Hypertension, Diuretic Use, and Risk of Hearing Loss

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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/m². 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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Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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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. As the life expectancy of individuals has increased, so has the prevalence of age-related hearing loss. Hearing loss can be disabling; therefore, identification of potential modifiable risk factors is an important public health issue.

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. Hypertension may increase the risk of hearing loss via decreased vascular supply to the stria vascularis. However, current evidence regarding the relation between hypertension and risk of hearing loss is inconsistent, with cross-sectional studies suggesting a positive association and a prospective study suggesting no association.

The Joint National Committee recommends thiazide diuretics as initial drug therapy for patients with uncomplicated hypertension. 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. The hearing loss is more likely to occur after intravenous drug administration but can also occur after oral dosing. The mechanism by which furosemide may cause hearing loss is unclear. Rodent models have shown that furosemide causes dysfunction of the stria vascularis, resulting in reduced endocochlear potential. Chronically impaired endocochlear potential has been shown to reduce auditory nerve activity, thereby impairing hearing.

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.
Ascertainment of Covariates

Covariates were selected on the basis of previously reported risk factors for hearing loss. Factors considered included age, race, body mass index, alcohol consumption, folate, beta-carotene, trans fats, beta-cryptoxanthin, vitamin A, vitamin B12, vitamin C, omega-3 fatty acids, potassium, magnesium, physical activity, smoking, diabetes, tinnitus, and use of acetaminophen, aspirin, and ibuprofen. For covariate adjustment, body mass index enzyme inhibitors was blocker, and beta-blocker use on the 1994 questionnaire and point onward. Person-time contribution of each participant were considered to have a history of hypertension from that reported having been diagnosed with hypertension, they considered women who reported being diagnosed with hypertension, 2813 (18%) who did not report a history of hypertension or medication use.

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 B12, 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.

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.

