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Original Contribution

Analgesic Use and the Risk of Hearing Loss in Women

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Use of analgesics is common and is associated with increased risk of hearing loss in men; however, the relation has not been examined prospectively in women. The authors prospectively examined the relation between frequency of aspirin, ibuprofen, and acetaminophen use and risk of hearing loss among 62,261 women aged 31–48 years at baseline (1995) in Nurses' Health Study II. The outcome was self-reported hearing loss ($n = 10{,}012$), and the follow-up period was 1995–2009. Cox proportional hazards regression was used to adjust for potential confounders. During 764,247 person-years of follow-up, ibuprofen use and acetaminophen use were independently associated with increased risk of hearing loss, but aspirin use was not. For ibuprofen, the multivariate-adjusted relative risk of hearing loss was 1.13 (95% confidence interval (CI): 1.06, 1.19) for use 2–3 days/week, 1.21 (95% CI: 1.11, 1.32) for use 4–5 days/week, and 1.24 (95% CI: 1.14, 1.35) for use ≥6 days/week (P-trend < 0.0001), compared with use less than once per week. For acetaminophen, the corresponding relative risks were 1.11 (95% CI: 1.02, 1.19), 1.21 (95% CI: 1.07, 1.37), and 1.08 (95% CI: 0.95, 1.22), respectively (P-trend = 0.0007). In this study, use of ibuprofen or acetaminophen (but not aspirin) 2 or more days per week was associated with an increased risk of hearing loss in women.

acetaminophen; analgesics; anti-inflammatory agents, non-steroidal; aspirin; hearing loss; ibuprofen

Abbreviations: NHANES, National Health and Nutrition Examination Survey; NHS II, Nurses' Health Study II; NSAID, nonsteroidal antiinflammatory drug.

Hearing loss is a common and disabling chronic condition. According to recent data from the National Health and Nutrition Examination Survey (NHANES), over 50% of US adults suffer from high-frequency hearing loss by age 60 years (1). Although the prevalence is higher in men, one-third of women in their 50s and almost two-thirds of women in their 60s suffer from hearing loss (1). Even mild hearing loss impairs communication and social interaction, adversely affecting work productivity, social connectivity, and quality of life (2, 3). The World Health Organization ranks adult-onset hearing loss as the sixth most common disease burden in high-income countries (4). Hearing loss represents an important public health concern, yet there are limited data on potentially modifiable risk factors for adult hearing loss.

Ibuprofen, acetaminophen, and aspirin are the 3 most commonly used medications in the United States (5). In NHANES III (1988–1994), more than 80% of women aged 25 years or older reported having used nonprescription analgesic agents within the past month (6). Potential ototoxicity (damage to the cochlea or auditory nerve) due to high doses of salicylates and nonsteroidal antiinflammatory drugs (NSAIDs) has been previously described (7–11) and may result from several mechanisms, such as impaired outer hair cell function, inhibition of prostaglandin-forming cyclooxygenase, and reduced cochlear blood flow. Potential ototoxicity from acetaminophen may be due to the depletion of glutathione (12), which has been shown to protect the cochlea from noise-induced damage (13, 14). Previously, we found that regular use (≥2 times/week) of NSAIDs, acetaminophen, or aspirin was associated with an increased risk of hearing loss in men (15).

To our knowledge, the relation between regular analgesic use and hearing loss in women has not been prospectively

examined. Given that use of analgesics by women is so common, we prospectively analyzed the association between analgesic use and the risk of hearing loss in 62,261 women.

MATERIALS AND METHODS

Study participants

Nurses' Health Study II (NHS II) originally enrolled 116,430 female registered nurses aged 25–42 years from 15 US states who answered a mailed questionnaire in 1989, and were thus aged 31–48 years at the 1995 baseline used for this study. Questionnaires are administered every other year, and the average follow-up rate over 22 years has exceeded 90%. We inquired about race and ethnicity and found that 2% of respondents were African-American, 2% were Hispanic, and 2% were Asian-American. The 2009 main questionnaire asked women whether they had a hearing problem and at what age a change in hearing was first noticed (see details below). Of the 77,956 women who returned the long-form questionnaire, 23.8% reported having a hearing problem. Those who reported that the hearing problem began before 1995 or who had a history of cancer other than nonmelanoma skin cancer (due to possible exposure to ototoxic chemotherapeutic agents) were excluded from the analysis. Because high doses of aspirin and NSAIDs have been associated with tinnitus (16–19), a strong risk factor for hearing loss (20–22), we also excluded women who reported tinnitus that occurred on 2 or more days per week. The number of women included in the analysis was 62,261.

