The Contribution of Ototoxic Medications to Hearing Loss among Older Adults

by

Yoonmee Joo

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

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Approved:

Margaret Wallhagen Chair

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Committee in Charge

Dedication

This dissertation is dedicated to my family; my husband Jihwi Kim, my son Jooahn and Joohyung. I have been very blessed to have all of you through my entire journey of the doctoral study for my joy and comfort.

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Along the long way, I have sometimes wondered if I was going a right way and why I was going this way. The questions brought me to the answer that Jesus is the way and the truth and the life. He called me and has worked through me for His purpose. I could complete my doctoral study by His grace.

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The Contribution of Ototoxic Medications to Hearing Loss among Older Adults

Yoonmee Joo, RN, PhD

Abstract

Background: Age-related hearing loss effects negatively on an individual's physical, psychosocial, and social status. Hearing loss may be accelerated in patients taking ototoxic medications. Given the high prevalence of hearing loss, drug-related ototoxicity among older adults may be a critical public health problem.

Objectives: The aims of this dissertation were: 1) to identify risk factors of age-related hearing loss from a literature review; 2) to explore the prevalence of ototoxic medication use and the associated factors for ototoxic medication use; 3) to investigate the association of ototoxic medication use with incidence and progression of hearing loss.

Methods: A search of the literature on risk factors for age-related hearing loss was performed using the electronic PubMed database. The research data were extracted from the Epidemiology of Hearing Loss Study datasets. The cohort was examined in 1993-1995 (n = 3753), 1998-2000 (n = 2800), and 2003-2005 (n = 2395) in Beaver Dam, Wisconsin. Medication use was obtained from the standardized questionnaire that was administered by the examiners. Hearing loss was defined as a pure tone average at 500, 1000, 2000, and 4000 Hz greater than 25 dB HL in either ear.

Results: The Literature review revealed that the most consistently strong risk factors for age-related hearing loss across the studies were genetics, current smoking, diabetes, cardiovascular diseases, and obesity. The prevalence of any ototoxic medication use increased from 84% to 91% over the 10-year follow-up period. Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and diuretics were common ototoxic medications taken by older adults.

Hypertension, diabetes, cardiovascular diseases, and history of smoking were associated with ototoxic medication use. Participants who took a loop diuretic had a high incidence of hearing loss for 10 years. Participants who took NSAIDs or a loop diuretic had worse progression of hearing loss over 10 years. Also, the use of concomitant ototoxic medications was associated with the incidence and severity of hearing loss.

Conclusion: Ototoxicity may interact with aging leading to a more severe hearing loss than that associated with age alone. The findings suggest that ototoxic medications should be considered a potentially modifiable contributor to age-related hearing loss.

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Chapter 1 Introduction

Problem Statement

Age-related hearing loss —also known as presbycusis— is a common sensory deficit among older adults (Van Eyken, Van Camp, & Van Laer, 2007). It is generally a bilateral sensorineural deficit and the progression of decline speeds up with age (National Institute on Deafness and other Communication Disorders [NIDCD], 2013). The condition usually begins with high tone hearing loss affecting the perception of consonants, such as the "s" and "th" sounds, and has a major adverse effect on communication, particularly in noisy situations. Over time, the ability to detect sounds in low frequencies is also impacted (Huang & Tang, 2010).

Age-related hearing loss is a very common chronic condition, yet it often goes unrecognized by older adults because the decline in hearing is gradual (Dalton et al., 2003). The need to treat hearing loss is also often unrecognized by older adults and health care providers because it is frequently perceived to be part of an inevitable aging process and is not life threatening (Kochkin, 1999; Wallhagen & Pettengill, 2008). However, some data suggest that age-related hearing loss may be prevented or delayed, rather than being accepted as a normal age-related progression (Zhan et al., 2010). Many older adults experience a decline in hearing with age, but these experiences vary, and the average hearing ability of a certain age group should not be generalized to all individuals in that age group (National Institute for Occupational Safety and Health [NIOSH], 1998). In addition to age, other risk factors may contribute to age-related hearing loss, and some older adults may experience more significant hearing problems than others in the same age group (NIOSH, 1998).

Background and Significance

The NIDCD (2010) reported that age-related hearing loss is the one of the four leading

chronic conditions among older adults; 30% of adults aged 65-74 years and approximately half of adults older than 75 years experience hearing loss. This prevalence of age-related hearing loss will continue to increase with the rapidly growing number of older adults in the population, and is expected to affect twice as many US adults aged 65 years and older by 2030 (Adminstration on Aging, 2008). The National Health and Nutrition Examination Survey reported that more than 30% of people aged 40-49 years are already experiencing hearing loss (Agrawal, Platz, & Niparko, 2008).

The effects of age-related hearing loss on an individual's physical, psychosocial, and social status are multiple (Karpa et al., 2010). Hearing loss impacts the quality of life of older adults. It is associated with diminished functional status as measured by activities of daily living (ADLs) such as walking, bathing, personal grooming, dressing, eating, transporting, using the toilet, and instrumental ADLs (IADLs) such as shopping, preparing meals, financing, using the telephone, doing heavy chores, doing light housework, and doing laundry (Dalton et al., 2003). Although ADLs are not likely to be directly related to hearing loss, older adults with hearing loss experience more difficulties with ADL functions even after controlling for other factors (Dalton et al., 2003; Strawbridge, Wallhagen, Shema, & Kaplan, 2000). Hearing loss also impairs IADL functions in older adults, as communication is a key element in maintaining these functions (Dalton et al., 2003).

Hearing loss is also adversely related to quality of life scores in both the physical and mental domains (Chia et al., 2007). Hearing loss affects not only the individuals who lose their hearing but also their family members, partly because it creates frustration related to communication difficulties (Lopez-Torres Hidalgo et al., 2009). Older adults with hearing loss may suffer from depression, low self-esteem, and loneliness due to communication difficulties

and social isolation (Wallhagen, Strawbridge, Shema, Kurata, & Kaplan, 2001). Frustration with the inability to hear in complex auditory environments can lead to a decreased willingness to engage in social relationships, resulting in a sense of isolation (Schneider et al., 2010). Despite these negative impacts, only 20% of people who could benefit from hearing aids try them, and adherence to hearing aids is even lower due to factors such as stigma, cost, and inconvenience (Wallhagen, 2010; Walling & Dickson, 2012).

Although hearing acuity may decline with aging, there is wide variation in age of onset, severity of hearing loss, and disease progression (Van Eyken, Van Camp, & Van Laer, 2007). Healthy older adults who have not been exposed to ototraumatic or ototoxic agents may have normal hearing acuity even at an advanced age (Van Eyken et al., 2007). The risk of age-related hearing loss is not only related to age, but also depends on individual susceptibility factors for hearing loss (Pyykko, Toppila, Zou, & Kentala, 2007). Gender and race may contribute to differences among individuals, and extrinsic damage and/or intrinsic diseases may accelerate age-related changes in the ear (National Institute of Health Consensus Development Program, 1990; Pyykko et al., 2007). Although it is a common condition and frequently unrecognized by older adults, age-related hearing loss should be considered like any other chronic disease that has preventable features.

Hearing loss may be accelerated in people taking ototoxic medications. Similar to people with age-related hearing loss, people with ototoxic drug-related hearing loss may also be ignoring the implications of disregarding the change in their hearing abilities. Given the high prevalence of hearing loss, drug-related ototoxicity among older adults may be a critical public health problem. At the same time, research into the association between ototoxic drugs and age-related hearing loss has not been very convincing. Although review articles state that ototoxic

medications frequently cause hearing loss in older adults (Liu & Yan, 2007; Van Eyken, Van Camp, & Van Laer, 2007), there is little evidence to support this conclusion. Most studies of hearing loss have been conducted with children or by using animal models. The majority of animal studies were done to determine the mechanisms underlying ototoxicity in the ear and the results may not be easily transferable to humans (Palomar Garcia, Abdulghani Martinez, Bodet Agusti, Andreu Mencia, & Palomar Asenjo, 2001). This highlights the importance of research exploring associations between ototoxic medication use and the incidence and progression of hearing loss in older adults.

Theoretical Perspectives

Age-related hearing loss is a complex condition that is not uniform in etiology. However, understanding the associated factors to age-related hearing loss could serve as a useful framework for age-related hearing loss research. A conceptual framework for the development of age-related hearing loss is shown in Figure 1.1. This is designed to evaluate the relative contribution of various factors to age-related hearing loss.

In addition to the aging process itself, other damages to the cochlea can accumulate over a lifetime and contribute to the decline in hearing experienced by older adults (Yamasoba et al., 2013). Genetic factors, environmental factors (noise and chemicals), lifestyle factors (smoking, alcohol, and diet), and individual health factors (ototoxic medications, diabetes, cardiovascular disease [CVD], and obesity) are related to increasing oxidative stress by production (Abdul-Ghani & DeFronzo, 2008; Huang & Tang, 2010; Kidd Iii & Bao, 2012; Kovacic & Somanathan, 2008). Oxidative stress damages cells and tissues in the cochlea (Huang & Tang, 2010). Antioxidant genes and antioxidant supplements may act against oxidative stress, and people with the deletion of certain antioxidant genes may be more prone to damage by reactive oxygen

species (ROS), and therefore more susceptible to hearing loss (Bielefeld, Tanaka, Chen, & Henderson, 2010). However, no definite conclusion can be drawn about antioxidant supplements (Bielefeld et al., 2010; Kidd Iii & Bao, 2012; Sha, Kanicki, Halsey, Wearne, & Schacht, 2012; Yamasoba et al., 2013).

Ototoxicity is cellular degeneration in the inner ear caused by a drug's side effects (Rybak & Ramkumar, 2007). Ototoxicity may interact with aging, leading to a more sever hearing loss than that associated with age alone (Weinstein, 2000). ROS and oxidative stress is often the common pathway by which medications cause ototoxicity within the cochlea (Kovacic & Somanathan, 2008; Pickles, 2008).

This conceptual framework provides the basis for exploration of variables, and can be used in the study to predict age-relate hearing loss in older adults. It may allow the investigation of the effects of ototoxic medications on age-related hearing loss while taking into consideration the large variation in individual susceptibility with other risk factors. Research exploring the association of ototoxic medications with age-related hearing loss in older adults should consider confounding factors as shown in the conceptual framework.

Overview of Dissertation

The purpose of this dissertation is to present the findings of a literature of review and the secondary analyses of data from the large Epidemiology of Hearing Loss Study dataset. The overall aim of the dissertation is to explore the association between ototoxic medication use and hearing loss in older adults.

The dissertation is presented in five chapters. In this chapter, the significance of age-related hearing loss, as well as theoretical perspectives for risk factors of age-related hearing loss, are discussed. Chapter 2 presents findings from a literature review for risk factors of age-

related hearing loss. Chapter 3 presents the prevalence of ototoxic medication use among older adults and the associated factors of ototoxic medication use. Chapter 4 presents findings of a longitudinal study investigating the association of ototoxic medication use with incidence and progression of hearing loss among older adults. Finally, Chapter 5 presents the conclusion from the three studies including implications for clinical practice and recommendations for future research.

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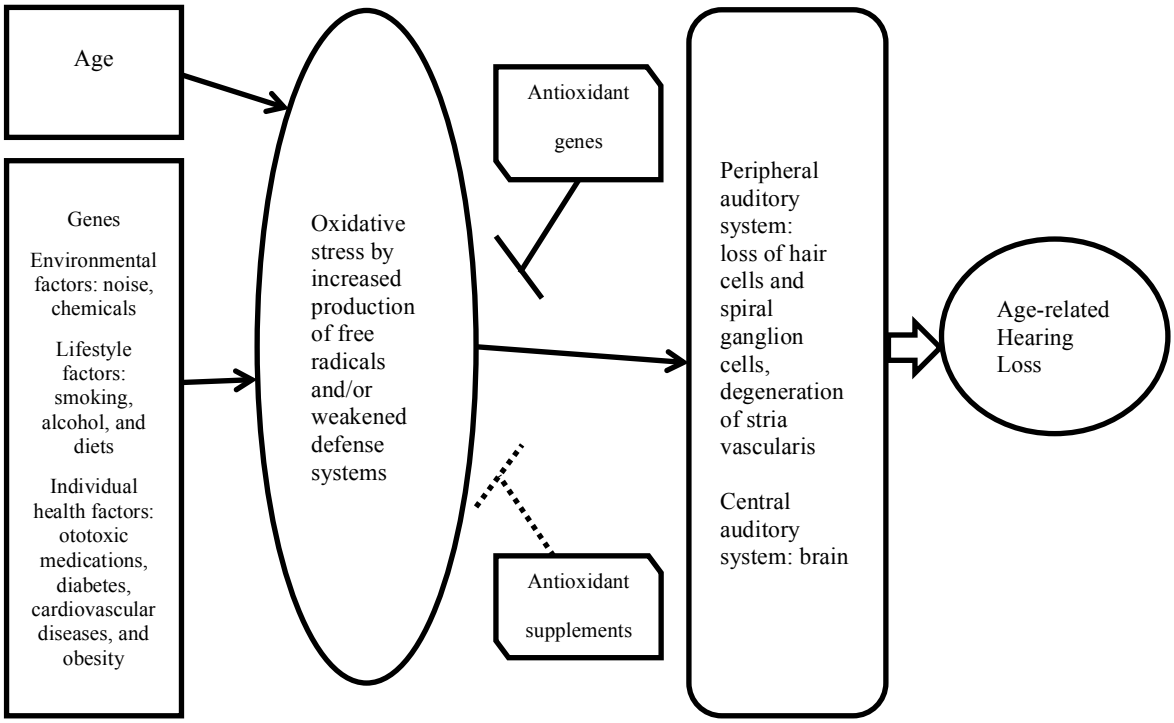

Figure 1.1. Conceptual Framework for Developing of Age-related Hearing Loss

Chapter 2 Risk Factors for Age-related Hearing Loss

Abstract

Background: Age-related hearing loss (ARHL) is generally a bilateral sensorineural deficit that increases at an accelerated rate with age. Strategies to prevent ARHL should focus on identifiable factors. The purpose of this study is to determine risk factors interacting with ARHL

Methods: The PubMed database was searched using the term "age-related hearing loss." Multiple combinations of terms were searched with the MeSH database using "hearing loss, aged" or "presbycusis" and "risk factors." Then, limits were applied: 1) published in English since 2000, 2) human adults, and 3) bilateral sensorineural hearing loss. Review articles were excluded.

