CLINICAL RESEARCH STUDY

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Hypertension, Diuretic Use, and Risk of Hearing Loss

Brian M. Lin, MD,[a,b,c] Sharon G. Curhan, MD, ScM,[b,c] Molin Wang, PhD,[b,d,e] Roland Eavey, MD,[f] Konstantina M. Stankovic, MD, PhD,[a,c] Gary C. Curhan, MD, ScD[b,c,d,g]

[a]The Massachusetts Eye and Ear Infirmary, Department of Otolaryngology-Head and Neck Surgery, Boston, Mass; [b]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass; [c]Harvard Medical School, Boston, Mass; [d]Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, Mass; [e]Department of Biostatistics, Harvard TH Chan School of Public Health, Boston, Mass; [f]Vanderbilt Bill Wilkerson Center for Otolaryngology and Communications Sciences, Vanderbilt University School of Medicine, Nashville, Tenn; [g]Renal Division, Department of Medicine, Brigham and Women's Hospital, Boston, Mass.

ABSTRACT

BACKGROUND: Hearing loss is highly prevalent among adults in the United States. Hypertension also is common and often treated with diuretics. Hypertension may increase the risk of hearing loss by decreasing vascular supply to the stria vascularis. Use of thiazides has been anecdotally associated with hearing loss. In small studies, furosemide use has been associated with hearing loss that is usually reversible, but can be permanent. We investigated the relation among hypertension, diuretic use, and hearing loss in a prospective cohort of 54,721 women in the Nurses' Health Study I, 1994 to 2012.

METHODS: Eligible participants included 54,721 female nurses aged 48 to 73 years in 1994 who provided information on thiazide diuretic and furosemide use in 1994, answered the question on hearing loss over their lifetime in 2012, and did not report hearing loss with date of onset before date of onset of hypertension diagnosis or medication use. The outcome was self-reported hearing loss. Cox proportional hazards regression was used to adjust for potential confounders.

RESULTS: During 774,096 person-years of follow-up, 19,296 cases of hearing loss were reported (incidence rate, 25 cases per 1000 person-years). At baseline in 1994, the mean age was 57.9 years and mean body mass index was 26.3 kg/m^2. Some 30.8% of participants had a history of hypertension. History of hypertension was independently associated with a modestly higher risk of hearing loss (multivariable adjusted relative risk, 1.04 [1.01-1.07]). Among women with a history of hypertension, neither thiazide diuretic (multivariable adjusted relative risk, 1.07 [0.99-1.16]) nor furosemide use (multivariable adjusted relative risk, 0.91 [0.75-1.09]) was significantly associated with risk of hearing loss when compared with women not taking antihypertensive medications. There was no significant effect modification by age.

CONCLUSIONS: History of hypertension was associated with a small increased risk of hearing loss. Thiazide diuretic use and furosemide use were not associated with risk of hearing loss among women with a history of hypertension.

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Requests for reprints should be addressed to Brian M. Lin, MD, Channing Division of Network Medicine, Brigham and Women's Hospital, 181 Longwood Ave, Boston, MA 02115.

E-mail address: brian_lin@meei.harvard.edu

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Hearing loss is highly prevalent in adults in the United States. Approximately one third of women aged 50 to 59 years and approximately two thirds of women aged 60 to 69 years have hearing loss.[1] As the life expectancy of individuals has increased, so has the prevalence of age-related hearing loss.[2] Hearing loss can be disabling; therefore, identification of potential modifiable risk factors is an important public health issue.[3,4]

Hypertension also is common in the United States and affects approximately 35% of women aged 40 to 59 years, and more than 65% of women aged more than 65 years.[5] Hypertension may increase the risk of hearing loss via decreased vascular supply to the stria vascularis.[6] However, current evidence regarding the relation between hypertension and risk of hearing loss is inconsistent, with cross-sectional studies suggesting a positive association[1,7] and a prospective study suggesting no association.[8]

The Joint National Committee recommends thiazide diuretics as initial drug therapy for patients with uncomplicated hypertension.[9] The relation between thiazides and hearing loss is largely anecdotal, with no published reports in the literature. Thus, the mechanism by which thiazides may alter hearing is unclear.