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. 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 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>
<thead>
<tr>
<th></th>
<th>No History of Hypertension (n = 34,523)</th>
<th>History of Hypertension (n = 15,401)</th>
<th>Thiazide No (n = 46,678)</th>
<th>Thiazide Yes (n = 3246)</th>
<th>Furosemide No (n = 49,323)</th>
<th>Furosemide Yes (n = 601)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>57.2 (6.4)</td>
<td>59.4 (6.4)</td>
<td>57.8 (6.4)</td>
<td>59.4 (6.5)</td>
<td>57.9 (6.5)</td>
<td>59.8 (6.6)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.5 (4.5)</td>
<td>28.2 (5.6)</td>
<td>26.2 (4.9)</td>
<td>28.8 (5.6)</td>
<td>26.3 (5.0)</td>
<td>30.0 (6.4)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>84.1 (12.9)</td>
<td>90.4 (14.3)</td>
<td>85.6 (13.5)</td>
<td>91.4 (14.2)</td>
<td>85.9 (13.6)</td>
<td>93.1 (16.2)</td>
</tr>
<tr>
<td>White</td>
<td>95.0%</td>
<td>93.1%</td>
<td>94.6%</td>
<td>92.7%</td>
<td>94.5%</td>
<td>93.7%</td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never smoker</td>
<td>46.5%</td>
<td>46.8%</td>
<td>46.6%</td>
<td>47.7%</td>
<td>46.7%</td>
<td>42.6%</td>
</tr>
<tr>
<td>Past smoker</td>
<td>41.5%</td>
<td>44.5%</td>
<td>42.3%</td>
<td>43.6%</td>
<td>42.3%</td>
<td>50.2%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>12.0%</td>
<td>8.5%</td>
<td>10.9%</td>
<td>8.6%</td>
<td>10.8%</td>
<td>7.0%</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>1.8 [0.0-6.5]</td>
<td>0.9 [0.0-5.3]</td>
<td>1.5 [0.0-6.2]</td>
<td>1.0 [0.0-5.8]</td>
<td>1.5 [0.0-6.1]</td>
<td>0.9 [0.0-3.5]</td>
</tr>
<tr>
<td>Daily nutrient intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin B12, µg</td>
<td>8.0 [5.0-12.0]</td>
<td>8.0 [5.0-12.0]</td>
<td>8.0 [5.0-12.0]</td>
<td>8.0 [5.0-12.0]</td>
<td>8.0 [5.0-12.0]</td>
<td>8.0 [5.0-13.0]</td>
</tr>
<tr>
<td>Vitamin E, mg</td>
<td>14.7 [8.3-114.3]</td>
<td>15.7 [8.6-182.9]</td>
<td>14.9 [8.4-115.7]</td>
<td>16.6 [8.8-186.0]</td>
<td>15.0 [8.4-116.7]</td>
<td>17.0 [8.5-185.6]</td>
</tr>
<tr>
<td>Folate, µg</td>
<td>404.7 [278.2-634.7]</td>
<td>414.7 [283.3-648.4]</td>
<td>406.8 [279.0-637.1]</td>
<td>422.1 [289.7-633.9]</td>
<td>408.0 [279.5-639.0]</td>
<td>408.9 [284.9-620.3]</td>
</tr>
<tr>
<td>Beta-cryptoxanthin, µg</td>
<td>155.7 [82.7-235.5]</td>
<td>170.7 [90.7-244.9]</td>
<td>159.1 [84.5-237.4]</td>
<td>178.2 [94.9-251.8]</td>
<td>160.2 [84.9-238.2]</td>
<td>176.8 [95.7-250.6]</td>
</tr>
<tr>
<td>Trans-fats, g</td>
<td>2.3 [1.6-3.2]</td>
<td>2.3 [1.6-3.2]</td>
<td>2.3 [1.6-3.2]</td>
<td>2.3 [1.6-3.2]</td>
<td>2.3 [1.6-3.2]</td>
<td>2.2 [1.5-3.2]</td>
</tr>
<tr>
<td>Omega-3 fatty acids, g</td>
<td>0.16 [0.09-0.27]</td>
<td>0.17 [0.10-0.28]</td>
<td>0.16 [0.09-0.27]</td>
<td>0.18 [0.10-0.29]</td>
<td>0.16 [0.10-0.27]</td>
<td>0.15 [0.09-0.27]</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>-</td>
<td>-</td>
<td>27.0%</td>
<td>86.7%</td>
<td>30.4%</td>
<td>71.4%</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>2.1%</td>
<td>7.3%</td>
<td>3.5%</td>
<td>6.7%</td>
<td>3.6%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Aspirin use, d/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>77.6%</td>
<td>70.1%</td>
<td>75.8%</td>
<td>67.8%</td>
<td>75.4%</td>
<td>66.6%</td>
</tr>
<tr>
<td>1-3</td>
<td>6.2%</td>
<td>5.6%</td>
<td>6.0%</td>
<td>5.9%</td>
<td>6.0%</td>
<td>5.2%</td>
</tr>
<tr>
<td>4+</td>
<td>16.0%</td>
<td>23.7%</td>
<td>17.8%</td>
<td>25.5%</td>
<td>18.2%</td>
<td>27.8%</td>
</tr>
<tr>
<td>Acetaminophen use, d/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>84.1%</td>
<td>79.5%</td>
<td>83.2%</td>
<td>75.7%</td>
<td>82.8%</td>
<td>71.2%</td>
</tr>
<tr>
<td>1-3</td>
<td>8.4%</td>
<td>9.5%</td>
<td>8.6%</td>
<td>11.0%</td>
<td>8.7%</td>
<td>13.4%</td>
</tr>
<tr>
<td>4+</td>
<td>5.2%</td>
<td>7.8%</td>
<td>5.8%</td>
<td>9.5%</td>
<td>5.9%</td>
<td>11.3%</td>
</tr>
<tr>
<td>Ibuprofen use, d/wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1</td>
<td>76.9%</td>
<td>70.6%</td>
<td>75.7%</td>
<td>64.5%</td>
<td>75.1%</td>
<td>62.2%</td>
</tr>
<tr>
<td>1-3</td>
<td>9.8%</td>
<td>9.8%</td>
<td>9.7%</td>
<td>11.5%</td>
<td>9.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>4+</td>
<td>7.6%</td>
<td>12.2%</td>
<td>8.6%</td>
<td>15.0%</td>
<td>8.9%</td>
<td>18.8%</td>
</tr>
</tbody>
</table>

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.
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 and 36 cases per 1000 person-years among men and women. 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. 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. It is hypothesized that hypertension may compromise the vascular supply to the stria vascularis, thereby leading to hearing loss. There is limited evidence regarding the relation between hypertension and risk of hearing loss.
studies have shown a higher prevalence of hearing loss among people with hypertension,\textsuperscript{1,7} whereas a prospective study in men has suggested no association between hypertension and hearing loss.\textsuperscript{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.\textsuperscript{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.\textsuperscript{10,12} However, the hearing loss can be irreversible and has been reported with oral dosing.\textsuperscript{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.\textsuperscript{13-17} Furthermore, long-term inhibition of the endocochlear potential has been associated with decreased auditory nerve activity,\textsuperscript{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.\textsuperscript{20-23} In addition, a recent review done for the US Preventive 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.\textsuperscript{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**


