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## Ubiquitous Aspirin: A Systematic Review of Its Impact on Sensorineural Hearing Loss

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### Abstract

**Objective**—This systematic review evaluates the impact of aspirin on audiometric outcomes with respect to: (1) doses exceeding 325 mg daily, (2) doses of 325 mg daily or less, (3) studies applicable to the general populace, and (4) studies applicable to those with inflammatory conditions. It also assesses the impact of aspirin on (a) self-reported hearing loss, (b) noise-induced audiometric changes, and (c) the adverse otological effects of aminoglycoside therapy.

**Data Sources**—Computerized searches of MEDLINE, PubMed, Cochrane, and EMBASE databases were performed, updated through January 2014, and supplemented by manual searches and inquiries to topic experts.

**Review Methods**—A systematic review was performed according to an a priori protocol. Data extraction was performed by 2 independent parties and focused on relevant audiological measurements, potential confounders, and study design elements associated with risk of bias, including utilization of randomization, prospective/retrospective data collection, and incorporation of blinding.

**Results**—The 37 criterion-meeting studies included a combined total of 185,155 participants. Aspirin ingestion 1.95 g/d was associated with worse audiometric results (4–112 dB threshold

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### Author Contributions

**Meghann Elizabeth Kyle**, acquisition of data, analysis and interpretation of data, drafting and editing manuscript, final approval; **James C. Wang**, acquisition of data, analysis and interpretation of data, contributing to manuscript, final approval; **Jennifer J. Shin**, analysis and interpretation of data, acquisition of data, drafting and editing manuscript, final approval.

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### Supplemental Material

Additional supporting information may be found at <http://otojournal.org/supplemental>.

shift); the effect was dose dependent and reversible in the short term. There were no audiometric data that confirm that long-term doses of 81 mg or 325 mg daily have no hearing consequences. Paradoxically, aspirin (in doses shown to be detrimental in isolation) had a protective effect when co-administered with intravenous gentamicin.

**Conclusions**—With the large-scale population utilization of aspirin for cardiovascular prophylaxis, the potential risks to hearing health should be considered for future longitudinal study, particularly given that short-term effects may be reversible.

### Keywords

hearing loss; sensorineural hearing loss; aspirin; public health

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### Introduction

Aspirin (acetylsalicylic acid, ASA) is ingested at the remarkable rate of 40,000 metric tons (120 billion tablets) per year, making it 1 of the 3 most utilized drugs worldwide.<sup>1,2</sup> Originally isolated from the bark of a willow tree, its antipyretic, analgesic, and anti-inflammatory properties have formed the foundation for its widespread use. In addition, this nonsteroidal anti-inflammatory agent now plays a noteworthy role in preventive regimens. More specifically, the United States Preventative Task Force recommends that prophylactic ASA be considered in males 45 to 79 years of age to obtain a potential 32% relative risk reduction for myocardial infarction. The Task Force also recommends that daily usage be considered in females age 55 to 79 years to effect a potential 17% relative risk reduction for stroke.<sup>3</sup> Therefore, ASA is likely to remain among the most ubiquitous of medications in active use.

Hearing loss is the most common sensory disorder in the United States, and its prevalence is increasing.<sup>4,5</sup> While 31.5 million American adults self-reported hearing loss in 2000, that number increased to 37 million in 2006.<sup>4</sup> With audiometric decline in older patients and aging of the overall population, the prevalence of hearing loss is of concern.<sup>6</sup> Given that such hearing loss often negatively impacts communication, academic performance, work productivity, and social integration, the Federal Interagency Workgroup has prioritized reducing hearing loss in the Healthy People 2020 objectives that elucidate the nation's health care objectives,<sup>7-9</sup> also noting that hearing loss may be caused by "sensitivity to certain drugs or medications," among other causes.<sup>9</sup>

Since hearing loss and ASA utilization are both so common, patients frequently present with both on their dossier. In fact, among the 45- to 79-year-old population subset where daily prophylactic ASA is routinely considered, there is a 13% to 68% prevalence of hearing loss.<sup>10-13</sup> While this population subset includes those with multiple cardiovascular risk factors whose presence would trump that of hearing-related health, ASA may also currently be utilized in those with limited cardiovascular risk but progressive and impactful sensorineural hearing loss. In these circumstances, it would behoove us to understand whether it would better serve our patients to withhold daily ASA either temporarily or until additional cardiovascular concern is raised. It would also behoove us to understand whether

the potential otological impact of ASA is dose dependent, so that such considerations would not trigger the drug's inappropriate cessation.

Conventional wisdom holds that high doses of ASA may be associated with hearing loss but that low doses do not cause adverse otological effects. At the outset of this systematic review, however, we knew of no studies that reported formal audiometric results to confirm the safety of longstanding low-dose ASA. Given the potential for widespread public health impact, as well as the frequency with which related clinical scenarios arise, we undertook a systematic review to evaluate the specific impact of ASA on the prevalence and pattern of hearing loss. Systematic reviews are distinct from traditional narrative reviews in that they are performed according to well-defined, rigorous procedures and provide a reproducible, thorough method to evaluate the current best evidence regarding a specific clinical question. As such, they often constitute the highest level of evidence available<sup>14-16</sup> and form the foundation for significant documents such as clinical practice guidelines<sup>17,18</sup> and global collaborative workgroups such as the Cochrane Collaboration. This systematic review evaluates the impact of ASA on audiometric outcomes with respect to: (1) doses exceeding 325 mg daily, (2) doses of 325 mg daily or less, (3) studies applicable to the general populace, and (4) studies applicable to those with inflammatory conditions. It also assesses the impact of aspirin on (a) self-reported hearing loss, (b) noise-induced audiometric changes, and (c) the adverse otological effects of aminoglycoside therapy.