In small studies, furosemide use has been associated with sudden sensorineural hearing loss that is usually reversible but can be permanent.[10-12] The hearing loss is more likely to occur after intravenous drug administration but can also occur after oral dosing.[10,12] The mechanism by which furosemide may cause hearing loss in humans is unclear. Rodent models have shown that furosemide causes dysfunction of the stria vascularis, resulting in reduced endocochlear potential.[13-17] Chronically impaired endocochlear potential has been shown to reduce auditory nerve activity, thereby impairing hearing.[18]

Although hypertension and diuretic use are common, the relation among hypertension, diuretic use, and hearing loss has not been prospectively studied in women. Therefore, we investigated the relation among hypertension, use of thiazide diuretics and furosemide, and hearing loss in a prospective cohort of 54,721 women in the Nurses' Health Study I. We also compared the use of thiazide diuretics and furosemide with the use of other hypertensive medications among hypertensive women to examine the relation between different hypertensive medications and risk of hearing loss.

CLINICAL SIGNIFICANCE

- Hypertension is independently associated with a higher risk of hearing loss in women.
- Use of thiazide diuretics and furosemide is not independently associated with risk of hearing loss in women.

MATERIALS AND METHODS

Study Participants

The Nurses Health Study I is a cohort of 121,700 female nurses aged 30 to 55 years when enrolled in 1976. Questionnaires are administered every 2 years, with an average follow-up rate of more than 90% of the eligible person-time. Participants were asked in 2012, "Do you have a hearing problem?" and, if so, "At what age did you first notice a change in your hearing?" Of the 63,966 women who answered the long-form questionnaire in 2012, 47% reported having a hearing problem. We excluded women who reported a hearing problem that began before 1994 (baseline year of our study) and those who had a history of nonmelanoma skin cancer due to potential exposure to chemotherapeutic agents that can be ototoxic. After excluding these participants, our study population was 54,721 women.

Ascertainment of Hypertension

On the 1976 questionnaire and every 2 years thereafter, participants were asked whether a clinician had diagnosed them as having high blood pressure. Self-reported hypertension has been shown to be highly reliable in this cohort of women.[19] We classified women who answered "yes" to this question as having a history of hypertension from that time onward.

Ascertainment of Medication Use

In 1994 and every 2 years thereafter, information on regular use of thiazide diuretics, furosemide, calcium channel blockers, and beta-blockers was obtained. In 1996, use of angiotensin-converting enzyme inhibitors was first ascertained. We considered women who answered "yes" to have taken the indicated medication for the previous 2 years.

Ascertainment of Hearing Loss

The outcome examined in this study was self-reported hearing loss. The 2012 questionnaire inquired whether the women had hearing loss, and if so, the age of onset. Year and age of onset were calculated from participant responses. We defined incident cases of hearing loss as participants who reported a hearing problem first noticed after this study's baseline of 1994.

The gold standard of evaluating hearing loss is pure-tone audiometry. However, it is logistically and financially challenging to obtain audiograms on all participants. Several studies have examined the correlation between self-reported hearing loss and hearing loss diagnosed by audiogram.[20-23] Studies found a single question on self-reported hearing loss to be a relatively reliable indicator of hearing loss.[24] Significant associations between several factors and risk of self-reported hearing loss have been observed using this manner of assessment in the Nurses' Health Study II.[25-27]

Ascertainment of Covariates

Covariates were selected on the basis of previously reported risk factors for hearing loss. Factors considered included age,[1] race,[1] body mass index,[25,28] waist circumference,[25] alcohol consumption,[26,29] folate,[30] beta-carotene,[31] trans fats,[31] beta-cryptoxanthin,[31] vitamin A, vitamin B_{12}, vitamin C,[31] vitamin E,[31] omega-3 fatty acids,[32] potassium,[33] magnesium,[34] physical activity,[25,35] smoking,[29] diabetes,[36] tinnitus,[37,38] and use of acetaminophen, aspirin, and ibuprofen.[27] For covariate adjustment, body mass index was categorized as <21 kg/m^2, 21 to 24 kg/m^2, 25 to 29 kg/m^2, 30 to 34 kg/m^2, 35 to 40 kg/m^2, and ≥ 40 kg/m^2. We also adjusted for waist circumference (<71 cm, 71-79 cm, 80-88 cm, ≥ 89 cm). Body mass index and waist circumference were also adjusted for as continuous variables to assess for residual confounding by these variables. We performed age-stratified analysis to assess for possible effect modification by age. Hypertension was not adjusted for in our regression models for diuretic use to avoid overadjustment.

