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Body Mass Index, Waist Circumference, Physical Activity and Risk of Hearing Loss in Women

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Abstract

BACKGROUND—Acquired hearing loss is highly prevalent, but prospective data on potentially modifiable risk factors are limited. In cross-sectional studies, higher body mass index (BMI), larger waist circumference, and lower physical activity have been associated with poorer hearing, but these have not been examined prospectively.

METHODS—We examined the independent associations between BMI, waist circumference and physical activity and self-reported hearing loss in 68,421 women in the Nurses' Health Study II from 1989 to 2009. Baseline and updated information on BMI, waist circumference and physical activity was obtained from biennial questionnaires.

RESULTS—After more than 1.1 million person-years of follow-up, 11,286 cases of hearing loss were reported to have occurred. Higher BMI and larger waist circumference were associated with increased risk of hearing loss. Compared with women with BMI <25 kg/m^2, the multivariate-adjusted relative risk (RR) for women with BMI ≥ 40 was 1.25 (95% CI 1.14,1.37). Compared with women with waist circumference <71 cm, the multivariate-adjusted RR for waist circumference >88 cm was 1.27 (95% CI 1.17, 1.38). Higher physical activity was inversely related to risk; compared with women in the lowest quintile of physical activity, the multivariate-adjusted RR for women in the highest quintile was 0.83 (95% CI 0.78,0.88). Walking 2 hours per week or more was inversely associated with risk. Simultaneous adjustment for BMI, waist circumference and physical activity slightly attenuated the associations but they remained statistically significant.

CONCLUSIONS—Higher BMI and larger waist circumference are associated with increased risk and higher physical activity is associated with reduced risk of hearing loss in women. These

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findings provide evidence that maintaining healthy weight and staying physically active, potentially modifiable lifestyle factors, may help reduce the risk of hearing loss.

Keywords

hearing loss; prospective study; body mass index; waist circumference; physical activity; epidemiology

Introduction

Acquired hearing loss is a highly prevalent disabling chronic condition. In the US, it is estimated that up to 1/3 of women in their fifties and 2/3 of women in their sixties suffer from some degree of hearing loss.[1] Hearing loss can impair communication and social interaction, and adversely affect psychosocial well-being and quality of life.[2,3] Therefore, identification of potentially modifiable risk factors for hearing loss is a compelling public health goal.

Obesity and its comorbidities, cardiovascular disease,[1,4–6] cerebrovascular disease,[7,8] diabetes,[9,10] hypertension,[6,11] and dyslipidemia,[6] may be related to the development of hearing loss, potentially due to compromised vascular supply to the stria vascularis and impaired cochlear function. Obese leptin-deficient mice develop sensorineural hearing loss earlier than their wild type counterparts.[12] In human cross-sectional studies, higher body mass index (BMI), a measure of overall obesity, and larger waist circumference, a measure of central adiposity, have been associated with poorer hearing thresholds.[13–15] However, the relation between obesity and hearing loss has not been prospectively examined.

Higher levels of physical activity may protect against hearing loss. Physical activity may have beneficial effects on the cochlear vascular endothelium, enhance detoxification of free radicals, and reduce inflammation. Small cross-sectional studies have reported relations between higher levels of physical activity, higher cardiorespiratory fitness, and better hearing sensitivity.[16,17] A number of conditions implicated in hearing loss, such as diabetes and cardiovascular disease, are inversely associated with higher levels of physical activity.[18,19] Yet, it is unclear whether physical activity is an independent risk factor for hearing loss.

We prospectively analyzed the association between these potentially modifiable factors and the risk of hearing loss in 68,421 female participants in the Nurses' Health Study II (NHS II).

METHODS

Study Participants

The Nurses' Health Study II is comprised of 116,430 female registered nurses aged 25–42 years from 14 states who answered a mailed questionnaire in 1989. Questionnaires were administered every other year and the average follow-up rate over 22 years exceeds 90%. The questionnaires elicited information on anthropometric measures, lifestyle factors, medication use, and medical conditions. Detailed information on diet was obtained every 4 years. The 2009 questionnaire asked participants whether they have a hearing problem and at what age a change in hearing was first noticed. We excluded women who reported hearing problem (n=2,530) or cancer (n=654) that began before 1989. We also excluded women who developed cancer during follow-up yet before the onset of hearing loss (n=4118). To refine the categorization of hearing "problem" as hearing "loss," we excluded participants who reported tinnitus that occurred more than once/week at baseline or during follow-up yet before the onset of hearing loss (n=6,490) because tinnitus is a strong risk factor for hearing loss.[20–22] We performed secondary analyses that included these women and stratified by tinnitus. The study protocol was approved by the Institutional Review Board of Brigham and Women's Hospital.

