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## Original Contribution

# Duration of Analgesic Use and Risk of Hearing Loss in Women

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Aspirin, nonsteroidal antiinflammatory drugs (NSAID), and acetaminophen are commonly used. Frequent use of analgesics has been associated with a higher risk of hearing loss. However, the association between duration of analgesic use and the risk of hearing loss is unclear. We investigated the relationship between duration of analgesic use and self-reported hearing loss among 55,850 women in the Nurses' Health Study. Cox proportional hazards regression was used to adjust for potential confounders. During 873,376 person-years of follow-up (1990–2012), longer durations of NSAID use (for >6 years of use compared with <1 year, multivariable-adjusted relative risk = 1.10, 95% confidence interval: 1.06, 1.15; *P* for trend < 0.001) and acetaminophen use (for >6 years of use compared with <1 year, multivariable-adjusted relative risk = 1.09, 95% confidence interval: 1.04, 1.14; *P* for trend < 0.001) were associated with higher risks of hearing loss. Duration of aspirin use was not associated with hearing loss (for >6 years of use compared with <1 year, multivariable-adjusted relative risk = 1.01, 95% confidence interval: 0.97, 1.05; *P* for trend = 0.35). In this cohort of women, longer durations of NSAID and acetaminophen use were associated with slightly higher risks of hearing loss, but duration of aspirin use was not. Considering the high prevalence of analgesic use, this may be an important modifiable contributor to hearing loss.

acetaminophen; aspirin; hearing loss; nonsteroidal antiinflammatory drug

Abbreviations: CI, confidence interval; NHS, Nurses' Health Study; NSAID, nonsteroidal antiinflammatory drug; RR, relative risk.

Hearing loss is common among adults in the United States. According to the National Health and Nutrition Examination Survey (NHANES), two-thirds of women in their sixties have hearing loss (1). Hearing loss can have a significant impact on quality of life; thus, identifying potential modifiable risk factors may help reduce the burden of this condition (2, 3).

Aspirin, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen are the most commonly used medications in the United States (4). Previous studies have suggested that use of high-dose NSAIDs or salicylates (aspirin) may be ototoxic. Ototoxicity may be mediated by several different mechanisms, including impairment of outer hair cell function, reduced vascular supply to the cochlea, and inhibition of cyclooxygenase (5–9). It is hypothesized that depletion of cochlear glutathione by acetaminophen (10) may result in greater susceptibility of the cochlea to noise-induced damage (11, 12). Furthermore, in rodent models, it has been demonstrated that acetaminophen and a metabolite of acetaminophen may cause ototoxicity through oxidative stress mechanisms (13).

In a cohort of younger women, we found that regular use (≥2 days/week) of ibuprofen and acetaminophen was associated with a higher risk of hearing loss (14). We therefore decided to examine this question in a cohort of older women and determine whether a longer duration of regular analgesic use was associated with the risk of hearing loss. Given the mechanisms by which analgesics are theorized to cause hearing loss, we hypothesized that longer duration of exposure to analgesics would be more likely to result in hearing

loss. We investigated the relationship between duration of analgesic use and risk of hearing loss among participants in the Nurses' Health Study (NHS) I.

## METHODS

### Study participants

NHS I is an ongoing cohort study of female nurses. In 1976, a total of 121,700 participants who were 30–55 years of age enrolled. Participants were 44–69 years of age in 1990, the baseline year of our study. In the NHS I, questionnaires are administered to the participants every 2 years, with an average follow-up rate of more than 90% of the eligible person-time. The NHS questionnaires are available online (15). In the Conservation of Hearing Study (CHEARS), an NHS substudy, researchers investigate factors associated with hearing loss in the NHS. On the 2012 long-form questionnaire, the women were asked whether they had a hearing problem, and if so, the age at which they first noticed a change in their hearing. In 2012, a total of 63,966 women answered the long-form questionnaire. Of these women, 47% reported having a hearing problem. Women who reported a hearing problem that began before 1990 (baseline year of the study) and those who reported a history of cancer other than nonmelanoma skin cancer were excluded from our study because of the potential exposure to ototoxic chemotherapeutic drugs. After applying these exclusion criteria, our study population comprised 55,850 women.