Results: Genetic factors (genes, race, and sex), environmental factors (noise, chemicals, smoking, and diet), and individual health factors (ototoxic medications, cardiovascular diseases, diabetes, and obesity) influence ARHL. The findings suggest that environmental and individual risk factors can accumulate over a lifetime and contribute to the hearing loss in older people. However, attempts to correlate specific risk factors to ARHL have resulted in conflicting results.

Conclusions: Many risk factors are modifiable and are possible targets for minimizing ARHL. Nurses can play an important role by screening potential risk factors in communities or clinics and educating people on the risk factors and lifestyle changes in order to delay ARHL.

Key words: age-related hearing loss, risk factors, older adults.

Background

Age-related hearing loss (ARHL) is generally a bilateral sensorineural deficit that increases at an accelerated rate with age (National Institute on Deafness and other Communication Disorders [NIDCD], 2013). More than 30% of people aged 40-49 years are already suffering from hearing loss (Agrawal, Platz, & Niparko, 2008) and according to data from NIDCD (2013) approximately half of adults older than 75 years of age experience hearing loss. ARHL has multiple negative effects on an individual's physical, psychosocial, and social status (Karpa et al., 2010).

Although many older adults experience hearing decline with age, other risk factors can contribute to ARHL and some elderly individuals may experience more significant hearing problems than others in the same age group depending on individual susceptibility and exposure to environmental factors that may damage hearing (Pyykko, Toppila, Zou, & Kentala, 2007). Strategies to prevent ARHL should focus on such identifiable factors. The purpose of this paper is to review the risk factors that interact with age in the development of ARHL as a basis for the development of targeted hearing conservation strategies. Specifically, this literature review will: 1) synthesize the literature examining the associations between risk factors and ARHL; 2) discuss the strengths and limitations of the current literature; and 3) discuss the recommendations for implications for public health care and future research.

Methods

Literature Search

A search of the literature on risk factors for ARHL was performed using the electronic PubMed database and the terms "age-related hearing loss" and "risk factors." In addition, multiple combinations of terms were searched with the MeSH database using "hearing loss,

aged" or "presbycusis" and "risk factors." PsychINFO and the Cochrane Library were also searched with similar terms. In addition, reference lists from every relevant paper were examined to determine whether pertinent studies had been missed through the data base searches.

Inclusion criteria included: 1) published in English and since 2000, 2) using human adult subjects, 3) addressing bilateral sensorineural hearing loss, and 4) clinical trials, randomized controlled trials or meta-analyses. A total of 305 articles were retrieved from the database using the various combinations of the keywords mentioned above. After applying the inclusion criteria, 71 articles were selected. Case reports (n = 7) excluded because the focus of this review is to critique primary research articles. Studies for treatment effect (n = 12) and studies for consequences of hearing loss (n = 7) were also excluded. Most studies focused on otological diseases and head trauma related to unilateral hearing loss; unilateral hearing impairment was excluded. Factors such as ear infections, otosclerosis, Meniere's disease, and head injury were exclusion criteria in the majority of ARHI studies. Therefore, studies focusing on these issues (n = 20) were excluded. Additionally, seven studies without risk factors were eliminated and eight articles were included from reference lists, yielding 33 research articles to be selected to review (Figure 2.1).

Study Quality

Each study was evaluated for study quality using a critical appraisal tool from Zaza et al. (2000). The evaluation included checking for bias in sampling, measurements, analysis, and interpretation of results. Based on the recommendations of Sanderson, Tatt, and Higgins (2007), no total numerical score was given, but each article was classified as moderate to high quality or low quality (Table 2.1). The criteria for moderate to high quality included: 1) adequate study population sample, 2) valid and reliable measures, 3) appropriate statistical analysis, 4)

appropriate interpretation of results. Additional criteria were: 5) clear study descriptions including potential confounding factors and 6) appropriate description of cases lost to follow-up in longitudinal studies.

Results

Table 2.1 shows a summary of characteristics of the studies regarding factors relating to ARHL. Major findings by risk factors for ARHL are summarized in Table. Helzner et al. (2005) and Fransen et al. (2008) studied for multi risk factors; therefore, their results are presented in different categories, when applicable.

Genetic Factors

Family history. Human research on ARHL supports that a family history of hearing loss is strongly correlated with ARHL (McMahon, Kifley, Rochtchina, Newall, & Mitchell, 2008; Christensen, Frederiksen, & Hoffman, 2001; Raynor et al., 2009). A maternal family history of hearing loss was more strongly associated with hearing loss in women compared to a paternal family history of hearing loss in men (McMahon et al., 2008). The heritability contribution to ARHL in older adults was estimated to be 40-50% (Chistensen et al., 2001; Raynor et al., 2009).

Ethnicity and sex. Susceptibility genes for ARHL are related to oxidative stress that may be part of the aging process (Liu & Yan, 2007). Glutathione S-transferase (GST) and N-acetyltransferase (NAT) are antioxidant enzymes that detoxify reactive oxygen species (ROS) in the inner ear, and are comprised of several gene classes. People who have the deletion of these antioxidant enzymes may be more prone to damage by ROS and, therefore, more susceptible to ARHL (Liu & Yan, 2007). Van Eyken et al. (2007) found the deletion of these two distinct susceptibility genes in the general European and the Finnish populations, originating from seven different countries. In the United States, White subjects with ARHL had more GSTM1 and

GSTT1 deletions and NAT2*6A mutations than a control group (Bared et al., 2010). The GSTM1 deletion was found more frequently in White Hispanics than in White non-Hispanics in the ARHL group. These data suggest that susceptibility genes may vary by ethnicity.

In a study by Pratt et al. (2009), ARHL was more common among men than women, and more common among White participants than Black participants. Low-frequency (500, 1000, and 2000 Hz) hearing loss was most common among White men, followed by White women, Black men, and Black women. High-frequency (2000, 4000, and 8000 Hz) hearing loss was most common among White men, followed by Black men, White women, and Black women (Helzner et al., 2005). Sex differences in hearing loss may be due to other factors besides sex-specific pathophysiologic mechanisms, such as occupational exposure, because men had modestly greater risk factors than women, even after adjusting for age.

Environmental Factors

Noise exposure. Noise-induced hearing loss (NIHL) has been extensively studied (Liu & Yan, 2007), but the contribution of noise exposure to the development of ARHL less so. It is difficult to distinguish between NIHL and ARHL in people with lifelong noise exposure because NIHL is bilateral sensorineural hearing loss that develops slowly over several years (Van Eyken, Van Camp, & Van Laer, 2007). Both hearing loss are related to deterioration of the cochlear structures, particularly hair cells (Gratton & Vazquez, 2003).

A European study found that there was a significant association between history of occupational noise exposure for more than one year and worse the high frequencies (2000, 4000, and 8000 Hz) hearing thresholds (Fransen et al., 2008). However, Cruickshanks et al. (2010) showed that noise exposure was not significantly correlated with the 10-year cumulative incidence of hearing loss in older adults. They noted that hearing loss tends to worsen with

current noise exposure, but progressive hearing loss among older adults may be mainly due to aging. Albera, Lacilla, Piumetto, and Canale (2010) also concluded that progressive hearing loss after noise exposure for at least 10 years was related more to age itself than to the duration of noise exposure. Ciorba et al. (2011) supported these findings in an Italian sample exposed to occupational noise for at least 3 years.

One cohort study evaluated the 15-year change in audiometric thresholds among men (Gates, Schmid, Kujawa, Nam, & D'Agostino, 2000). NIHL is typically shown as a discrete elevation (notch) of the hearing thresholds in the 3000 to 6000 Hz region in the audiogram (Cooper & Owen, 1976), while ARHL usually progressive across the high frequencies. The finding showed less threshold changes over the 15 years in the notch frequencies but significant changes in the adjacent frequency at 2000 Hz and 8000 Hz among notch groups. The impact of noise causing the "notch" at the given frequency results in no further or few changes across time, while frequencies around the notch tend to catch up in terms of loss with aging. However, notched audiograms should be interpreted cautiously as a notch may not be due to noise (Nondahl et al., 2009). It is difficult to conclude from the studies whether noise exposure contributes to ARHL in older adults because there is great variation in the number of noisy jobs a person has, the age of the first exposure, the noise levels, and the duration of exposure.

Chemical exposure. In addition to noise, industrial chemicals are considered environmental risk factors for ARHL. Chemical toxins reach the inner ear via the bloodstream and damage inner ear structures and their hearing functioning. Furthermore, more central effects have been seen, notably with solvent exposures (Morata, 2007).

A cross-sectional study conducted with male workers in Taiwan to investigate the effect of toluene and noise exposure on hearing loss (Chang et al., 2006) found that workers exposed to

toluene and noise had four times greater risk than those exposed to noise only. There was no significant dose effect of toluene exposure. Sliwinska-Kowalska et al. (2003) found that workers exposed to styrene had approximately four times greater risk of hearing loss than unexposed workers. Those exposed to both styrene and noise had two to three times greater risk of hearing loss than the styrene or noise only exposure groups. The group exposed to styrene, toluene and noise had 21.5 times greater risk of hearing loss than unexposed group. Morata et al. (2002) also studied the effect of styrene on workers' hearing using urine samples as a biological exposure marker. They found that styrene was significantly related to bilateral high frequency hearing loss, consistent with the previous study.

Exposure to pesticide is also a risk factor for hearing loss. A study conducted with pesticide applicators (Crawford et al., 2008) found that lifetime days of any pesticide use were significantly associated with developing hearing loss. In addition, a longitudinal study of veterans (Park et al., 2010) found that patella lead levels were significantly correlated with poor high frequencies hearing, while tibial lead was significantly correlated with a progressive increase in hearing thresholds over 20 years.

Most chemical exposure studies have conducted in the occupational settings. Multiple exposures to noise and chemicals may have synergistic ototoxic effects on hearing loss. However, there is little research investigating the effect of occupational chemical exposure on ARHL in the general population after retirement or termination of exposure.

Lifestyle Factors

Cigarette smoking and alcohol consumption. It been suggested before that smoking and alcohol consumption are related to cardiovascular effects, which then extend to risk of

hearing loss (Fransen et al., 2008). Smoking itself may cause oxidative damage in the inner ear and nicotine reduces the blood supply to the cochlea (Cruickshanks et al., 1998).

There was a significant association between current smoking and prevalent hearing loss among older adults (Itoh et al., 2001; Gopinath et al., 2010a), but found no significant association between pack-years of smoking and hearing loss or incident hearing loss over 5 years (Gopinath et al., 2010a). However, a European study (Fransen et al., 2008) found that the number of pack-years of smoking was significantly associated with hearing loss among ever-smokers aged 53-67 years. Cruickshanks et al. (1998) also found a significant dose-response effect among participants aged 60-69 years.

In contrast to smoking, light to moderate alcohol consumption (≤2drinks/day or <30g/day) had a significant positive correlation with hearing function in older adults (Gopinath et al., 2010a; Itoh et al., 2001). The apparent protective effect of regular moderated alcohol consumption on hearing is similar to its effects on the cardiovascular system (Fransen et al., 2008). Interestingly, cross sectional studies from Europe and Japan found that there was no increased risk for hearing loss with heavy alcohol consumption (Fransen et al., 2008; Gopinath, et al., 2010a; Itoh et al., 2001).

Nutrition. Nutrition may play a role in the pathogenesis of auditory disorders, and poor nutrition among older adults may affect ARHL (Bales & Ritchie, 2004). Vitamin B-12 and folate deficiency is a common problem among older adults, and micronutrient status may affect cellular metabolism, nerve function, and vascular function in the auditory system among older adults (Gates & Mills, 2005). A randomized controlled trial by Park et al. (2007) found that hearing-impaired participants had a higher prevalence of vitamin B-12 deficiency than those with normal hearing. However, three-month of vitamin B-12 supplementation did not significantly improve

hearing levels in vitamin B-12 deficient individuals.

Several studies examined the association between diet and ARHL in the Blue Mountain Hearing Study participants. Higher glycemic load intake and higher cholesterol intake, and higher carbohydrate and sugar intake were significantly related to the 5-year incidence of hearing loss (Gopinath et al., 2010b; Gopinath et al., 2011). In addition, fat and retinol intakes were related to poorer hearing ability (Spankovich et al., 2011). However, higher carbohydrate intakes were associated with better hearing ability (Spankovich et al., 2011), which is not consistent with the finding of Gopinath, et al. (2010b).

Several possible mechanisms may explain the association between diet and ARHL. High carbohydrate and cholesterol diets are associated with cardiovascular diseases and diabetes, which cause disruption to the cochlear blood flow and are considered risk factors for ARHL (Nakashima et al., 2003). Atherosclerotic diets result in thickening of the stria vascularis and hair cell loss in the cochlear in the animal models (Guo, Zhang, Du, Nair, & Yoo, 2005). Additionally, oxidative stress generated by hyperglycemia could damage the cochlear (Seidman, 2000). However, it may be difficult to evaluate the effects of individual nutrients on hearing as people often take combinations of nutrients daily.

Individual Health Factors

Ototoxic medications. Although review articles state that ototoxic medications (aminoglycoside antibiotics, chemotherapeutics, salicylates, and loop diuretics) frequently cause ARHL (Van Eyken, Van Camp, & Van Laer, 2007), there is little human research, especially for older adults, on this topic and less evidence to support these conclusions.

Helzner et al.(2005) reported that people who used salicylates, quinine, and loop diuretics currently did not have a higher risk of hearing loss. Conversely, salicylates had a protective

effect on hearing loss in the cohort.

Two studies were focused on the association between hearing loss and analgesic uses such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), and acetaminophen in large population-based studies (Curhan, Eavey, Shargorodsky, & Curhan, 2010; Curhan, Shargorodsky, Eavey, & Curhan, 2012).

Curhan et al. (2010) conducted a study with men using self-reported professionally diagnosed hearing loss over 20 years. The risk of hearing loss in regular users of analgesia (≥2 times/week) was 12% higher for aspirin, 21% higher for NSAIDs, and 22% higher for acetaminophen, compared to subjects who used these medications less than 2 times per week. The risk of hearing loss was significantly higher in men younger than 50 years for aspirin, NSAIDs, and acetaminophen. Also, the risk of hearing loss was positively associated with duration of regular use. The same authors did a similar study with women using self-reported hearing loss over 22 years (Curhan et al., 2012). The risk of hearing loss was significantly higher with the regular use of ibuprofen and acetaminophen than with the use of these medications less than 2 times per week. The risk of hearing loss was significantly greater in younger (< 50 years) women who used ibuprofen more than 6 days per week. However, there was no significance between aspirin use and the risk of hearing loss. Furthermore, the effect of multi analgesic agents was not greater than total of each individual analgesic use. However, there was no information on the analgesic doses that participant took in either study.

