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Menopause and Postmenopausal Hormone Therapy and Risk of Hearing Loss

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Abstract

Objective—Menopause may be a risk factor for hearing loss and postmenopausal hormone therapy (HT) has been proposed to slow hearing decline; however, there are no large prospective studies. We prospectively examined the independent relations between menopause and postmenopausal HT and risk of self-reported hearing loss.

Methods—Prospective cohort study among 80,972 women in the Nurses' Health Study II, baseline age 27-44 y, followed from 1991 to 2013. Baseline and updated information was obtained from detailed validated biennial questionnaires. Cox proportional hazards regression models were used to examine independent associations between menopausal status and postmenopausal HT and risk of hearing loss.

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Conflict of Interest

Dr. Sharon Curhan is a consultant for Decibel Therapeutics. Dr. A. Heather Eliassen has no conflict of interest. Dr. Brian Lin has no conflict of interest. Dr. Molin Wang has no conflict of interest. Dr. Roland Eavey has no conflict of interest. Dr. Gary Curhan is a consultant for Decibel Therapeutics.

Results—After 1,410,928 person-years of follow-up, 18,558 cases of hearing loss were reported. There was no significant overall association between menopausal status, natural or surgical, and risk of hearing loss. Older age at natural menopause was associated with higher risk. The multivariable-adjusted relative risk (MVRR) of hearing loss among women who underwent natural menopause at age 50+ years compared with <50 was 1.10 (95% CI 1.03, 1.17). Among postmenopausal women, oral HT [(estrogen therapy (ET) or estrogen plus progestogen therapy (EPT)] was associated with higher risk of hearing loss, and longer duration of use was associated with higher risk (p-trend <0.001). Compared with women who never used HT, the MVRR of hearing loss among women who used oral HT for 5-9.9 years was 1.15 (95% CI 1.06, 1.24) and for 10+ years was 1.21 (95% CI 1.07, 1.37).

Conclusion—Older age at menopause and longer duration of postmenopausal HT are associated with higher risk of hearing loss.

Keywords

Hearing Loss; Hormone Therapy; Women's Health; Epidemiology; Public Health

Introduction

Hearing loss is a common, often disabling, condition that afflicts ~48 million Americans,[1] with global prevalence expected to grow as the world's population ages.[2] The adverse influence of hearing loss on communication, social well-being, health and quality of life are considerable.[3] Acquired hearing loss is often irreversible and treatment options are limited, underscoring the need to identify potentially modifiable risk factors that could aid in prevention.

The influence of estrogen and progestogens on auditory function is complex and incompletely understood. Estrogen receptors are present in peripheral and central auditory structures.[4,5] Human and animal studies have shown low estrogen levels can impair hearing, possibly through alterations in cochlear blood flow, neuroregulatory mechanisms, neuronal physiology or bone metabolism in the otic capsule.[6-13] Reduced estrogen levels after menopause may be associated with hearing loss in women.[14] Age is a strong risk factor for both hearing loss[15] and menopause, however cross-sectional studies that reported poorer hearing in postmenopausal than in premenopausal women did not adjust for age.[16,17] A cross-sectional study of postmenopausal women found a lower prevalence of hearing loss in those with higher serum estradiol.[18] A possible adverse influence of progestogens has been suggested, whether during the luteal phase of the menstrual cycle or as part of postmenopausal hormone therapy (HT).[17,19] Mechanisms for potential negative effects of progestogens on hearing have been proposed, including down-regulation of estrogen receptors or reduced cochlear blood flow,[20] yet whether progestogens have a direct effect on the cochlea is unknown.

Postmenopausal HT has been proposed to slow the development of age-related hearing loss, but previous studies have been small. Cross-sectional findings suggested that postmenopausal women who did not take HT had poorer hearing thresholds than those who used HT or premenopausal women, and postmenopausal women who used estrogen therapy

(ET) had better hearing than those who received estrogen plus progestogen (EPT) or no HT.[17,20,21] The relation between HT and risk of hearing loss has not previously been examined prospectively. Clarification of the relations between hormones and hearing could provide insight into underlying mechanisms and contribute to informed decision-making regarding HT.