Ascertainment of analgesic use

On the 1995 questionnaire and every 2 years thereafter, women were asked about their average frequency of use of NSAIDs, acetaminophen, and aspirin. In 1995, women were asked to report the number of days each month on which they used the individual analgesics. In 1997, women were asked about the average number of days per week of use (never, once/week, 2–3 times/week, 4–5 times/week, or ≥6 times/week) of aspirin, NSAIDs (e.g., ibuprofen, Advil (Pfizer Inc., Kings Mountain, North Carolina), Midol (Bayer HealthCare LLC, Leverkusen, Germany), Aleve (Bayer HealthCare)), and acetaminophen (e.g., Tylenol (McNeil Consumer Healthcare, Fort Washington, Pennsylvania)), and these were the categories used in the analysis. In 1999 and thereafter, women were asked specifically about average use of ibuprofen (e.g., Advil, Motrin (McNeil Consumer Healthcare), Nuprin (McNeil Consumer Healthcare)) and regular use (≥2 times/week) of other NSAIDs (e.g., Aleve, Naprosyn (Roche Pharmaceuticals, Basel, Switzerland), Relafen (GlaxoSmithKline, London, United Kingdom), ketoprofen, Anaprox (Roche Pharmaceuticals)). Our main analyses examined frequency of use of ibuprofen, acetaminophen, and aspirin. We considered NSAID use reported in 1995 and 1997 to be ibuprofen use. In secondary analyses, we examined regular use (≥2 times/week) of ibuprofen and of other antiinflammatory analgesics separately. If information on analgesic intake was missing for a 2-year time period, person-time for that participant was not included for that time period. Analgesic use assessed in this manner has been shown to be associated with a number of important outcomes, such as hypertension (23, 24), renal cell carcinoma (25), Parkinson's disease (26), survival after breast cancer (27), and colon cancer (28).

Ascertainment of outcome

The primary outcome, self-reported hearing loss, was determined on the basis of responses to the 2009 long-form questionnaire. The question asked, "Do you have a hearing problem?" (response categories were no, mild, moderate, or severe) and "If so, at what age did you first notice a change in your hearing?".

We defined incident cases as a reported hearing problem first noticed after 1995. The follow-up period was 1995–2009. We excluded women who reported having tinnitus, so we considered the remaining cases of self-reported hearing problems to be hearing loss. Although standard pure-tone audiometry is considered the gold standard for evaluation of hearing loss, due to the cost and logistic limitations of audiometric screening of large populations, questionnaires have been used. Self-reported hearing loss has been found to be a reasonably reliable measure of hearing loss (1, 29–32).

Ascertainment of covariates

We selected covariates purported to be risk factors for hearing loss. Covariates considered in the multivariate analysis included: age (1); race (1); body mass index (weight (kg)/height $(m)^2$) (33); alcohol consumption (34); intakes of folate (35), vitamin B_{12} (36), potassium (37), magnesium (38), and vitamin A (39); physical activity (40); smoking (34); hypertension (41); diabetes (42); and menopausal status (43).

Covariate information was obtained from the biennial questionnaires. In 2005, participants were asked whether they described themselves as Spanish, Hispanic, or Latina and also whether they described themselves as white, black/African-American, Asian, Native American/Alaska Native, Native Hawaiian/Pacific Islander, or other. Intakes of alcohol, folate, vitamin B_{12}, potassium, magnesium, and vitamin A were calculated from semiquantitative food frequency questionnaires that were mailed to participants every 4 years. Information on tinnitus was obtained from the 2009 main questionnaire, which included a question about tinnitus and its frequency and age of onset. We excluded women who reported having tinnitus that occurred before the onset of hearing loss on 2 or more days per week.