Assessment of Body Mass Index (BMI)

BMI was calculated based on height, reported at study entry in 1989, and weight, reported on each biennial questionnaire, and these measurements were used to calculate biennially updated BMI. In a validation study, self-reported height and weight and direct measurements were highly correlated (height, r=0.94 and weight, r=0.96) [23,24] in a similar cohort of women.

Assessment of Waist Circumference

Waist circumference was assessed at two time points, in 1993 and 2005. Participants were sent a measuring tape and asked to report their waist circumference to the nearest ¼ inch. Self-measured waist circumference was found to be correlated with technician-measured waist circumference measurements (r=0.89).[25] Information on waist circumference was available for 50% of study participants.

Assessment of Physical Activity

Information on physical activity was first collected in 1989 and again in 1991, 1997, 2001, 2005, and 2009. Participants completed a physical activity grid, modified slightly on successive questionnaires, and reported average time spent per week in the previous year in a variety of recreational activities: walking for exercise, walking to work, hiking outdoors, jogging (>10 min/mile), running (≤ 10 min/mile), bicycling (including stationary machine), calisthenics/aerobics/aerobic dance/rowing machine, tennis, squash, racquetball, lap swimming, other aerobic activity (e.g. aerobics, dance, ski/stair machine), lower intensity exercise (e.g. yoga, stretching, toning), other vigorous activities, weight training or resistance exercise. Participants also reported flights of stairs climbed daily. Energy expenditure in metabolic-equivalent tasks (METs) in hours/week[26] was calculated using the Ainsworth classification.[27] One MET is the amount of energy expended while sitting quietly, hence an activity with MET score of 5 requires five times the energy as sitting quietly. Total physical activity was derived from the reported hours spent per week in recreational activities plus the reported number flights of stairs climbed daily. Walking pace was used to determine the MET score for calculating MET-hrs/wk from walking.[28] The reproducibility and validity of the physical activity questionnaire have been demonstrated in a representative sample of 147 NHS II participants. The questionnaire-based estimate of physical activity was highly correlated with one-week recall (r=0.79) and four 1-week diaries completed over the course of one year (r=0.62).[29]

Assessment of Hearing Loss

The primary outcome, self-reported hearing loss, was determined based on responses to the 2009 question "Do you have a hearing problem?" with response categories: "no," "mild," "moderate," or "severe," and, "If so, at what age did you first notice a change in your hearing?" Of the 80,096 women who responded to this questionnaire, 23.3% reported a hearing problem.

We defined an incident case as hearing problem first noticed after 1989. We excluded those who reported tinnitus; therefore, we considered the remaining cases of self-reported hearing problem to be hearing loss. Although hearing loss is usually insidious in onset, we defined incident cases as hearing loss when first noticed by the participant. We did not have information on severity of hearing loss at the time of onset, thus we were not able to perform prospective analyses that considered severity of hearing loss as the outcome. Pure-tone audiometry is considered the gold standard for hearing loss evaluation, but cost and logistic limitations precluded such assessment in this large population. Studies that assessed the reliability of self-reported hearing loss using a single question found this method to be a reasonably reliable measure.[30–32] A recent validation study of individuals aged 30–65 years evaluated the performance of a single question as compared to results from pure-tone audiometry and found the sensitivity and specificity were 79.6% and 77.4%, respectively.[33]

Assessment of covariates

We considered covariates purported to be risk factors for hearing loss, including age,[1] race,[1] smoking,[34] intake of alcohol,[34] folate,[35] vitamin B12,[36] magnesium,[37] potassium, vitamin A,[38] hypertension,[6] diabetes,[9] acetaminophen use and ibuprofen use.[39] Covariate information was obtained from the biennial questionnaires. Intakes of alcohol, folate, B12, potassium, magnesium, and vitamin A were calculated from semiquantitative food frequency questionnaires (FFQ) mailed first in 1991 and every 4 years thereafter. Beginning in 1995 and every 2 years thereafter, participants were asked about average frequency of use of analgesics.