To investigate these issues, we prospectively examined the associations between menopausal status, oral HT and risk of self-reported hearing loss in 80,972 women in the Nurses' Health Study II.

Methods

Study Population

The Conservation of Hearing Study (CHEARS) examines risk factors for hearing loss among participants in the Nurses' Health Study II, an ongoing cohort study of 116,430 female registered nurses in the US, aged 25-42 at enrollment in 1989. Participants have been followed by biennial mailed questionnaires that elicit updated information on diet, lifestyle, and various health outcomes; the follow-up rate over 24 years exceeds 90% of the eligible person-time. We limited the study to women who provided information on hearing on the 2009 or 2013 questionnaire. Of these 86,853 women, we excluded those who reported a hearing problem that began before baseline for the current analysis (1991) (n=3254) or did not report date of onset (n=437), reported cancer other than non-melanoma skin cancer (n=1101), date of menopause was before baseline or could not be determined (n=300), and used HT before the onset of menopause (n=789). A total of 80,972 women were included in the menopause analyses. For the HT analyses, we included only postmenopausal women. Women who reached menopause during follow-up were included in the analysis beginning at menopause. We excluded women who had missing information on HT for each time period. The total number of women included in the HT analyses was 47,360. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

Ascertainment of Menopause and HT Use

On each questionnaire, the participant was asked whether her menstrual periods had ceased permanently and at what age and for what reason (natural/surgical). Self-reported type of menopause and age at time of menopause in a similar cohort (NHS) were highly accurate compared with medical records.[22] Women were defined as postmenopausal if they reported permanent cessation of menstrual periods or had bilateral oophorectomy (surgical menopause). Age at menopause was defined as 12 months after the age at which women reported their natural periods had ceased. Women who had unknown menopausal status or had hysterectomy without bilateral oophorectomy, had incomplete availability of data on the extent of pelvic surgery, or had permanent cessation of menses due to radiation therapy were considered postmenopausal when they reached the age at which natural menopause occurred in 90% of the cohort, 54 years or older for smokers or 56 years or older for nonsmokers.[22]

On each questionnaire, participants were also asked whether they had ever used HT and, if so, the type of hormone used most recently during the previous 2 years. Women were asked about use of specific preparations, including oral and non-oral preparations. Women reported their use of ET and EPT. This information was used to categorize participants by duration of use and the type of hormone(s) used.

Ascertainment of outcome

The primary outcome of this study is self-reported hearing loss. Self-reported hearing loss was determined based on responses to the 2009 and 2013 questionnaires on which participants were asked about their hearing and provided the age at which a change in hearing was first noticed. We defined incident cases of hearing loss as a change in hearing that was first noticed by the participant after 1991 (baseline). Several studies have evaluated the use of questionnaires to elicit information on self-reported hearing loss in large populations in comparison with hearing loss determined by conventional audiometry and found reasonably similar and predictable relationships between impairment and self-assessment findings.[23-25] For example, a study that compared the use of a single question, "Do you feel you have a hearing loss?" with hearing loss measured by audiometry found the sensitivity of the single question among women similar in age to our study population was 79%, 95% and 100% for the detection of mild, moderate and marked hearing loss, respectively, and the specificity was 72%, 65%, and 64% for mild, moderate and marked hearing loss, respectively.[25] In another study that evaluated the validity of self-reported hearing loss by questionnaire with hearing loss defined as a four frequency (0.5, 1, 2, 4 kHz) pure tone average greater than 25 dBHL in the worse ear, the sensitivity of a single question ("Do you feel you have a hearing loss?") was 77.4% and the specificity was 75.8%.[23] The use of questionnaires to assess hearing loss in large populations has been effective in detecting significant relations in this and similar cohorts.[26-30]