Data on covariates were obtained from the biennial questionnaires. Women were asked in 2004 whether they described themselves as white, black/African American, Asian, Native American/Alaska Native, Native Hawaiian/Pacific Islander, or other. Intake of alcohol, folate, vitamin B_{12}, vitamin A, vitamin C, potassium, magnesium, vitamin E, trans fat, omega-3 fatty acids, beta-carotene, and beta-cryptoxanthin was derived from semiquantitative food frequency questionnaires mailed to study participants every 4 years. Information derived from the semiquantitative food frequency questionnaires starting in 1994 was used in our analysis. The validity and reproducibility of these questionnaires have been reported.[39,40]

The other covariates have been shown to be valid measures for this cohort and other similar cohorts. For example, correlations for weight and physical activity were 0.97 and 0.79, respectively.[41-43]

Statistical Analysis

All analyses were performed in a prospective manner using information on hypertension and medication use that was collected before the reported onset of hearing loss. We considered women who reported being diagnosed with hypertension in or before 1994 as having a history of hypertension. If on a subsequent questionnaire, participants reported having been diagnosed with hypertension, they were considered to have a history of hypertension from that point onward. Person-time contribution of each participant was assigned on the basis of their response to questions regarding thiazide diuretic, furosemide, calcium channel blocker, and beta-blocker use on the 1994 questionnaire and every 2 years thereafter. Use of angiotensin-converting enzyme inhibitors was first asked in 1996, and thus, person-time contribution of each participant was assigned on the basis of their response to the question in 1996. Participants were censored at the time of onset of hearing loss or diagnosis of cancer. Multivariable-adjusted relative risks were calculated using Cox proportional hazards regression models. The Anderson-Gill data structure was used to handle left truncation and time-varying covariates efficiently.[44] To control as finely as possible for confounding by age, we stratified the analysis jointly by age at the start of follow-up and calendar year of the current questionnaire cycle. Duration of medication use was also used in our analyses. In these analyses, we excluded women who answered "yes" to the use of the medication in question in the first year it was ascertained on the questionnaire to eliminate potential use of the medication beyond the 2 years preceding the baseline question. Answers in the affirmative on subsequent questionnaires for use of the medication were classified as 2 years of medication use. We examined the association between duration of medication use as continuous variables and categoric variables (no use, <2 years, 2-3 years, 4-5 years, 6-7 years, 8+ years). To examine whether the association between thiazide and furosemide use with hearing loss differed by history of hypertension, we performed analyses stratified by history of hypertension. We also tested for possible effect modification of the relation among use of thiazide diuretics, furosemide, and age (categorized by <60 years and ≥ 60 years). Because diuretic use may be associated with tinnitus, we also performed a secondary analysis that excluded participants who reported onset of tinnitus before onset of hearing loss. Covariate status from the 1994 questionnaire was updated on each subsequent questionnaire. All P values are 2-sided, with 95% confidence intervals (CIs) calculated for all relative risks. SAS software version 9.4 (SAS Institute Inc, Cary, NC) was used to perform all statistical analyses. This study was approved by the Partners Healthcare institutional review board.

RESULTS

Participant characteristics at baseline according to history of hypertension and medication use are shown in **Table 1**. Women who reported a history of hypertension or use of thiazide diuretics or furosemide tended to be older, had higher body mass index and waist circumference, were less physically active, and were more likely to have a history of smoking or diabetes compared with women who did not report a history of hypertension or medication use.

At baseline, 15,401 women (31%) had a history of hypertension. Among women with hypertension, 2813 (18%) were taking thiazide diuretics alone, 429 (3%) were taking furosemide alone, and 22 (0.1%) were taking both thiazide diuretics and furosemide.