### Ascertainment of medication use

In 1990 and every 2 years thereafter, women were asked about their average use of aspirin (e.g., Anacin (Insight Pharmaceuticals, Langhoren, Pennsylvania), Bufferin (Dr. Reddy's Laboratories Ltd., Hyderabad, India), Midol (Bayer AG, Leverkusen, Germany), and Alka-Seltzer (Bayer AG, Leverkusen, Germany)), acetaminophen (e.g., Tylenol (McNeil Consumer Healthcare, Fort Washington, Pennsylvania)), and other antiinflammatory medications (e.g., ibuprofen, Naprosyn (Atnahs Pharma, London, United Kingdom), and Advil (Pfizer, Groton, Connecticut)). Specifically, participants were asked, "On average, how many days each month do you take any of the following medications: acetaminophen (e.g., Tylenol); aspirin (e.g., Anacin, Bufferin, Midol, Alka-Seltzer, etc.); other antiinflammatory (e.g., ibuprofen, Naprosyn, Advil)?" Starting in 2000, participants were asked about their average use of ibuprofen (e.g., Advil, Motrin (Johnson & Johnson, New Brunswick, New Jersey), and Nuprin (Shasun Pharmaceuticals, Chennai, India)). We considered participants who reported using other antiinflammatory analgesics (e.g., ibuprofen, Naprosyn, Advil) between 1990–1999 and ibuprofen (e.g., Advil, Motrin, Nuprin) between 2000–2012 to be NSAID users. Participants with missing information on analgesic intake over any 2-year questionnaire period were excluded from that time period. Analgesic use assessed in this manner has been associated with colon cancer (16), renal cell carcinoma (17), Parkinson disease (18), hypertension (19, 20), and breast cancer survival (21).

Duration of medication use was derived by assigning 2 years of use to women who reported using the medication 2 or more days/week on average, starting at baseline (1990), and then adding 2 additional years of use for answers in the affirmative on subsequent questionnaires. Women who reported using analgesics less than 2 days/week on average were categorized as participants with "no regular use" for that questionnaire cycle. Duration of medication use was categorized as less than 1 year, 1–2 years, 3–4 years, 5–6 years, and more than 6 years. Women who reported "no regular use" of analgesics were categorized as having less than 1 year of use. We were unable to ascertain information on duration of use of aspirin, NSAIDs, or acetaminophen before 1990.

### Ascertainment of hearing loss

The outcome in the present study was self-reported hearing loss. In 2012, participants were asked, "Do you have a hearing problem?" If they answered in the affirmative, they were asked, "At what age did you first notice a change in your hearing?" We defined cases of hearing loss as women who reported a hearing problem after 1990. The gold standard for evaluating hearing loss is pure-tone audiometry. From a logistical and financial standpoint, it is challenging to obtain audiograms in such a large cohort. It has been shown in previous studies that compared with hearing loss diagnosed by audiogram, self-reported hearing loss is a relatively reliable indicator of hearing loss (22–25). In addition, significant associations between other factors and risk of self-reported hearing loss have been observed using this method of assessment in NHS I and NHS II (14, 26–29).

### Ascertainment of covariates

Covariates were selected based on previously reported risk factors for hearing loss. These factors included age (1); race (1); body mass index (27, 30); waist circumference (27); alcohol consumption (28, 31); intakes of folate (32), β-carotene (29), *trans* fatty acids, omega-3 fatty acids (33), β-cryptoxanthin (29), vitamin A, vitamin $B_{12}$, vitamin C (29), vitamin E, potassium (34), and magnesium (35); physical activity level (27, 36); smoking (31); diabetes (37); hypertension (26); and tinnitus (38, 39).

Updated covariate data were obtained from the biennial questionnaires. Dietary intakes (alcohol, folate, vitamin $B_{12}$, vitamin A, potassium, magnesium, vitamin E, *trans* fatty acids, omega-3 fatty acids, β-carotene, and β-cryptoxanthin) were derived from semiquantitative food frequency questionnaires, which are mailed to study participants every 4 years. The validity and reproducibility of the food frequency questionnaires have previously been reported (40, 41). Many of the other covariates used in our models have been shown to be valid measures in this and other similar cohorts (42–44).

### Calculation of the population attributable fraction

In the event that duration of analgesic use was found to be associated with risk of hearing loss, we calculated the population attributable fraction (PAF) of hearing loss among women in our study using the method of Bruzzi et al. (45).

This method has been shown to provide valid estimates of the population attributable fraction with multicategory exposures (46). This calculation is based on the assumption that there is a causal relation.