## Methods

### Search Strategy

A combination of computerized and manual searches was performed to identify all relevant data. A computerized PubMed search of MEDLINE ranging from 1965 through January 2014 was performed, updating the search through the latter date. Articles mapping to the exploded medical subject heading *hearing loss* or containing *hearing loss* in the title were combined into one group. Medical subject headings *anti-inflammatory agents, non-steroidal, ibuprofen, aspirin, or acetaminophen* were exploded and the articles were collected into a second group. The 2 groups were then cross-referenced and limited to human studies in the English language. Parallel searches using similar terms were performed in EMBASE and the Cochrane Library. The combined searches yielded 356 references. Titles and abstracts were then evaluated according to the inclusion/exclusion criteria described in the following. Reference lists for relevant narrative reviews and criteria-meeting publications were searched manually for additional studies. Two parties from audiology and otolaryngology performed searches independently, blinded to each other's results. Topic experts were also contacted to determine if additional studies or unpublished data could be identified. Titles and abstracts for all identified studies were reviewed, and 37 articles were ultimately included in the analysis (Figure 1).

### Inclusion/Exclusion Criteria

Articles identified by the computerized and manual search strategy described previously were evaluated to meet these inclusion criteria: (1) patients of any age, ethnicity, health status, or socioeconomic background (patient population); (2) exposure to any ASA regimen

of any dose, as confirmed via blood laboratory analysis, medical report, or self-report (intervention); (3) comparison to a control or non-ASA-exposed baseline data (comparison); (4) outcome measured in terms of sensorineural or mixed hearing loss via conventional audiometry, otoacoustic emissions (OAE), and/or psychophysical measurements; self-reported hearing assessments were included but tracked in a separate secondary group (outcomes); and (5) all study designs with all follow-up times in the search strategy timeframe were included (timeframe/studies). An additional discussion of the measures of hearing outcome is presented in Appendix 1 (available at [www.otojournal.org](http://www.otojournal.org)).

Articles were excluded if (1) no hearing results were reported, (2) hearing results resulted in non-sensorineural hearing loss (eg, acute otitis media and otitis media with effusion), (3) hearing results were unclear regarding the type of audiometric criteria used to determine hearing loss, (4) a population of solely nonhearing patients were evaluated (nonapplicable denominator), and (5) they were abstracts without subsequent full manuscript publication.

### Data Extraction

Data extraction focused on items relevant to the study results, potential sources of heterogeneity among those results, and study identification (author, year of publication, full reference citation). Extracted data included (1) number/percentage with maintenance, improvement, or deterioration of hearing thresholds; (2) number of subjects in each group; (3) specific drug regimen evaluated; (4) *P* value, confidence interval, standard error of the mean, proportions, or descriptive statistics reported; and (5) follow-up time. Data collection also included multiple potential sources of heterogeneity among studies: (a) dosing and duration of the drug regimen, (b) control regimen details if applicable, (c) audiological criteria used for stratification of data, (d) primary study endpoints, and (e) study design.<sup>19</sup> In accordance with data demonstrating that specific “study quality” ranking scales may be misleading or give heterogeneous results,<sup>19–22</sup> rather than utilizing a summary scale, we focused on evaluation of data quality by consistent factual description of individual elements of study design with specific attention to: whether randomization was performed, prospective/retrospective analysis, incorporation of blinding (participants and/or assessors), and whether hearing assessments were the primary outcome.

### Quantitative Data Analysis

An a priori plan was made to perform a quantitative meta-analysis of the following null hypotheses if the data were permissive: (1) ASA has no impact on the prevalence or pattern of sensorineural hearing loss and (2) any such impact is not dose dependent. However, due to large variation in study designs, audiometric criteria, affected frequency ranges, and reporting parameters, a pooled analysis was not appropriate.

If the primary study reported a statistical analysis, it was included in the extracted data. If the primary study did not describe a statistical comparison, when possible, post hoc calculations for the 95% confidence interval of the prevalence of hearing loss were calculated according to the standard binomial distribution (Stata 12.0, College Station, Texas).

## Results

### Study Characteristics

The 37 criterion-meeting studies included a total of 185,155 participants. Clinical and research audiometric evaluations included standard pure-tone thresholds and speech discrimination scores, OAE, and psychophysical measurements. Non-audiometric data consisted of self-reported hearing loss via survey results. There were 3 randomized controlled trials and 9 studies that employed blinding. The bulk of the data suggested ASA had a deleterious effect, but data from 2 randomized controlled trials demonstrated a protective effect as well.

Given the inherent variability in these studies' patient populations, ASA exposures, and outcome measurements, we describe the results in categories. First, we present results measured by standard audiometry (ie, pure-tone averages, speech scores). Among these studies, we show data categorized by (1) ASA dosage (>325 mg/d, 325 mg/d) and (2) relevance to the general population or those with inflammatory conditions (eg, rheumatoid arthritis). Second, we briefly summarize the result of other audiometric outcomes, specifically OAE and psychophysical testing. Third, we describe the mixed results of studies of self-reported hearing symptoms, which include the studies with the largest sample sizes and longest follow-up periods; data are again categorized by the absence/presence of a focus on subjects with inflammatory conditions. Fourth, we evaluate the impact of ASA in the setting of other audiometrically detrimental exposures: noise and aminoglycosides.