In summary, results of human studies on both the protective and toxic impact of ototoxic drug use on hearing loss remain controversial.

Cardiovascular disease. CVD may affect the microvascular system of the stria vascularis that provides a large capillary blood supply to the cochlear. Because the blood supply of the

cochlear is most prominent at its apex where the low frequency sounds are transduced, microvascular changes are most likely to affect low frequency hearing (Gates, Cobb, D'Agostino, & Wolf, 1993).

Women with a history of myocardial infarction (MI) had nearly twice the risk of cochlear loss than those with no history of MI, but a similar risk was not found in men (Torre, Cruickshanks, Klein, Klein, & Nondahl, 2005). Hutchinson, Alessio, and Baiduc (2010) also evaluated the relationship between CV health and hearing function among four age groups. They found significantly that participants with low CV fitness in the older age group (49-78 years) had more hearing loss compared to those in the same age group with good CV fitness. Cochlear function was also better among older persons with high CV fitness compared to those with medium or low CV fitness. In addition, Gopinath and collegues (2009) showed that participants with moderate to severe hearing loss had a significantly greater history of stoke.

Diabetes. Diabetes may affect auditory function by microangiopathy, cellular changes to the peripheral nervous system, and metabolic changes from generation of ROS within the cochlear (Frisina, Mapes, Kim, Frisina, & Frisina, 2006). Mitchell et al. (2009) evaluated the relationship between diabetes and ARHL. Fifty percent of those with diabetes had ARHL compared to 38% of those without diabetes. Five-year incidence percentages of hearing loss were similar for both groups, but participants with newly diagnosed diabetes showed significant progression of hearing loss over 5 years compared to participants without diabetes. Frisina et al. (2006) found that hearing function was significantly worse in pure-tone thresholds, wide-band noise thresholds, speech reception thresholds, and otoacoustic emissions among older adults with diabetes as compared to those without diabetes.

In addition, veterans aged 60 years or younger with as compare to those without diabetes

had greater hearing loss, especially in the high frequencies (Vaughan, James, McDermott, Griest, & Fausti, 2006). A similar relationship was not found in veterans older than 60 years of age. Similar differences were found with participants in Japan (Uchida, Sugiura, Ando, Nakashima, & Shimokata, 2010).

Diabetes appears to speed up the progression of ARHL in younger population, but age still appears to play a significant role.

Obesity. Obesity itself may be an independent risk factor for ARHL by obesity-related oxidative stress beside obesity-induced systemic diseases (Hwang, Wu, Hsu, Liu, & Yang, 2009). Waist circumference was positively correlated to pure tone average (Hwang et al., 2009). Men younger than 55 years with a larger waist circumference had poorer hearing after controlling for body mass index, diabetes and CVD. Women older than 55 years had the same association between waist circumference and pure tone average at high frequencies. This age-sex specific difference of ARHL is similar to that of heart disease (Lee & Foody, 2008). Fransen et al. (2008) found that participants with higher body mass index had worse hearing function after controlling CVD and smoking.

Discussion

Extensive research has been undertaken to elucidate the contribution of risk factors to ARHL. The findings discussed in this review support the conclusion that environmental, lifestyle, and individual health risk factors can accumulate over a lifetime and contribute to the hearing loss experienced by older people. Genetic factors and the aging process itself are also critical factors associated with degeneration in hearing ability. Furthermore, the interaction of intrinsic-extrinsic factors, such as co-exposures to chemicals and noise and CVD risk factors related to diet, has been discussed to reveal the underlying complex associations of risks for

ARHL.

The most consistently strong risk factors for ARHL across the studies are genetics, current smoking, diabetes, CVD, and obesity. Noise was related to early development of hearing loss but its relationship to the progression of ARHL remains unclear. Occupational exposure to organic solvents such as styrene and toluene has been found to relate to hearing loss, with ototoxic effects exacerbated with coexposure to noise, but most studies are limited to occupational settings. Diet and ototoxic medications showed conflicting results for ARHL, but are considered as potentially strong risk factors.

There are a number of limitations in the literature that need to be addressed. The studies relying on self-reported historical information could be affected by recall bias in the medical or personal histories of the participants. Also, information from self-administered questionnaires may attenuate the association between risk factors and hearing loss because older adults may accept hearing loss as a natural part of the aging process.

Attempts to correlate specific risk factors to ARHL have resulted in conflicting results. This may be due to different inclusion and exclusion criteria used to define ARHL. Also, the adjusted confounding factors used in the analyses varied among studies that used the same outcome. Further, the variations in study samples with different age ranges, measurements, and research questions make comparisons across studies difficult.

Measurements ranged from simple questionnaires to full audiological assessments using pure tone audiometry. Even with standardized PTA, the definition of hearing loss was not the same across studies. There is no universally accepted definition of hearing loss. Therefore, some studies may have failed to find an association due to their use of a different definition of hearing loss.

Implications for practice and research

The need to treat AHRL is often unrecognized by older adults and health care providers as it is thought to be part of an inevitable aging process and is not a life-threatening condition (Wallhagen & Pettengill, 2008). However, ARHL should be considered a disorder that may be prevented or delayed and treated like any other chronic disease that has preventable features (Zhan et al., 2010).

Although some of the risk factors for hearing loss in this literature review are factors such as age, sex, and race that cannot be changed, many are modifiable and potential targets for prevention of ARHL. The effect of risk factors for ARHL seems greater in the younger population. Early detection of hearing loss through screening could help adults benefit by delaying ARHL and its progression (Chou, Dana, Bougatsos, Fleming, & Beil, 2011). Public health nurses and providers can screen for hearing loss in those at risk populations and educate them regarding lifestyle factors, such as smoking and diet, that may minimize hearing loss. Screening hearing should be a part of health checklist, especially for people who have CVD and diabetes, just like annual eye exams. Public health providers may consider ototoxicity as an adverse effect when they prescribe medications. Also they need to refer high-risk populations for hearing loss to an audiologist for further evaluation and treatment.

Single global questions like "Do you have a hearing problem?" may be useful to capture subjective hearing problems and to identify people who need a referral for formal audiometric testing. A simple question in the community setting is inexpensive, quick, and easy to administer without special equipment or training. Several simple objectives measures may be useful along with the single item in the identification of hidden or unrecognized hearing loss (Bagai, Thavendiranathan, & Detsky, 2006).

Although many risk factors associated with ARHL have been described, some may yet be discovered. It is still not known how many environmental and genetic factors contribute to the etiology of ARHL, how they interact with each other, or what their individual contributions are. Many studies for hearing loss are still limited to young adults or occupational settings for noise and chemical. Retired older adults need further evaluation for the long-term effects of risk factors for ARHL.

Several studies found the effects of diet and medications were still controversial. Because it is difficult to know whether risk factors preceded hearing loss or vice versa in cross-sectional studies, longitudinal studies that can assess the impact of long–term exposure to various risk factors are needed to clarify their association with hearing loss in older adults. Identifying further risk and protective factors for ARHL and developing appropriate interventions are a worthy goal for further research.

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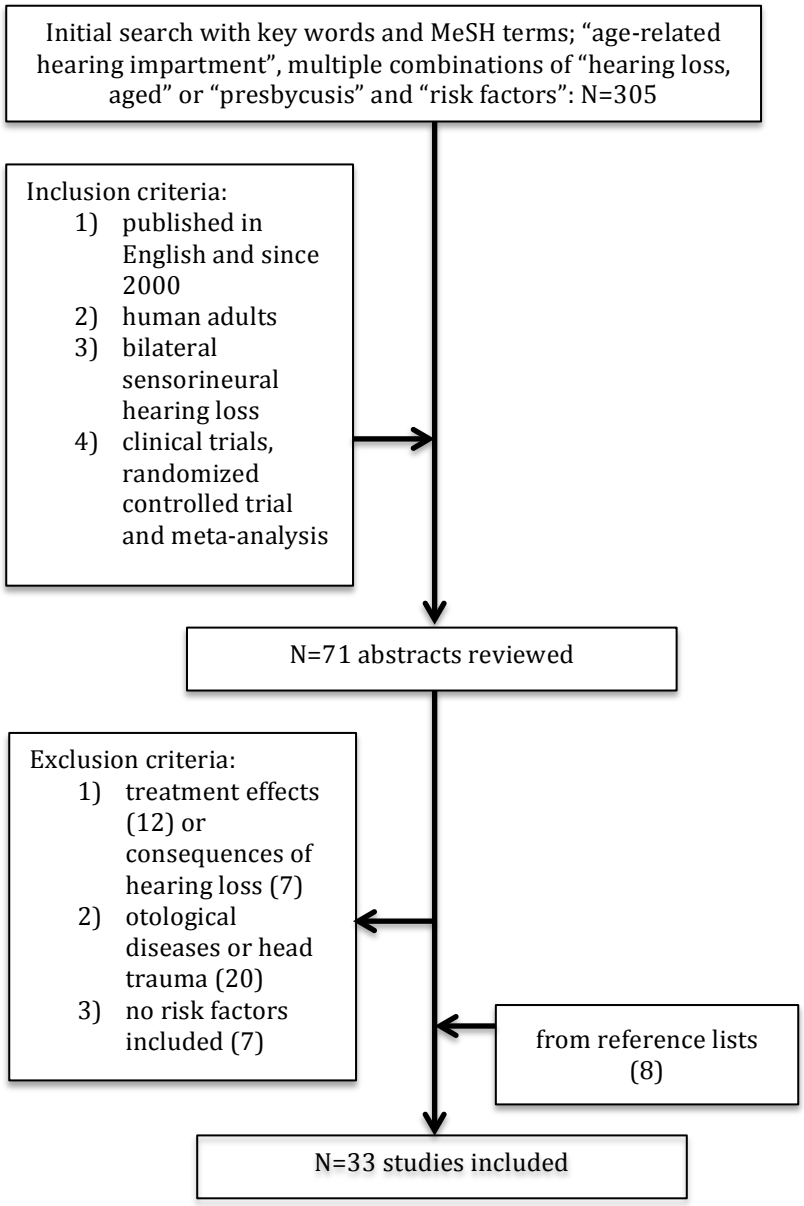

Figure 2.1. Flow Chart Showing the Selection of Studies in the Literature Review

Table 2.1. Characteristics of Age-related Hearing Loss Studies by Risk Factors

Investigator, Year	Country of study	Design	Subjects	Measurement	QL[1]
Genetic Factors: **Family history**					
Christensen et al., 2001	Denmark	Prospective cohort	Twins from the Danish Twin Registry (3928)	Self-reported HL[2]	-
McMahon, et al., 2008	Australia	Prospective cohort	Adults from BMHS[3] (2669)	HL on PTA[4] at 500, 1000, 2000, 4000 Hz > 25 dB, family history	+
Raynor, et al., 2009	US	Prospective cohort	Adults from EHLS[5] (3510)	HL on PTA at 500 to 4000Hz >25 dB, family history	+
Ethnicity and Sex					
Van Eyken, et al., 2007	Belgium, UK, The Netherlands, Germany, Denmark, Italy, Finland	Clinical trial	Adults from nine centers (2111)	PTA thresholds at 125 to 8000 Hz, genotypes	+
Pratt, et al., 2009	US	Cross-sectional	Adults from Cardiovascular Health Study (548)	HL on PTA at 250 to 8000 Hz >25 dB, sex, race	-
Bared, et al., 2010	US	Case-control	HL group (55) vs. Control group (79)	HL on PTA at 500 to 4000Hz >30 dB, DNA	+
Environmental Factors: **Noise exposure**					
Gate, et al., 2000	US	Prospective cohort	Men from Framingham Heart Study (203)	PTA thresholds from 250 to 8000 Hz, no notch (< 15 dB elevation), small notch (15-34 dB elevation), and large notch (≥ 35 dB elevation) in the 3000-6000 Hz	+
Albera, et al., 2010	Italy	Cross-sectional	Men (568)	HL on PTA at 2000, 3000, 4000 Hz >25 dB, occupational noise exposure	+
Cruickshanks, et al., 2010	US	Prospective cohort	Adults rom the EHLS (3753)	HL on PTA at 500 to 4000 Hz >25 dB, occupational noise exposure	+

[1] QL=Quality Level
[2] HL=hearing loss
[3] BMHS=Blue Mountains Hearing Study
[4] PTA=Pure tone average
[5] EHLS=Epidemiology of Hearing Loss Study

Table 2.1. Characteristics of Age-related Hearing Loss Studies by Risk Factors (continued)

Investigator, Year	Country of study	Design	Subjects	Measurement	QL
Ciorba, et al., 2011	Italy	Cross-sectional	Older adults (460)	PTA thresholds at 250 to 8000 Hz, occupational noise exposure	-
Chemical exposure					
Crawford, et al., 2008	US	Cross-sectional	White men licensed private pesticide applicators from the Agricultural Health Study (14229)	Self reported HL, pesticides exposure	-
Park, et al., 2010	US	Cross-sectional	Men from the Normative Aging Study (448)	HL on PTA at 500 to 4000 Hz > 25 dB, bone lead levels	+
Co-exposure to Noise and Chemical					
Morata, et al., 2002	US	Case-control	Workers at fiberglass product industry (313) Workers at metal products industry (78) Workers at a mail distribution terminal (81)	HL on PTA at 1000 to 8000 Hz > 25 dB, styrene exposure, noise exposure	+
Sliwinska-Kowalska, et al., 2003	Poland	Case-control	Workers at yacht yards and plastic factory (290) Workers with no styrene exposure (223)	HL on PTA at 1000 to 8000 Hz > 25 dB, styrene exposure, noise exposure	+
Chang, et al., 2006	Taiwan	Case-control	Male workers at an adhesive materials manufacturing plant (58) Male workers exposed to noise exposure only (58) Male administrative clerks (58)	HL on PTA at 1000 to 6000 Hz ≥ 25 dB, toluene exposure, noise exposure	-
Lifestyle Factors: **Cigarette smoking and alcohol consumption**					
Itoh, et al., 2001	Japan	Case-control	Adults with HL (496) Age-matched older adults without HL (2807)	HL on PTA at 4000 Hz > 40 dB, smoking and alcohol intake	-
Gopinath, et al., 2010	Australia	Cross-sectional	Adults from the BMHS (2815)	HL on PTA at 500 to 4000 Hz > 25 dB, smoking status, alcohol intake	+
Nutrition					
Park, et al., 2006	US	Randomized, controlled trial	Older adults (93)	HL on PTA at 500 to 4000 Hz > 25 dB, vitamin B-12 status	+
Gopinath, et al., 2010	Australia	Cross-sectional	Adults from the BMHS (2956)	HL on PTA at 500 to 4000 Hz > 25 dB, glycemic load value	+
Gopinath, et al., 2011	Australia	Cross-sectional	Adults from the BMHS (2956)	HL on PTA at 500 to 4000Hz > 25 dB, cholesterol level, dietary fat	+