### Statistical analysis

All analyses were performed in a prospective manner. Person-time for each participant was assigned based on their responses to questions about aspirin, NSAID, and acetaminophen use on the 1990 questionnaire and was updated every 2 years subsequently. Participants were censored at the reported onset of hearing loss or cancer diagnosis. Multivariable-adjusted relative risks were calculated using Cox proportional hazards regression models. The Anderson-Gill data structure was used to deal with left truncation and time-varying covariates in an efficient manner (47). To control for confounding by age as finely as possible, we stratified our analysis jointly by age at start of follow-up and calendar year of a given questionnaire cycle. We also tested for possible effect modification of the relationships of use of aspirin, NSAID, and acetaminophen with age (categorized as <60 years and ≥60 years). Age 60 years was chosen based on the distribution of participant ages and previous studies in which effect modification by age was investigated. Given that analgesic use may be associated with tinnitus, we performed a secondary analysis in which we excluded women who reported onset of tinnitus before onset of hearing loss. *P* values are all 2-sided, with 95% confidence intervals for all relative risks. SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina) was used for all statistical analyses. This study was approved by the Partners Healthcare Institutional Review Board.

## RESULTS

At study baseline (1990), the mean participant age was 53.9 (standard deviation, 6.5) years, and the mean participant body mass index, calculated as weight in kilograms divided by height in meters squared, was 25.5 (standard deviation, 4.7). At baseline, 16.2% of participants reported regular (≥2 days/week) aspirin use, 11.1% of participants reported regular NSAID use, and 7.9% of participants reported regular acetaminophen use; 8.8% of participants reported regular use of multiple analgesics.

Characteristics of participants by duration of aspirin, NSAID, and acetaminophen use in 2002 (the approximate midpoint of the study period) are shown in Tables 1–3. Women with longer durations of aspirin use tended to be older, were more physically active, were more likely to be current smokers, and were more likely to have a history of hypertension or diabetes. Women with longer durations of NSAID use tended to have higher body mass indices and waist circumferences, were less physically active, consumed less alcohol, and were more likely to have a history of hypertension or diabetes. Women with longer durations of acetaminophen use tended to have higher body mass indices and waist circumferences,

**Table 1.** Age-Adjusted Characteristics of Participants According to Duration of Regular Aspirin Use, Nurses' Health Study I[a], 1990–2002

| Variable | Duration of Regular Aspirin Use, years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <1 (*n* = 14,347) | | 1–2 (*n* = 6,953) | | 3–4 (*n* = 5,567) | | 5–6 (*n* = 4,017) | | >6 (*n* = 8,994) | |
| | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % |
| Age, years[b,c,d] | 64.1 (5.8) | | 64.7 (5.8) | | 65.3 (5.8) | | 65.7 (6.0) | | 66.6 (5.9) | |
| Body mass index[c,d,e] | 26.6 (5.2) | | 27.1 (5.3) | | 27.1 (5.3) | | 27.1 (5.3) | | 27.0 (5.3) | |
| Waist circumference, cm[c] | 85.4 (13.1) | | 86.5 (13.5) | | 86.6 (13.1) | | 86.5 (12.8) | | 86.6 (13.0) | |
| White race[c,d] | | 93.7 | | 94.9 | | 94.4 | | 95.2 | | 95.5 |
| Physical activity level, METs[c,f] | 18.8 (23.2) | | 18.7 (24.5) | | 18.4 (20.6) | | 18.5 (20.3) | | 19.8 (22.1) | |
| Smoking status[c,d] | | | | | | | | | | |
| Never smoker | | 47.7 | | 46.4 | | 45.5 | | 45.4 | | 44.7 |
| Past smoker | | 44.5 | | 46.4 | | 47.3 | | 47.4 | | 47.3 |
| Current smoker | | 7.6 | | 7.0 | | 7.1 | | 7.0 | | 7.8 |
| Alcohol consumption, g/day[c] | 6.0 (10.4) | | 6.0 (10.7) | | 6.2 (10.5) | | 6.3 (10.3) | | 7.0 (11.4) | |
| History of hypertension[c,d] | | 41.8 | | 48.8 | | 53.1 | | 52.8 | 56.3 | |
| History of diabetes[c,d] | | 5.9 | | 7.7 | | 8.2 | | 8.8 | 8.7 | |

Abbreviations: MET, metabolic equivalent of task; SD, standard deviation.