The cumulative incidence of hearing loss among participants was 35%. During 774,096 person-years of follow-up time, 19,296 cases of hearing loss were reported (incidence rate, 25 cases per 1000 person-years). History of hypertension was independently associated with a modestly higher risk of hearing loss (multivariable adjusted relative risk,

Table 1 Baseline Characteristics of Participants According to Furosemide Use and Thiazide Use, Nurses' Health Study I, 1994

	No History of Hypertension (n = 34,523)	History of Hypertension (n = 15,401)	Thiazide No (n = 46,678)	Thiazide Yes (n = 3246)	Furosemide No (n = 49,323)	Furosemide Yes (n = 601)
Age, y	57.2 (6.4)	59.4 (6.4)	57.8 (6.4)	59.4 (6.5)	57.9 (6.5)	59.8 (6.6)
BMI, kg/m^2	25.5 (4.5)	28.2 (5.6)	26.2 (4.9)	28.8 (5.6)	26.3 (5.0)	30.0 (6.4)
Waist circumference, cm	84.1 (12.9)	90.4 (14.3)	85.6 (13.5)	91.4 (14.2)	85.9 (13.6)	93.1 (16.2)
White	95.0%	93.1%	94.6%	92.7%	94.5%	93.7%
Physical activity in 2001, METs	14.3 [5.4-28.5]	11.5 [4.0-25.0]	13.5 [5.0-27.5]	11.7 [4.0-25.0]	13.5 [5.0-27.4]	11.6 [3.3-25.1]
Smoking status						
Never smoker	46.5%	46.8%	46.6%	47.7%	46.7%	42.6%
Past smoker	41.5%	44.5%	42.3%	43.6%	42.3%	50.2%
Current smoker	12.0%	8.5%	10.9%	8.6%	10.8%	7.0%
Alcohol consumption, g/d	1.8 [0.0-6.5]	0.9 [0.0-5.3]	1.5 [0.0-6.2]	1.0 [0.0-5.8]	1.5 [0.0-6.1]	0.9 [0.0-3.5]
Daily nutrient intake						
Vitamin A, IU	1521 [840-2553]	1633 [861-2620]	1543 [847-2570]	1647 [860-2630]	1550 [847-2574]	1664 [849-2684]
Vitamin B12, µg	8.0 [5.0-12.0]	8.0 [5.0-12.0]	8.0 [5.0-12.0]	8.0 [5.0-12.0]	8.0 [5.0-12.0]	8.0 [5.0-13.0]
Vitamin C, mg	213 [136-433]	220 [143-438]	214 [138-433]	227 [147-463]	215 [138-435]	226 [155-417]
Vitamin E, mg	14.7 [8.3-114.3]	15.7 [8.6-182.9]	14.9 [8.4-115.7]	16.6 [8.8-186.0]	15.0 [8.4-116.7]	17.0 [8.5-185.6]
Folate, µg	404.7 [278.2-634.7]	414.7 [283.3-648.4]	406.8 [279.0-637.1]	422.1 [289.7-633.9]	408.0 [279.5-639.0]	408.9 [284.9-620.3]
Potassium, mg	3200 [2571-3907]	3259 [2620-3999]	3207 [2577-3921]	3386 [2710-4171]	3214 [2583-3932]	3501 [2708-4283]
Magnesium, mg	334 [266-412]	336 [267-413]	335 [266-413]	336 [270-413]	335 [267-413]	330 [260-410]
Beta-carotene, µg	4570 [3029-7014]	4695 [3108-7231]	4604 [3042-7064]	4759 [3215-7365]	4614 [3055-7079]	4626 [3123-7444]
Beta-cryptoxanthin, µg	155.7 [82.7-235.5]	170.7 [90.7-244.9]	159.1 [84.5-237.4]	178.2 [94.9-251.8]	160.2 [84.9-238.2]	176.8 [95.7-250.6]
Trans-fats, g	2.3 [1.6-3.2]	2.3 [1.6-3.2]	2.3 [1.6-3.2]	2.3 [1.6-3.2]	2.3 [1.6-3.2]	2.2 [1.5-3.2]
Omega-3 fatty acids, g	0.16 [0.09-0.27]	0.17 [0.10-0.28]	0.16 [0.09-0.27]	0.18 [0.10-0.29]	0.16 [0.10-0.27]	0.15 [0.09-0.27]
History of hypertension	-	-	27.0%	86.7%	30.4%	71.4%
History of diabetes	2.1%	7.3%	3.5%	6.7%	3.6%	12.5%
Aspirin use, d/wk						
<1	77.6%	70.1%	75.8%	67.8%	75.4%	66.6%
1-3	6.2%	5.6%	6.0%	5.9%	6.0%	5.2%
4+	16.0%	23.7%	17.8%	25.5%	18.2%	27.8%
Acetaminophen use, d/wk						
<1	84.1%	79.5%	83.2%	75.7%	82.8%	71.2%
1-3	8.4%	9.5%	8.6%	11.0%	8.7%	13.4%
4+	5.2%	7.8%	5.8%	9.5%	5.9%	11.3%
Ibuprofen use, d/wk						
<1	76.9%	70.6%	75.7%	64.5%	75.1%	62.2%
1-3	9.8%	9.8%	9.7%	11.5%	9.8%	9.2%
4+	7.6%	12.2%	8.6%	15.0%	8.9%	18.8%