Questionnaire-derived information for this cohort or similar cohorts has been validated for many of the covariates by comparison with directly measured values and detailed diaries, with correlations of 0.97 for weight (44), 0.90 for alcohol consumption (45), and 0.79 for physical activity (46). The reproducibility and validity of the food

frequency questionnaire has been documented previously (47, 48).

Statistical analysis

All analyses were prospective, using information on analgesic use that was collected before the report of onset of hearing loss. Frequency of use of each analgesic was categorized as <1 day/week, 1–2 days/week, 3–4 days/week, 5–6 days/week, or ≥6 days/week. For each participant, person-time was allocated on the basis of the updated response to the analgesic questions at the beginning of each follow-up period. Participants were censored at the date of reported hearing loss, cancer, or death, whichever came first. Age- and multivariate-adjusted relative risks were calculated using Cox proportional hazards regression models, which were adjusted simultaneously for use of the other types of analgesics. To examine whether the association between analgesic use and hearing loss varied by age, we performed analyses stratified by age group (<50 years vs. ≥50 years). We considered all covariates that might be potential confounders and removed from the model any that were found not to be statistically significant, except for diabetes mellitus ($P = 0.29$) and folate intake ($P = 0.07$ for the highest quintile of intake). Although these variables were not significant, we chose to be conservative and to retain these 2 covariates because of recent reports of a cross-sectional association between diabetes and hearing loss and because of the borderline significance of folate intake.

For all relative risks, we calculated 95% confidence intervals. All *P* values are 2-tailed. Statistical tests were performed using SAS software, version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Tables 1–3 show the characteristics of participants at baseline according to frequency of analgesic use. Of the 93% of women who described themselves as white, 0.7% reported that they were of Hispanic ethnicity. The most frequent users of aspirin were slightly older, had a higher body mass index, were more likely to be past or current smokers, and were more likely to have hypertension and diabetes. Similarly, the most frequent users of ibuprofen were slightly older, had a higher body mass index, were more likely to be past or current smokers, and were more likely have hypertension and diabetes. The most frequent users of acetaminophen had a higher body mass index, were less physically active, and were more likely to smoke, to have hypertension, and to have diabetes.

During 764,247 person-years of follow-up, 10,012 cases of hearing loss were reported. Both ibuprofen use and acetaminophen use were independently associated with an increased risk of hearing loss, but aspirin use was not (Table 4). Compared with women who used ibuprofen less than once per week, the multivariate relative risk of hearing loss increased with increasing frequency of ibuprofen use. The multivariate relative risk of hearing loss for women who used acetaminophen also increased with increasing frequency of use, compared with women who used acetaminophen less than once per week.

The magnitudes of association between ibuprofen and acetaminophen use and hearing loss tended to be greater in women younger than age 50 years; however, the *P* value for interaction was significant only for the ibuprofen category of ≥6 days/week (Table 5). There was no association between aspirin use and the risk of hearing loss in either age group.

We performed a subanalysis using 2001 as the baseline, when detailed information on low-dose aspirin versus regular-dose aspirin was first elicited, and it included low-dose aspirin and regular-dose aspirin separately in the full multivariate model. There was no association between the use of low-dose or regular-dose aspirin and the risk of hearing loss.

Regular use (defined as ≥2 days/week) of other NSAIDs (e.g., naproxen, ketoprofen) was not significantly associated with an increased risk of hearing loss. As compared with women who used these analgesics less than twice per week, the multivariate relative risk of hearing loss for use ≥2 times/week was 1.05 (95% confidence interval: 0.98, 1.13). In contrast, the relation between regular use of ibuprofen and an increased risk of hearing loss was highly significant (relative risk = 1.16, 95% confidence interval: 1.11, 1.22).

The association between hearing loss and regular use of more than 1 class of analgesics did not appear to be greater than the sum for use of each individual analgesic (Table 6).

DISCUSSION

The use of ibuprofen and the use of acetaminophen were independently associated with an increased risk of hearing loss in women. The magnitude of the risk related to ibuprofen and acetaminophen use tended to increase with increasing frequency of use. There was no relation observed between aspirin use and the risk of hearing loss.