Statistical analysis

All analyses were prospective, using exposure information collected before the reported onset of hearing problem. BMI was calculated and categorized as <25, 25–29, 30–34, 35–39, and 40+, which conform with WHO categories for healthy weight (BMI <25), pre-obese (BMI 25–29), obese class I (30–34), obese class II (35–39), and obese class III (BMI 40+). Waist circumference was categorized according to previously used cutpoints: <71 cm, 71–79 cm, 80–88 cm and >88 cm.[40] Physical activity, expressed as METs/week, was categorized in quintiles. Intensity of physical activity was categorized as strenuous (activities with a MET value >6) and moderate (activities with a MET value 3.5 to 6). Hours per week of walking was categorized into 4 categories, <1 hour/week, 1–1.5 hours/week, 2–4 hours/week, and 4+ hours/week, in a way that is consistent with previous examinations of the relation between walking and other health outcomes in this cohort. [41,42]

For each participant, person-time was allocated based on the most recent responses to the weight, waist circumference and physical activity questions at the beginning of each follow-up period. Participants were censored at the age of reported hearing loss or cancer, whichever came first. Missing categories were created for data on covariates that were not available. Age- and multivariate-adjusted relative risks (RRs) were estimated using Cox proportional hazards regression models, with the Anderson-Gill data structure.[43] 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. To examine whether the associations vary by age, we performed likelihood ratio tests comparing models with and without the age*exposure interaction terms.

For all RRs, we calculated 95% confidence intervals (CIs). All P values are 2-tailed. Tests of linear trend across increasing categories of exposure were conducted by treating the BMI, waist circumference, and physical activity categories as continuous variables and assigning the median value for each category. All analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc., Cary, NC).

RESULTS

Characteristics of participants at baseline are summarized in Table 1. The mean age was 34.5 years, the median BMI was 22.6 kg/m^2 (IQR 20.7–25.6), the median waist circumference in 1993 was 73.7 cm (IQR 68.6–83.8), and the median level of physical activity was 13.9 METs/week (IQR 5.4–30.2). Walking for exercise one hour/week or more was reported by 58% of the women. Participants who answered the 2009 main questionnaire, on which hearing loss was first assessed, did not differ appreciably with respect to baseline characteristics from those participants who did not.

After 1,159,460 person-years of follow-up, 11,286 cases of hearing loss were reported to have occurred. The age- and multivariate-adjusted relative risks (RRs) of hearing loss according to category of BMI are presented in Table 2. Higher BMI was independently associated with an increased risk of hearing loss. In a multivariate-adjusted model that did not include physical activity, compared with women with BMI<25, the RR for hearing loss in those with BMI ≥ 40 was 1.25 (95% CI 1.14,1.37; p-trend <0.001). Further adjusting for physical activity and for waist circumference slightly attenuated the association; however, a BMI of 25 or greater remained independently associated with risk of hearing loss.

Larger waist circumference was also independently associated with an increased risk of hearing loss (Table 3). In a multivariate-adjusted model that did not include BMI or physical activity, compared with women with waist circumference <71 cm, the RR for hearing loss in those with waist circumference >88 cm was 1.27 (95% CI 1.17,1.38; p-trend <0.001). Further adjusting for physical activity and for BMI attenuated the association; however, waist circumference >88 cm remained independently associated with risk of hearing loss (multivariate-adjusted RR = 1.17 (95% CI 1.06,1.29)).

Higher level of physical activity was inversely associated with the risk of hearing loss (Table 4). In a multivariate model that did not include BMI or waist circumference, the RR for hearing loss for women in the highest quintile compared with the lowest quintile of physical activity was 0.83 (95% CI 0.78,0.88; p-trend<0.001). Further adjusting for BMI slightly attenuated the association (multivariate-adjusted RR=0.86 (95% CI 0.81,0.92)).

Walking was the most common form of physical activity; therefore, we examined the relation between walking and risk of hearing loss. After multivariate adjustment, walking 2 or more hours/week was associated with lower risk of hearing loss (p-trend <0.001) (Table 5). For example, compared with women who walked <1 hour/week, the multivariate-adjusted RR of hearing loss for women who walked 4 or more hours per week was 0.85 (95% CI 0.80,0.91).

We examined the relation between strenuous physical activity, moderate physical activity, walking and risk of hearing loss. We did not observe additional reduction in risk with more strenuous exercise. Similarly, when we examined the relation between walking, jogging, and running and risk of hearing loss, there was no additional reduction in risk with jogging or running (data not shown).