Values are mean (standard deviation), median [interquartile range], or percent.
Waist circumference values were taken from the 1996 questionnaire.
BMI = body mass index; MET = metabolic equivalent.

Table 2 Age- and Multivariable-Adjusted Relative Risks of Incident Hearing Loss According to History of Hypertension, Nurses' Health Study I, 1994-2012

	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
History of hypertension						
No	8289	417,000	1.00	Reference	1.00	Reference
Yes	11,007	357,096	1.08	1.05-1.12	1.04	1.01-1.07

CI = confidence interval; RR = relative risk.

*Adjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity, nutrient (folate, magnesium, potassium, vitamin A, vitamin B_{12}, vitamin C, vitamin E, beta-carotene, beta-cryptoxanthin, trans-fat) intake, smoking status, diabetes, tinnitus, and acetaminophen, aspirin, and ibuprofen use.

1.04; 95% CI, 1.01-1.07) (Table 2). Thiazide use was independently associated with a higher risk of hearing loss (relative risk, 1.08; 95% CI, 1.04-1.12), but furosemide use was not (relative risk, 1.01; 95% CI, 0.93-1.08). After limiting the analysis to those women with a history of hypertension, none of the medications were significantly associated with risk of hearing loss when compared with women not taking medication (Table 3). Tests for effect modification by age for thiazide and furosemide use were not significant ($P = .61$ and .11, respectively). Adjusting for waist circumference and body mass index as continuous variables did not significantly change the results. After excluding participants with a history of tinnitus, the results were not materially different (data not shown).

Duration of thiazide, furosemide, calcium channel blocker, beta-blocker, and angiotensin-converting-enzyme inhibitor use was not associated with risk of hearing loss (data not shown).

DISCUSSION

History of hypertension was associated with a modest higher risk of hearing loss. After accounting for history of hypertension and adjusting for other antihypertensive medication use, there was no association between use of thiazide diuretics or furosemide and risk of hearing loss. There was also no association between duration of thiazide or furosemide use and risk of hearing loss. Use of other antihypertensive medications was not associated with risk of hearing loss.

The incidence rate of hearing loss in our cohort was 25 cases per 1000 person-years. In comparison, the approximate incidences of hearing loss in 2 previous prospective cohorts, in whom hearing loss was defined as a change in pure-tone average of >25 decibels, were 72 cases per 1000 person-years among women[45] and 36 cases per 1000 person-years among men and women.[46] Although the precise reasons for differing rates of hearing loss in these studies are unclear, potential explanations include differences in age and sex of the study populations and the method of outcome ascertainment.

The stria vascularis is located in the lateral cochlear wall and is responsible for sending auditory signals from the cochlea to the central nervous system.[47] Vascular supply to the stria vascularis is derived from the terminal arteries with no collateral supply. Therefore, it is particularly sensitive to events that compromise vascular supply, with animal studies showing reduced endocochlear potential and hearing loss occurring promptly after an anoxic event.[48] It is hypothesized that hypertension may compromise the vascular supply to the stria vascularis, thereby leading to hearing loss.[6] There is limited evidence regarding the relation between hypertension and risk of hearing loss.[1,7,8] Cross-sectional

Table 3 Age- and Multivariable-Adjusted Relative Risks of Incident Hearing Loss Among Women with a History of Hypertension, According to Antihypertensive Medication Use, Nurses' Health Study I, 1994-2012