[a] Regular aspirin use was defined as ≥2 days/week. Data are representative of participants who contributed person-time in 2002. These are characteristics at the approximate midway point of follow-up to provide representative results. The actual period-specific results were used in the analysis.

[b] Value is not age adjusted.

[c] Values are standardized to the age distribution of the study population.

[d] Values of polytomous variables may not sum to 100% because of rounding.

[e] Weight (kg)/height $(m)^2$.

[f] Metabolic equivalents from recreational and leisure-times activities.

**Table 2.** Age-Adjusted Characteristics of Participants According to Duration of Regular Use of Nonsteroidal Antiinflammatory Drugs, Nurses' Health Study I[a], 1990–2002

| Variable | Duration of Regular NSAID Use, years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <1 (*n* = 19,169) | | 1–2 (*n* = 6,843) | | 3–4 (*n* = 4,694) | | 5–6 (*n* = 3,404) | | >6 (*n* = 5,768) | |
| | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % |
| Age, years[b,c,d] | 65.6 (6.0) | | 64.9 (5.9) | | 64.6 (5.8) | | 64.5 (5.8) | | 64.4 (5.7) | |
| Body mass index[c,d,e] | 26.2 (4.9) | | 27.0 (5.1) | | 27.5 (5.6) | | 27.7 (5.5) | | 28.1 (5.8) | |
| Waist circumference, cm[c] | 84.5 (12.5) | | 86.5 (12.8) | | 87.5 (13.7) | | 88.0 (13.6) | | 89.1 (14.1) | |
| White race[c,d] | | 94.1 | | 94.9 | | 94.7 | | 95.2 | | 95.2 |
| Physical activity level, MET hours/week[c,f] | 19.8 (22.9) | | 18.7 (24.2) | | 18.3 (22.0) | | 17.8 (21.2) | | 17.8 (21.6) | |
| Smoking status[c,d] | | | | | | | | | | |
| Never smoker | | 48.0 | | 45.6 | | 43.9 | | 45.9 | | 43.4 |
| Past smoker | | 43.9 | | 46.8 | | 49.1 | | 47.5 | | 50.1 |
| Current smoker | | 8.0 | | 7.4 | | 6.8 | | 6.5 | | 6.2 |
| Alcohol consumption, g/day[c] | 6.3 (11.0) | | 6.3 (10.5) | | 6.1 (10.1) | | 6.2 (10.1) | | 6.5 (10.7) | |
| History of hypertension[c,d] | | 44.3 | | 49.9 | | 52.3 | | 54.1 | | 57.4 |
| History of diabetes[c,d] | | 6.7 | | 7.6 | | 8.6 | | 7.6 | | 8.8 |

Abbreviations: MET, metabolic equivalent of tasks; NSAID, nonsteroidal antiinflammatory drug; SD, standard deviation.

[a] Regular NSAID use was defined as ≥2 days/week. Data are representative of participants who contributed person-time in 2002. These are characteristics at the approximate midway point of follow-up to provide representative results. The actual period-specific results were used in the analysis.

[b] Value is not age adjusted.

[c] Values are standardized to the age distribution of the study population.

[d] Values of polytomous variables may not sum to 100% because of rounding.

[e] Weight (kg)/height $(m)^2$.

[f] Metabolic equivalents from recreational and leisure-times activities.

were less physically active, consumed less alcohol, and were more likely to have a history of hypertension and diabetes.

During 873,376 person-years of follow-up, 18,663 incident cases of hearing loss were reported. Increasing duration of regular NSAID use (for >6 years of use compared with <1 year use, multivariable-adjusted relative risk (RR) = 1.10, 95% confidence interval (CI): 1.06, 1.15; *P* for trend < 0.001) and regular acetaminophen use (for >6 years of use compared with <1 year use, multivariable-adjusted RR = 1.09, 95% CI: 1.04, 1.14; *P* for trend < 0.001) were independently associated with higher risks of hearing loss, but increasing duration of aspirin use was not (for >6 years of use compared with <1 year use, multivariable-adjusted RR = 1.01, 95% CI: 0.97, 1.05; *P* for trend = 0.35) (Table 4). Adjusting for body mass index and waist circumference as continuous variables and excluding participants with a history of tinnitus did not significantly change the results. There was no significant effect modification of duration by age (data not shown).