Ascertainment of Covariates

We used an *a priori* selection of potential confounders to include in the multivariable models. Based on previous literature, we *a priori* selected factors that were purported to be risk factors for hearing loss for inclusion in our multivariable analyses. Potential confounders that were considered included age,[15] race,[15] smoking,[31] body mass index (BMI),[27] waist circumference,[27] physical activity,[27] intake of alcohol,[31] history of hypertension,[29] diabetes,[32] acetaminophen,[26] ibuprofen,[26] tinnitus,[33] and parity. We also adjusted for intake of nutrients that have been found to be associated with hearing loss in this cohort or others: folate,[28] vitamin B12,[34] Vitamin C,[28] magnesium,[35] omega-3 long chain PUFA,[30] trans-fat, beta-carotene,[28] and beta-cryptoxanthin.[28] Covariate information was obtained from biennial questionnaires and semiquantitative food frequency questionnaires, administered every four years, and updated throughout the analysis whenever new information became available.

In 2012, a web-based Hearing Study Supplementary Questionnaire (HSSQ) that elicited additional information related to hearing health was completed by a subcohort of participants (n=33,102). The characteristics of the women who completed the HSSQ did not differ materially from those of the overall cohort. Information on a variety of hearing-related

factors was collected, including detailed information on lifetime recreational, occupational and impulse noise exposure. For example, participants provided information on the average amount of time that they were engaged in a number of specified activities or exposed to specified types of noises during each decade of life. Exposure to Very Loud Noise (VLN) was defined as exposure to "noise that is so loud that you have to shout in order to be understood by someone standing 3 feet away from you." Examples of very loud noises were included for illustrative purposes. Women were also asked about exposure to "extremely intense noise of brief duration (noise that is so loud it is painful)" and examples that were provided (e.g. gunfire). This method has been used previously in this cohort to examine relations between noise exposure and hearing loss.[36]

Statistical analysis

The study design was prospective, and information on menopause and HT was collected before the report of onset of hearing loss. Person-time of follow-up was calculated from the date of return of the 1991 questionnaire until the date of self-reported hearing loss or end of follow-up in 2013. Participants who reported cancers other than non-melanoma skin cancer were censored when reported during follow-up. Women who reported use of hormones other than oral ET or EPT (e.g. transdermal, vaginal or unknown type) were categorized separately. Participants with missing HT data were skipped for that time period.

Characteristics of women according to menopausal status in 2001 were examined to provide a representation of these characteristics at an intermediate time point during the follow-up period. Secondary analyses that examined age at menopause and risk of hearing loss were restricted to women who had experienced natural menopause and to women with no HT use.

We used Cox proportional hazards regression models to estimate relative risks (RR) and 95% confidence intervals (CI). Premenopausal women were the referent group in the analysis of menopausal status. Postmenopausal women who reported "never use" were the referent group in the analysis of HT. We used the Anderson-Gill[37] data structure, with a new data record created for each biennial questionnaire, to handle time-varying covariates efficiently. To control as finely as possible for confounding by age, calendar time and any possible two-way interactions between these two time scales, we stratified the analysis jointly by age in months at start of follow-up and calendar year of the current questionnaire cycle. The time scale for the analysis was then measured as months since the start of the current questionnaire cycle, which is equivalent to age in months. Tests for linear trend for duration of HT were performed by assigning the median value of each category to all participants in that group. All P values are two-tailed. Statistical tests were performed with SAS statistical software, version 9.4 (SAS Institute Inc.).

Results

Midpoint characteristics (2001) according to menopausal status are presented in Table 1. Participants were predominantly white (>94%) and the mean (SD) ages of the pre- and postmenopausal women were 45.0 (4.1) and 50.7 (3.5) years, respectively. Postmenopausal women had higher BMI and larger waist circumference. Among the postmenopausal women, over 60% reported having ever used oral HT, almost 18% reported use of other

forms of HT (either non-oral or unknown type), and over 20% had never used any form of HT.

