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## 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 is also common and is 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 between hypertension, diuretic use, and hearing loss in a prospective cohort of 54,721 women in Nurses' Health Study I (NHSI), 1994–2012.

**Methods**—Eligible participants included 54,721 female nurses aged 48–73 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

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All authors had access to the data and a role in writing the manuscript.

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**Conflicts of Interest:** None declared

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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<sup>2</sup>. 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 anti-hypertensive 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.

### Keywords

Hearing loss; hypertension; thiazide diuretics; furosemide; prospective study

## INTRODUCTION

Hearing loss is highly prevalent in adults in the United States. Approximately one-third of women in their fifties and approximately two-thirds of women in their sixties have hearing loss <sup>1</sup>. As the life expectancy of individuals has increased, so has the prevalence of age-related hearing loss <sup>2</sup>. Hearing loss can be disabling, therefore, identification of potential modifiable risk factors is an important public health issue <sup>3,4</sup>.

Hypertension is also common in the United States, and affects approximately 35% of women in their forties and fifties, and more than 65% of women older than sixty-five years of age <sup>5</sup>. Hypertension may increase the risk of hearing loss via decreased vascular supply to the stria vascularis <sup>7</sup>. However, current evidence regarding the relation between hypertension and risk of hearing loss is inconsistent, with cross-sectional studies suggesting a positive association <sup>1,8</sup>, and a prospective study suggesting no association <sup>9</sup>.

The Joint National Committee (JNC) recommends thiazide diuretics as initial drug therapy for patients with uncomplicated hypertension <sup>10</sup>. 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 <sup>11–13</sup>. The hearing loss is more likely to occur following intravenous drug administration but can also occur after oral dosing <sup>11,13</sup>. 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 <sup>14–18</sup>. Chronically impaired endocochlear potential has been shown to reduce auditory nerve activity, thereby impairing hearing <sup>19</sup>.

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

## MATERIALS AND METHODS

### Study Participants

The Nurses Health Study I (NHS I) is a cohort of 121,700 female nurses aged 30–55 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), those who had a history of non-melanoma 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<sup>20</sup>. We classified women who answered, “yes” to this question as having a history of hypertension from that time onwards.

### Ascertainment of medication use

In 1994 and every two 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 two 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<sup>21–24</sup>. Studies found a single question on self-reported hearing loss

to be a relatively reliable indicator of hearing loss<sup>25</sup> Significant associations between several factors and risk of self-reported hearing loss have been observed using this manner of assessment in Nurses' Health Study II<sup>26–28</sup>.

### Ascertainment of covariates

Covariates were selected based on previously reported risk factors for hearing loss. Factors considered included age<sup>1</sup>, race<sup>1</sup>, body mass index<sup>26, 29</sup>, waist circumference<sup>26</sup>, alcohol consumption<sup>27, 30</sup>, folate<sup>31</sup>, beta-carotene<sup>32</sup>, trans fats<sup>32</sup>, beta-cryptoxanthin<sup>32</sup>, vitamin A, vitamin B<sub>12</sub>, vitamin C<sup>32</sup>, vitamin E<sup>32</sup>, omega-3 fatty acids<sup>33</sup>, potassium<sup>34</sup>, magnesium<sup>35</sup>, physical activity<sup>26, 36</sup>, smoking<sup>30</sup>, diabetes<sup>37</sup>, tinnitus<sup>38, 39</sup>, and use of acetaminophen, aspirin, and ibuprofen<sup>28</sup>. For covariate adjustment, body mass index was categorized as <21 kg/m<sup>2</sup>, 21–24 kg/m<sup>2</sup>, 25–29 kg/m<sup>2</sup>, 30–34 kg/m<sup>2</sup>, 35–40 kg/m<sup>2</sup>, and 40 kg/m<sup>2</sup>. 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 over-adjustment.

Data on covariates was 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<sub>12</sub>, vitamin A, potassium, magnesium, vitamin E, trans fat, 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 has previously been reported<sup>40, 41</sup>.

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<sup>42–44</sup>.

### 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 prior to 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 based on 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 based on 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<sup>45</sup>. To control as finely as possible for confounding by age, we stratified the analysis jointly by age at 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 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 two years preceding the baseline question. Answers in the affirmative on subsequent questionnaires for use of the medication were classified as two years of medication use. We examined the association between duration of medication use as continuous variables and categorical 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 between 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 prior to onset of hearing loss. Covariate status from the 1994 questionnaire was updated on each subsequent questionnaire. All p-values are two-sided, with 95% confidence intervals calculated for all relative risks. SAS software, version 9.4 (SAS Institute Inc., Cary, North Carolina) was used to perform all statistical analyses. This study was approved by the Partners Healthcare IRB.

