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Prospective Study of Gastroesophageal Reflux, Use of Proton Pump Inhibitors and H2-Receptor Antagonists, and Risk of Hearing Loss

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Abstract

Objectives—Gastroesophageal reflux disease (GERD) is common and often treated with proton pump inhibitors (PPIs) or H2-receptor antagonists (H2-RAs). GERD has been associated with exposure of the middle ear to gastric contents, which could cause hearing loss. Treatment of GERD with PPIs and H2-RAs may decrease exposure of the middle ear to gastric acid, and decrease the risk of hearing loss. We prospectively investigated the relation between GERD, use of PPIs and H2-RAs, and the risk of hearing loss in 54,883 women in Nurses' Health Study II.

Design—Eligible participants, aged 41–58 years in 2005, provided information on medication use and GERD symptoms in 2005, answered the question on hearing loss in 2009 or in 2013, and did not report hearing loss starting before the date of onset of GERD symptoms or medication use.

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The primary outcome was self-reported hearing loss. Cox proportional hazards regression was used to adjust for potential confounders.

Results—During 361,872 person-years of follow-up, 9,842 new cases of hearing loss were reported. Compared with no GERD symptoms, higher frequency of GERD symptoms was associated with higher risk of hearing loss (multivariable adjusted relative risks: <1 time/month 1.04 [0.97, 1.11], several times/week 1.17 [1.09, 1.25], daily 1.33 [1.19, 1.49]; p-value for trend <0.001). After accounting for GERD symptoms, neither PPI nor H2-RA use was associated with the risk of hearing loss.

Conclusions—GERD symptoms are associated with higher risk of hearing loss in women, but use of PPIs and H2-RAs are not independently associated with the risk.

Keywords

Hearing loss; gastroesophageal reflux disease; proton pump inhibitors; H2-receptor antagonists; prospective study

INTRODUCTION

Hearing loss is the most common sensory disorder and is highly prevalent among adults in the United States(Agrawal et al. 2008). Although the prevalence of high frequency hearing loss is lower in women compared with men, it affects one-third of women in their 50's and close to two-thirds of women in their 60's (Agrawal et al. 2008). The adverse impact of hearing loss on an individual's quality of life can be considerable (Cacciatore et al. 1999; Olusanya et al. 2006), thus identifying potential modifiable risk factors for hearing loss is important.

Gastroesophageal reflux disease (GERD) is also common and affects approximately 10–20% of people in the Western world (Dent et al. 2005). The mainstays of medical therapy for patients with GERD are proton pump inhibitors (PPIs) and H2-receptor antagonists (H2-RAs), with some studies suggesting PPIs are more effective than H2-RAs (Bate et al. 1990; Chiba et al. 1997). GERD may lead to exposure of the middle ear to gastric enzymes, which in mouse models has been associated with Eustachian tube dysfunction, impaired clearance of middle ear contents, and hearing loss (Develioglu et al. 2013; Heavner et al. 2001; White et al. 2002; Yuksel et al. 2013).

Treatment of GERD with PPIs or H2-RAs may decrease exposure of the middle ear to gastric acid, thereby decreasing the risk of hearing loss. PPIs inhibit the hydrogen/potassium adenosine triphosphate enzyme system of gastric parietal cells, thereby inhibiting secretion of hydrogen ions into the gastric lumen. This enzyme is also expressed in the lateral wall of the cochlea (Lecain et al. 2000), and plays a critical role in formation of the endocochlear potential (Shibata et al. 2006). Thus, inhibition of this enzyme by PPI treatment could increase the risk of hearing loss. H2-RAs are competitive antagonists of gastric parietal cell H2-receptors, which suppress normal secretion of hydrogen ions. Use of H2-RAs is not known to influence inner ear function.

Although GERD and its treatment with PPIs and H2-RAs are common, the relation between GERD, these medications, and hearing loss has not been prospectively examined. Thus, we investigated the relation between GERD, regular use of PPIs and H2-receptor antagonists, and hearing loss in a prospective cohort of 54,883 women in the Nurses' Health Study II.