Menopause and risk of hearing loss

After 1,410,928 person-years of follow-up, 18,558 cases of hearing loss were reported. No overall association between menopausal status, whether natural or surgical, and risk of hearing loss was observed (Table 2). Compared with women who were premenopausal, the multivariable-adjusted relative risk (MVRR) for hearing loss among women who had undergone natural menopause was 1.00 (95% CI 0.94, 1.05), and among those who had undergone surgical menopause was 0.95 (0.89, 1.02). In an analysis restricted to women who did not use HT, no association was observed among women who underwent natural menopause [MVRR = 0.98 (95% CI 0.92, 1.05)] (Supplemental Table 1). The risk of hearing loss among women who underwent surgical menopause and did not use HT was 31% lower than among women who were premenopausal [MVRR = 0.69 (95% CI 0.60, 0.80)], however, there were only 223 cases of self-reported hearing loss in this group.

Older age at natural menopause was associated with higher risk; the risk among women who underwent natural menopause at age 50 or older was 10% higher than among those who underwent natural menopause before age 50 [MVRR 1.10 (95%CI 1.03, 1.17)] (Table 3). No significant association between older age at surgical menopause and risk was observed, but power was limited due to the number of cases. We also conducted an analysis restricted to women who underwent natural menopause and who did not use HT (Supplemental Table 2). The MVRR for hearing loss for women who underwent natural menopause at age 50-54 years was 1.21 (95% CI 1.10, 1.34) and at age 55+ years was 1.29 (95% CI 1.11, 1.50), compared with women who underwent natural menopause before age 50. When restricted to women who had reported their age of menopause (excluding women with derived age at menopause), the results were unchanged.

HT and risk of hearing loss

Among postmenopausal women, use of oral HT was associated with higher risk of hearing loss and the magnitude of the risk tended to increase with longer duration of use (p-trend <0.001)(Table 4). Compared with women who never used any type of HT, the MVRR of hearing loss among women who used oral HT for 1-1.9 years was 1.10 (95% CI 1.00, 1.21), for 2-4.9 years was 1.08 (95% CI 1.00, 1.16), 5-9.9 years was 1.15 (95% CI 1.06, 1.24) and for 10+ years was 1.21 (95% CI 1.07, 1.37).

When specific types of oral HT were examined, longer duration of use of both oral ET or EPT were each associated higher risk (Table 5). Fewer women reported use of progestogen-only oral HT, yet among these women a higher risk was suggested but not significant [MVRR 1.15 (95% CI 0,98, 1.35)]. Transdermal HT use was less common, but the associations observed were similar to those with oral HT. When examined separately by type of menopause, the results for HT were similar (data not shown).

In the subcohort of women for whom we had detailed information on self-reported lifetime noise exposure (n=33,102), the proportion of women who reported frequent very loud noise or impulse noise exposure was small (<4%) and did not differ by menopausal status or HT

use (data not shown). In analyses that adjusted for history of very loud noise exposure and history of impulse noise exposure, the results were not materially changed (data not shown).

Discussion

In this prospective study among 80,972 women, we did not observe an overall independent association between menopausal status and risk of hearing loss. However, the risk among women who underwent natural menopause at an older age was higher. We also found that use of oral HT, whether ET or EPT, was associated with higher risk, and the magnitude of the risk was greater with longer duration of use. These findings suggest that oral HT, particularly longer duration of use, may have implications for hearing.

The role of sex hormones in audition is complex and incompletely understood, with both direct effects on the cochlea and central auditory pathways and indirect actions, such as modulation of blood flow that may influence peripheral and central hearing function. Sex differences in auditory anatomy, physiology, and rates of aging-related auditory decline have been demonstrated in animal models and humans.[16,38-42] Despite potentially dissimilar lifetime noise exposure in men and women, studies in mouse models demonstrated sex differences in rates of hearing decline with age even when noise exposure was minimized, and endogenous and exogenous sex hormones may influence hearing.[38,43-45] Although differences in sex hormones have been suggested to contribute to hearing disparities in humans,[42] their influence on aging-related hearing decline remains unclear.