Table 2.1. Characteristics of Age-related Hearing Loss Studies by Risk Factors (continued)

Investigator, Year	Country of study	Design	Subjects	Measurement	QL
Spankovich, et al., 2011	Australia	Cross-sectional	Adults from the BMHS (2111)	HL on PTA thresholds from 250 to 8000Hz, TEOAE[6], dietary status	+
Individual Health Factors: **Ototoxic medications**					
Curhan, et al., 2010	US	Longitudinal	Men from the Health Professionals Fellow-up Study (26917)	Self-reported professionally diagnosed HL, regular use of aspirin, NSAIDs[7] and acetaminophen	+
Curhan, et al., 2012	US	Longitudinal	Women from the Nurses' Health Study II (62261)	Self-reported HL, regular use of aspirin, NSAIDs and acetaminophen	+
Cardiovascular disease (CVD)					
Torre et al., 2005	US	Cross-sectional	Adults from the EHLS (1501)	Cochlear function on DPOAEs[8], self-reported CVD	+
Gopinath, et al., 2009	Australia	Cross-sectional	Adults from the BMHS (3654)	HL on PTA at 500, 1000, 2000, 4000 Hz >25 dB, stroke	+
Hutchinson, et al., 2010	US	Cross-sectional	Youth (26), Young adults (27), Middle-aged adults (26), Old adults (22)	PTA thresholds at 1000 to 4000 Hz and DPOAEs, cardiovascular fitness levels by VO_2 peak parameters	-
Diabetes					
Frisina, et al., 2006	US	Case-control	Diabetic type II group (30) vs. control group (30)	PTA at 250 to 8000 Hz, otoacoustic emissions, gap detection, speech perception, sentence perception	+
Vauhan, et al., 2006	US	Prospective cohort	Diabetic veterans (342) vs. non-diabetic veterans (353)	HL on PTA at 250 to 4000 Hz > 25 dB	+
Mitchell, et al., 2009	Australia	Prospective cohort	Diabetic participants (210) vs. non-diabetic participants (1648) from the BMHS	HL on PTA at 500, 1000, 2000, 4000 Hz > 25 dB	+
Uchida, et al., 2009	Japan	Cross-sectional	Adults (2306)	HL on PTA at 500, 1000, 2000, 4000 Hz > 25 dB, diabetes	+

[6] TEOAE=Transient evoked otoacustic emissions
[7] NSAIDs= nonsteroidal anti-inflammatory drugs
[8] DPOAEs=distortion product otoacoutic emissions

Table 2.1. Characteristics of Age-related Hearing Loss Studies by Risk Factors (continued)

Investigator, Year	Country of study	Design	Subjects	Measurement	QL
Obesity					
Hwang, et al., 2009	Taiwan	Cross-sectional	Adults (690)	PTA thresholds at 250 to 8000 Hz, waist circumference, BMI[9]	+
Multi risk factors					
Helzner, et al., 2005	US	Cross-sectional	Older adults (2052)	HL on PTA of 500, 1000, 2000 Hz > 25 dB and of 2000, 4000, 8000 Hz > 40 dB, ototoxic medication use, occupational noise exposure, lifestyle factors, and medical history	+
Fransen, et al., 2008	Belgium, UK, The Netherlands, Germany, Denmark, Italy, Finland	Cross-sectional, multicenter study	Adults from nine centers (4083)	Hearing thresholds at 250, 500, 1000, 2000, 4000, 8000 Hz, BMI, smoking, CVD, noise, chemical exposure, alcohol consumption, and medications	+

[9] BMI=Body mass index

Table 2.2. Major Findings by Risk Factors for Age-related Hearing Loss

Risk factors	Investigator, Year	Major findings
Family history	Christensen, et al., 2001	• Monozygotic twin pairs with self-reported hearing loss compared to dizygotic twin pairs (OR[10] 4.5; 95% CI[11] 2.7-6.8 vs. OR 1.5: 95% CI 1.0-2.2)
	McMahon, et al., 2008	• Maternal family history of hearing loss in women (OR 3.0; 95% CI 1.6-5.6) • Paternal family history of hearing loss in men (OR 2.0, 95% CI 1.01-3.9)
	Raynor, et al., 2009	• Family history in all (OR 4.69) and in women only (OR 5.49)
Ethnicity and sex	Van Eyken, et al., 2007	• GSTT1[12] ($p < 0.01$) and GSTM1[13] ($p < 0.01$) in the Finnish population • NAR2*6[14] ($p = 0.035$) in the general European population
	Pratt, et al., 2009	• Men and White participants ($p < 0.01$)
	Bared, et al., 2010	• GSTT1 null genotype (OR 2.84; 95% CI 1.4-5.9), GSTM1 null genotype (2.43; 1.2-5.1), and NAT2*6 mutant genotype (2.88; 1.4-6.1) in White subjects
Noise exposure	Gates, et al., 2000	• Greater mean 15-year threshold change in large notches (N2) group only at 2000 Hz as compared to a small notch (N1) and absence of a notch (N0) groups ($p < 0.01$) • Greater change at 8000 Hz in the N1 group than the N0 or N2 groups ($p < 0.01$)
	Albera, et al., 2010	• Progressive hearing loss after the first 10-year of noise exposure was more related to age than to duration of noise exposure ($p < 0.01$)
	Cruickshanks, et al., 2010	• Noise exposure was not significantly correlated with the 10-year cumulative incidence of hearing loss.
	Ciorba, et al., 2011	• No difference of hearing thresholds after adjusting age and sex.
Chemical exposure	Crawford, et al., 2008	• The highest quartile of insecticides exposure (OR 1.19; 95% CI 10.4-1.35) and organophosphate insecticides exposure (1.17; 1.03-1.31)
	Park, et al., 2010	• Tibia lead and patella lead for lowering hearing thresholds ($p < 0.05$) • Patella lead (OR 1.14; 95% CI 1.14-1.91)
Co-exposure to noise and chemical	Morata, et al., 2002	• Every dB above 85 of noise exposure (OR 1.18; 95% CI 1.01-1.34), and each millimore of mandelic acid per gram of creatinine in urine (styrene) (2.44; 1.01-5.89)
	Sliwinska-Kowalska, et al., 2003	• Styrene exposure (OR 5.2; 95% CI 2.9-8.9), noise only (3.4; 1.7-6.4), styrene and noise (10.9; 4.9-24.2), styrene and toluene (13.1; 4.5-37.7), and styrene, toluene, and noise (21.5; 5.1-90.1)
	Chang, et al., 2006	• Toluene and noise exposure (OR 22.6; 95% CI 7.8-65.6) and noise only (5.4; 1.8-15.6)
Cigarette smoking and alcohol consumption	Itoh, et al., 2001	• Current smokers (OR 2.10; 95% CI 1.53-2.89) • No increased risk for heavy drinkers
	Gopinath, et al., 2010	• Current smoking (OR 1.63; 95% CI 1.01-2.64)
Nutrition	Park, et al., 2006	• Higher mean serum MMA[15] concentrations and prevalence of B12 deficiency ($p < 0.01$)
	Gopinath, et al., 2010	• Higher mean dietary glycemic load dietary (OR 1.41; 95% CI 1.01-1.97)
	Gopinath, et al., 2011	• Highest quartile of dietary cholesterol intake (OR 1.33; 95% CI 1.01-1.74)

[10] OR= odds ratio
[11] CI= confidence interval
[12] GSTT1=Glutathione S-transferase theta 1
[13] GSTM1=Glutathione S-transferase mu 1
[14] NAT2*6=N-acetyltransferase 2*6A
[15] MMA= methylmalonic acid

Table 2.2. Major Findings by Risk Factors for Age-related Hearing Loss (continued)

Risk factors	Investigator, Year	Major findings
	Spankovich, et al., 2011	• Higher cholesterol, fat and retinol intakes with poorer TEOAE and PTA[16] ($p < 0.05$)
Ototoxic medications	Curhan, et al., 2010	• Aspirin (OR1.12; 95% CI 1.04-1.20), NSAIDs[17] (1.21; 1.11-1.33), acetaminophen (1.22; 1.07-1.39) in regular user (≥ 2times/week), compared with user less than 2 times per week
	Curhan, et al., 2012	• Ibuprofen for use 2-3 days/week (RR[18] 1.13; 95% CI 1.06-1.19), for use 4-5 days/week (1.21; 1.11-1.32), for use ≥6 days/week (1.24; 1.14-1.35) • Acetaminophen for use 2-3 days/week (RR 1.11; 95% CI 1.02-1.19), for use 4-5 days/week (1.21; 1.07-1.37), for use ≥6 days/week (1.08; 0.95-1.22) • No significance with aspirin.
Cardiovascular disease	Torre et al., 2005	• Self-reported history of myocardial infarction with cochlear impairment in women (OR 2.0; 95% CI 1.15-3.46), but not significant in men.
	Gopinath, et al., 2009	• Stroke (OR 2.04, 95% CI 1.20-3.49)
	Hutchinson, et al., 2010	• Low cardiovascular fitness in the old age group (49-78 years) with worse pure-tone hearing at 2000 and 4000Hz ($p < 0.05$)
Diabetes	Frisina, et al., 2006	• Diabetic group with lower hearing ability, wideband noise and speech reception thresholds and otoacoustic emissions ($p < 0.05$)
	Vauhan, et al., 2006	• Diabetic participants with aged younger than 60 years only in the highest frequencies ($p < 0.05$)
	Mitchell, et al., 2009	• Diabetes (OR 1.55, 95% CI 1.11-2.17) • Newly diagnosed diabetes with progression of hearing loss over 5 years (OR 2.71; 95% CI 1.07-6.86)
	Uchida, et al., 2009	• Diabetes on hearing thresholds in the younger group (40-64 years) at the high frequencies ($p < 0.01$), but no difference in the older group (65-86 years)
Obesity	Hwang, et al., 2009	• Waist circumference with PTA-low ($p=0.034$) and PTA-high ($p=0.024$), but BMI[19] with PTA-low ($p < 0.001$) and PTA-high ($p = 0.035$) only in men younger than 55 years
Multi risk factors	Helzner, et al., 2005	• Age (OR 1.88; 95% CI 1.57-2.24), White (1.63; 1.30-2.04), diabetes (1.42; 1.10-1.83), cerebrovascular disease (1.56; 1.12-2.18), current smoking (1.68; 1.11=2.54), and occupational noise exposure (1.55; 1.24-1.94) • In White men, higher diastolic blood pressure (OR 1.27; 95% CI 1.07-1.50), diabetes (2.12; 1.29-3.48), cerebrovascular disease (2.29; 1.17-4.49), and occupational noise exposure (2.18; 1.52-3.11); in White women, cerebrovascular disease (1.90; 1.03-3.50), and diabetes (1.89; 1.07-3.35) • In Black men, cardiovascular diseases (OR 3.23; 95% CI 1.20-8.72); in Black women, current smoking (2.86; 1.20-6.84)
	Fransen, et al., 2008	• Occupational noise exposure, smoking, high BMI ($p < 0.05$)

[16] PTA=pure tone average
[17] NSAIDs=non-steroidal anti-inflammatory drugs
[18] RR=relative risk
[19] BMI=body mass index

Chapter 3 Prevalence of Ototoxic Medication Use among Older Adults in Beaver Dam, Wisconsin

Abstract

Background: Drug related ototoxicity may exacerbate age related hearing loss, yet few data are available on the prevalence of ototoxic medication use in older adults. The purpose of this study is to investigate the prevalence of ototoxic medication use and to explore factors associated with ototoxic medication use among older adults.

Methods: Cross-sectional analyses were conducted using the large the Epidemiology of Hearing Loss Study database. Medication use was assessed using a standardized questionnaire that asked about medications that participants were taking at least once per week.

Results: Ninety-one percent of the sample was taking a reported ototoxic medication. Non-steroidal anti-inflammatory drugs were the most commonly used (75.2%), followed by acetaminophen (39.9%) and diuretics (35.6%). The prevalence of concomitant ototoxic medications use was 50%. Hypertension, diabetes, cardiovascular disease, and history of smoking were associated with ototoxic medication use. Participants with hearing loss were taking a significantly greater number of ototoxic medications than those without hearing loss.

Conclusion: Epidemiological studies are needed to refine our understanding of the relationship between potentially ototoxic medications and age-related hearing loss. Also, providers need to consider appropriate substitutions or drugs with less ototoxicity and monitor hearing periodically when they prescribe medications to older adults.

Key words: ototoxicity, medication use, older adults

Introduction

Age-related hearing loss is the one of the four leading chronic conditions in older adults as 30% of adults aged 65-74 years old and approximately half of adults older than 75 years have hearing loss (National Institute on Deafness and Other Communication Disorders, 2010). Age-related hearing loss has multiple negative effects on an individual's physical, psychosocial, and social status (Karpa et al., 2010). For example, it is associated with diminished functional status as measured by activities of daily living (Dalton et al., 2003) as well as quality of life scores in both the physical and mental domains (Chia et al., 2007). Older adults with hearing loss may suffer from depression, low self-esteem, and loneliness due to communication difficulties and social isolation (Wallhagen, Strawbridge, Shema, Kurata, & Kaplan, 2001). Hearing loss affects not only the individual, but also his or her family members, who may become frustrated as a result of communication difficulties (Lopez-Torres Hidalgo et al., 2009).

Age is the most common factor associated with developing hearing loss in the adult population (Bielefeld, Tanaka, Chen, & Henderson, 2010). Hearing acuity typically declines by approximately 1 dB annually after 60 years old (Walling & Dickson, 2012). However, age and exposure to life experiences that damage the ear contribute together to the development of hearing loss (Peterson, 1994). Older adults are often on multiple medications for concurrent chronic illnesses (Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002). Hearing loss might be accelerated in patients taking ototoxic medications. Ototoxic drug-related hearing loss has been characterized as a bilateral sensorineural loss affecting the higher frequencies, similar to age-related hearing loss (Rybak & Ramkumar, 2007). Similar to people with age-related hearing loss, people with ototoxic drug-related hearing loss may take their hearing problem for granted.