MATERIALS AND METHODS

Study Participants

The Nurses' Health Study II is a cohort of 116,430 female registered nurses originally enrolled in 1989 who were aged 25–42 years. Participants were aged 41–58 years in 2005 (the baseline year for our analysis). Questionnaires are administered biennially, with an average follow-up rate exceeding 90% of the eligible person-time. These biennial questionnaires assess participants' dietary habits, lifestyle habits, and medical history. They are available at the following website: http://www.channing.harvard.edu/nhs/?page_id=246. The majority of the women in the cohort are non-Hispanic whites, with a small percentage being Asian-American (2%), African-American (2%), and Hispanic (2%). The 2009 long-form questionnaire inquired for the first time whether the women had a hearing problem and, if so, age of onset. Of the 77,956 women who answered this questionnaire in 2009, 24% reported they had a hearing problem. We excluded women who reported having a hearing problem before 2005 (when information on GERD was first collected), those who did not answer the question on GERD symptoms, and those who had a history of non-melanoma skin cancer due to potential exposure to ototoxic chemotherapeutic agents. After applying these exclusion criteria, our study population was 54,883 women. The study protocol was approved by the institutional review board at Partners Healthcare. Completion of the self-administered questionnaire was considered implied informed consent.

Ascertainment of gastroesophageal reflux (GERD) symptoms

On the 2005 questionnaire, women were asked for the first time whether they had ever regularly had heartburn/acid reflux one or more times a week. If they answered "yes", they were asked how long this has been occurring (5 years or less, 6–14 years, 15 years or longer), and how often they had symptoms in the past year (none in the last year, less than once a month, once a month, about once a week, several times a week, or daily). In 2009, GERD status was updated when participants were again asked how often they had heartburn or acid-reflux. Our analysis examined self-reported GERD symptoms (yes vs. no), as well as frequency and duration of symptoms. Women who answered the question on GERD symptoms but did not specify frequency or duration of symptoms were excluded from the analysis by GERD symptom frequency and duration.

Ascertainment of medication use

On the 2003 questionnaire and every 2 years thereafter, women were asked whether they regularly used PPIs or H2-RAs. Our analysis examined regular usage of PPIs or H2-RAs starting in 2005. If information on PPI or H2-RA use was missing for a 2-year time period, person-time for that participant was not included for that time period.

Ascertainment of hearing loss

The outcome examined in this study was self-reported hearing loss. Participants were asked in 2009, “Do you have a hearing problem?”, and if so, “At what age did you first notice a change in your hearing?”. In 2013, participants were again asked about their hearing. We defined incident cases of hearing loss as participants who reported a hearing problem (a little hearing trouble, moderate hearing trouble, or deaf) that was first noticed after 2005.

The gold standard of evaluating hearing loss is pure-tone audiometry. Because it is costly and logistically challenging to obtain audiometric tests on all study participants, self-reported hearing loss has been used successfully in several large population based studies. Studies have found a single question on self-reported hearing loss to be a relatively reliable indicator of hearing loss (Nondahl et al. 1998). The sensitivities and specificities for detecting hearing loss range from 77–100% and 70–84%, respectively (Gomez et al. 2001; Hannula et al. 2011; Salonen et al. 2011; Swanepoel de et al. 2013). Significant associations have been observed between several factors and risk of self-reported hearing loss assessed in this manner in Nurses’ Health Study II (Curhan et al. 2013; Curhan et al. 2014; Curhan et al. 2012).

Ascertainment of covariates

Covariates were selected based on previously reported risk factors for hearing loss. Factors considered included age (Agrawal et al. 2008), race (Agrawal et al. 2008), body mass index (Curhan et al. 2013; Seidman 2000), waist circumference (Curhan et al. 2013), alcohol consumption (Curhan et al. 2014; Itoh et al. 2001), diet (folate (Durga et al. 2007), vitamin A (Le Prell et al. 2007), vitamin B_{12} (Houston et al. 1999), vitamin C, vitamin E, potassium (Wangemann 2006), magnesium (Haupt et al. 2003), trans fats, omega-3 fatty acids (Curhan et al. 2014), beta-carotene, beta cryptoxanthin), physical activity (Curhan et al. 2013; Li et al. 2006), smoking (Itoh et al. 2001), diabetes (Bainbridge et al. 2008), hypertension (Lin et al. 2015), tinnitus (Hasson et al. 2010; Nondahl et al. 2002), diuretic (thiazides or furosemide) use (Gallagher et al. 1979), and analgesic (acetaminophen, aspirin, and ibuprofen) use (Curhan et al. 2012).