Use of aspirin, ibuprofen, and acetaminophen is commonplace (5). In NHS II, ibuprofen and acetaminophen were used more frequently than aspirin. At baseline, approximately 69% of the women used NSAIDs, 62% used acetaminophen, and 30% used aspirin at least once per week. Of these women, 4.9% used NSAIDs ≥6 days/week, which is consistent with 1999–2000 NHANES data showing that 4% of US women used NSAIDs every day for as long as a month (49).

The current findings for ibuprofen, the most commonly used NSAID, and acetaminophen are consistent with our previous findings that regular use of NSAIDs and regular use of acetaminophen (≥2 times/week) were associated with an increased risk of hearing loss in men (15), but the findings for aspirin differ. In the male cohort, which was followed in a manner similar to the NHS II cohort, the outcome examined was self-reported professionally diagnosed hearing loss. Compared with men who used aspirin less 2 times per week, regular users of aspirin were 12% more likely to have hearing loss. In men, the magnitudes of the associations with all 3 types of analgesics were greater in those younger than age 50 years: Regular users of

Table 1. Age-Standardized Baseline Characteristics of Participants According to Frequency of Aspirin Use, Nurses' Health Study II, 1995[a]

	Frequency of Aspirin Use, days/week									
	<1 (*n* = 32,780)		1 (*n* = 9,333)		2–3 (*n* = 2,595)		4–5 (*n* = 720)		≥6 (*n* = 1,616)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years[b]	39.8 (4.7)		40.8 (4.4)		41.6 (4.3)		42.0 (4.2)		42.8 (4.0)	
Body mass index[c]	25.5 (5.8)		25.4 (5.7)		25.9 (6.1)		26.5 (6.5)		26.8 (6.8)	
Physical activity[d] in 1997, METs	18.4 (22.3)		19.4 (23.4)		18.7 (21.5)		16.9 (19.2)		19.6 (23.6)	
Smoking status										
Never smoker		68.5		64.8		63.1		61.4		62.5
Past smoker		22.6		24.6		25.6		25.6		23.7
Current smoker, cigarettes/day										
1–4		1.7		2.3		2.2		1.7		1.8
5–14		2.7		3.3		3.1		4.4		4.3
≥15		4.4		4.9		5.9		7.0		7.6
Alcohol consumption, g/day	3.2 (6.1)		4.4 (7.6)		4.8 (8.2)		4.3 (7.2)		3.7 (7.9)	
Daily nutrient intake										
Vitamin B_{12}, μg	9.9 (14.4)		10.0 (13.5)		9.8 (11.5)		12.3 (22.5)		11.5 (14.5)	
Folate, μg	463.0 (284.4)		447.0 (250.4)		448.0 (243.3)		484.9 (264.9)		529.3 (312.2)	
Potassium, mg	3,113.3 (640.1)		3,125.5 (625.9)		3,110.1 (635.5)		3,085.3 (669.4)		3,188.4 (715.2)	
Magnesium, mg	332.5 (87.3)		335.4 (83.0)		332.8 (77.5)		334.7 (91.9)		347.1 (105.4)	
Vitamin A, IU	14,327 (10,037)		14,306 (9,682)		14,313 (9,796)		15,557 (12,177)		16,345 (11,661)	
History of hypertension		8.4		8.5		11.0		12.0		18.8
History of diabetes		1.1		1.0		0.6		2.8		4.0
Non-Hispanic white race		92.9		94.3		95.3		93.6		94.9

Abbreviations: METs, metabolic equivalents; SD, standard deviation.
[a] Data were standardized to the age distribution of the study population.
[b] Values were not age-adjusted.
[c] Weight (kg)/height $(m)^2$.
[d] Recreational and leisure-time activity.

Table 2. Age-Standardized Baseline Characteristics of Participants According to Frequency of Ibuprofen Use, Nurses' Health Study II, 1995[a]