Estrogen receptors (ER) have been demonstrated in inner and outer hair cells, spiral ganglion cells, the spiral ligament and the stria vascularis,[9] and estrogen influences both peripheral and central auditory pathways.[16,46] Progesterone receptors were not found in these structures,[47] suggesting indirect action, possibly by interacting with inner ear glucocorticoid receptors and altering aldosterone-mediated regulation of sodium and potassium ionic balance.[48] A protective role for estrogen has been suggested;[18,21] fluctuations in hearing sensitivities have been demonstrated throughout the menstrual cycle, with poorer hearing during the menstrual phase when estrogen is the lowest.[19,49] A cross-sectional study of postmenopausal women found lower serum estradiol was associated with poorer auditory sensitivity.[18] However, estrogen and progestogen exacerbated hearing loss and increased vulnerability to acoustic damage in mouse models of adult-onset hearing loss, and greater degeneration of hair cells and central auditory neurons was found in mice with intact ovaries compared with ovariectomized mice.[43]

To our knowledge, this is the first large prospective study to examine the independent relation of menopausal onset and risk of hearing loss. Based on limited data, it was previously suggested that the menopausal transition was a trigger for hearing decline[14,50] Although a small longitudinal study in Sweden (n=143) reported accelerated rates of threshold decline with increasing time since menopause, the dropout rate was high and the study did not perform age-specific comparisons to examine whether menopause itself was an independent risk factor.[14] A small cross-sectional study in Turkey (n=55) compared hearing thresholds among similarly aged premenopausal and postmenopausal women and did not

observe significant differences.[51] Our prospective study found that menopausal onset is not an independent risk factor for hearing loss.

Our finding that older age at natural menopause was associated with higher risk of hearing loss was unexpected and the mechanism is unclear. The determinants of the age at which natural menopause occurs are incompletely understood, but may include genetics, lifestyle factors, reproductive history, and demographic factors.[52] In our analyses, careful adjustment for these factors, particularly age, did not materially influence the results. Although older age at natural menopause may be a marker of healthy aging,[53,54] it has also been associated with adverse health outcomes.[55-57] The risk of hearing loss among women who underwent surgical menopause and did not use HT was lower than among women who were premenopausal; however, this finding should be interpreted with caution given that relatively few women who underwent surgical menopause did not use HT and thus there was a relatively small number of cases among those who did not use HT.

This is also the first large prospective study to examine the independent relation of HT and risk of hearing loss. Findings from previous studies in animals and humans have been conflicting. A study in mice showed worse hearing in those administered EPT compared with ET or placebo, and that peripheral and central auditory influences of estrogen may differ.[45] A study in guinea pigs found administration of estrogen, progestin, or both resulted in poorer hearing measures, as well as adverse histologic changes, including inflammatory infiltrates and vacuolization of the stria vascularis.[58] In humans, case reports of adverse reactions to HT have included sudden sensorineural hearing loss, tinnitus and vertigo.[59] Some small retrospective and cross-sectional studies have found poorer hearing measures among postmenopausal women who used combination EPT compared with users of ET or no HT,[8,17,20,21] and a randomized controlled trial among 24 postmenopausal women reported improved hearing after treatment with a synthetic steroid HT with estrogenic and progestogenic action.[60] Although some studies suggest a possible protective influence of ET, our findings indicate that use of either oral ET or EPT may adversely influence hearing.

Current considerations for HT include timing, dose, type, and duration, along with risks and benefits.[61] Our findings suggest that hearing may also be a consideration for women treated with HT.

Strengths of this study include the large size of the study population, large number of cases of incident hearing loss, prospective study design, long duration of follow-up, and decades of detailed information on HT use. The availability of detailed and validated information on health, diet, lifestyle, reproductive and menopausal factors, allowed us to control for a number of potential confounding factors. For our analyses, we used updated exposures in our Cox models, thus we were able to include women in our HT analysis as they became postmenopausal and account for changes in hormone use during follow-up.