Data on covariates were obtained from the biennial questionnaires. Women were asked in 2005 whether they described themselves as white, black/African-American, Asian, Native American/Alaska Native, Native Hawaiian/Pacific Islander, or other. Nutritional intake (alcohol, folate, vitamin A, vitamin B_{12}, vitamin C, vitamin E, potassium, magnesium, trans fats, 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 questionnaire in 2003 was used in our analysis, and updated in 2007. The validity and reproducibility of these questionnaires has previously been reported (Rimm et al. 1992; Willett et al. 1985). In addition, the validity of covariate data provided by this cohort or other similar cohorts has been shown to be reliable in previous studies (Colditz et al. 1986; Rimm et al. 1992; Rimm et al. 1990; Willett et al. 1985; Wolf et al. 1994).

Statistical analysis

All analyses were performed in a prospective manner using information on GERD symptoms and medication use that was collected before the report of hearing loss onset. Person-time contribution of each participant was assigned based on their response to questions regarding GERD symptoms on the 2005 and updated based on the response in 2009, and PPI and H2-RA use on the 2005 and updated in 2007, 2009, and 2011. Participants were censored at the time of cancer diagnosis. 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 (Therneau et al. 2000). 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 at start of follow-up and calendar year of the current questionnaire cycle. We performed analyses stratified by frequency of GERD symptoms to examine whether the association between PPI use and H2-RA use with hearing loss differed by these factors. Duration of GERD symptoms was only asked in 2005; however, if participants answered the question on duration of symptoms in 2005, symptom duration was updated based on responses to the question on GERD in 2009. If participants reported GERD symptoms for the first time in 2009, they were assigned a symptom duration of 2 years. Covariate status from the 2005 questionnaire was used as baseline, and the status of covariates was updated based on participant responses on each subsequent questionnaire. For covariate adjustment, body mass index was categorized as <25 kg/m^2, 25–29 kg/m^2, 30–34 kg/m^2, 35–39 kg/m^2, and ≥40 kg/m^2, and waist circumference was categorized as (<71 cm, 71–79 cm, 80–88 cm, >88 cm). Nutrients were categorized as quintiles of daily intake or in pre-specified categories. 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.

RESULTS

The characteristics of participants at baseline according to self-reported GERD symptom status, PPI use, and H2-RA use are shown in Table 1. Women who reported having GERD symptoms had higher body mass index, higher waist circumference, were less physically active, were more likely to be past or current smokers, and were more likely to have a history of hypertension and diabetes.

At baseline (2005), 18,157 women (33%) reported having GERD symptoms. Of the women with GERD symptoms, 2,679 (15%) were taking PPIs alone, 1,018 (6%) were taking H2-RAs alone, and 115 (1%) were taking both PPIs and H2-RAs.

During 361,872 person-years of follow-up, 9,842 cases of hearing loss were reported. Compared with participants who reported no GERD symptoms in the past year, the multivariable-adjusted relative risk of hearing loss was higher with increasing frequency of GERD symptoms (daily GERD symptoms multivariable-adjusted relative risk = 1.33; 95% confidence interval = 1.19, 1.49; p-value for trend <0.001) (Table 2). Compared with participants who reported no GERD symptoms in the past year, the multivariable-adjusted relative risk of hearing loss was higher with increasing duration of GERD symptoms (15 or

more years of symptoms multivariable-adjusted relative risk = 1.20; 95% confidence interval = 1.10, 1.32; *P* for trend <0.0001) (Table 3). Gamma statistic between frequency of GERD symptoms and duration of GERD symptoms was 0.89 (p = 0.001). The biggest confounders were body mass index and waist circumference.

Before taking into account GERD symptoms, PPI use was independently and significantly associated with increased risk of hearing loss (multivariable-adjusted relative risk = 1.16, 95% confidence interval = 1.08, 1.24), but H2-RA use was not (multivariable-adjusted relative risk = 1.10, 95% confidence interval = 0.97, 1.24). After taking into account GERD symptoms, there was no significant association between PPI use and hearing loss (Table 4). There was no significant association between H2-RA use and hearing loss in any stratum (Table 4).

Adjusting for body mass index and waist circumference as continuous variables did not materially change the results. After excluding participants with a history of tinnitus, the results were not materially changed for GERD symptoms, PPI use, or H2-RA use (data not shown).