	Frequency of Ibuprofen Use, days/week									
	<1 (*n* = 17,867)		1 (*n* = 24,957)		2–3 (*n* = 10,324)		4–5 (*n* = 2,045)		≥6 (*n* = 2,861)	
	Mean (SD)	%[b]	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years[c]	40.1 (4.7)		39.9 (4.6)		40.5 (4.5)		41.1 (4.5)		42.0 (4.2)	
Body mass index[d]	25.1 (5.6)		25.2 (5.5)		26.2 (6.0)		27.5 (6.7)		28.5 (7.4)	
Physical activity[e] in 1997, METs	18.9 (23.2)		18.8 (22.0)		18.6 (22.6)		18.5 (23.5)		16.2 (20.3)	
Smoking status										
Never smoker		69.0		66.6		65.2		63.7		62.7
Past smoker		21.9		23.9		24.2		24.5		26.0
Current smoker, cigarettes/day										
1–4		1.6		2.0		2.1		1.4		1.9
5–14		2.8		3.0		3.1		3.2		3.0
≥15		4.5		4.4		5.3		7.0		6.4
Alcohol consumption, g/day	3.1 (6.3)		3.7 (6.6)		3.8 (6.8)		4.0 (7.5)		3.5 (7.1)	
Daily nutrient intake										
Vitamin B_{12}, μg	10.1 (16.4)		9.9 (13.1)		10.0 (17.7)		10.1 (12.5)		10.6 (13.2)	
Folate, μg	475.5 (306.8)		455.0 (265.5)		443.5 (245.2)		442.3 (248.2)		476.2 (272.2)	
Potassium, mg	3,110.9 (639.8)		3,133.1 (628.7)		3,112.6 (633.2)		3,103.9 (671.6)		3,093.4 (699.0)	
Magnesium, mg	332.0 (86.8)		334.1 (86.4)		332.5 (83.3)		333.2 (85.4)		335.7 (95.3)	
Vitamin A, IU	14,470 (10,324)		14,484 (10,149)		14,222 (9,539)		14,406 (10,100)		14,697 (10,327)	
History of hypertension		8.2		7.7		10.3		13.1		16.6
History of diabetes		1.2		1.0		1.2		1.3		2.6
Non-Hispanic white race		91.5		94.1		94.9		94.2		94.5

Abbreviations: METs, metabolic equivalents; SD, standard deviation.
[a] Data were standardized to the age distribution of the study population.
[b] Percentages for smoking may not add up to 100% because of missing information.
[c] Values were not age-adjusted.
[d] Weight (kg)/height $(m)^2$.
[e] Recreational and leisure-time activity.

Table 3. Age-Standardized Baseline Characteristics of Participants According to Frequency of Acetaminophen Use, Nurses' Health Study II, 1995[a]

	Frequency of Acetaminophen Use, days/week									
	<1 (*n* = 20,518)		1 (*n* = 25,429)		2–3 (*n* = 6,145)		4–5 (*n* = 1,133)		≥6 (*n* = 969)	
	Mean (SD)	%[b]	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years[c]	40.6 (4.6)		39.6 (4.7)		40.0 (4.6)		40.7 (4.7)		41.9 (4.3)	
Body mass index[d]	25.3 (5.7)		25.5 (5.6)		26.3 (6.1)		27.5 (6.8)		27.5 (7.4)	
Physical activity[e] in 1997, METs	19.6 (23.7)		18.0 (21.6)		17.1 (20.7)		15.6 (18.7)		15.8 (19.4)	
Smoking status										
Never smoker		66.7		68.6		66.3		64.0		60.9
Past smoker		23.5		22.4		23.7		24.8		23.8
Current smoker, cigarettes/day										
1–4		1.9		1.7		1.7		2.6		1.0
5–14		2.9		2.8		3.1		3.3		4.2
≥15		4.8		4.2		5.1		5.2		9.7
Alcohol consumption, g/day	3.8 (6.9)		3.3 (6.3)		3.2 (6.0)		3.0 (6.4)		3.7 (8.9)	
Daily nutrient intake										
Vitamin B_{12}, μg	10.3 (17.1)		9.7 (12.1)		9.9 (11.9)		11.3 (38.7)		10.4 (13.4)	
Folate, μg	472.0 (289.6)		452.9 (268.4)		450.4 (264.5)		445.5 (258.8)		458.6 (275.0)	
Potassium, mg	3,155.3 (655.7)		3,103.9 (620.7)		3,059.1 (625.3)		3,036.6 (619.3)		3,016.1 (741.6)	
Magnesium, mg	340.2 (90.0)		329.0 (82.9)		326.3 (84.1)		322.1 (76.5)		324.8 (107.0)	
Vitamin A, IU	15,083 (10,914)		14,010 (9,387)		13,621 (9,052)		13,816 (9,044)		13,447 (9,275)	
History of hypertension		8.0		8.4		11.4		14.2		17.5
History of diabetes		1.2		1.1		1.2		2.2		2.4
Non-Hispanic white race		92.8		93.6		93.3		94.8		93.1