### Pure-tone Threshold Audiometry and Speech Discrimination Scores Associated with Aspirin in Subjects without Inflammatory Conditions

**Doses exceeding 325 mg daily**—Four prospective studies suggested that ASA had a deleterious audiometric effect when administered in doses of at least 1.95 g daily in patients without rheumatoid arthritis or connective tissue disease (Table 1).<sup>23–26</sup> Three of these analyses compared audiometry after ASA ingestion to subjects' baseline hearing, while 1 evaluated patients taking ASA for analgesia after tonsillectomy in comparison to controls. Two showed statistically significant worsening of audiometry (Table 2); the magnitude of loss ranged from 4 dB to 112 dB and was dose dependent in the single study that evaluated a range of doses on the same participants. Ingestion of less than 4 g per day was associated with pure-tone threshold worsening of 4.4 dB to 12.7 dB, while ingestion of 4 to 10 g per day was associated with changes of 15 dB to 112.5 dB. Speech discrimination scores were not evaluated. Two additional studies suggested a deleterious audiometric effect but did not report statistical analyses of their ASA-related findings (Table 3); in these instances, it was not that effects were present that were not statistically significant; a statistical analysis was simply not reported. In all 4 prospective analyses, the hearing loss was reversible. The maximum follow-up time in these studies was 3 weeks. There were also 7 case reports of patients unaffected by rheumatoid arthritis that described worsening audiometry with ASA; all instances except 1 improved after ASA was discontinued (Appendix 2, available at [www.otojournal.org](http://www.otojournal.org)).<sup>27–32</sup>

**Doses of 325 mg daily or less**—There were no studies that evaluated the impact of ASA doses of 325 mg or less per day. In fact, there were no studies that evaluated hearing outcomes with doses of less than 1.95 g per day in this more general patient population. Not only were there no data showing that these lower daily doses were not associated with either short-term or long-term audiometric effects, but there were also no data evaluating these dose ranges in subjects representative of the general population (ie, those not ingesting ASA for control of inflammatory conditions). Therefore, with regard to the prophylactic daily regimens administered at doses of 81 or 325 mg daily to the general population, there are currently no pure-tone audiometry or speech discrimination data on which to base decisions for hearing-related health.

### **Pure-tone Threshold Audiometry and Speech Discrimination Scores Associated with Aspirin in Subjects with Rheumatoid Arthritis and Connective Tissue Diseases**

**Doses exceeding 325 mg daily**—Seven studies evaluated the impact of ASA on pure-tone averages and speech recognition (Table 4).<sup>33–39</sup> One randomized, double-blind placebo-controlled study demonstrated that those receiving ASA had statistically significantly worse pure-tone thresholds, speech recognition, and word discrimination in background noise (Table 5). All subjects met diagnostic criteria for rheumatoid arthritis. The pharmacological reporting in this paper was somewhat vague in that it specified 325 mg doses during a 7-day interval but did not specify the frequency with which this dose was administered. An attempt was made to contact authors of this 1978 publication, but at the time of this writing, the dosing intervals and thus total daily ingestion remain unspecified (we received word that the 5 authors listed are either retired or deceased). The magnitude of audiometric worsening ranged from 6.8 dB to 26.8 dB, with more loss in the higher frequencies and at higher blood serum levels (Table 4); these findings were statistically significant. Drops in hearing were reversible and follow-up time was 7 days.

The remaining 6 studies suggest worsening of audiometric thresholds, but the primary reports did not contain statistical analyses (Tables 6, 7). The magnitude of change in pure-tone thresholds ranged from 0 dB to 45 dB and crossed all measured frequencies (Table 4). In most instances, frequency-specific information was not reported. One of these studies evaluated speech discrimination<sup>33</sup> and found that monaural testing was impacted more than binaural testing. When specified in these 6 studies, doses were typically high (3.6–9.0 g/d), but in 1 instance, data from those ingesting less than 1 g per day were merged with those taking more than 4 g per day.<sup>35</sup> The longest follow-up times among these studies was 3 weeks.

**Doses of 325 mg daily or less**—There were no studies that specifically evaluated the impact of long-term low dose ASA in patients with rheumatoid arthritis or connective tissue diseases. While the aforementioned randomized controlled trial may have included patients taking 325 mg of ASA daily,<sup>37</sup> any data specific to that total daily dose was merged with data from those who may have been taking more. Likewise, there was 1 cohort study whose study population included those ingesting less than 1 g daily but provided no audiometric results specific to the lower dose range. Therefore, among those with rheumatoid arthritis

and connective tissue diseases, there are likewise no dose-specific data to guide audiometric decisions with regard to patients taking either 81 mg or 325 mg daily.

### **Aspirin-Associated Otoacoustic Emissions and Psychophysical Measurements**

While formal pure-tone audiometry and speech scores are the most immediately interpretable metric for hearing loss, related results may also be quantified via evaluation of OAE or psychophysical measurements. Eight small studies evaluated the impact of ASA on OAE: 1 prospective placebo-controlled, double-blinded crossover study<sup>40</sup> and 7 prospective cohort studies.<sup>23,41–46</sup> These reports suggested a deleterious effect and are described in further detail in Appendix 3 (available at [www.otojournal.org](http://www.otojournal.org)). Similarly, 5 prospective studies assessed the impact of ASA on psychophysical measurements, all of which suggested an adverse effect on hearing (Appendix 4, available at [www.otojournal.org](http://www.otojournal.org)).<sup>24,36,47–49</sup> When specified, follow-up times in these 13 studies was less than 3 weeks.