Antihypertensive Medication	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
No medication	2361	84,079	1.00	Reference	1.00	Reference
Thiazides	917	24,991	1.21	1.12-1.31	1.07	0.99-1.16
Furosemide	121	3160	1.03	0.86-1.24	0.91	0.75-1.09
Calcium channel antagonists	694	24,040	1.03	0.94-1.12	1.01	0.93-1.10
Beta-blockers	1170	38,996	1.11	1.04-1.19	1.01	0.94-1.09
ACEIs	881	30.288	1.12	1.04-1.21	1.04	0.96-1.13
Other antihypertensive medication	740	28,213	1.03	0.95-1.12	1.00	0.92-1.09
Multiple antihypertensive medications	3590	101,804	1.15	1.09-1.21	1.03	0.97-1.08

ACEI = angiotensin-converting enzyme inhibitor; CI = confidence interval; RR = relative risk.

*Adjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity, nutrient (folate, magnesium, potassium, vitamin A, vitamin B_{12}, vitamin C, vitamin E, beta-carotene, beta-cryptoxanthin, trans fat) intake, smoking status, diabetes, tinnitus, and acetaminophen, aspirin, and ibuprofen use, and all the antihypertensive medications shown in the table.

studies have shown a higher prevalence of hearing loss among people with hypertension,[1,7] whereas a prospective study in men has suggested no association between hypertension and hearing loss.[8] In our prospective cohort of women, hypertension was associated with a slightly increased risk of hearing loss.

Given that we observed a small increased risk of hearing loss among women with a history of hypertension, we restricted our analysis of diuretic use to women with a history of hypertension. Despite anecdotal accounts that use of thiazides may be associated with risk of hearing loss, we observed no association between thiazide diuretic use and hearing loss in our prospective study of women.

Furosemide use has been associated with risk of hearing loss in humans and rodent models.[10-12,14] In humans, use of furosemide has been associated most commonly with hearing loss when administered intravenously, and the hearing loss is usually reversible.[10,12] However, the hearing loss can be irreversible and has been reported with oral dosing.[11] Although the mechanism by which this clinical hearing loss may occur is unclear, rodent models suggest that it may occur via inhibition of the endocochlear potential and alteration of Organ of Corti mechanics.[13-17] Furthermore, long-term inhibition of the endocochlear potential has been associated with decreased auditory nerve activity,[18] which may impair hearing. However, in our cohort of women, we found no association between furosemide use and risk of hearing loss.

Study Limitations

The study population was predominantly white women. Further investigation is required to examine these associations in other populations. The outcome in our study was self-reported hearing loss. Although pure-tone audiometry is often considered the gold standard for evaluating hearing loss, self-reported hearing loss has been shown to be reliable as an indicator for hearing loss.[20-23] In addition, a recent review done for the US Preventative Services Task Force revealed that a single question about perceived hearing loss was almost as accurate as a more detailed questionnaire or a portable audiometric device for detection of hearing loss.[49]

CONCLUSIONS

History of hypertension was associated with a small increased risk of hearing loss. Thiazide diuretic use and furosemide use were not associated with risk of hearing loss among women with a history of hypertension.