Our study has limitations. Assessment of hearing loss was based on self-report. Hearing decline can be subtle, thus there is imprecision in the date of onset. Standard pure-tone audiometry is the gold-standard measure for evaluating hearing loss, however, assessments based on self-report have been found to be reasonably reliable,[23,62] and have been used to

detect significant associations in this cohort previously.[26-28,30] Notably, the prevalence of self-reported hearing loss in this cohort was similar to nationally representative findings for women in this age group (National Health Interview Survey).[63] Assessment of hearing loss and date of onset were collected in 2009 and 2013, but all information on exposures and covariates was collected before the reported date of onset of hearing loss; therefore, we were able to examine these relations prospectively. We carefully adjusted for many potentially confounding variables in our analyses, yet residual confounding is still a possibility. Our study was limited to predominantly non-Hispanic white women, thus further studies in additional populations are needed.

Conclusion

These findings suggest that women who undergo menopause at an older age and women who use oral HT have a higher risk of hearing loss. In addition, longer duration of use of oral HT is associated with higher risk of hearing loss among postmenopausal women. Hearing health may be a consideration for women when evaluating the risks and benefits of HT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Age-standardized Midpoint Characteristics of the Study Population According to Menopausal Status, Nurses' Health Study II (2001)[a]

Characteristic	Premenopausal Women (n=48749)	Postmenopausal Women (n=16546)
Age, y[b]	45.0 (4.1)	50.7 (3.5)
Body Mass Index, kg/m^2	26.6 (6.2)	27.5 (6.5)
Waist Circumference (1993), cm	77.8 (12.6)	79.1 (13.7)
Physical Activity, MET-hrs/wk[c]	13.1 (4.5-28.8)	11.5 (4.0-26.2)
Smoking Status, %		
Never	68.5	62.4
Past	24.5	25.3
Current	6.7	12.0
History of Hypertension, %	15.1	21.8
History of Diabetes, %	2.1	3.8
History of Tinnitus, %	6.4	8.4
White Race, %	94.7	94.3
Ibuprofen Use[d] %	20.9	21.8
Acetaminophen Use[d], %	8.8	12.6
Alcohol Intake, g/d	1.1(0-4.9)	1.1 (0-4.7)
Never Use of HT[e], %	--	20.5
Oral HT (ever), %	--	61.6
Non-oral HT (ever), %	--	16.6
HT, unknown type (ever), %	--	1.3

[a]Values, except for age, are standardized to the age distribution of the study population. Polytomous variables may not sum to 100% because of rounding. Characteristics at the approximate study midpoint (2001) are presented to provide a representation of the population at an intermediate time point during follow-up period.

[b]Mean (SD) for all such values.

[c]Median (IQR) for all such values, not age-standardized. METS, metabolic equivalent tasks from recreational and leisure-time activities.

[d]Two days per week or more.

[e]HT, hormone therapy

Table 2

Menopausal Status and Risk of Hearing Loss, Nurses' Health Study II (1991-2013)

Menopausal Status	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR[a] (95% CI)
Premenopausal	9,859	1,014,791	1.00 (ref)	1.00 (ref)
Postmenopausal	8,699	396,137	1.05 (1.01, 1.10)	0.98 (0.93, 1.04)
Natural	6,058	266,734	1.04 (0.99, 1.09)	1.00 (0.94, 1.05)
Surgical	2,352	115,173	1.09 (1.04, 1.15)	0.95 (0.89, 1.02)

[a]Multivariable models adjusted for age; race; body mass index; waist circumference; physical activity; smoking; hypertension; diabetes; intake of alcohol, folate, vitamin B12, vitamin C, magnesium, long chain omega-3 fatty acids, trans-fat, beta-carotene and beta-cryptoxanthin; ibuprofen use; acetaminophen use; tinnitus; parity; and duration of hormone therapy.