### **Self-reported Evaluation of Hearing Results Associated with Aspirin**

The studies with the most impressive sample sizes and follow-up times focused on self-reported hearing loss; 7 studies had mixed results (Tables 8, 9).<sup>35,50–55</sup> The largest prospective observational cohort study was conducted through the Nurses' Health Study II and evaluated 62,261 adult women's self-reported hearing loss and ASA consumption.<sup>50</sup> Subjects responded to survey questions: "Do you have a hearing problem?" (no/mild/moderate/severe) and "If so, at what age did you first notice a change in hearing?" Subjects were grouped by self-reported frequency of analgesic use as assessed by questionnaire every 2 years from 1995 to 2009. Women who reported tinnitus >2 days per week were excluded from the analysis. Self-reported hearing results showed no association between ASA and hearing loss, regardless of the frequency of use (multivariate relative risk [RR] 1.07 [95% CI, 0.97–1.18] for 2 to 3 d/w; 0.98 [95% CI, 0.87–1.11] for 4 to 5 d/w; 1.00 [95% CI, 0.94–1.07] for 6 d/w). The results are limited to the frequency and duration of ASA and omit numeric dose information. A subanalysis of the present study using 2001 as the baseline evaluated "low-dose" versus "regular-dose" ASA and revealed no association between frequency of "low-dose" or "regular-dose" ASA and the risk of hearing loss. While "low-dose" and "high-dose" were not specifically defined within the report, review of the distributed questionnaires suggested that low-dose therapy was described as 100 mg or less per day. As these were self-reported ingestions and hearing perceptions, the participants were not blinded. These findings were not corroborated with formal audiometry.

The second recent prospective observational cohort study was conducted through the Health Professionals Follow-up Study and evaluated 26,917 adult male patients with regard to ASA usage regularly (2×/w) or non-regularly (2×/w).<sup>51</sup> Self-reported hearing loss was measured in response to the survey questions: "Have you been professionally diagnosed with hearing loss?" or "Do you feel you have a hearing loss?" The survey was given every 2 years beginning in 1986. The characterization of ASA usage is limited to the frequency and duration and does not describe specific dose information. The multivariate-adjusted hazard ratio revealed a statistically significant increase in risk of self-reported hearing loss with twice weekly consumption of ASA (1.12 [95% CI, 1.04–1.20]), in contrast to the results

from the Nurses' Health Study II. Since these were self-reported medications and symptoms, the participants were not blinded. The pure-tone thresholds and speech scores associated with the self-reported results were not investigated.

Also focusing on self-reported hearing symptoms were 3 prospective evaluations of consecutive inpatients from a program spanning 22 hospitals in the US and abroad. Self-reported hearing results were described in ASA exposed patients (<0.6–>4.8 g/d), but not the unexposed or pre-exposed, so no relative risks were reported.<sup>52–54</sup> All demonstrated at least some percentage (0.3%–28%) of subjective hearing loss among ASA consumers. Again, these patients were aware of their ASA ingestion status and audiometry was not simultaneously reported.

Two studies evaluated the impact of ASA on self-reported hearing in rheumatoid arthritis patients.<sup>19,32</sup> One was a prospective, double-blind, controlled study, which evaluated ASA (6 g/d) in comparison to fenoprofen (2.4 g/d) and found that the ASA group was significantly more likely to report tinnitus or hearing problems than the fenoprofen group.<sup>32</sup> The other study prospectively evaluated subjects with “regular” ASA usage for rheumatoid arthritis in comparison to healthy controls.<sup>35</sup> There was no significant difference between groups. This was the only study to describe concomitant self-reported and audiometric results in the setting of ASA usage. The self-reported prevalence of hearing loss was mildly higher than the audiometrically demonstrated sensorineural changes (31% vs 28%) in the ASA group. No audiometric data were obtained in the control group.

### **Impact of Aspirin on Hearing Changes after Noise Exposures**

Three small studies evaluated whether concurrent ASA ingestion potentiates the hearing effect seen by noise with mixed results (Table 10).<sup>47,56,57</sup> One study determined that noise resulted in worse temporary threshold shifts with ASA than without (18–27 dB vs 14 dB) and recommended that ASA should be avoided prior to loud exposures.<sup>57</sup> The second study also supported a worse effect with ASA, while the third study suggested that ASA had no synergistic effect with noise.<sup>56</sup>

### **Protective Effects of Aspirin When Co-Administered with Aminoglycoside Therapy**

Remarkably, 2 of the most rigorous studies of the impact of ASA on audiometric outcomes showed that it had a protective effect on hearing, although when co-administered with an aminoglycoside. Two randomized double-blind placebo-controlled trials showed ASA significantly mitigated the hearing effects of intravenous gentamicin (Table 11).<sup>58,59</sup> The larger of these (n = 195) evaluated the impact of ASA on pure-tone audiometry (6000, 8000 Hz) in adults receiving intravenous gentamicin therapy.<sup>59,60</sup> Randomization was effective; age, sex, weight, and pretreatment audiometry were balanced between groups. The treatment group received ASA 1 g every 8 hours (3 g/d) for 14 days, while the control group received placebo on the same schedule. The ASA group had significantly fewer patients with high frequency hearing thresholds worse than 15 dB after treatment (3% vs 13%, *P* = .013).

The smaller trial (n = 60) evaluated the impact of ASA on pure-tone audiometry in normal-hearing adults scheduled for intravenous gentamicin treatment.<sup>58</sup> Randomization resulted in



similar sex, age, weight, and pure-tone thresholds in the experimental and control groups at the outset. The treatment group received 500 mg ASA every 8 hours (1.5 g/d) for 7 days, while the control group received placebo on the same schedule. Pure-tone audiometry and speech discrimination scores were tested at day 0, day 8, and day 15. Hearing results were again better in the ASA group (3.3% vs 20%–36% with thresholds >15 dB;  $P = .001$  at 4000 Hz,  $P = .04$  at 8000 Hz).