## 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, 2,813 (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 = 1.04; 95% CI = 1.01, 1.07) (Table 2). Thiazide use was independently associated with higher risk of hearing loss (RR = 1.08; 95% CI = 1.04, 1.12), but furosemide use was not (RR = 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=0.61 and 0.11, 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 very 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 two previous prospective cohorts, where hearing loss was defined as a change in pure tone average of >25 decibels, were 72 cases per 1000 person-years among women<sup>46</sup>, and 36 cases per 1000 person-years among men and women<sup>47</sup>. 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<sup>48</sup>. Vascular supply to the stria vascularis is derived from 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<sup>49</sup>. It is hypothesized that hypertension may compromise the vascular supply to the stria vascularis thereby leading to hearing loss<sup>7</sup>. There is limited evidence regarding the relation between hypertension and risk of hearing loss<sup>1, 8, 9</sup>. Cross-sectional studies have shown higher prevalence of hearing loss among people with hypertension<sup>1, 8</sup>, whereas a prospective study in men has suggested no association between hypertension and hearing loss<sup>9</sup>. In our prospective cohort of women, hypertension was associated with a very 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 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<sup>11–13, 15</sup>. In humans, use of furosemide has been most commonly associated with hearing loss when administered intravenously and the hearing loss is usually reversible<sup>11, 13</sup>. However, the hearing loss can be irreversible and has been reported with oral dosing<sup>12</sup>. Although the mechanism by which this clinical hearing loss may occur unclear, rodent models suggest that it may occur via inhibition of the endocochlear potential

and alteration of Organ of Corti mechanics<sup>14–18</sup>. Furthermore, long-term inhibition of the endocochlear potential has been associated with decreased auditory nerve activity<sup>19</sup>, which may impair hearing. However, in our cohort of women, we found no association between furosemide use and risk of hearing loss.

Our study has 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<sup>21–24</sup>. In addition, a recent review done for the United States 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<sup>50</sup>.

In conclusion, 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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**Clinical Significance**

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

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**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=3,246)	Furosemide No (n=49,323)	Furosemide Yes (n=601)
Age, years	57.2 (6.4)	59.4 (6.4)	57.8 (6.4)	59.4 (6.5)	57.9 (6.5)	59.8 (6.6)
Body mass index, kg/m <sup>2</sup>	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/day	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, gm	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, gm	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, days/week						

	No History of Hypertension (n=34,523)	History of Hypertension (n=15,401)	Thiazide No (n=46,678)	Thiazide Yes (n=3,246)	Furosemide No (n=49,323)	Furosemide Yes (n=601)
<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, days/week						
<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, days/week						
<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

Abbreviations: METs = metabolic equivalents

Waist circumference values were taken from the 1996 questionnaire

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

**Table 2**

	No. of Cases	Person- Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
History of Hypertension						
No	8,289	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

RR denotes relative risk

\* Adjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity, nutrient (folate, magnesium, potassium, vitamin A, vitamin B12, vitamin C, vitamin E, beta-carotene, beta-cryptoxanthin, trans-fat) intake, smoking status, hypertension, diabetes, tinnitus, and acetaminophen, aspirin, and ibuprofen use.

**Table 3**

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

Anti-Hypertensive Medication	No. of Cases	Person-Years	Age-Adjusted RR	95% CI	Multivariable- Adjusted RR*	95% CI
No Medication	2,361	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	3,160	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
ACE Inhibitors	881	30,288	1.12	1.04, 1.21	1.04	0.96, 1.13
Other Anti-Hypertensive Medication	740	28,213	1.03	0.95, 1.12	1.00	0.92, 1.09
Multiple Anti-Hypertensive Medications	3,590	101,804	1.15	1.09, 1.21	1.03	0.97, 1.08

RR denotes relative risk

\* Adjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity, nutrient (folate, magnesium, potassium, vitamin A, vitamin B12, vitamin C, vitamin E, beta-carotene, beta-cryptoxanthin, trans fat) intake, smoking status, hypertension, diabetes, tinnitus, and acetaminophen, aspirin, and ibuprofen use, and all the antihypertensive medications in the table.