Longer durations of aspirin, NSAID, and acetaminophen use were significantly correlated with increasing frequency of aspirin, NSAID, and acetaminophen use (Spearman correlation coefficients = 0.61, 0.48, and 0.59, respectively). There was a higher risk of hearing loss among women who reported regular (≥2 days/week) NSAID use (multivariable-adjusted RR = 1.07, 95% CI: 1.01, 1.13) and regular acetaminophen use (multivariable-adjusted RR = 1.07, 95% CI: 1.01, 1.13) compared with women who reported average use of less than 2 days/week. Regular aspirin use was not associated with risk of hearing loss (multivariable-adjusted RR = 1.01, 95% CI: 0.98, 1.05). Regular use of multiple analgesics was also associated with higher risk of hearing loss (for regular use of aspirin, NSAIDs, and acetaminophen compared with no regular use, multivariable-adjusted RR = 1.19, 95% CI: 1.08, 1.32) (Appendix Table 1).

Assuming a causal relation between analgesic use and hearing loss among women in our study, the population attributable fraction for regular NSAID use was 4.0%, and that for acetaminophen use was 1.6%. The total population attributable fraction for NSAID use and acetaminophen use among women in our study was 5.5%.

## DISCUSSION

In our large prospective study, longer durations of regular (≥2 days/week) NSAID use and acetaminophen use were associated with higher risks of hearing loss. If this is a causal relation, it suggests that a substantial proportion of hearing loss attributable to use of analgesics is potentially preventable.

Ototoxicity is a well-known potential side effect of very high-dose salicylates (5). Salicylates have been associated with decreased blood flow to the cochlea, impaired outer hair cell motility, and inhibition of the endocochlear

**Table 3.** Age-Adjusted Characteristics of Participants According to Duration of Regular Acetaminophen Use, Nurses' Health Study I[a], 1990–2002

| Variable | Duration of Regular Acetaminophen Use, years | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | <1 (*n* = 23,719) | | 1–2 (*n* = 6,239) | | 3–4 (*n* = 3,561) | | 5–6 (*n* = 2,419) | | >6 (*n* = 3,940) | |
| | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % | Mean (SD) | % |
| Age, years[b,c,d] | 65.1 (5.9) | | 65.0 (5.9) | | 65.0 (5.9) | | 65.0 (5.9) | | 65.3 (6.0) | |
| Body mass index[c,d,e] | 26.5 (5.0) | | 27.4 (5.4) | | 27.7 (5.6) | | 27.6 (5.5) | | 27.9 (5.8) | |
| Waist circumference, cm[c] | 85.1 (12.8) | | 87.1 (13.4) | | 87.7 (13.5) | | 87.5 (13.3) | | 89.1 (13.8) | |
| White race[c,d] | | 94.5 | | 94.6 | | 94.3 | | 94.5 | | 94.9 |
| Physical activity level, MET hours/week[c,f] | 20.0 (22.5) | | 18.5 (23.8) | | 17.7 (24.6) | | 17.1 (21.2) | | 16.1 (20.4) | |
| Smoking status[c,d] | | | | | | | | | | |
| Never smoker | | 47.0 | | 45.5 | | 45.5 | | 45.8 | | 43.6 |
| Past smoker | | 45.1 | | 47.3 | | 47.3 | | 47.5 | | 49.3 |
| Current smoker | | 7.7 | | 7.0 | | 7.0 | | 6.5 | | 7.0 |
| Alcohol consumption, g/day[c] | 6.8 (11.1) | | 5.9 (10.1) | | 5.7 (10.7) | | 5.4 (9.6) | | 5.1 (9.7) | |
| History of hypertension[c,d] | | 45.1 | | 51.7 | | 54.4 | | 54.9 | | 59.6 |
| History of diabetes[c,d] | | 6.6 | | 8.2 | | 8.4 | | 9.1 | | 9.7 |

Abbreviations: MET, metabolic equivalent of tasks; SD, standard deviation.

[a] Regular acetaminophen use was defined as ≥2 days/week. Data are representative of participants who contributed person-time in 2002. These are characteristics at the approximate midway point of follow-up to provide representative results. The actual period-specific results were used in the analysis.

[b] Value is not age adjusted.

[c] Values are standardized to the age distribution of the study population.

[d] Values of polytomous variables may not sum to 100% because of rounding.

[e] Weight (kg)/height $(m)^2$.