This protective effect of 1.5 to 3.0 g daily in the setting of gentamicin therapy in these 2 randomized studies appears paradoxical in the setting of the data demonstrating statistically significant worsening in pure-tone audiometry after administering similar doses of ASA alone.

### Study Designs and Risk of Bias

This systematic review uncovered reports of a variety of study designs (Tables 12, 13). Randomized controlled trials were limited to 3 double-blinded studies in which hearing results were the primary outcome; 1 demonstrated a statistically significantly worse audiometric results in patients with rheumatoid arthritis who received at least 325 mg daily, while the other 2 showed a statistically significant protective effect when 1.5 to 3.0 g daily are administered to those undergoing intravenous gentamicin therapy. Nine studies employed blinding and hearing results were the primary outcome in the vast majority of studies.

### Discussion

The data uncovered by this systematic review were multifaceted. First, results confirmed conventional wisdom regarding high-dose ASA therapy; the preponderance of data suggested a deleterious effect when administered in doses at or exceeding 1.95 g daily in both those with and without rheumatoid arthritis and connective tissue disorders. Studies with statistically significant results described a magnitude of impact ranging from 4 dB to 112 dB, which was both dose-dependent and reversible, and follow-up periods were limited to less than a month.

Second, there were no studies that evaluated audiometry results in relation to ASA daily dosages of 81 or 325 mg. In addition, studies with follow-up times exceeding 20 weeks were limited to those with self-reported hearing outcomes without audiometric corroboration. There are no data reporting pure-tone thresholds or speech scores in patients undergoing long-term low-dose ASA therapy, and it is possible that those who seek medical care more frequently may be more likely to both take ASA and be aware of hearing deficits due to surveillance bias.<sup>61</sup> No data exist to confirm conventional wisdom that low dose ASA administration over long periods does not have an impact on audiometry. In addition, it is unknown whether any such potential effect would still be reversible after an extended course, as the bulk of studies demonstrating reversibility have follow-up times of less than 1 month.

Third, the data regarding the concomitant exposure of ASA and other elements detrimental to hearing showed somewhat paradoxical results. While the data regarding simultaneous

noise exposure were mixed, the data from randomized, placebo-controlled, double-blind trials with formal audiometry as the primary outcome measure demonstrated a protective effect of ASA on gentamicin ototoxicity at doses of 1.5 to 3.0 g daily.

### Clinical Implications of the Results

Clinically, these findings suggest that with regard to hearing, ASA therapy should be tailored to specific clinical scenarios. In 1 scenario, a hearing-impaired patient ingesting 1.95 g of ASA daily would be expected to have an audiometric benefit from stopping the medication as the effects are typically reversible, at least in short-term studies. In a second, more common scenario of a patient with hearing loss or at risk of hearing loss who is ingesting 81 or 325 mg daily for the foreseeable future, there are no data to guide decisions regarding ASA usage; at this point, there are no data to support a trial off the medication to assess for a potentially reversible effect, so the proven cardiovascular protective effects would take precedent. In the less common third scenario where a patient requires gentamicin treatment, there is level 1 evidence to support the co-administration of ASA for improved audiometric results.

Multiple studies demonstrate that the effect of ASA on hearing is reversible, particularly when administered over a short timeframe.<sup>24,26–31,33,35,37,44,47,54,57</sup> However, the duration of studied ASA therapy and follow-up times after ASA cessation in many instances are limited. Therefore, it remains unclear whether regimens of longer duration retain that reversible effect.

### Potential Protective Effects of ASA on Hearing

While data suggest that ASA doses of 1.5 to 3 g daily worsen hearing when administered in isolation, when the same regimens are given with gentamicin, ASA becomes protective. This apparently paradoxically protective effect of ASA may occur through an antioxidant mechanism, which protects the outer hair cells from aminoglycoside-released reactive oxygen species that would otherwise subsequently result in apoptotic cochleotoxicity.<sup>60</sup> Aminoglycosides displace calcium from its binding sites resulting in a restriction of calcium dependent physiological mechanisms in the inner ear, which impairs natural antioxidant generation.<sup>58</sup> Additional research into the related NF- $\kappa$ B pathway may provide future insight into the protective mechanism.<sup>62</sup> One wonders whether a study of ASA administration concomitant with intratympanic gentamicin for Meniere's disease might also someday demonstrate a hearing-protective effect.

The ASA/gentamicin randomized controlled trials also raise the question of whether there might be other instances where ASA utilization might be of benefit. Accordingly, the potential for ASA to protect from cisplatin-related ototoxicity is under investigation in a randomized, phase II, double-blind, placebo-controlled, 2-arm trial.<sup>59,63,64</sup>

In addition, in a related topic not without controversy, there are mixed results regarding the impact of cardiovascular disease on hearing loss.<sup>65–69</sup> Since ASA is recommended for cardiovascular prophylaxis,<sup>70,71</sup> if there is a true association between cardiovascular disease and hearing loss, then ASA might be indirectly protective of hearing in some patients through preventive effects.

## Potential Additional Effect Modifiers of the Impact of ASA on Hearing

The results of large prospective observational cohorts suggest that ASA may have a differential effect in males and females. These data are, however, currently based on self-reported hearing assessments without audiometric confirmation. Nonetheless, they were large-scale analyses with a decade of follow-up. Of note, patients with tinnitus more than twice weekly were removed from the female analysis, potentially removing patients with associated hearing loss in either the exposed or unexposed group. Future studies may help elucidate whether a true gender effect exists based on audiometric testing.

Similarly, some data suggest that eye color or an associated feature may alter the ASA-associated effect; dark-eyed subjects may show larger ASA-related threshold shifts than light-eyed listeners.<sup>47</sup> Understanding any such effect modifiers may ultimately provide insight to allow for more selective counseling of individual patients.