DISCUSSION

In this large prospective study of women, increasing frequency and duration of GERD symptoms were independently associated with a higher risk of hearing loss. However, use of PPIs or H2-RAs was not associated with hearing loss after accounting for GERD symptoms.

Recent studies have shown evidence of gastric contents in middle ear effusions of children with recurrent otitis media (McCoul et al. 2011). Animal models suggest that exposure of the middle ear to gastric contents may cause Eustachian tube dysfunction, impaired mucociliary clearance of middle ear contents, and sensorineural hearing loss (Develioglu et al. 2013; Heavner et al. 2001; White et al. 2002; Yuksel et al. 2013).

The mechanism by which GERD may increase the risk of hearing loss is unclear. Exposure of the inner ear to gastric contents via diffusion or active transport of gastric contents through the round window membrane, which has been shown to occur with several other compounds, may result in damage to the inner ear and sensorineural hearing loss (Kim et al. 1990; Miriszlai et al. 1978; Richardson et al. 1971; Schuknecht 1957). Alternatively, exposure of the round window membrane to gastric contents may result in increased permeability of this membrane, as is the case with middle ear infections, making the inner ear more susceptible to damage (Ikeda et al. 1988; Ikeda et al. 1990). However, the pathophysiology is not well understood and warrants further investigation.

Previous studies in rodent models have demonstrated that PPIs inhibit the hydrogen/potassium adenosine triphosphate enzyme system in the lateral wall of the cochlea (Lecain et al. 2000), thereby inhibiting formation of the endocochlear potential (Shibata et al. 2006). Conversely, in people with GERD, PPI use may decrease exposure of the middle ear to gastric acid and decrease risk of hearing loss. Although PPI use was associated with an increased risk of hearing loss in our study before accounting for frequency of GERD symptoms, there was no overall association between PPI use and hearing loss after

accounting for GERD symptom frequency, an example of confounding by indication. We observed no relation between use of H2-RAs and hearing loss.

Our study has limitations. The study population was predominantly non-Hispanic white women. Although this cohort of women may not be representative of the United States adult female population, information provided by this cohort is highly reliable and the follow-up rates are high. Further investigation is needed to examine these associations in other populations. Our data are dependent on the accuracy of participants' self-report. However, the validity of information on a variety of exposures provided by this cohort of women has been shown to be reliable in previous studies (Colditz et al. 1986; Rimm et al. 1992; Rimm et al. 1990; Willett et al. 1985; Wolf et al. 1994). Assessment of GERD symptoms was based on self-reported frequency of symptoms. Given the high between frequency of GERD symptoms and duration of GERD symptoms, we were unable to ascertain whether the risk of hearing loss is independently associated with frequency of GERD symptoms, duration of GERD symptoms, or both. The outcome of our study was self-reported hearing loss. Although pure-tone audiometry is considered the gold-standard for evaluation of potential hearing loss, and allows for differentiation between conductive and sensorineural hearing loss, self-reported hearing loss has been shown to be a reliable indicator of hearing loss (Gomez et al. 2001; Hannula et al. 2011; Salonen et al. 2011; Swanepoel de et al. 2013). Furthermore, a recent review performed for the United States Preventive Services Task Force on the accuracy of screening tools for hearing loss revealed that a single question about perceived hearing loss was almost as accurate as a more detailed questionnaire or portable audiometric device in hearing loss detection (Chou et al. 2011). Although there may be residual confounding, we adjusted as finely as possible for many known risk factors for hearing loss. We did not have information on frequency of PPI or H2-RA use.

In conclusion, higher frequency and duration of GERD symptoms is associated with a higher risk of hearing loss in women. No relation was observed between PPI use or H2-RA use and hearing loss after accounting for GERD symptoms. Given the high prevalence of GERD symptoms in the general population, these findings suggest a common modifiable risk factor may contribute to the development of hearing loss.

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Table 1

Baseline Characteristics of Participants According to Gastroesophageal Reflux Symptoms, Proton Pump Inhibitor (PPI) Use, and Histamine H2-Receptor Antagonist (H2-RA) Use, Nurses' Health Study II, 2005.