Missing natural/surgical menopause (n=289 cases)

Table 3

Age at Menopause and Risk of Hearing Loss Among Postmenopausal Women, Nurses' Health Study II (1991-2013)

Age at Menopause	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR[a] (95% CI)
Natural				
<50 years	2,589	122,303	1.00 (ref)	1.00 (ref)
50+ years	3,399	140,178	1.06 (1.00, 1.13)	1.10 (1.03, 1.17)
Surgical				
<50 years	1,597	73,764	1.00 (ref)	1.00 (ref)
50+ years	301	12,674	0.96 (0.84, 1.09)	1.00 (0.87, 1.15)

P-interaction = 0.07

[a]Multivariable models adjusted for age; race; body mass index; waist circumference; physical activity; smoking; hypertension; diabetes; intake of alcohol, folate, vitamin B12, vitamin C, magnesium, long chain omega-3 fatty acids, trans-fat, beta-carotene and beta-cryptoxanthin; ibuprofen use; acetaminophen use; tinnitus; parity; and duration of hormone therapy.

Table 4

Duration of Postmenopausal Hormone Therapy and Risk of Hearing Loss Among Postmenopausal Women, Nurses' Health Study II (1991-2013)

Duration of Oral HT Use	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted RR[a] (95% CI)
Never	3267	149,062	1.00 (ref)	1.00 (ref)
Ever Oral HT				
<1 yr	388	19,214	1.12 (1.00, 1.24)	1.09 (0.98, 1.21)
1–1.9 yrs	544	27,465	1.13 (1.03, 1.24)	1.10 (1.00, 1.21)
2-4.9 yrs	1064	49,993	1.10 (1.02, 1.18)	1.08 (1.00, 1.16)
5-9.9 yrs	1018	40,488	1.14 (1.06, 1.23)	1.15 (1.06, 1.24)
10+ yrs	399	12,983	1.20 (1.08, 1.34)	1.21 (1.07, 1.37)
p-trend			<0.001	<0.001

[a]Multivariable models adjusted for age; race; body mass index; waist circumference; physical activity; smoking; hypertension; diabetes; intake of alcohol, folate, vitamin B12, vitamin C, magnesium, long chain omega-3 fatty acids, trans-fat, beta-carotene and beta-cryptoxanthin; ibuprofen use; acetaminophen use; tinnitus; parity; use of non-oral HT; type of menopause; and age at menopause.

HT, hormone therapy

Table 5

Duration By Type of Oral Postmenopausal Hormone Therapy and Risk of Hearing Loss Among Postmenopausal Women, Nurses' Health Study II (1991-2013)

Duration of Oral HT Use	Cases	Person-years	Age-adjusted RR (95% CI)	Multivariable -adjusted RR[a] (95% CI)
Never	3267	149062	1.00 (ref)	1.00 (ref)
Oral ET				
< 1 yr	116	6043	1.21 (1.01, 1.46)	1.21 (1.00, 1.46)
1-4.9 yrs	549	28933	1.11 (1.01, 1.21)	1.10 (0.99, 1.21)
5+ yrs	786	30075	1.17 (1.09, 1.27)	1.18 (1.07, 1.30)
Oral EPT				
< 1 yr	215	10885	1.04 (0.90, 1.19)	1.01 (0.88, 1.16)
1-4.9 yrs	972	44760	1.10 (1.02, 1.18)	1.07 (1.00, 1.16)
5+ yrs	616	22604	1.14 (1.04, 1.24)	1.14 (1.04, 1.26)
Oral Progestins				
Ever use	159	6843	1.19 (1.01, 1.40)	1.15 (0.98, 1.35)

[a]Multivariable models adjusted for age; race; body mass index; waist circumference; physical activity; smoking; hypertension; diabetes; intake of alcohol, folate, vitamin B12, vitamin C, magnesium, long chain omega-3 fatty acids, trans-fat, beta-carotene and beta-cryptoxanthin; ibuprofen use; acetaminophen use; tinnitus; parity; use of non-oral HT; type of menopause; and age at menopause.

HT, hormone therapy

ET, estrogen therapy

EPT, estrogen plus progestogen therapy