## Risk of Bias

The 3 randomized controlled trials and the preponderance of data as a whole suggest that ASA has an impact on hearing, either detrimental with higher doses in isolation or protective when co-administered with gentamicin. When considering these largely positive findings, the risk of publication bias must be considered<sup>72,73</sup>; it is possible that studies with negative findings were simply less likely to advance to publication.

## Conclusions

ASA ingestion of 1.95 g per day is associated with worse audiometric results (4–112 dB threshold shift), and data suggest that the effect is dose-dependent and reversible in the short term. There are no audiometric data that confirm that long-term doses of 81 mg or 325 mg daily have no hearing consequences and no data to suggest that these doses should be stopped in the setting of hearing loss. Paradoxically, ASA (in doses shown to be detrimental in isolation) has a protective effect when co-administered with intravenous gentamicin. With the large-scale population utilization of aspirin for cardiovascular prophylaxis, the potential risks to hearing health should be considered for future longitudinal study, particularly given that short-term effects may be reversible.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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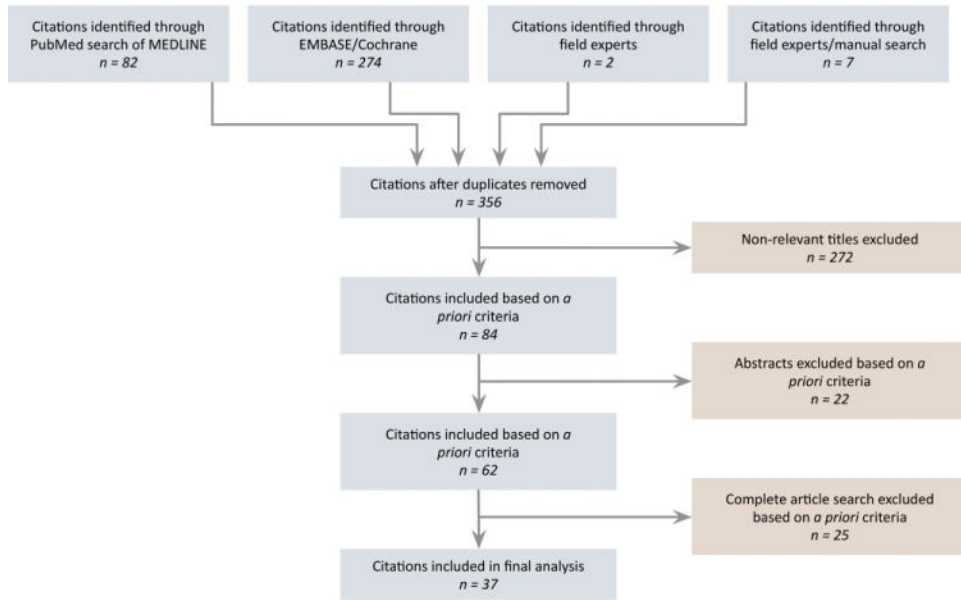
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**Figure 1.**  
Flow diagram showing the stages of identification of studies by citation source.



**Table 1**

Change in Mean Audiogram Results Post- versus Pre-ASA: Patients without Inflammatory Conditions.<sup>a</sup>

Author, Year	0.5 kHz	1 kHz	1.5 kHz	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	Mean of 0.25, 0.5, 1, 2, 4, and 8 kHz	Mean of 0.125–8 kHz	Speech Recognition Scores	Reversibility of Hearing Loss	Comments
Abdala, 2005 <sup>b,23</sup>	NR	NR	-12.7 (3.9 g/d)	NR	NR	NR	-14.3	NR	NR	NR	NR	Yes	Comparison to baseline
Day, 1989 <sup>b,25</sup>	NR	NR	NR	NR	NR	NR	NR	NR	-4.38 (1.95 g/d)	NR	NR	Yes	Change from baseline; mean hearing loss in dB at each frequency examined
Bonding, 1979 <sup>24</sup>	NR	-15–40 (4 g/d)	NR	NR	NR	NR	NR	NR	-11.56 (3.25 g/d) -46.56 (4.55 g/d) -112.5 (5.85 g/d)	NR	NR	Yes	Flat hearing loss configurations
Johnsen, 1982 <sup>26</sup>	NR	NR	NR	NR	NR	NR	NR	NR	-10–15 (10 g/d)	-10–15 (10 g/d)	NR	Yes	

Abbreviations: ASA, aspirin (acetylsalicylic acid); NR, not reported.

<sup>a</sup>Negative numbers reflect worse hearing after ASA. For example, if the mean pre-ASA threshold was 10 dB and the mean post-ASA threshold was 40 dB, then the change in mean is -30 dB. Positive numbers conversely reflect better hearing after ASA. Numbers reported are audiometry in units of decibels (ASA dose).

<sup>b</sup> Study demonstrated statistically significant effects.

**Table 2**

Studies Demonstrating a Statistically Significant Deleterious Effect of ASA on Pure-tone Thresholds or Speech Discrimination in Patients without Inflammatory Conditions.