The observed relations between BMI, waist circumference, physical activity and hearing loss did not vary by age (p-interaction > 0.20 for global interaction with age for each exposure). In addition, the results were materially unchanged when relevant covariates were included as continuous rather than categorical (data not shown). We also performed analyses that did not exclude women with tinnitus and the results were not materially changed (data not shown).

DISCUSSION

In this large prospective study of women, higher BMI and larger waist circumference were independently associated with an increased risk of hearing loss. The risk decreased with increasing level of physical activity; even walking 2 hours/week or more was associated with a lower risk. These findings may provide insight into potential mechanisms that underlie acquired hearing loss and suggest possible strategies for prevention.

This prospective study confirms previous cross-sectional findings of an association between obesity and increased prevalence of hearing loss. Higher BMI was associated with poorer hearing sensitivities in a multinational European study[14] and the Health ABC Study.[13] Moreover, our findings that larger waist circumference was independently associated with increased risk of hearing loss even after adjusting for BMI, similar to previous cross-sectional findings,[15] suggest that waist circumference provides additional information about risk beyond BMI and that central adiposity may itself be a risk factor for hearing loss.

This study also provides prospective evidence consistent with cross-sectional studies that reported higher levels of cardiorespiratory fitness associated with better hearing sensitivities.[16] Our findings suggest that walking 2 hours per week or more may reduce risk of hearing loss. Adjustment for BMI and waist circumference only modestly attenuated the association, suggesting the association is not primarily mediated through effects of physical activity on adiposity.

Mechanisms that may underlie the relation between obesity, physical activity and hearing function include hypoxia and ischemic damage, oxidative stress and formation of reactive species, and resultant death of cochlear and spiral ganglion cells that leads to hearing loss. The Beaver Dam Offspring Study found cross-sectional associations between larger central retinal venular equivalent (CRVE), an indicator of microvascular inflammation and endothelial dysfunction, as well as between carotid intima media thickness, a subclinical measure of macrovascular atherosclerotic disease, and poorer hearing thresholds.[5] Obesity-related atherosclerosis may lead to stiffening and constriction of the internal auditory artery and reduction in cochlear blood flow.[44] Reduced blood supply to the cochlea, whether due to microvascular or macrovascular compromise, can lead to capillary constriction within the stria vascularis, cell death, and poorer hearing sensitivity.[4,6,45,46]

Oxidative stress has also been implicated in acquired hearing loss.[47,48] Antioxidants may prevent hearing loss due to exposure to ototoxic drugs or noise.[49] Animal studies of cochlear changes that accompany age-related hearing loss demonstrate decreased antioxidant activity[50] and a decline in the ability to protect against free radical damage. Obesity-related oxidative stress and resultant damage to the auditory epithelia due to accumulation of reactive oxidative species may contribute to hearing loss.[51]

Our findings suggest that larger waist circumference, a marker of central adiposity,[52] may increase the risk of hearing loss, beyond higher BMI. Greater central fat mass is associated with dyslipidemia, hypertension, and hypercoagulability.[53] Low adiponectin plasma concentrations related to larger waist circumference may increase risk of hearing loss.[54]

Higher levels of physical activity or better cardiorespiratory fitness may protect against hearing loss by improving vascular supply to the cochlea,[55] preventing auditory neurodegeneration and neurotransmitter loss,[56] and possibly moderating noise-induced damage.[57] Higher levels of physical activity are also inversely related to a number of purported risk factors for hearing loss, including diabetes, vascular dysfunction, and cardiovascular disease.[18,19,58] Physical activity may improve endothelial function, leading to endothelium-mediated arterial vasodilation and enhanced blood flow to the stria vascularis.[55] Physical activity increases endothelial nitric oxide formation and improves endothelium-dependent vasodilation of cardiac and renal vasculature[58,59] and could have similar protective effects on cochlear vasculature. Even moderate levels of physical activity can improve cardiorespiratory fitness.[60] Higher cardiorespiratory fitness may be associated with protection against hypertension in the internal auditory artery and neuroprotective effects in the central nervous system, such as preservation of central auditory processing, attenuation of aging-related neurotransmitter loss, increased brain-derived neurotrophic factor expression and increased resistance to auditory neurodegeneration.[61] Higher levels of physical activity and cardiorespiratory fitness may also enhance resistance to noise-induced auditory damage.[57,62]