[f] Metabolic equivalents from recreational and leisure-times activities.

potential via alteration of membrane permeability, conductance, and afferent cochlear nerve function (7, 9, 48–50). However, use of high-dose aspirin has been uncommon for more than 2 decades. We found no association between duration of regular (≥2 days/week) aspirin use and risk of hearing loss. Data from a previous study in which investigators examined cumulative use of aspirin in our cohort suggested that participants tended to use aspirin at doses within the recommended daily range (51), which is much lower than the high doses previously described to be associated with hearing loss. To our knowledge, this represents the first published study in which the relationship between duration of aspirin use and risk of hearing loss in women has been prospectively examined.

High-dose NSAIDs have been associated with ototoxicity in rodent models and small human case reports (52). In NHS II, we found that regular use of NSAIDs was associated with a higher risk of hearing loss, and more frequent use tended to be associated with a higher risk (14). In a prospective study in men, Curhan et al. (53) found a higher risk of hearing loss associated with a longer duration of NSAID use. Previous data have shown that the average use of NSAIDs within the NHS I cohort is, on average, much less than 3.2 g/day, the recommended maximum daily dose (51). Our data are consistent with these findings and represent the first published study in which the association between duration of NSAID use and the risk of hearing loss in women has been described.

Acetaminophen has been hypothesized to decrease levels of cochlear glutathione, which may reduce protection of the cochlea from noise-induced hearing loss (11, 12). In a previous study in men, researchers demonstrated that a longer duration of acetaminophen use was associated with a higher risk of hearing loss (53). Our data in women are consistent with these findings. Previous data have shown that use of acetaminophen within this cohort is, on average, far less than 4 g/day, the recommended maximum daily dose (51). To our knowledge, this represents the first prospective study in women to describe the relation between duration of acetaminophen use and the risk of hearing loss.

Although the magnitude of the higher risk of hearing loss with analgesic use in our cohort was modest, given the high prevalence of analgesic use, a small increase in risk could have important public health implications. We calculated the population attributable fraction of hearing loss for NSAID and acetaminophen use and, assuming causality, 5.5% of the cases of hearing loss in our cohort could be attributable to NSAID and acetaminophen use. Although limited by the assumption of causality, our estimates serve as an important reminder that small increases in risk associated with common exposures could have potentially important implications on a population level.

**Table 4.** Multivariable-Adjusted Relative Risk of Hearing Loss, According to Duration of Regular Analgesic Use, Nurses' Health Study I, 1990–2012[a]

| Analgesic and Duration of Use, years | No. of Cases | No. of Person-Years | Age-Adjusted RR | 95% CI | Multivariable-Adjusted RR[b] | 95% CI |
|---|---|---|---|---|---|---|
| Aspirin | | | | | | |
| <1 | 5,842 | 413,837 | 1.00 | Referent | 1.00 | Referent |
| 1–2 | 2,695 | 147,431 | 1.02 | 0.98, 1.07 | 0.98 | 0.94, 1.03 |
| 3–4 | 2,285 | 96,035 | 1.11 | 1.05, 1.16 | 1.03 | 0.98, 1.09 |
| 5–6 | 2,002 | 68,849 | 1.14 | 1.08, 1.20 | 1.04 | 0.98, 1.09 |
| >6 | 5,839 | 147,225 | 1.22 | 1.18, 1.27 | 1.01 | 0.97, 1.05 |
| *P* for trend | | | <0.01 | | 0.35 | |
| NSAIDs | | | | | | |
| <1 | 8,711 | 494,753 | 1.00 | Referent | 1.00 | Referent |
| 1–2 | 3,103 | 148,865 | 1.15 | 1.11, 1.20 | 1.07 | 1.03, 1.12 |
| 3–4 | 2,120 | 87,836 | 1.24 | 1.19, 1.31 | 1.07 | 1.02, 1.12 |
| 5–6 | 1,591 | 57,483 | 1.29 | 1.22, 1.36 | 1.08 | 1.02, 1.14 |
| >6 | 3,138 | 84,439 | 1.46 | 1.40, 1.52 | 1.10 | 1.06, 1.15 |
| *P* for trend | | | <0.01 | | <0.01 | |
| Acetaminophen | | | | | | |
| <1 | 10,393 | 573,821 | 1.00 | Referent | 1.00 | Referent |
| 1–2 | 2,946 | 131,952 | 1.10 | 1.06, 1.15 | 1.02 | 0.98, 1.07 |
| 3–4 | 1,668 | 66,963 | 1.14 | 1.08, 1.20 | 1.01 | 0.96, 1.07 |
| 5–6 | 1,170 | 40,737 | 1.17 | 1.10, 1.24 | 1.02 | 0.96, 1.08 |
| >6 | 2,486 | 59,903 | 1.37 | 1.31, 1.43 | 1.09 | 1.04, 1.14 |
| *P* for trend | | | <0.01 | | <0.01 | |