Author, Year	Study Design (sample size)	Patient Description	ASA Regimen Evaluated	Hearing Evaluation	Follow-up Time	ASA Exposure Results	No ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
Abdala, 2005 <sup>23</sup>	Prospective cohort (n = 41, 10 of which were ASA exposed)	Adult ASA recipients: age 22–37 years (n = 10) Children with mild SNHL (n = 8) Healthy term-born neonates (n = 23)	ASA 975 mg (3 tablets of 325 mg)/Q6h for 4 d	Air and bone conduction audiogram Immittance testing DP-gram DPOAE	Baseline, then 72 h and 96 h afterward	Mean audiometric threshold increase at 96 h: 12.7 dB at 1500 Hz, 14.3 dB at 6000 Hz. Significant correlation between serum level and audiometry ( $r = 0.75, P = .19$ )	Subjects were compared to their own baseline	72.96 h	Audiometric results were not directly correlated with DPOAE results
Day, 1989 <sup>25</sup>	Prospective cohort, double-blinded (n = 8)	Age 22–46 years with normal hearing at the outset Male healthy volunteers	ASA in 4 serial scheduled doses: (1) 1.95 g/d (2) 3.25 g/d (3) 4.55 g/d (4) 5.85 g/d for 7 d each	Pure-tone thresholds measured at 250–8000 Hz	On the seventh day of each treatment period	Mean HL per frequency (dB HL) 1.95 g/d = 4.38 3.25 g/d = 11.56 4.55 g/d = 40.56 5.85 g/d = 112.5 Mean Tinnitus intensity (dB HL) 1.95 g/d = 25.50 3.25 g/d = 36.38 4.55 g/d = 51.00 5.85 g/d = 62.13	Subjects were compared to their own baseline. HL expressed as mean decrease from pretreatment thresholds in both ears	Effect present at 1 week	Hearing and tinnitus had a dose-dependent response to ASA level ( $P < .05$ ).

Abbreviations: ASA, aspirin (acetylsalicylic acid); DPOAE, distortion product otoacoustic emissions; HL, hearing loss; SNHL, sensorineural hearing loss.

**Table 3**

Studies Suggesting a Potential Deleterious Effect of ASA on Pure-tone Thresholds and/or Speech Discrimination in Patients without Inflammatory Conditions.

Author, Year	Study Design (sample size)	Patient Description	ASA Regimen Evaluated	Hearing Evaluation	Follow-up Time	ASA Exposure Results	No ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
Bonding, 1979 <sup>24</sup>	Prospective controlled study (n = 21)	ASA: Age 16–29 years, 4 males, 12 females undergoing tonsillectomy who utilized ASA for postoperative pain control Control: 5 non-ASA subjects All had normal hearing at the outset	ASA 4 g every 24 h for 2–3 d	“Tested audiometrically and if a pure-tone SNHL was present, the patient’s CB at 1 kHz was determined,” estimations using loudness summation	Control audiometry and CB estimations were performed 2–3 weeks after HL developed	15–40 dB HL at 1 kHz 56% (9/16) had a wider CB with temporary ASA induced HL	Sensitivity curves remained unchanged in controls	Effect present after 2–3 d of treatment	Reversible
Johnsen, 1982 <sup>26</sup>	Prospective cohort (n = 2)	1 female, age 29 years with PT <15 dB HL audiometry 1 male, age 42 years with PT <20 dB HL AS and no response in AD	ASA 10 g/d × 1 d	HL defined as > 15–20 dB HL at 125–8000 Hz Pure-tone thresholds	Immediately before and after ingestion of ASA and again 2 days later	PT threshold was elevated to 25–30 dB HL and the response pattern of TEOAEs were altered	Subjects were compared to their own baseline	NR	Hearing thresholds returned to normal 48 h post exposure

Abbreviations: AD, right ear; AS, left ear; ASA, aspirin (acetylsalicylic acid); CB, critical band; HL, hearing loss; NR, not reported; PT, pure tone; SNHL, sensorineural hearing loss; TEOAE, transient evoked otoacoustic emissions.

**Table 4** Change in Mean Audiogram Results Post- versus Pre-ASA: Patients with Rheumatoid Arthritis and Connective Tissue Diseases.<sup>a</sup>

Author, Year	0.25 kHz	0.5 kHz	1 kHz	2 kHz	3 kHz	4 kHz	6 kHz	8 kHz	Speech Recognition Scores in Quiet	Reversibility of Hearing Loss	Comment
Jardini, 1978 <sup>b,37</sup>	-7.84 (BSL 5.79) -6.84 (BSL 11.44)	-9.5 (BSL 5.79) -7.34 (BSL 11.44)	-11.47 (BSL 5.79) -9.13 (BSL 11.44)	-19.88 (BSL 5.79) -15.31 (BSL 11.44)	NR	-21 (BSL 5.79) -19.16 (BSL 11.44)	NR	-24 (BSL 5.79) -26.84 (BSL 11.44)	-1.89% (BSL 5.79) -2.79% (BSL 11.44)	Yes	Comparison of placebo to ASA thresholds; dose 325 mg × 7 d (dosing frequency NR).
Davis, 1979 <sup>34</sup>	11% (95% CI, 1.4%–34.7%) 28% (95% CI, 9.7%–53.5%)	had new hearing loss (defined by “a threshold shift”) after ASA (3.6 g/d), 28% (95% CI, 9.7%–53.5%) of those with hearing loss had progression (defined by “a threshold shift”) after ASA (3.6 g/d).								NR	Data were not reported in a measured frequency-specific fashion.
Halla, 1988 <sup>35</sup>	17.9% (95% CI, 11.8%–25.4%)	had audiometry worse than 25 dB after ASA administration (< 1 g/d to > 4 g/d; dose-specific hearing results NR).								NR	
Myers, 1965 <sup>38</sup>	In the group with normal hearing at the outset, “hearing loss ranged from 20 to 40 dB” after ASA (6–8 g/d). This HL was characterized in most cases as a bilateral, symmetrical threshold elevation at all frequencies. As the plasma salicylate level approached 30 mg/100 ml, a deficit between 30–40 dB was seen.										
Heyworth, 1972 <sup>36</sup>	75% (95% CI, 42.8%–94.5%)	had audiometry worse than 20 dB after ASA administration (specific dose per day NR).								Yes (4 of 9)	
Bernstein, 1967 <sup>33</sup>	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-25 to 45 (6–8 g/d)	-20% (5 out of 12 patients) (6–8 g/d)	Yes	Bekesy tracking revealed flat loss of 25dB to 45 dB at 0.125 kHz to 8 kHz.
Young, 1982 <sup>39</sup>	0 (6–9 g/d)	-1 (6–9 g/d)	-2 (6–9 g/d)	-1 (6–9 g/d)	NR	0 (6–9 g/d)	NR	-9 (6–9 g/d)	-4% (6–9 g/d)	NR	Average thresholds of 5 subjects

Abbreviations: ASA, aspirin (acetylsalicylic acid); BSL, blood serum level (mg/100 ml); NR, not reported.