Strengths of this study include its prospective design, large sample size, high follow-up rate, and validated methods to quantify BMI, waist circumference, and physical activity. The study population was relatively homogeneous with respect to education and occupation, reducing variability in those factors.[63] Limitations include assessment of hearing loss based on self-report. Although sudden sensorineural hearing loss occurs, hearing loss is commonly insidious in onset, thus imprecision in the assessment of date of onset exists. We defined incident hearing loss as when a hearing problem was first noticed by the participant. Standard pure-tone audiometry is the gold standard measure for evaluation of hearing loss, however, assessment of hearing loss based on self-report has been found to be reasonably reliable.[30,31,33,64] Assessment of hearing loss was based on participant report in 2009 regarding date of onset, however all information on exposures and covariates was collected prior to reported date of hearing loss onset; therefore, the relations were examined prospectively. We did not have information on hearing loss severity at the time of onset, thus severity of hearing loss could not be considered. Although some participants were lost to follow-up since the inception of this cohort and/or did not answer the 2009 questionnaire, the baseline characteristics of participants who did and did not answer the 2009 questionnaire did not appreciably differ. Our study was limited to predominantly non-Hispanic White women, thus further research in additional populations and is warranted.

CONCLUSION

Higher body mass index and larger waist circumference are associated with an increased risk and higher level of physical activity is associated with a decreased risk of hearing loss in women.

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Table 1

Baseline Characteristics of Nurses' Health Study II Women

	(n=68,421)
Age, years	34.5 (4.6)
Caucasian, %	93.1
Body mass index, kg/m^2	22.6 (20.7–25.6)
Waist Circumference, cm	73.7 (68.6–83.8)
Physical activity, METs[a]/week	13.9 (5.4–30.2)
Never smoker, %	66.7
Past smoker, %	21.3
Current smoker, %	11.6
Alcohol, g/d	0.9 (0.0–3.50)
Vitamin B12, mcg/d	7.0 (5.0–11.0)
Folate, mcg/d	372 (280–609)
Potassium, mg/d	2940 (533)
Magnesium, mg/d	316 (74)
Vitamin A, IU/d	11,113 (7702–15,722)
History of hypertension, %	5.0
History of diabetes, %	0.6
Ibuprofen use[b], %	18.3
Acetaminophen use[b], %	20.6
Walking, %	
<1 hour/wk	41.9
1–1.5 hrs/wk	24.8
2–3 hrs/wk	17.0
4+ hrs/wk	16.3

Values are means (SD), medians (interquartile range) or percentages.

Dietary factors assessed in 1991.

Waist circumference assessed in 1993.

Ibuprofen and acetaminophen use assessed in 1995.

[a]Metabolic equivalent tasks from recreational and leisure-time activities.

[b]Regular use 2+ times per week

Table 2

Body Mass Index and Risk of Self-Reported Hearing Loss Among Women in the Nurses' Health Study II (1989–2009)

	Categories of Body Mass Index (kg/m^2)					
	<25	**25–29**	**30–34**	**35–39**	**40+**	**P-trend**
Cases	4899	3059	1577	762	535	
Age-adjusted RR (95% CI)	1.00 (ref)	1.14 (1.09,1.19)	1.21 (1.14,1.28)	1.29 (1.19,1.39)	1.34 (1.23,1.47)	<0.001
Multivariate-adjusted* RR (95% CI) (without PA)	1.00 (ref)	1.12 (1.07,1.17)	1.17 (1.10,1.24)	1.22 (1.12,1.31)	1.25 (1.14,1.37)	<0.001
Multivariate-adjusted RR (95% CI) (with PA)**	1.00 (ref)	1.11 (1.06,1.16)	1.14 (1.08,1.21)	1.18 (1.09,1.28)	1.21 (1.10,1.32)	<0.001
Multivariate-adjusted* RR (95% CI) (with PA and WC)**	1.00 (ref)	1.08 (1.03,1.14)	1.11 (1.03,1.18)	1.16 (1.06,1.26)	1.19 (1.07,1.32)	<0.001

*Adjusted for age, race, smoking, alcohol intake, intake of B12, magnesium, potassium, vitamin A, and folate, baseline hypertension, baseline diabetes, acetaminophen use, ibuprofen use.