Abbreviations: METs, metabolic equivalents; SD, standard deviation.
[a] Data were standardized to the age distribution of the study population.
[b] Percentages for smoking may not add up to 100% because of missing information.
[c] Values were not age-adjusted.
[d] Weight (kg)/height $(m)^2$.
[e] Recreational and leisure-time activity.

Table 4. Age- and Multivariate-Adjusted[a] Relative Risks of Incident Hearing Loss According to Use of Analgesics, Nurses' Health Study II, 1995–2009[b]

Analgesic and Frequency of Use	No. of Cases ($n = 10,012$)	Person-Years of Follow-up ($n = 764,247$)	Age-Adjusted RR	95% CI	Multivariate-Adjusted RR	95% CI
Aspirin, days/week						
<1	7,371	575,819	1.00		1.00	
1	370	40,551	0.85	0.77, 0.95	0.97	0.87, 1.08
2–3	419	28,345	1.03	0.93, 1.13	1.07	0.97, 1.18
4–5	275	16,638	0.99	0.88, 1.12	0.98	0.87, 1.11
≥6	1,349	67,927	1.03	0.97, 1.09	1.00	0.94, 1.07
P-trend			0.50		0.64	
Ibuprofen, days/week						
<1	5,595	423,739	1.00		1.00	
1	1,483	141,202	1.04	0.98, 1.10	1.01	0.95, 1.08
2–3	1,560	109,995	1.20	1.13, 1.27	1.13	1.06, 1.19
4–5	550	33,327	1.28	1.17, 1.40	1.21	1.11, 1.32
≥6	605	34,413	1.26	1.16, 1.37	1.24	1.14, 1.35
P-trend			<0.0001		<0.0001	
Acetaminophen, days/week						
<1	7,344	537,682	1.00		1.00	
1	1,125	116,553	1.00	0.94, 1.07	1.01	0.94, 1.07
2–3	777	55,101	1.17	1.08, 1.26	1.11	1.02, 1.19
4–5	265	14,751	1.29	1.14, 1.46	1.21	1.07, 1.37
≥6	269	14,425	1.14	1.01, 1.28	1.08	0.95, 1.22
P-trend			0.06		0.0007	

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age; race; body mass index; alcohol consumption; physical activity; intakes of folate, vitamin B_{12}, magnesium, potassium, and vitamin A; smoking status; hypertension; diabetes; and use of the other analgesics.

[b] Numbers of cases and person-years may not add up to totals because of missing data.

aspirin were 33% more likely, regular users of NSAIDs were 61% more likely, and regular users of acetaminophen were 99% more likely to have hearing loss than nonregular users of the same age (15).

Although ototoxicity due to high-dose salicylates has been well demonstrated (7), the mechanisms are not fully understood. A reduction in auditory sensitivity has been associated with compromised blood supply to the cochlea (50), and salicylates induce vascular changes and decreased cochlear blood flow, possibly mediated through the inhibition of prostaglandin synthesis. Salicylates also impair outer hair cell electromotility by binding to the motor protein prestin, and they may induce biochemical and electrophysiologic changes in outer hair cells that alter membrane conductance, permeability, and possibly afferent cochlear nerve function (9, 11, 51, 52). We cannot explain why we observed a positive association between aspirin use and risk of hearing loss in men but no relation in women. In men, the definition of the outcome was self-reported professionally diagnosed hearing loss, whereas in women the outcome was a self-reported hearing problem. It is unclear whether differences in the findings are due to differences in the outcome assessment or whether there exists a difference between men and women for the relation between aspirin use and hearing loss.

We considered the possibility that extensive use of aspirin in the low-dose form might explain the lack of association between aspirin use and risk of hearing loss. In 2001, when information on low-dose versus regular-dose aspirin was first elicited, only 7% of women reported using low-dose aspirin; however, frequency of use increased as the participants aged. Nevertheless, when we included both low-dose aspirin and regular-dose aspirin separately in the full multivariate model, there was no association between frequency of use of low-dose or regular-dose aspirin and the risk of hearing loss.