Given the high prevalence of hearing loss and its impact on health and daily living in older adults, drug-related ototoxicity may be a critical public health problem.

Although some studies have evaluated select medications in specific population such as infants or patients in hospitals, there are few data on the prevalence of known ototoxic medication use among older adults in the community. The purpose of this study is to investigate the prevalence of ototoxic medication use and to explore factors associated with ototoxic medication use among older adults in Beaver Dam, Wisconsin.

Aging and Ototoxicity for Age-related Hearing Loss

From the cochlea to the brain, several structural and chemical changes accompany advancing age. Older adults may have both conductive and senosorineural hearing loss in addition to cognitive difficulties that affect sound interpretation (Walling & Dickson, 2012). However, the vast majority of older adults with hearing loss have age-related sensorineural loss within the cochlea that is associated with problems in transducing hydro-mechanical vibrations to electrical potential in the cochlea and/or in auditory nerve transmission to the brain. This usually results from permanent damage in the organ of Corti (Walling & Dickson, 2012). Vulnerable sites in the cochlea that are affected by aging include the hair cells, the nerve, and the stria vascularis (Pickles, 2008). Loss of hair cells is more serious in the basal region of the cochlea among older adults, which leads to high frequency hearing loss (Weinstein, 2000). Hair cells cannot be replaced and are susceptible to accumulated damage over time from a combination of aging and toxicity from ototoxic medications (Lin et al., 2012). The stria vascularis provides the blood supply to the organ of Corti and maintains the endocochlear resting potential (Lin et al., 2012). Damage from age-related changes in the stria vascularis result in loss of the endocochlear resting potential, leading to a less effective cochlear amplifier and elevated

hearing thresholds (Lin et al., 2012). These changes cause a gradual, symmetric hearing loss predominantly of high frequencies (Yueh, Shapiro, MacLean, & Shekelle, 2003).

Free radicals (reactive oxygen species, or ROS) are considered to be important causative factors in age-related hearing loss (Liu & Yan, 2007). The ability to balance oxidative processes becomes less efficient with age, leading to the damage of key cell components such as mitochondria DNA. This oxidative damage accumulates over time in the cochlea and causes tissue dysfunction during aging (Yamasoba et al., 2013). In addition to the aging process itself, other damages to the cochlea can accumulate over a lifetime and contribute to the decline in hearing experienced by older adults (Huang & Tang, 2010). Ototoxicity is cellular degeneration in the inner ear caused by a drug's side effects (Rybak & Ramkumar, 2007). The most common reported ototoxic drugs in clinical use are aminoglycoside antibiotics, macrolide antibiotics, salicylates, and chemotherapeutic agents such as cisplatin, loop diuretics, antimalarials, non-steroidal anti-inflammatory drugs (NSAIDs), quinine, and acetaminophen (Rybak & Ramkumar, 2007; Tabuchi et al., 2011; Walling & Dickson, 2012). For example, aminoglycosides can activate the formation of ROS, which can damage mitochondria in the cochlea and lead to hair cell death (Kovacic & Somanathan, 2008; Pickles, 2008). Cisplatin affects the outer hair cells, the spiral ganglion cells, and the stria vascularis. Loop diuretics mainly target the stria vascularis (Pickles, 2008; Rybak & Ramkumar, 2007). High dose of salicylates and NSAIDs may reduce cochlear blood flow and damage outer hair cells (Cazals, 2000; Jung, Rhee, Lee, Park, & Choi, 1993). Quinine induces vasoconstriction and decrease cochlear blood flow (Jung et al., 1993). Acetaminophen can impair hair cells from degenerative effect by oxidative stress (Yorgason, Kalinec, Luxford, Warren, & Kalinec, 2010). However, the key mechanisms by which medications cause ototoxicity is still not clear. The effects on hair cells over the short term in

vitro may not be the same as ototoxicity produced in vivo where the damage develops over longer periods and where much lower concentrations can be ototoxic (Pickles, 2008). Furthermore, ototoxic drug-related hearing loss in older adults could be a more significant cause of hearing loss than in younger groups because of the high prevalence of ototoxic drug use for co-morbid chronic diseases and the increased vulnerability to ototoxic drug effects because of impaired renal function (Howarth & Shone, 2006).

Methods

Study design and participants

Cross-sectional analyses were conducted using select variables extracted from the Beaver Dam Eye Study (BDES) Epidemiology of Hearing Loss Study (EHLS) datasets. The cohort was examined in 1993-1995 (n = 3753), 1998-2000 (n = 2800), and 2003-2005 (n = 2395) in Beaver Dam, Wisconsin, when the participants ranged in age from 48-92 (Cruickshanks et al., 2010). This study included data from the baseline examination in 1993-1995 and the 10-year follow-up in 2003-2005 in order to allow for comparison of two points in time but did not include a longitudinal analysis. Participants who completed the survey for medication use were included in his study

Measures

Medication use among the EHLS participants was obtained from the concurrent BDES on the same cohort. Medication use among the EHLS participants was obtained from the standardized questionnaire (Klein & Klein, 1999) that was administered by the examiners (Klein, Klein, Lee, Cruickshanks, & Gangnon, 2006). Participants were asked to bring all prescription and over-the-counter medications that they were regularly taking at least once per week. The examiner recorded the medication from the label of the bottle and checked whether the

medication bottle was the correct one for the medicine the participant reported taking. The examiner also asked whether there were other medications being taken that were not brought to the interview. If so, the interviewer then phoned the participant at home to have the participant read the name of the medication over the phone. When necessary to verify medication and reason for use, the examiner phoned the participants, their physicians, and/or their pharmacies. In addition, participants were asked whether they had a history of hospitalization with fever requiring intravenous antibiotics and if they had a history of receiving chemotherapy. If yes to the latter, they were asked about the type of chemotherapy received, duration of chemotherapy, and age at first chemotherapy. Medications selected for the current study and defined here as "ototoxic medications" were those that have been identified as ototoxic in the literature reviewed above. These included diuretics, NSAIDs, antibiotics, chemotherapeutic agents, quinine, and acetaminophen. Concomitant ototoxic medications use was defined by the use of more than one of these medications.

Hearing loss is defined as a pure tone average (PTA) at 500, 1000, 2000, and 4000 Hz greater than 25 dB HL in either ear. Pure-tone air-conduction thresholds were measured by clinical audiometers for each ear at 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz Assessments were obtained in sound-treated booths (Cruickshanks et al., 2010). All audiometers were calibrated every six months during the study periods according to American National Standards Institute standard (American National Standard Institute, 2004).

Trained interviewers administrated the questionnaire at the baseline and 10-year follow-up examination for medical history, noise exposure, and socioeconomic status (Cruickshanks et al., 2010). Medical history included self-reported physician diagnosis of diabetes, and cardiovascular disease (CVD) (stroke, heart attack, or angina). Diabetes was defined as a

hemoglobin A1c level greater than or equal to 6.5% at the time of the examination, as well as self-reported physician diagnosis. Noise exposure was assessed by current (within past year) noise job. Hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, or a self-reported physician diagnosis of hypertension and current use of antihypertensive medication. Smoking status was categorized as non-smoker, past smoker, or current smoker.

Statistical analysis

Descriptive analyses are presented as means with standard deviations for continuous variables and as frequencies and percentages for categorical variables. Comparison analyses used the chi-square test of association for categorical variables, and t-tests of differences in means for continuous variables. To evaluate the factors associated with the use of ototoxic medication, logistic regression was used. Ototoxic medication use was dichotomous (No/Yes) variable and number of ototoxic medication use was continuous variable. Multicollinearity was checked among independent variables. Statistical significance was defined as $p < .05$. All statistical analyses were conducted using SPSS software, version 22 (SPSS, Inc., Chicago, IL).

Results

The descriptive characteristics of the participants are shown in Table 3.1. The mean age of the 3614 participants at baseline was 65 (SD=10.4), more than half were women, 46% had hearing loss, and 51% had hypertension. At 10-yr follow-up, the mean age of the 2902 participants was 71.7 (SD=8.7), more than half were women, 70% had hearing loss, and 76% had hypertension. The prevalence of hearing loss and chronic disease, such as hypertension, diabetes and CVD, increased greatly over 10 years.

Participants taking ototoxic medications were more likely to be older and female, and to have hypertension, diabetes, CVD, and cancer at baseline. At 10-year follow-up, participants taking ototoxic medications were only more likely to have hypertension.

Prevalence of ototoxic medication use

Overall, 84 % of participants were using any ototoxic medications at baseline, and the prevalence of ototoxic medication use increased to 91.1% over 10 years (Table 3.1). The most common ototoxic medication taken by older adults was NSAIDs (75.2%), followed by acetaminophen (39.9%) and diuretics (35.6%) (Table 3.2). The users of NSAIDs and diuretics had increased by 17% and 12.6 % respectively over 10 years.

Among ototoxic medication users, half of participants were taking more than one class of ototoxic medication at baseline, and 60% were concomitant users at 10-year follow-up. The mean number of ototoxic medications used was 1.88 (±0.89) and more than 21% of participants were combined users of 3 or more ototoxic medications at 10-year follow-up (Figure 3.1). Participants with hearing loss were taking a greater number of ototoxic medications than those without hearing loss at both baseline and 10-year follow-up (Table 3.3).

Factors associated with ototoxic medication use/change

Females had significantly greater odds of taking ototoxic medication at baseline (odds ratio [OR]=2.44, 95% confidence interval [CI] 1.98, 3.0), but this sex difference was not significant at the 10-year follow up. CVD (OR=3.52, 95% CI 2.28, 5.43), hypertension (OR=1.82, 95% CI 1.48, 2.24), diabetes (OR=1.88, 95% CI 1.23, 2.89) and history of smoking (OR=1.29, 95% CI 1.05, 1.58) were significantly associated to ototoxic medication use at baseline, while CVD (OR=2.86, 95% CI 1.37, 6.0) and hypertension (OR=2.45, 95% CI 1.70, 3.51) were significantly associated at 10-year follow-up (Table 3.4)

Further analysis was conducted with a subgroup of participants not using ototoxic medications at baseline. Among participants who were not taking any ototoxic medication (n=560) at baseline, 385 participants remained at 10-year follow-up. Of these 385 participants, 312 participants were taking ototoxic medication at 10-year follow-up. Age (OR for 10yr=1.68, 95% CI 1.11-2.54) and hypertension (OR=2.95, 95% CI 1.58-5.52) were associated with change of ototoxic medication use over 10 years (Table 3.5).

Discussion

The prevalence of any ototoxic medication use increased from 84% to 91% over the 10-year follow-up period among older adults in this population-based study. NSAIDs (75.2%), acetaminophen (39.9%) and diuretics (35.6%) were common ototoxic medications taken by older adults at 10-year follow-up. This high prevalence may be related to the increased prevalence of chronic diseases with age (Forman, Rimm, & Curhan, 2007). Chronic diseases such as hypertension, CVD, or diabetes were associated with ototoxic medication use in this study.

A study using data from the National Health and Nutrition Examination Survey (NHANES) found 25% of adults aged 20 to 69 years used ototoxic medications including aminoglycoside antibiotics (0.03%), loop diuretics (1.5%), antineoplastic drugs (5%), and NSAIDs (7.3%) (Bainbridge, Hoffman, & Cowie, 2008). The prevalence of ototoxic medication use was greater in the hearing impaired group than in the normal hearing group (p=0.001). Additional large population-based studies have focused on the association between hearing loss and analgesic uses such as aspirin, NSAIDs, and acetaminophen (Curhan, Eavey, Shargorodsky, & Curhan, 2010; Curhan, Shargorodsky, Eavey, & Curhan, 2012). In Nurses' Health Study II, women aged 31 to 48 years commonly used NSAIDs (69%), acetaminophen (62%), and aspirin (30%) at least once a week (Curhan et al., 2012). The Health Professionals Follow-up Study found that in men

aged 40 to 75 years the prevalence of NSAIDs, aspirin, and acetaminophen was 4.9%, 26.8%, and 5.6% respectively (Curhan et al., 2010). In these two studies, NSAIDs and acetaminophen were significantly associated with the risk of self-reported hearing loss, but findings for aspirin were conflicting. Conflicting results for aspirin were also found in other studies (Chen et al., 2007; Jung et al., 1993; Sha, Qiu, & Schacht, 2006). Aspirin was included within the NSAIDs category in the current study and not isolated out. In addition, the Health, Aging and Body Composition study reported that participants were aged from 73 to 84 years and were taking salicylates (44%), loop diuretics (9.7%), and quinine (1.2%) (Helzner et al., 2005). Also, the Framingham Heart Study reported that only a very small percentage (0.4%) of the 2293 participants aged 57 to 89 years were taking ototoxic medications (Moscicki, Elkins, Baum, & McNamara, 1985). However, they did not describe in the article which classes of medications were included in their analyses.

We found a much higher prevalence of any ototoxic medication use than in other previous studies. This might be related to the inclusion of a greater number of known ototoxic medications than those included in other studies. However, in the current study the prevalence of use of each individual category of ototoxic medication, whether NSAIDs, diuretics, or antibiotic was also higher than in other prevalence studies. The fact that our study included older participants were older than NHANES and many of the other studies, and this study continued to follow up people who have entered nursing homes and assisted living unlike most other studies, therefore tend to take more multiple medications might be reasons for this finding. Additionally, the assessment of ototoxic medication use in the current study involved actually identifying and confirming the medications used and was not just based on self-report.

More than half of participants used multiple ototoxic medications. The association between number of ototoxic medication use and hearing loss was significant in this study. A previous study documented that the impact of concomitant use of more than one class of aspirin, acetaminophen, or NSAIDs on self-reported hearing loss was additive (Curhan et al., 2010). This may be partly explained by the fact that different classes of ototoxic medications affect auditory function through different mechanisms (Curhan et al., 2010).

Hypertension, diabetes, and CVD are frequently confounded as comorbid diseases with cardiovascular complications (Sowers, Epstein, & Frohlich, 2001), although their correlations were low ($r < .20$) in this study (not shown in the result). Therefore, it is difficult to tease out the unique variance of each factor on ototoxic medication use. However, they may add significant risk for hearing loss among ototoxic medication users because these diseases themselves are also risk factors for age-related hearing loss (Frisina, Mapes, Kim, Frisina, & Frisina, 2006; Gates, Cobb, D'Agostino, & Wolf, 1993).