**Adjusted for all of the above, as well as for physical activity (PA).

***Adjusted for all of the above, as well as for physical activity (PA) and waist circumference (WC).

Information on WC was first obtained in 1993. Information on analgesic use was first obtained in 1995.

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Table 3

Waist Circumference and Risk of Self-Reported Hearing Loss Among Women in the Nurses' Health Study II (1993–2009)

	Categories of Waist Circumference (cm)				
	<71	**71–79**	**80–88**	**>88**	**P-trend**
Cases	777	2160	1949	2866	
Age-adjusted RR (95% CI)	1.00 (ref)	1.16 (1.07,1.26)	1.24 (1.14,1.35)	1.48 (1.36,1.61)	<0.001
Multivariate-adjusted* RR (95% CI) (without BMI or PA)	1.00 (ref)	1.07 (0.99,1.16)	1.11 (1.02,1.21)	1.27 (1.17,1.38)	<0.001
Multivariate-adjusted RR (95% CI) (with PA)**	1.00 (ref)	1.07 (0.98,1.16)	1.09 (1.00,1.19)	1.23 (1.14,1.34)	<0.001
Multivariate-adjusted* RR (95% CI) (with BMI and PA)**	1.00 (ref)	1.05 (0.97,1.14)	1.05 (0.95,1.15)	1.17 (1.06,1.29)	0.001

* Adjusted for: age, race, smoking, alcohol intake, intake of B12, magnesium, potassium, vitamin A, and folate, baseline hypertension, baseline diabetes, acetaminophen use, ibuprofen use

** Adjusted for all of the above as well as for physical activity (PA)

*** Adjusted for all of the above as well as for body mass index (BMI) and physical activity (PA)

Information on WC was first obtained in 1993. Information on analgesic use was first obtained in 1995.

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Table 4

Physical Activity and Risk of Self-Reported Hearing Loss Among Women In the Nurses' Health Study II (1989–2009)

	Physical Activity (METs/week) Quintiles					
	1	**2**	**3**	**4**	**5**	**P-trend**
1989 Mets/Week, median (range)[a]	1.9 (<4.0)	6.5 (4.0–9.6)	13.6 (9.7–18.9)	25.4 (19.0–36.5)	56.7 (36.6+)	
Cases	2264	2233	2278	2036	1923	
Age-adjusted RR (95% CI)	1.00 (ref)	0.96 (0.90,1.01)	0.95 (0.90,1.01)	0.85 (0.80,0.90)	0.83 (0.78,0.88)	<0.001
Multivariate-adjusted[*] RR (95% CI) (without BMI)	1.00 (ref)	0.95 (0.90,1.01)	0.95 (0.90,1.01)	0.86 (0.81,0.91)	0.83 (0.78,0.88)	<0.001
Multivariate-adjusted[**] RR (95% CI) (with BMI)	1.00 (ref)	0.96 (0.91,1.02)	0.97 (0.91,1.03)	0.88 (0.83,0.93)	0.86 (0.81,0.92)	<0.001

[*] Adjusted for: age, race, smoking, alcohol intake, intake of B12, magnesium, potassium, vitamin A, and folate, baseline hypertension, baseline diabetes, acetaminophen use, ibuprofen use

[**] Adjusted for all of the above as well as for body mass index (BMI)

[a] 1989 values are presented to be representative, however PA was updated in the analyses

Information on WC was first obtained in 1993. Information on analgesic use was first obtained in 1995.

Table 5

Walking and Risk of Self-Reported Hearing Loss Among Women in the Nurses' Health Study II (1989–2009)

	Walking (Hours/Week)				
	<1	**1–1.5**	**2–3**	**4+**	**P-trend**
Cases	4672	2551	1839	1305	
Multivariate-adjusted* RR (95% CI) (without BMI)	1.00 (ref)	0.98 (0.94,1.03)	0.90 (0.85,0.95)	0.85 (0.80,0.91)	<0.001
Multivariate-adjusted RR (95% CI) (with BMI)**	1.00 (ref)	0.99 (0.94,1.03)	0.92 (0.87,0.97)	0.87 (0.81,0.92)	<0.001

*Adjusted for: age, race, smoking, alcohol intake, intake of B12, magnesium, potassium, vitamin A, and folate, baseline hypertension, baseline diabetes, acetaminophen use, ibuprofen use

**Adjusted for all of the above as well as for body mass index (BMI)

Information on WC was first obtained in 1993. Information on analgesic use was first obtained in 1995.