Ototoxicity due to high doses of NSAIDs has been suggested in animal studies and human case reports (53). NSAIDs may reduce cochlear blood flow because of inhibition of cyclooxygenase and decreased prostaglandin activity (7). To our knowledge, there are no other published prospective studies of the relation between ibuprofen use and hearing loss in women.

Acetaminophen may deplete levels of endothelial thiols, such as endogenous cochlear glutathione (12), which is present in the cochlea in substantial amounts and may

Table 5. Multivariate Relative Risk[a] of Incident Hearing Loss According to Use of Analgesic Agents and Age Group, Nurses' Health Study II, 1995–2009

Analgesic and Frequency of Use	Age Group, years						*P* for Interaction
	<50			≥50			
	No. of Cases	RR	95% CI	No. of Cases	RR	95% CI	
Aspirin, days/week							
<1	3,582	1.00		3,789	1.00		
1	209	0.97	0.84, 1.13	161	0.97	0.83, 1.14	0.98
2–3	161	1.06	0.90, 1.24	258	1.08	0.95, 1.23	0.83
4–5	81	0.90	0.72, 1.12	194	1.03	0.89, 1.18	0.34
≥6	279	0.95	0.84, 1.08	1,070	1.02	0.95, 1.09	0.48
Ibuprofen, days/week							
<1	2,302	1.00		3,293	1.00		
1	824	1.02	0.94, 1.11	659	1.01	0.92, 1.10	0.87
2–3	752	1.11	1.01, 1.20	808	1.15	1.06, 1.24	0.50
4–5	252	1.25	1.10, 1.43	298	1.18	1.05, 1.33	0.51
≥6	259	1.48	1.29, 1.68	346	1.10	0.99, 1.23	0.0007
Acetaminophen, days/week							
<1	3,145	1.00		4,199	1.00		
1	648	1.00	0.91, 1.09	477	1.02	0.92, 1.12	0.76
2–3	380	1.13	1.01, 1.26	397	1.08	0.97, 1.19	0.48
4–5	115	1.35	1.12, 1.63	150	1.12	0.95, 1.32	0.13
≥6	76	1.03	0.82, 1.30	193	1.09	0.94, 1.26	0.74

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age; race; body mass index; alcohol consumption; physical activity; intakes of alcohol, folate, vitamin B_{12}, magnesium, potassium, and vitamin A; smoking status; hypertension; diabetes; and use of the other analgesics.

protect the cochlea from noise-induced damage (13, 14). We found an increased risk of hearing loss associated with acetaminophen use that was statistically significant for the categories 2–3 days/week and 4–5 days/week; however, it is unclear why no relation was observed for women who used acetaminophen ≥6 days/week. Although there was a suggestion that the magnitude of the association was greater in women younger than age 50 years, the *P* value for interaction was not statistically significant.

Table 6. Multivariate Relative Risk[a] of Incident Hearing Loss According to Regular Use (≥2 Times/Week) of Individual and Multiple Analgesic Agents, Nurses' Health Study II, 1995–2009

Analgesic(s) Used	No. of Cases	Relative Risk	95% Confidence Interval
No regular use	5,315	1.00	
Aspirin only	1,275	1.01	0.95, 1.08
Ibuprofen only	1,653	1.17	1.11, 1.24
Acetaminophen only	483	1.09	0.99, 1.19
Aspirin + ibuprofen	463	1.16	1.05, 1.27
Ibuprofen + acetaminophen	408	1.28	1.16, 1.42
Aspirin + acetaminophen	243	1.23	1.08, 1.40
All 3 analgesics	172	1.34	1.15, 1.56

[a] Adjusted for age; race; body mass index; alcohol consumption; physical activity; intakes of folate, vitamin B_{12}, magnesium, potassium, and vitamin A; smoking status; hypertension; and diabetes.