The strengths of the present study are that little research has been done on this topic and we had good quality data with a large population-based cohort of community-dwelling older adults. Data were collected using standardized protocols and methodologies for measuring medication use. However, our study has limitations. The population is mostly non-Hispanic White from Beaver Dam and, thus, the results may not be generalizable to other ethnic groups. There was an association between number of ototoxic medication use and hearing loss, but the association between any ototoxic medication use and hearing loss was not statistically significant (not shown in the result) in this study. Because this study was cross sectional, it is difficult to know whether ototoxic medications preceded the hearing loss or vice versa in cross-sectional studies. A longitudinal analysis could help to clarify the association between the incidence of hearing loss

and ototoxicity from medications used by older adults. The short-term ototoxic effect of medications is relatively well documented and is generally known to clinicians. However, long-term consequences of ototoxic drug use, especially at lower doses than commonly thought to cause ototoxicity, have not been adequately studied, and more research still needs to be done in this field. Future studies in other large population-based subjects of older adults are needed to generalize our findings.

Implications

Our findings support that known ototoxic medications are widely used for treating various conditions and ototoxicity may interact with aging leading to a more severe hearing loss than that associated with age alone. Given the high prevalence of hearing loss and its impact on health and daily living, the high prevalence of ototoxic medication use by older adults may be a critical public health problem. They highlight the potential for increased hearing loss as a result of the increased use of ototoxic medications to treat chronic illnesses loss across time. They also raise important public issue. Providers may discount ototoxic side effects compared to the main effect of the drug when they choose medications for certain diseases (Albert et al., 2011). Also, providers need to consider adding potential ototoxic medications to people who have diabetes, hypertension, or CVD, which may increase risk of age-related hearing loss. This study emphasizes the importance of understanding the potential for drug's side effects, the need for proper monitoring, and the consideration of appropriate substitutions or drugs with less ototoxicity when taking care of older adults. Also, it is important for their health providers to discuss with older people who are taking multiple ototoxic medications whether to stop or change the medications before their hearing is declined. If the medications cannot be stopped or changed, they need to be cautious about monitoring hearing closely.

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Table 3.1. Characteristics of Participants at Baseline (1993-1995) and 10-year Follow-up (2003-2005)

		Ototoxic medication (1993-1995)				Ototoxic medication (2003-2005)		
	Baseline	Yes	No		10-yr follow-up	Yes	No	
Characteristic, n (%)	n=3753	n=2996	n=560	p-Value	n=2902	n=2078	N=202	p-Value
Age*	65.1 (10.4)	65.4 (10.5)	63.4 (10.0)	< .001	71.7 (8.7)	71.6 (8.6)	71.1 (8.9)	.374
Age group								
48-59	1246 (35.0)	1018 (34.0)	228 (40.7)		74 (3.4)	66 (3.3)	8 (4.7)	
60-69	1056 (29.7)	872 (29.1)	184 (32.9)	< .001	927 (42.4)	849 (42.1)	78 (46.2)	.482
70-79	892 (25.1)	786 (26.2)	106 (18.9)		702 (32.1)	652 (32.4)	50 (29.6)	
≥ 80	362 (10.2)	320 (10.7)	42 (7.5)		482 (22.1)	448 (22.2)	33 (19.5)	
Sex (female)	2164 (57.7)	1771 (87.8)	257 (44.1)	< .001	1414 (59.0)	1206 (55.8)	107 (54.0)	.192
Education (years)								
< 12	847 (23.8)	728 (24.3)	119 (21.3)		394 (16.5)	336 (16.4)	28 (14.2)	
12	1632 (45.9)	1366 (45.6)	266 (47.6)	.348	1165 (48.6)	996 (48.6)	96 (48.7)	.829
13-15	549 (15.4)	466 (15.6)	83 (14.8)		413 (17.3)	351 (17.1)	34 (17.3)	
≥ 16	527 (14.8)	436 (14.6)	91 (16.3)		421 (17.6)	367 (17.9)	39 (19.8)	
Hearing loss (> 25dB)	1631 (45.5)	1381 (46.0)	225 (44.2)	.431	2197 (69.9)	1180 (57.6)	103 (57.9)	.943
Current noise job	296 (8.3)	248 (8.3)	48 (8.6)	.819	69 (3.2)	65 (3.2)	4 (2.4)	.545
Smoking history								
Non smoker	1600 (45.9)	1368 (45.9)	232 (45.9)		1032 (48.3)	957 (47.9)	75 (54.0)	
Ex-smoker	1375 (39.4)	1185 (39.7)	189 (37.4)	.355	918 (42.9)	867 (43.3)	51 (36.7)	.301
Current smoker	513 (14.7)	429 (14.4)	84 (16.6)		188 (8.8)	175 (8.8)	13 (9.4)	
Hypertension	1760 (50.2)	1584 (53.3)	176 (33.8)	< .001	2359 (75.9)	1392 (67.6)	94 (52.8)	< .001
Diabetes	369 (10.4)	334 (11.5)	25 (4.6)	< .001	647 (27.1)	389 (19.3)	23(15.9)	.303
Cardiovascular disease	504 (14.2)	480 (16.1)	24 (4.4)	< .001	763 (30.3)	386 (19.2)	20 (13.2)	.064
History of cancer	584 (16.8)	520 (17.4)	64 (13.1)	.019	571 (25.5)	536 (26.0)	35 (20.2)	.095
History of kidney disease	83 (2.4)	74 (2.5)	9 (1.6)	.212	113 (5.2)	109 (5.5)	4 (2.4)	.084

* Mean (SD)

Table 3.2. Categories of Ototoxic Medication Use

	1993-1995	2003-2005
Medication	n (%)	n (%)
NSAIDs	2025 (58.3)	1610 (75.2)
Acetaminophen	1275 (36.5)	892 (39.9)
Antibiotics (oral)	173 (5.0)	173 (7.7)
Antibiotics (IV)	657 (19.3)	314 (14.8)
Diuretics	793 (23.0)	795 (35.6)
Chemo	68 (1.9)	98 (4.5)
Quinine	38 (1.1)	15 (0.7)

Table 3.3. Number of Ototoxic Medications and Hearing Loss

	Number of ototoxic medications			
	1993-1995		2003-2005	
Hearing loss	Mean (SD)	p-Value	Mean (SD)	p-Value
Yes	1.47(1.0)	0.001	1.78 (1.0)	0.016
No	1.36 (0.9)		1.67 (1.0)	

Table 3.4. Odds Ratios (OR) with 95% of Confidence Interval (CI) for Ototoxic Medication Use at Baseline and 10-year Follow-up

	Baseline	10-yr follow-up
	OR (95% CI)	OR (95% CI)
Sex (female)	2.44 (1.99-3.0)**	1.40 (0.98-2.02)
Age	1.01 (.998-1.02)	1.02 (0.99-1.04)
CVD	3.52 (2.28-5.43)**	2.86 (1.37-6.0)*
Hypertension	1.82 (1.48-2.24)**	2.45 (1.70-3.51)**
Diabetes	1.88 (1.23-2.89)*	1.28 (0.74-2.21)
History of smoking	1.29 (1.05-1.58)*	1.33 (0.92-1.91)

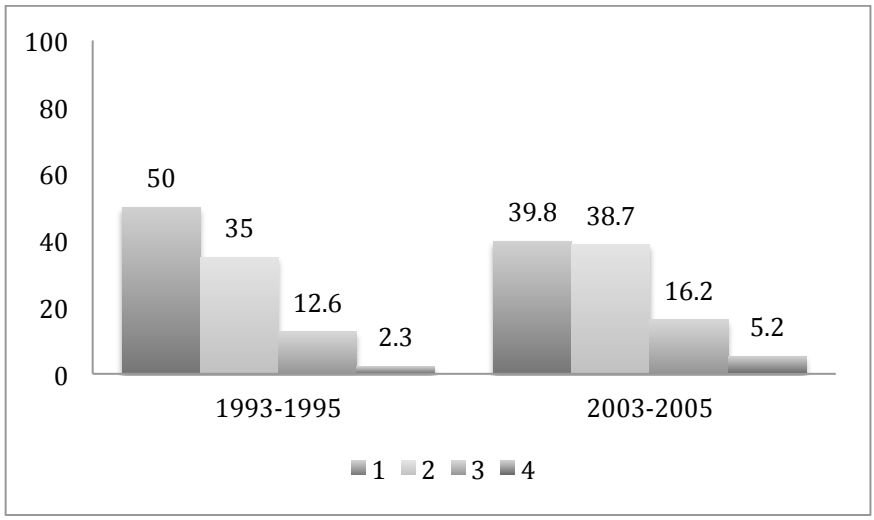
* $p < .05$
** $p < .001$

Table 3.5. Odds Ratios (OR) with 95% of Confidence Interval (CI) for Change of Ototoxic Medication Use from Baseline to 10-year Follow-up (n=385)

	OR (95% CI)
Sex (female)	0.88 (0.47-1.66)
Age (10yr)	1.68 (1.11-2.54)*
CVD	2.12 (0.47-9.57)
Hypertension	2.95 (1.58-5.52)*
Diabetes	1.29 (0.47-3.56)
History of smoking	1.45 (0.76-2.74)

* $p < .05$

Figure 3.1. Number of Ototoxic Medication Use (%)



Chapter 4 The Contribution of Ototoxic Medications to Hearing Loss among Older Adults

Abstract

Background: Ototoxicity is cellular degeneration in the inner ear caused by a drug's side effects. Research into the association between ototoxic drugs and age-related hearing loss has not been very convincing. The purpose of this study is to explore the association between ototoxic medication use and the incidence and progression of hearing loss in older adults.

Methods: Epidemiology of Hearing Loss Study participants in 1993-1995 (n = 3753), 1998-2000 (n = 2800), and 2003-2005 (n = 2395). Medication use was assessed using a standardized questionnaire by the examiners at each examination every five years. The ototoxic medications include loop diuretics, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, chemotherapeutic agents, quinine, and acetaminophen in this study. Hearing loss was defined as a pure tone average (PTA) at 500, 1000, 2000, and 4000 Hz greater than 25 dB HL in either ear. Progression of hearing loss was defined as a PTA change at 5-year or 10-year follow-up that was equal to or greater than 10 dB HL from the baseline PTA among those who had mild to moderate hearing loss. Generalized estimating equations model was used as a proportional hazard discrete time analysis.

Results: Number of ototoxic medications was associated with risk of developing hearing loss during the 10-year follow-up period (Hazard Ratio (HR)= 1.15, 95% confidence interval (CI) 1.06, 1.25) after adjusting for age, sex, smoking and body mass index. Loop diuretics (HR=1.40, 95% CI 1.05, 1.87) were associated with the 10-year incidence of hearing loss. NSAIDs (HR=1.45, 95% CI 1.22, 1.72) and loop diuretics (HR=1.33 95% CI 1.08, 1.63) were associated with risk of progressive hearing loss over 10 years.

Conclusion: Several ototoxic medications are commonly used in older adults and should be

considered as potentially modifiable contributors to incidence and severity of age-related hearing loss.

Key words: Ototoxic medication, hearing loss, age-related hearing loss, older adults

Introduction

Age-related hearing loss is a sensory deficit that is common among older adults (Van Eyken, Van Camp, & Van Laer, 2007). Age is the most common factor associated with developing hearing loss in the older adult population (Bielefeld, Tanaka, Chen, & Henderson, 2010). An analysis of data from the National Health and Nutrition Examination Survey found that more than two thirds of adults over 75 years old have hearing loss (Lin, Thorpe, Gordon-Salant, & Ferrucci, 2011). However, both age and exposure to life experiences that damage the ear contribute to the development of age-related hearing loss (Peterson, 1994). Sex and race may also contribute to the differences found among individuals, and the cumulative effects of extrinsic damage and/or intrinsic diseases may accelerate age-related changes in the auditory system (National Institute of Health Consensus Development Program, 1990; Pyykko, Toppila, Zou, & Kentala, 2007).

Ototoxicity may interact with aging, leading to a more severe hearing loss than that associated with age alone (Weinstein, 2000). Ototoxicity is cellular degeneration in the inner ear caused by a drug's side effects (Rybak & Ramkumar, 2007). Research into the association between ototoxic drugs and age-related hearing loss has not been very convincing. Although review articles state that ototoxic medications frequently cause hearing loss in older adults (Liu & Yan, 2007; Van Eyken et al., 2007), there is little evidence to support this conclusion. Most studies of medication-related hearing loss have been conducted with children or animal models. The majority of animal studies were done to determine the mechanisms underlying ototoxicity in the ear and the results may not be easily transferable to humans (Palomar Garcia, Abdulghani Martinez, Bodet Agusti, Andreu Mencia, & Palomar Asenjo, 2001). In addition, although the

short-term ototoxic effects of medications are relatively well documented and generally known to clinicians, the long-term consequences of ototoxic drug use have not been adequately studied.

The purpose of this study is to explore the association between ototoxic medication use and the 10-year cumulative incidence and progression of hearing loss in older adults.

Methods

Study design and participants

This study was conducted using selected variables extracted from the ongoing longitudinal Beaver Dam Eye Study (BDES) and the Epidemiology of Hearing Loss Study (EHLS) datasets. Researchers conducting the BDES identified individuals 43 to 84 years of age from a private census conducted during 1987 and 1988 in Beaver Dam and invited them to participate in a study of age-related ocular disorders (Linton, Klein, & Klein, 1991). The BDES participants alive as of March 1, 1993 were eligible for baseline examination for the EHLS (Cruickshanks et al., 1998). This cohort was examined in 1993-1995 (n = 3753), 1998-2000 (n = 2800), and 2003-2005 (n = 2395) with a high follow-up rate among living participants (Figure 4.1) (Cruickshanks et al., 2003; Cruickshanks et al., 2010). Cohort and follow-up characteristics according to differences between participants and non-participants have been published previously (Cruickshanks et al., 2003; Cruickshanks et al., 2010).

At baseline, 1955 participants in the EHLS had normal hearing and were, therefore, at risk of developing incident hearing loss by the follow up examinations. Participants who had mild to moderate hearing loss at baseline were included for evaluating the progression of hearing loss (n=1439).

A signed informed consent was obtained from all study participants at the baseline and follow-up examinations. This study was approved by the Health Sciences Institutional Review

Board of the University of Wisconsin. The current study received a waiver of review from the Human Research Protection Program Committee on Human Research of the University of California, San Francisco because only de-identified data were utilized (reference # 059824)).