	GERD yes (n=18,157)	GERD no (n=36,726)	PPI yes (n=2,873)	PPI no (n=52,010)	H2-RA yes (n=1,123)	H2-RA no (n=53,760)
Age, years	48.6 (4.6)	48.1 (4.6)	49.1 (4.5)	48.2 (4.6)	49.3 (4.4)	48.2 (4.6)
Body mass index, kg/m^2	28.8 (6.8)	26.2 (5.9)	30.4 (7.3)	26.9 (6.2)	30.0 (7.6)	27.0 (6.3)
Waist circumference, cm	91.5 (15.6)	85.1 (13.9)	95.3 (16.8)	86.8 (14.5)	93.7 (16.4)	87.1 (14.7)
Non-Hispanic white	94.9%	95.1%	95.8%	95.0%	95.2%	95.0%
Physical activity in 2001, METs	10.8 [3.5–24.8]	14.5 [5.1–30.4]	8.8 [2.7–21.5]	13.4 [4.6–29.0]	9.2 [3.1–22.9]	13.1 [4.6–28.7]
Smoking status						
Never smoker	62.9%	68.3%	61.8%	66.8%	57.4%	66.7%
Past smoker	29.0%	25.1%	30.3%	26.2%	32.1%	26.3%
Current smoker, cigarettes/day						
1–4	1.4%	1.1%	1.3%	1.2%	2.3%	1.2%
5–14	2.7%	2.4%	2.4%	2.5%	2.7%	2.5%
≥15	3.9%	2.8%	4.1%	3.1%	5.4%	3.1%
Alcohol consumption, g/day	2.0 [0.0–6.7]	2.3 [0.0–7.8]	1.2 [0.0–5.3]	2.2 [0.0–7.6]	1.2 [0.0–5.6]	2.2 [0.0–7.6]
Daily nutrient intake						
Vitamin A, IU	11421 [8181–15485]	11730 [8478–15947]	11251 [8044–15455]	11654 [8396–15806]	11315 [8001–15038]	11640 [8388–15798]
Vitamin B12, μg	10.0 [5.9–18.5]	9.7 [5.8–16.5]	10.8 [6.2–22.2]	9.8 [5.8–16.9]	11.0 [6.2–26.0]	9.8 [5.8–17.0]
Vitamin C, mg	164.5 [107.7–298.7]	169.9 [112.1–294.5]	165.2 [107.0–298.2]	168.4 [111.0–295.7]	177.6 [112.3–384.7]	168.0 [110.7–293.9]
Vitamin E, mg	19.7 [8.3–157.2]	19.1 [8.3–127.7]	21.4 [8.7–170.6]	19.2 [8.3–136.9]	22.6 [9.2–179.6]	19.3 [8.3–137.3]
Folate, μg	677 [446–882]	673 [455–887]	707 [451–899]	672 [452–884]	712 [462–919]	674 [452–885]
Potassium, mg	3123 [2745–3529]	3167 [2795–3579]	3115 [2733–3549]	3156 [2782–3562]	3063 [2703–3484]	3155 [2780–3563]
Magnesium, mg	347 [293–419]	350 [297–420]	351 [292–424]	349 [296–420]	351 [291–427]	349 [296–420]
Beta-Carotene, μg	4530 [3032–6530]	4718 [3190–6746]	4358 [2915–6430]	4672 [3155–6695]	4479 [2920–6201]	4657 [3145–6694]
Beta-Cryptoxanthin, μg	108.3 [66.8–173.3]	120.7 [74.3–193.2]	101.9 [62.0–160.0]	117.3 [72.2–187.9]	102.3 [61.5–164.9]	116.8 [71.9–187.2]
Trans Fats, gm	3.8 [2.9–4.8]	3.7 [2.8–4.6]	3.9 [2.9–4.9]	3.7 [2.8–4.7]	4.0 [3.0–5.0]	3.7 [2.8–4.7]
Omega-3 fatty acids, gm	0.16 [0.07–0.32]	0.17 [0.07–0.32]	0.16 [0.07–0.34]	0.16 [0.07–0.32]	0.16 [0.07–0.32]	0.16 [0.07–0.32]
History of hypertension	33.0%	20.9%	44.1%	23.8%	43.7%	24.5%