References

1. Agrawal Y, Platz EA, Niparko JK. Prevalence of hearing loss and differences by demographic characteristics among US adults: data from the National Health and Nutrition Examination Survey, 1999-2004. *Arch Intern Med*. 2008;168:1522-1530.
2. Wallhagen MI, Strawbridge WJ, Cohen RD, Kaplan GA. An increasing prevalence of hearing impairment and associated risk factors over three decades of the Alameda County Study. *Am J Public Health*. 1997;87:440-442.
3. Cacciatore F, Napoli C, Abete P, Marciano E, Triassi M, Rengo F. Quality of life determinants and hearing function in an elderly population: Osservatorio Geriatrico Campano Study Group. *Gerontology*. 1999;45:323-328.
4. Olusanya BO, Ruben RJ, Parving A. Reducing the burden of communication disorders in the developing world: an opportunity for the millennium development project. *JAMA*. 2006;296:441-444.
5. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics−2015 update: a report from the American Heart Association. *Circulation*. 2015;131:e29-e322.
6. Friedland DR, Cederberg C, Tarima S. Audiometric pattern as a predictor of cardiovascular status: development of a model for assessment of risk. *Laryngoscope*. 2009;119:473-486.
7. Gates GA, Cobb JL, D'Agostino RB, Wolf PA. The relation of hearing in the elderly to the presence of cardiovascular disease and cardiovascular risk factors. *Arch Otolaryngol Head Neck Surg*. 1993;119:156-161.
8. Shargorodsky J, Curhan SG, Eavey R, Curhan GC. A prospective study of cardiovascular risk factors and incident hearing loss in men. *Laryngoscope*. 2010;120:1887-1891.
9. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311:507-520.
10. Wigand ME, Heidland A. Ototoxic side-effects of high doses of furosemide in patients with uraemia. *Postgrad Med J*. 1971;47(Suppl):54-56.
11. Rifkin SI, de Quesada AM, Pickering MJ, Shires DL Jr. Deafness associated with oral furosemide. *South Med J*. 1978;71:86-88.
12. Gallagher KL, Jones JK. Furosemide-induced ototoxicity. *Ann Intern Med*. 1979;91:744-745.
13. Ruggero MA, Rich NC. Furosemide alters organ of corti mechanics: evidence for feedback of outer hair cells upon the basilar membrane. *J Neurosci*. 1991;11:1057-1067.
14. Chodynicki S, Kostrzewska A. Effect of furosemide and ethacrynic acid on endolymph potential in guinea pigs. *Otolaryngol Pol*. 1974;28:5-8.
15. Brusilow SW. Propranolol antagonism to the effect of furosemide on the composition of endolymph in guinea pigs. *Can J Physiol Pharmacol*. 1976;54:42-48.
16. Kusakari J, Ise I, Comegys TH, Thalmann I, Thalmann R. Effect of ethacrynic acid, furosemide, and ouabain upon the endolymphatic potential and upon high energy phosphates of the stria vascularis. *Laryngoscope*. 1978;88:12-37.
17. Rybak LP. Ototoxicity of loop diuretics. *Otolaryngol Clin North Am*. 1993;26:829-844.
18. Lang H, Jyothi V, Smythe NM, Dubno JR, Schulte BA, Schmiedt RA. Chronic reduction of endocochlear potential reduces auditory nerve activity: further confirmation of an animal model of metabolic presbyacusis. *J Assoc Res Otolaryngol*. 2010;11:419-434.
19. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol*. 1986;123:894-900.
20. Swanepoel de W, Eikelboom RH, Hunter ML, Friedland PL, Atlas MD. Self-reported hearing loss in baby boomers from the Busselton Healthy Ageing Study: audiometric correspondence and predictive value. *J Am Acad Audiol*. 2013;24:514-521, quiz 529.
21. Hannula S, Bloigu R, Majamaa K, Sorri M, Maki-Torkko E. Self-reported hearing problems among older adults: prevalence and comparison to measured hearing impairment. *J Am Acad Audiol*. 2011;22:550-559.
22. Salonen J, Johansson R, Karjalainen S, Vahlberg T, Isoaho R. Relationship between self-reported hearing and measured hearing impairment in an elderly population in Finland. *Int J Audiol*. 2011;50:297-302.