Measures

Ototoxic medication use. Medication use among the EHLS participants was obtained from the concurrent BDES on the same cohort (Klein, Klein, Lee, Cruickshanks, & Gangnon, 2006). Medication use was assessed using a standardized questionnaire by the examiners at each examination every five years (Klein & Klein, 1999). Participants were asked to bring all prescription and over-the-counter medications that they were regularly taking at least once per week. The examiner recorded the medication from the label of the bottle and checked whether the medication bottle was the correct one for the medicine the participant reported taking. The examiner also asked whether there were other medications being taken that were not brought to the interview. If so, the interviewer then phoned the participant at home to have the participant read the name of the medication over the phone. When necessary to verify medication and reason for use, the examiner phoned the participants, their physicians, and/or their pharmacies. In addition, EHLS participants were asked whether they had a history of hospitalization with fever requiring intravenous antibiotics and if they had a history of receiving chemotherapy. If yes to the latter, they were asked about the type of chemotherapy received, duration of chemotherapy, and age at first chemotherapy.

Medications selected for the current study and defined as "ototoxic medications" here were those that have been identified as ototoxic in the literature reviewed (Liu & Yan, 2007; Van Eyken et al., 2007). The ototoxic medications included loop diuretics, NSAIDs, antibiotics, chemotherapeutic agents, quinine, and acetaminophen. Concomitant ototoxic medications were

considered if a participant was taking more than one ototoxic medication.

Outcome. Incidence of hearing loss and severity of hearing loss were the main dependent variables. Hearing loss was defined as a pure tone average (PTA) at 500, 1000, 2000, and 4000 Hz greater than 25 dB HL in either ear. Participant with hearing loss at baseline were considered to be at risk of hearing loss progression. Progression of hearing loss was defined as a PTA at 500, 1000, 2000, and 4000 Hz in the either ear at any follow-up that was equal to or greater than 10 dB HL as compared to the baseline PTA among those who had mild to moderate hearing loss (25 dB HL < PTA ≤ 60 dB HL).

To evaluate hearing, pure-tone air-conduction and bone-conduction audiometry were used in the three EHLS cycles. Pure-tone air-conduction thresholds were measured by clinical audiometers for each ear at 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz in sound-treated booths according to guideline (American Speech-Languag-Hearing Association, 1987). Masking was used when necessary.

At the baseline examination, Virtual 320 clinical audiometers (Virtual Corporation, Seattle, WA) equipped with TDH-50 earphones and insert earphones (Cabot Safety Corp., Indianapolis, IN) were used. At the follow-up examinations, GSI 61 clinical audiometers (Grason-Stadler, Inc., Madison, WI) equipped with TDH- 50 earphones and insert earphones were used. Participants unable to travel to the clinic site were tested using a Beltone 112 portable audiometer (Beltone Electronic Corp., Chicago, IL). All audiometers were calibrated every six months during the study periods according to American National Standards Institute (ANSI) standards (ANSI, 1996, 2004). Ambient noise levels were obtained at each visit and were routinely monitored at the examination site to ensure the testing conditions complied with ANSI standards (ANSI, 1991, 1999).

Covariates. Covariates include family history of hearing loss, noise exposure, diabetes, hypertension, cardiovascular disease (CVD), smoking and body mass index (BMI).

Trained interviewers administrated a questionnaire at the baseline and follow-up examinations for ear and hearing-related medical history, noise exposure, family history of hearing loss, lifestyle factors, and general medical history. Medical history included self-reported physician diagnosis of diabetes and CVD (stroke, heart attack, or angina). Diabetes was defined as a hemoglobin A1c level greater than or equal to 6.5% at the time of the examination, as well as self-reported physician diagnosis. Noise exposure was assessed by history of hunting or target shooting, occupational noise exposure, and current (within past year) noise job. Hypertension was defined as systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, or a self-reported physician diagnosis of hypertension and current use of antihypertensive medication. Smoking status was categorized as non-smoker, past smoker, or current smoker. Height and weight were measured and BMI (kg/m^2) was calculated.

Statistical analysis

Chi-square tests were used for association with categorical variables and t-tests were used with continuous data for univariate analyses.

Generalized estimating equations (GEE) model with the complementary log-log (cloglog) link function was used as a proportional hazard discrete time model because of small number of follow-up intervals in this study (Garson, 2013). That is, the cloglog model treats data grouped by time interval and thus is a form of interval-censored survival model. GEE is an extension of generalized linear models to cover repeated measures and, therefore, can handle time varying variables. In addition, time varying covariates were incorporated to update the ototoxic

medication exposure during all three exams. GEE is a population-averaged approach, thus the focus is not on individuals' odds ratios but on the average odds ratios of the two groups. Exp (b) for cloglog models is a discrete time hazard ratio estimate in one group for a binary predictor (Garson, 2013). This model was used to evaluate the association of ototoxic medication use and the incidence and progression of hearing loss.

Ototoxic medication exposure was dichotomized into users and non-users. For each participant, person-time was allocated based on the response to the ototoxic medication use questions at the beginning of each follow-up period. Participants were censored at the exam of diagnosis of hearing loss for the incidence analysis, or censored at the exam of progression equal to greater than 10 dB HL than baseline for the progression analysis. The number of ototoxic medication use was continuous variable for concomitant ototoxic medications.

Selected risk factors (family history of hearing loss, smoking, diabetes, CVD, hypertension, BMI and noise exposure) included those associated with hearing loss in published research. Age- and sex-adjusted models were first run for each potential individual risk factor. Those that were significantly associated with the incidence or progression of hearing loss were entered into multivariate models. The associations between covariates and hearing loss were examined for possible interactions with age and sex.

Statistical significance is defined as $p < .05$. All statistical analyses were conducted using SPSS software, version 22 (SPSS, Inc., Chicago, IL).

Results

Baseline characteristics

Participants' mean age was 65.1(SD 10.4) years and more than half were women at baseline. Approximately 46% of participants already had hearing loss at the baseline exam.

Participants' characteristics according to hearing loss are shown in Table 4.1. The most common ototoxic medication taken by older adults was non-steroidal anti-inflammatory drugs (NSAIDs) (58.3%), followed by acetaminophen (36.5%) and diuretics (23.0%). Among ototoxic medication users, half were taking more than one class of ototoxic medication at baseline. Older age, male sex, current noisy job, history of noise exposure, smoking, CVD, diabetes, hypertension, diuretics, and number of ototoxic medications were associated with hearing loss.

Incidence of hearing loss

The 10-year cumulative prevalence of incidence and progression of hearing loss in this population was previously published (Cruickshanks et al., 2010). Age (HR=2.01 for 5 years of age 95% CI 1.88, 2.16) and male sex (HR=2.00 95% CI 1.58, 2.54) were associated with increased risk of developing hearing loss during 10-year follow-up. Among other covariates, smoking and BMI were significantly predictors for increased risk of developing hearing loss in the age-sex-adjusted model. After adjusting for age, sex, smoking and BMI, each additional increase in the total number of ototoxic medications (HR=1.15, 95% CI 1.06, 1.25) and taking loop diuretics (HR=1.40 95% CI 1.05, 1.87) were associated with the incidence of hearing loss (Table 4.2).

Progression of hearing loss

Intravenous antibiotics and quinine were not associated with progression of hearing loss before adjusting for any other covariates. They were not included for further analysis. Age and male sex were associated with risk of progressive hearing loss over 10-year period. Among other covariates, hypertension and diabetes were significant predictors for progressive hearing loss in the age-sex- adjusted model. Adjusting for age, sex, hypertension, and diabetes, each additional increase in the total number of ototoxic medications (HR= 1.09, 95% CI 1.01, 1.18), and taking

either NSAIDs (HR=1.45, 95% CI 1.22, 1.72) or loop diuretics (HR=1.33, 95% CI 1.08, 1.63) were associated with risk of progression of mild to moderate hearing loss (Table 4.3).

Discussion

The present study found that older adults who took a loop diuretic have a high incidence of hearing loss and that those who took NSAIDs or loop diuretics have worse progression of hearing loss over 10 years compared with those who do not. The use of multiple ototoxic medications was also found to affect the incidence and severity of hearing loss among community-dwelling older adults. These findings have important implications because both loop diuretics and NSAIDs are commonly used medications among older adults.

The association between hearing loss and analgesic use, such as aspirin, NSAIDs, and acetaminophen, has also been the focus of recent large population-based studies. Curhan, Eavey, Shargorodsky, and Curhan (2010) conducted a study with men aged 40-74 years from the Health Professionals Follow-up Study using self-reported professionally diagnosed hearing loss over 20 years. They excluded participants aged 75 years or older. The same authors investigated the association with women aged 31-48 years in the Nurses' Health Study II, using self-reported hearing loss over 22 years (Curhan, Shargorodsky, Eavey, & Curhan, 2012). In these two studies, they found that the risk of self-reported hearing loss in regular users of analgesia ($\geq$ 2 times/week) was higher for NSAIDs and acetaminophen compared to subjects who used these medications less than two times per week, but findings for aspirin were conflicting. We included aspirin in NSAIDs category and it was not associated with risk of developing hearing loss over 10years, however its effect on hearing was controversial in other studies (Chen et al., 2007; Jung, Rhee, Lee, Park, & Choi, 1993). Also, our study did not find that acetaminophen was associated with risk of incidence or progression of hearing loss. The fact that our study included more older

people might be one reason for the differences since aging is a key risk factor for age-related hearing loss. Additionally, the assessment of ototoxic medication use in the current study involved actually identifying and confirming the medications used and was not just based on self-report. Furthermore, hearing loss was measured by pure tone audiometric tests in our study, compared to self-reported hearing loss in the studies of Curhan et al.

In contrast to the findings from this study, the Health, Aging and Body Composition study reported that people who were using salicylates, loop diuretics, and quinine at the time of the study did not have higher odds of having hearing loss (Helzner et al., 2005). Similarly, the Framingham Heart Study reported that participants were taking ototoxic medications and found no significant association between ototoxic medication use and hearing loss (Moscicki, Elkins, Baum, & McNamara, 1985). However, they did not describe in the article which classes of medication were included as ototoxic medication.

The main manifestations of the pathology of age-related hearing loss in the aging cochlea are the loss of hair cells and spiral ganglion cells, and the degeneration of the lateral wall including stria vascularis (Lin et al., 2012; Dubno, Eckert, Lee, Matthews, & Schmiedt, 2013: Pickles, 2008). The consequence of increasing oxidative imbalance in the inner ear is very similar to the signs of aging cochlea (Liu & Yan, 2007). Reactive oxidative species (ROS) and oxidative stress is often the common pathway by which medications cause ototoxicity within the cochlea (Weinstein, 2000). The oxidative damage by excess ROS accumulates over time in the cochlea, and the balance of oxidative processes becomes less efficient with age and contributes tissue dysfunction or death, resulting in hearing loss (Huang & Tang, 2010; Yamasoba et al., 2013). Aminoglycosides and acetaminophen can activate the formation of ROS, which can lead to hair cell death (Kovacic & Somanathan, 2008; Pickles, 2008; Yorgason, Kalinec, Luxford,

Warren, & Kalinec, 2010). Cisplatin affects the outer hair cells, the spiral ganglion cells, and the stria vascularis, while loop diuretics mainly target the stria vascularis that is a highly vascularized and metabolically active region of the cochlea (Pickles, 2008; Rybak & Ramkumar, 2007). NSAIDs may also contribute to strial degeneration (Gratton & Schulte, 1995; Nelson & Hinojosa, 2006). Quinine induces vasoconstriction and decrease cochlear blood flow (Jung et al., 1993). These different mechanisms may explain that some different classes of ototoxic medications may impair auditory function, thus the use of multiple ototoxic medications added significantly to developing or progressing hearing loss in our study. Curhan et al. (2010) also found similar results with concomitant use of more than one class of aspirin, acetaminophen, or NSAIDs. However, our study did not find the effects of antibiotics, quinine, and chemo agents on risk of hearing loss and it might be due to the low proportion of people using those medications (5%, 1.1 % and 1.9 %, respectively) or short-term effect of therapeutic periods.

Participants who were taking loop diuretic had 40% higher risk of developing hearing loss and 33% higher risk of progressing hearing loss over 10 years, compare to those who did not take it. Even though NSAIDs were not associated with 10-year cumulative incidence of hearing loss, participants who were taking NSAIDs had 45% greater risk of progressing hearing loss than those who did not take it. Therefore, older people who take these ototoxic medications may need to make important decisions with health providers to stop or change the medications before their hearing is affected. For cases in which the medications cannot be stopped or changed, they need to be cautious about monitoring hearing periodically.

The strengths of this study are a longitudinal population-based cohort study over 10 years with a large sample size and high follow-up rates throughout the period. Data were collected using standardized protocols and methodologies for measuring medication use and hearing

thresholds, and multiple measures of socioeconomic status. This study is a novel study using objective audiometric test for the long-term contribution of ototoxic drug use to age-related hearing loss among a community-based cohort.

There are some important limitations to the study. First, it is a not a randomized controlled study to assess the association between ototoxic medication use and hearing loss. We have limitations to controlling confounding factors. However, it would be ethically problematic to randomize individuals to these various medications that are used for the treatment of multiple chronic conditions. Second, the population was mostly non-Hispanic White from Beaver Dam and, thus, the results may not be generalizable to other ethnic groups. Also, we did not have information on the exact duration and dose of the ototoxic medications, so it was difficult to investigate duration-dose related ototoxicity. Last, longitudinal studies using survivor cohorts could have underestimated new cases with hearing loss and/or lost people who died from related diseases such as CVD or diabetes in the older population. Attrition and/or missing data may still be a problem in a longitudinal study using survivor cohorts despite high retention rates. Of 1955 participants with normal hearing, 473 (24.2%) participants died or were lost to follow-up at the last follow-up. However, there was no difference in the incidence of hearing loss when data were analyzed with all those lost to follow-up coded as having developed hearing loss vs. when data were analyzed with all those lost to follow-up coded as maintaining normal hearing.

The known ototoxic medications are widely used for treating a variety of conditions, and providers may perceive the main effect of the drug to outweigh ototoxic side effects when they choose medications to treat certain conditions (Albert et al., 2011). However, ototoxic drug-related hearing loss in older adults could be more significant as a cause of hearing loss than in younger groups due to the high use of ototoxic drugs to treat chronic diseases, and an increased

vulnerability to ototoxic drugs because of age-related impaired renal function (Howarth & Shone, 2006).

Future studies in other large population-based cohorts of older adults are needed to generalize our findings to other ethnic groups. Also, long-term consequences of duration-dosage related ototoxicity with ototoxic drug use, especially at lower doses than commonly thought to cause ototoxicity, have not been adequately studied, and more research still needs to be conducted in this field.