	GERD yes (n=18,157)	GERD no (n=36,726)	PPI yes (n=2,873)	PPI no (n=52,010)	H2-RA yes (n=1,123)	H2-RA no (n=53,760)
History of diabetes	5.5%	3.1%	10.0%	3.6%	7.5%	3.9%
Aspirin use, days/week						
None	69%	74%	63%	73%	62%	73%
1–3	7%	7%	6%	7%	7%	7%
4+	23%	18%	30%	19%	30%	20%
Acetaminophen use, days/week						
None	72%	82%	67%	79%	59%	79%
1–3	19%	13%	20%	15%	23%	15%
4+	8%	4%	12%	5%	16%	5%
Ibuprofen use, days/week						
None	56%	62%	58%	60%	50%	60%
1–3	30%	28%	27%	29%	31%	28%
4+	13%	8%	14%	10%	18%	10%
Furosemide use	2%	1%	4%	1%	3%	1%
Thiazide use	12%	7%	17%	8%	16%	8%
History of Tinnitus	10%	6%	12%	7%	12%	7%

Abbreviations: METs = metabolic equivalents

Values are mean (standard deviation) or median [interquartile range]

Table 2

Age- and Multivariable-Adjusted Relative Risks of Incident Hearing Loss According to Frequency of GERD Symptoms, Nurses' Health Study II, 2005–2013.

GERD Symptom Frequency	Incident Cases of Hearing Loss	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
No GERD	6,027	239,198	1.00	Reference	1.00	Reference
Less than once/month	1,090	38,832	1.12	1.05, 1.19	1.04	0.97, 1.11
Once/month	559	17,684	1.26	1.15, 1.37	1.16	1.06, 1.26
Once/week	928	31,140	1.19	1.11, 1.27	1.08	1.00, 1.16
Several times/week	922	27,133	1.35	1.26, 1.45	1.17	1.09, 1.25
Daily	316	7,885	1.59	1.42, 1.78	1.33	1.19, 1.49

P for trend (multivariable-adjusted) <0.001

RR denotes relative risk

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

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Table 3

Age- and Multivariable-Adjusted Relative Risks of Incident Hearing Loss According to Duration of GERD Symptoms, Nurses' Health Study II, 2005–2013.

GERD Symptom Duration	Incident Cases of Hearing Loss	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
None	6,027	239,198	1.00	Reference	1.00	Reference
5 years or less	2,069	61,847	1.32	1.25, 1.39	1.13	1.07, 1.19
6–14 years	1,134	46,476	1.13	1.06, 1.20	1.11	1.04, 1.18
15 or more years	526	15,795	1.34	1.22, 1.46	1.20	1.10, 1.32

P for trend (multivariable-adjusted) <0.001

RR denotes relative risk

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

Table 4

Age- and Multivariable-Adjusted Relative Risks of Incident Hearing Loss for PPI Use and H2-RA Use, Stratified by Frequency of GERD Symptoms, Nurses' Health Study II, 2005–2013.

GERD Symptom Frequency	Incident Cases of Hearing Loss	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
PPIs						
Less than once/month						
No PPI use	5,952	236,849	1.00	Reference	1.00	Reference
PPI use	75	2,349	1.27	1.01, 1.60	1.20	0.96, 1.52
Once/month						
No PPI use	455	14,435	1.00	Reference	1.00	Reference
PPI use	104	3,249	1.02	0.82, 1.26	1.04	0.83, 1.31
Once/week						
No PPI use	770	26,517	1.00	Reference	1.00	Reference
PPI use	158	4,623	1.18	0.99, 1.40	1.11	0.93, 1.33
At least several times/week						
No PPI use	951	27,431	1.00	Reference	1.00	Reference
PPI use	287	7,587	1.09	0.96, 1.25	1.07	0.93, 1.23
H2-RAs						
Less than once/month						
No H2-RA use	6,000	238,383	1.00	Reference	1.00	Reference
H2-RA use	27	815	1.32	0.90, 1.92	1.19	0.82, 1.74
Once/month						
No H2-RA use	537	16,859	1.00	Reference	1.00	Reference
H2-RA use	22	826	0.84	0.55, 1.28	0.81	0.52, 1.25
Once/week						
No H2-RA use	874	29,468	1.00	Reference	1.00	Reference
H2-RA use	54	1,671	1.09	0.83, 1.43	1.00	0.76, 1.33
At least several times/week						
No H2-RA use	1,118	31,838	1.00	Reference	1.00	Reference

GERD Symptom Frequency	Incident Cases of Hearing Loss	Person-Years	Age-Adjusted RR	95% CI	Multivariable-Adjusted RR*	95% CI
H2-RA use	120	3,180	1.07	0.89, 1.30	1.01	0.83, 1.23

RR denotes relative risk

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

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