23. Gomez MI, Hwang SA, Sobotova L, Stark AD, May JJ. A comparison of self-reported hearing loss and audiometry in a cohort of New York farmers. *J Speech Lang Hear Res*. 2001;44:1201-1208.
24. Kamil RJ, Genther DJ, Lin FR. Factors associated with the accuracy of subjective assessments of hearing impairment. *Ear Hear*. 2015;36: 164-167.
25. Curhan SG, Eavey R, Wang M, Stampfer MJ, Curhan GC. Body mass index, waist circumference, physical activity, and risk of hearing loss in women. *Am J Med*. 2013;126:1142.e1-1142.e8.
26. Curhan SG, Eavey R, Wang M, Stampfer MJ, Curhan GC. Prospective study of alcohol consumption and self-reported hearing loss in women. *Alcohol*. 2015;49:71-77.
27. Curhan SG, Shargorodsky J, Eavey R, Curhan GC. Analgesic use and the risk of hearing loss in women. *Am J Epidemiol*. 2012;176:544-554.
28. Seidman MD. Effects of dietary restriction and antioxidants on presbyacusis. *Laryngoscope*. 2000;110:727-738.
29. Itoh A, Nakashima T, Arao H, et al. Smoking and drinking habits as risk factors for hearing loss in the elderly: epidemiological study of subjects undergoing routine health checks in Aichi, Japan. *Public Health*. 2001;115:192-196.
30. Durga J, Verhoef P, Anteunis LJ, Schouten E, Kok FJ. Effects of folic acid supplementation on hearing in older adults: a randomized, controlled trial. *Ann Intern Med*. 2007;146:1-9.
31. Curhan SG, Stankovic KM, Eavey RD, Wang M, Stampfer MJ, Curhan GC. Carotenoids, vitamin A, vitamin C, vitamin E, and folate and risk of self-reported hearing loss in women. *Am J Clin Nutr*. 2015;102:1167-1175.
32. Curhan SG, Eavey RD, Wang M, Rimm EB, Curhan GC. Fish and fatty acid consumption and the risk of hearing loss in women. *Am J Clin Nutr*. 2014;100:1371-1377.
33. Wangemann P. Supporting sensory transduction: cochlear fluid homeostasis and the endocochlear potential. *J Physiol*. 2006;576:11-21.
34. Haupt H, Scheibe F, Mazurek B. Therapeutic efficacy of magnesium in acoustic trauma in the guinea pig. *ORL J Otorhinolaryngol Relat Spec*. 2003;65:134-139.
35. Li Y, Healy EW, Drane JW, Zhang J. Comorbidity between and risk factors for severe hearing and memory impairment in older Americans. *Prev Med*. 2006;43:416-421.
36. Bainbridge KE, Hoffman HJ, Cowie CC. Diabetes and hearing impairment in the United States: audiometric evidence from the National Health and Nutrition Examination Survey, 1999 to 2004. *Ann Intern Med*. 2008;149:1-10.
37. Hasson D, Theorell T, Westerlund H, Canlon B. Prevalence and characteristics of hearing problems in a working and non-working Swedish population. *J Epidemiol Community Health*. 2010;64: 453-460.
38. Nondahl DM, Cruickshanks KJ, Wiley TL, Klein R, Klein BE, Tweed TS. Prevalence and 5-year incidence of tinnitus among older adults: the epidemiology of hearing loss study. *J Am Acad Audiol*. 2002;13:323-331.
39. Rimm EB, Giovannucci EL, Stampfer MJ, Colditz GA, Litin LB, Willett WC. Reproducibility and validity of an expanded self-administered semiquantitative food frequency questionnaire among male health professionals. *Am J Epidemiol*. 1992;135:1114-1126, discussion 1127−1136.
40. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. *Am J Epidemiol*. 1985;122:51-65.
41. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology*. 1990;1:466-473.
42. Willett W. *Nutritional Epidemiology*. 3rd ed. Oxford; New York: Oxford University Press; 2013.
43. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;23:991-999.
44. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York: Springer; 2000.
45. Cruickshanks KJ, Wiley TL, Tweed TS, et al. Prevalence of hearing loss in older adults in Beaver Dam, Wisconsin. The Epidemiology of Hearing Loss Study. *Am J Epidemiol*. 1998;148:879-886.
46. Mitchell P, Gopinath B, Wang JJ, et al. Five-year incidence and progression of hearing impairment in an older population. *Ear Hear*. 2011;32:251-257.
47. Nin F, Hibino H, Doi K, Suzuki T, Hisa Y, Kurachi Y. The endocochlear potential depends on two K+ diffusion potentials and an electrical barrier in the stria vascularis of the inner ear. *Proc Natl Acad Sci U S A*. 2008;105:1751-1756.
48. Morizane I, Hakuba N, Shimizu Y, et al. Transient cochlear ischemia and its effects on the stria vascularis. *Neuroreport*. 2005;16:799-802.
49. Chou R, Dana T, Bougatsos C, Fleming C, Beil T. Screening adults aged 50 years or older for hearing loss: a review of the evidence for the U.S. preventive services task force. *Ann Intern Med*. 2011;154: 347-355.