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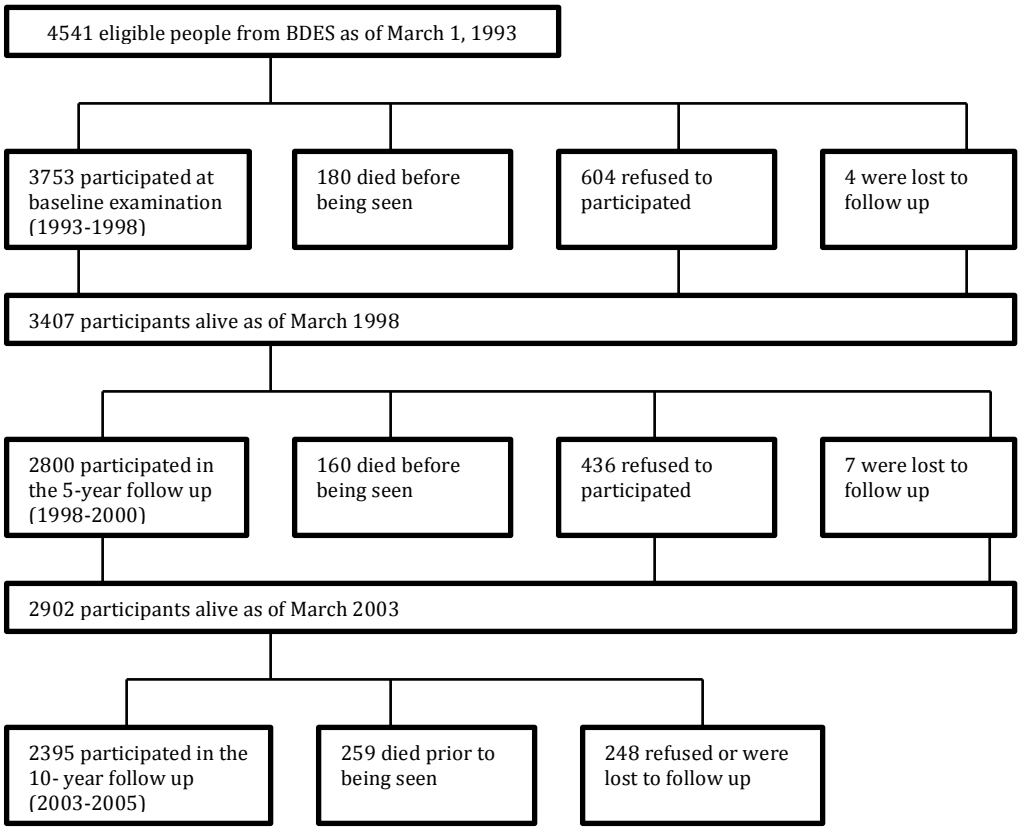

Figure 4.1. Participation in the Epidemiology of Hearing Loss Study, 1993-1995, 1998-2000, and 2003-2005.

Table 4.1. Baseline Characteristics of Participants according to Hearing Loss

	All	Hearing loss		P value
	n=3614	No (n=1955)	Yes (n=1631)[a]	
Age, yr (mean ±standard deviation)	65.1 ±10.4	60.56 ± 8.5	70.5 ±9.9	< .001
Age group, yr (%)				
48-59	35.0	51.4	15.7	
60-69	29.7	30.9	28.3	< .001
70-79	25.1	15.7	36.1	
80+	10.2	2.0	19.9	
Sex (male) (%)	43.3	33.1	55.2	< .001
Current noisy job (%)	8.3	10.1	6.3	< .001
History of noise exposure (%)	55.1	50.4	61.3	< .001
Family history of hearing loss (%)	38.8	40.2	37.2	.08
Smoking status (%)				
Never	45.9	48.2	43.1	
Past	39.4	36.3	42.7	.001
Current	14.7	15.2	14.2	
CVD (%)	14.2	8.2	21.7	< .001
Diabetes (%)	10.4	8.1	13.2	< .001
Hypertension (%)	50.2	45.6	56.0	< .001
Any ototoxic medication use (%)	84	83.7	84.7	.10
NSAIDs	58.3	59.4	57.0	.157
Acetaminophen	36.5	37.3	35.6	.227
Diuretics	23.0	17.8	29.1	< .001
Antibiotics (IV)	19.3	17.8	21.3	.010
Antibiotics (oral)	5.0	4.9	5.1	.730
Chemo	1.9	1.8	2.1	.489
Quinine	1.1	0.7	1.6	.012
Concomitant ototoxic medications (%)	50.0	44.4	52.0	< .001
Body mass index (mean ±standard deviation)	29.6 ± 5.5	29.6±5.6	29.5±5.4	.44
Hearing loss (%)	45.5	-	-	

[a] Included severe hearing loss (PTA> 60 dB HL)

Table 4.2. Hazard Ratio of Incident Hearing Loss according to Ototoxic Mediation Use

Risk factors	Age-sex adjusted Hazard ratio (95% CI)	Multivariate adjusted [a] Hazard ratio (95% CI)
Number of ototoxic medications [b]	1.17 (1.08, 1.27)**	1.15 (1.06, 1.25)*
NSAIDs	1.16 (0.96, 1.41)	1.14 (0.95, 1.38)
Acetaminophen	1.06 (0.86, 1.31)	1.05 (0.85, 1.29)
Loop diuretic	1.37 (1.02, 1.84)*	1.40 (1.05, 1.87)*
Antibiotics (IV)	1.14 (0.88, 1.48)	1.09 (0.85, 1.41)
Antibiotics (oral)	1.03 (0.69, 1.54)	1.05 (0.71, 1.56)
Chemo	1.29 (0.72, 2.32)	1.28 (0.75, 2.21)
Quinine	2.08 (0.72, 5.98)	2.04 (0.77, 5.38)

[a] Adjusted for age, sex, smoking, and body mass index
[b] Each additional increase
* $p < .05$, ** $p < .001$

Table 4.3. Hazard Ratio of Progression of Hearing Loss according to Ototoxic Medication Use

Risk factors	Age-sex adjusted Hazard ratio (95% CI)	Multivariate adjusted [a] Hazard ratio (95%CI)
Number of ototoxic medications [b]	1.08 (1.00, 1.16)*	1.09 (1.01, 1.18)*
NSAIDs	1.41 (1.22, 1.70)**	1.45 (1.22, 1.72)**
Acetaminophen	1.02 (0.87, 1.19)	1.01 (0.86, 1.19)
Loop diuretic	1.34 (1.10, 1.63)*	1.33 (1.08, 1.63)*
Antibiotics (oral)	1.28 (0.96, 1.71)	1.24 (0.92, 1.69)
Chemo	1.28 (0.69, 1.53)	1.03 (0.68, 1.55)

[a] Adjusted for age, sex, diabetes, and hypertension
[b] Each additional increase (continuous variable)
* $p < .05$, ** $p < .001$

Chapter 5 Conclusion

Summary of Findings

Findings from the literature review

The literature review (Chapter 2) revealed that the most consistently strong risk factors for age-related hearing loss across the studies are; genetics (Bared et al., 2010; Christensen, Frederiksen, & Hoffman, 2001; Helzner et al., 2005; McMahon, Kifley, Rochtchina, Newall, & Mitchell, 2008; Pratt et al., 2009; Raynor et al., 2009; Van Eyken, Van Camp, Fransen, et al., 2007), current smoking (Cruickshanks et al., 1998; Fransen et al., 2008; Gopinath, Flood, McMahon, Burlutsky, Smith, et al., 2010; Itoh et al., 2001), diabetes (Frisina et al., 2006; Mitchell et al., 2009; Uchida, Sugiura, Ando, Nakashima, & Shimokata, 2010; Vaughan, James, McDermott, Griest, & Fausti, 2006), cardiovascular diseases (Gopinath, Schneider, Rochtchina, Leeder, & Mitchell, 2009; Hutchinson, Alessio, & Baiduc, 2010; Torre, Cruickshanks, Klein, Klein, & Nondahl, 2005), and obesity (Fransen et al., 2008; Hwang, Wu, Hsu, Liu, & Yang, 2009).

Noise was related to early development of hearing loss but its relationship to the progression of age-related hearing loss remains unclear (Albera, Lacilla, Piumetto, & Canale, 2010; Ciorba et al., 2011; Cruickshanks et al., 2010; Fransen et al., 2008). In addition, occupational chemical exposure to toluene and styrene has been found to relate to hearing loss from chemicals' ototoxic effects that are also exacerbated by coexposure to noise, but most studies are limited to occupational settings (Chang, Chen, Lien, & Sung, 2006; Morata et al., 2002; Sliwinska-Kowalska et al., 2003).

Diet and ototoxic medications showed conflicting results for age-related hearing loss, but are considered potentially strong risk factors. (Gopinath, Flood, McMahon, Burlutsky, Brand-

Miller, et al., 2010; Gopinath, Flood, Teber, McMahon, & Mitchell, 2011; Park et al., 2007). However, it may be difficult to tease out the unique effect of each nutrient or medication on hearing as people often take combinations of nutrients or medications daily.

Findings from the research studies

A cross-sectional study (Chapter 3) was conducted using select variables extracted from the Epidemiology of Hearing Loss Study (EHLS) datasets. The prevalence of any ototoxic medication use increased from 84% to 91% over the 10-year follow-up period among older adults. Non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and diuretics were common ototoxic medications taken by older adults. More than half of participants were taking more than one class of ototoxic medication among ototoxic medication users. Participants with hearing loss were taking a greater number of ototoxic medications than those without hearing loss. Hypertension, diabetes, cardiovascular diseases, and history of smoking were associated with ototoxic medication use. Age and hypertension were associated with change of ototoxic medication use over 10 years. However, there was no significant association between any ototoxic medication use and hearing loss in the cross-sectional analysis.

In the longitudinal analysis with EHLS datasets (Chapter 4), participants who took loop diuretics had a high incidence of hearing loss over 10 years, after adjusting age, sex, body mass index, and smoking history. Participants who took NSAIDs or a loop diuretic had worse progression of mild to moderate hearing loss over 10 years, after adjusting age, sex, diabetes, and hypertension. Also, the use of concomitant ototoxic medications was associated with the incidence and severity of hearing loss.

In addition, the conceptual framework (Figure 1.1) discussed in Chapter 1 was noting the potential contributions of multiple factors to the hearing loss that occurs with age. The findings

of the research studies support sex, smoking, diabetes, hypertension, obesity, and ototoxic medications as risk factors. Gaps remain in our understanding of oxidative stress.

Implications for Practice

The effect of risk factors on age-related hearing loss appears greater in the younger population. Early detection of hearing loss through screening could help adults benefit by delaying onset of age-related hearing loss and its progression (Chou, Dana, Bougatsos, Fleming, & Beil, 2011). However, the rate of addressing hearing loss among older adults in primary care settings is relatively low (Schneider et al., 2010; Wallhagen & Pettengill, 2008). Nurses can serve a key role in initiating communication with older adults about hearing and providing information for risk factors and further evaluation. Nurses and providers in primary care settings can screen for hearing loss in those at risk populations and educate them about lifestyle changes that can reduce their risk for hearing loss, such as quitting smoking, the use of dieting, and weight control. Hearing screenings should be a part of health checklist, especially for people who have cardiovascular diseases and diabetes, just like annual eye exams. Also, high-risk populations for hearing loss should be referred to an audiologist for further evaluation and treatment.

Reported ototoxic medications in the literature were widely used for treating various conditions in this dissertation study. Ototoxicity of medications may interact with aging leading to a more severe hearing loss than that associated with age alone. Therefore, this dissertation research suggests that ototoxic medications should be considered a potentially modifiable contributor to age-related hearing loss. Providers need to reconsider adding potentially ototoxic medications to people who have diabetes, hypertension, or cardiovascular diseases, which may increase the risk of age-related hearing loss. This study emphasizes the importance of

understanding the potential for hearing loss from loop diuretics or NSAIDs, the need for proper monitoring of hearing, and the consideration of appropriate substitutions or drugs with less ototoxicity when taking care of older adults. Also, it is important for their healthcare providers to discuss with older people who are taking multiple ototoxic medications whether to stop or change the medications before their hearing is affected.

Recommendations for Future Research

Identifying further risk and protective factors for age-related hearing loss and developing appropriate interventions are a worthy goal for further research.

The Health, Aging and Body Composition study and the Framingham Heart Study found no significant association between ototoxic medication use and hearing loss in the cross sectional analysis (Helzner et al., 2005; Moscicki, Elkins, Baum, & McNamara, 1985), while the studies of Curhan et al. found significant associations in the longitudinal analysis (Curhan, Eavey, Shargorodsky, & Curhan, 2010; Curhan, Shargorodsky, Eavey, & Curhan, 2012). Similarly, this dissertation found that the association between hearing loss and ototoxic medication use was not significant in the cross sectional study with EHLS datasets, but was significant in the longitudinal study. The importance of addressing the long-term effect of ototoxic medication use should be considered in any research design. Future research may need to consider the frequency of performing hearing evaluations when attempting to elucidate the long-term effects of potentially ototoxic medication use on age-related hearing loss among older adults. Additionally, the long-term consequences of taking a potentially ototoxic medication at various doses across time as it relates to hearing loss have not been adequately studied. More research still needs to be conducted with large populations in order to categorize the effects of individual medication on hearing loss. Medication compliance may be critical issues in conducting valuable studies with

older adults.

Future studies in other large population-based cohorts of older adults are needed to generalize our findings to other ethnic groups. Future research is also needed to determine the contribution of ototoxic medication use among high-risk populations, such as people with hypertension, diabetes, and cardiovascular diseases, to age-related hearing loss.

The conceptual framework could guide future research exploring the relationship between ototoxic medications and age-related hearing loss. Oxidative stress as a contributing factor to age-related hearing loss has been intensively studied. Despite these advances, the underlying events that cause the aging cochlea are not yet fully understood. The free radical theory may be a part of the aging process in the cochlea, but several other mechanisms may contribute to age-related hearing loss (Kidd Iii & Bao, 2012). Studying the effects of genetic factors on hearing loss alone is difficult because most people have been exposed to other risk factors for hearing loss over a lifetime. However, this conceptual framework provides a potential way to begin to isolate the independent contribution of each factor and/or the variance explained by each factor. It will also eventually involve an interactive model since these are not truly independent risk factors among older adults. These risk factors may explain the large variations in the onset and extent of age-related hearing loss among older adults.

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