Abbreviations: CI, confidence interval; NSAIDs, nonsteroidal antiinflammatory drugs; RR, relative risk.
[a] Regular analgesic use was defined as ≥2 days/week.
[b] Adjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity level, nutrient intake (folate, magnesium, potassium, vitamin A, vitamin $B_{12}$, vitamin C, vitamin E, β-carotene, β-cryptoxanthin, *trans* fatty acids, omega-3 fatty acids), smoking status, hypertension, diabetes, tinnitus, and duration of use of the other analgesics.

Our study has limitations. Our cohort comprised mostly older white women. Further investigation is required to examine the associations in other populations. Although we were able to assess duration of analgesic use, our study lacked information on the cumulative amounts of analgesic intake in participants. Analgesic use was self-reported, and we lacked information on duration of use prior to baseline. Given that analgesic use data were based on self-reports, the possibility of misclassification of analgesic use cannot be excluded. However, data in the present study were prospectively collected over 22 years, and information from this and other similar cohorts has been shown to be highly reliable in previous studies (40, 41, 44, 54). The outcome of our study was self-reported hearing loss. Although pure-tone audiometry is considered the gold standard for diagnosing hearing loss, self-reported hearing loss has been shown to be a reliable indicator of hearing loss (22–25). Furthermore, in a recent literature review, Chou et al. (55) showed that a single question on perceived hearing loss was almost as accurate as a more detailed questionnaire or portable audiometric device for detecting hearing loss. Misclassification of the age at which participants reported they first noticed a change in their hearing cannot be excluded.

In conclusion, longer duration of regular (≥2 days/week) NSAID use and longer duration of regular acetaminophen use were associated with higher risks of hearing loss, but longer duration of aspirin use was not. Considering the high prevalence of analgesic use and the high probability of frequent and/or prolonged exposure in women of more advanced age, our findings suggest that NSAID use and acetaminophen use may be modifiable risk factors for hearing loss.

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**Appendix Table 1.** Multivariable-Adjusted Relative Risk of Hearing Loss According to Regular Use of Analgesics, Alone or in Combination, Nurses' Health Study I[a], 1990–2012

| Analgesic | No. of Cases | No. of Person-Years | Age-Adjusted RR | 95% CI | Multivariable-Adjusted RR[b] | 95% CI |
|---|---|---|---|---|---|---|
| None | 7,277 | 410,152 | 1.00 | Referent | 1.00 | Referent |
| Aspirin alone | 5,600 | 215,017 | 1.05 | 1.01, 1.09 | 1.01 | 0.98, 1.05 |
| NSAIDs alone | 1,535 | 93,663 | 1.11 | 1.05, 1.18 | 1.07 | 1.01, 1.13 |
| Acetaminophen alone | 1,465 | 64,903 | 1.11 | 1.05, 1.18 | 1.07 | 1.01, 1.13 |
| Aspirin and NSAIDs | 1,098 | 43,660 | 1.19 | 1.11, 1.26 | 1.08 | 1.01, 1.15 |
| NSAIDs and acetaminophen | 460 | 29,732 | 1.14 | 1.04, 1.26 | 1.10 | 1.00, 1.21 |
| Aspirin and acetaminophen | 1,303 | 39,324 | 1.14 | 1.08, 1.21 | 1.06 | 0.99, 1.12 |
| Aspirin, NSAIDs, and acetaminophen | 416 | 14,732 | 1.35 | 1.22, 1.49 | 1.19 | 1.08, 1.32 |

Abbreviations: CI, confidence interval; NSAID, nonsteroidal antiinflammatory drug; RR, relative risk.
[a] Regular analgesic use was defined as ≥2 days/week.
[b] Adjusted for age, race, body mass index, waist circumference, alcohol consumption, physical activity level, nutrient intake (folate, magnesium, potassium, vitamin A, vitamin $B_{12}$, vitamin C, vitamin E, β-carotene, β-cryptoxanthin, *trans* fatty acids, omega-3 fatty acids), smoking status, hypertension, diabetes, tinnitus, and frequency of use of the other analgesics.