The prevalence of hearing loss in women increases with age (1, 54). Data from the 1999–2004 NHANES showed that for non-Hispanic white women, the prevalence of bilateral hearing loss (average threshold at 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz ≥25 dB) increases from 4.4% among women in their 40s to 20% among women in their 60s (1). Similarly, the prevalence of high-frequency hearing loss (average threshold at 3 kHz, 4 kHz, and 6 kHz ≥25 dB in either ear) increases from 20% of women in their 40s to 65% of women in their 60s (1). The magnitude of the association between frequent ibuprofen or acetaminophen use and hearing loss tended to be greater in women younger than age 50 years. Of particular note, the relative risk of hearing loss was 48% higher in younger women who used ibuprofen ≥6 days/week, and the interaction with age was highly significant. The cause of acquired hearing loss is multifactorial. In a given individual, potential contributors to hearing loss include processes associated with aging, noise exposure, inherited genetic factors, and otologic and systemic conditions. The relative contribution of some risk factors, such as analgesic use, to hearing loss may be larger

in younger persons, before the cumulative effects of aging, noise, and other factors have substantially affected hearing.

Although regular use of ibuprofen was associated with increased risk of hearing loss, we did not observe a relation with regular use of other NSAIDs (e.g., naproxen, ketoprofen). Potentially, this could be due to differences in the pharmacologic activity of the various 2-arylpropionic acid derivatives ("profens") or, since comparatively fewer women used these other NSAIDs frequently, lack of power to detect an association. In a subcohort of 4,024 NHS II participants who completed a supplementary questionnaire on analgesic use in 1998, among those women who used any NSAIDs at least once per month, over 80% reported using ibuprofen (our unpublished data). This important relation deserves further study.

Our study had limitations. Assessment of hearing loss was based on self-report. Although standard pure-tone audiometry is considered the gold standard for hearing loss evaluation, self-reported hearing loss has been demonstrated to be reliable (29–31, 55, 56). Gomez et al. (29) examined the agreement between self-report and audiometry and found that for bilateral midfrequency hearing loss, the sensitivity of self-reporting was 77% and the specificity was 82%. Nondahl et al. (31) compared self-reporting with audiometry; the sensitivity of self-reporting was 71%, the specificity was 70%, and the prevalence of hearing loss based on self-reporting was within 1.9% of that measured by audiometry. Using a slightly different audiometric definition of hearing loss, Schow et al. (30, 56) found that the sensitivity of self-reporting was 73% and the specificity was 84%. Moreover, a recent evidence review of the accuracy of hearing-loss screening methods among older adults by the US Preventive Services Task Force found that a single question regarding perceived hearing loss was nearly as accurate as a more detailed hearing loss questionnaire or a handheld audiometric device for detecting hearing loss (57).

We did not have information on lifetime noise exposure. Excessive noise exposure is a risk factor for hearing loss, and while the physiologic effects of noise on the ear may be modified by salicylates (58), the relation between noise exposure, NSAIDs, acetaminophen, and hearing loss has not been examined. We also did not have information on dose or indications for analgesic use in the entire cohort. However, on the supplementary NHS II analgesic questionnaire, the most commonly reported reasons for aspirin use were headache, cardiac disease prevention, muscle/joint pain, backache, and menstrual cramps; for NSAID or acetaminophen use, the common indications were muscle/joint pain, headache, menstrual cramps, and backache (our unpublished data). Although we did not have sufficient detail about dose to examine this separately, the relation between analgesic dose and hearing loss merits further research. We were not able to examine the association between use of narcotic analgesics and hearing loss.

The present study examined a population of predominantly non-Hispanic white women. Although the participants in the NHS II cohort may not be representative of the adult female population in the United States, follow-up rates are high and the information provided is highly reliable. Further studies are needed to examine these associations in other demographic groups. To better understand possible differences between men and women regarding the association between analgesic use and hearing loss, further research that uses the same methods to examine both sexes in a single data set would be informative.

In conclusion, this prospective study showed that use of ibuprofen or acetaminophen 2 or more days per week is associated with an increased risk of hearing loss in women and that the magnitude of the risk tends to be greater with increasing frequency of use. There was no relation observed between aspirin use and the risk of hearing loss. Given the prevalence of hearing loss and the frequent use of analgesics, these findings could have important public health implications, as they suggest a potentially modifiable contributor to hearing loss.

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