<sup>a</sup>Negative numbers reflect worse hearing after ASA. For example, if the mean pre-ASA threshold was 10 dB and the mean post-ASA threshold was 40 dB, then the change in mean is –30 dB. Positive numbers conversely reflect better hearing after ASA. Numbers reported are audiometry in units of decibels (ASA dose).

<sup>b</sup>Study demonstrated statistically significant effects. Study is a randomized controlled trial.

**Table 5**

Study Demonstrating a Statistically Significant Deleterious Effect of ASA on Pure-tone Thresholds or Speech Discrimination in Patients with Rheumatoid Arthritis and Connective Tissue Disorders.

Author, Year	Study Design (sample size)	Patient Description	ASA Regimen Evaluated	Hearing Evaluation	Follow-up Time	ASA Exposure Results	No ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
Jardini, 1978 <sup>37</sup>	Randomized placebo-controlled study (n = 30)	All diagnosed with RA ASA: 13 women, 2 men Age 19–69 years (mean S3) Placebo: 14 women, 1 man Age 29–76 (mean 51)	ASA 325 mg (5 grain (1 grain = 65 mg) capsules) × 7 d (dosing frequency not specified) Lactose placebo × 7 d	PT air/bone conduction thresholds at 250–8000 Hz SRT;SDS in quiet (recorded CID W-22) and in noise (–4 dB competing SNR)	Days 0, 3, and 7	ASA group had significantly increased PT threshold shifts at 250–8000 Hz except at 2000 Hz as compared to control ( $P < .05$ ). ASA group had significantly poorer SRTs ( $P < .05$ ). ASA group had significantly worse discrimination in background noise ( $P < .05$ ).	No ASA Exposure Results	Effect present at day 3	Moderate BSL (35 mg/100 mL) may adversely affect auditory sensitivity. Thresholds recovered over the course of 1 week.

Abbreviations: ASA, aspirin (acetylsalicylic acid); BSL blood serum level; CID W-22, word recognition list W-22 created by Central Institute for the Deaf; PT, pure tone; RA: rheumatoid arthritis; SDS, speech discrimination scores; SNR, signal to noise ratio; SRT, speech reception threshold.

Table 6

Studies Suggesting a Potential Deleterious Effect of ASA on Pure-tone Thresholds and/or Speech Discrimination in Patients with Rheumatoid Arthritis and Connective Tissue Disorders.

Author, Year	Study Design (sample size)	Patient Description	ASA Regimen Evaluated	Hearing Evaluation	Follow-up Time	ASA Exposure Results	No ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
Hallia, 1988 <sup>35</sup>	Prospective controlled study (n = 316)	Exposure: ASA/salicylate for RA (n = 134; 20–88 y, mean 58.3) Controls: healthy volunteers (n = 182; 20–61 y, mean 34.3)	*Regular* ASA use for > 1 w prior to study ( 1 g–4 g/d) Controls received no ASA.	HL defined as >25 dB HL pure-tone thresholds	NR	17.9% (24/134) had abnormal audiometry (post hoc 95% CI, 11.8%–25.4%) 71% (17/24) with abnormal audio had salicylate level > 1.42 mmol/l	No audiometric data were collected on the control group.	NR	Primary goal to determine if hearing symptoms could be used to titrate NSAID doses in RA patients Consecutive NSAID patients
Davis, 1979 <sup>34</sup>	Cohort within a randomized controlled double-blind trial (n = 40)	Age 22–68 years with RA	ASA 900 mg Q6h for 1 y or Pirprofen 200 mg Q6h for 1 y after a single blind placebo washout	HL defined as a "threshold shift"	Prior to active drug, 20 w after, and at the study conclusion	10% (2/18) of ASA subjects had new HL, 28% (5/18) of ASA group had progression of HL. Post hoc 95% CI, 1.4%–34.7% (new), 9.7%–53.5% (progression).	Subjects were followed from their baseline	NR	67% (12/18) of ASA subjects had either a CHL or SNHL upon entering the study. Hearing loss was a secondary outcome. 5 subjects withdrew due to GI effects, urticarial rash, SNHL, and serum SGOT elevations.
Myers, 1965 <sup>38</sup>	Prospective cohort (n = 25)	Ages 13–78 years with RA or other connective-tissue diseases	ASA 6–8 g/d and magnesium aluminum hydroxide	Pure-tone thresholds measured at 250–8000 Hz and word discrimination tests	Audiogram was usually repeated 1 week after acute intoxication	84% (21/25) had reversible bilateral symmetric HL; post hoc 95% CI, 63.4%–95.5%.	Subjects were compared to their own baseline	Effect present at 1 week	The threshold was associated with plasma salicylate level. Characteristic loss was 30–40 dB threshold worsening.
Heyworth, 1972 <sup>36</sup>	Prospective cohort (n = 33)	Age 26–83 years with RA 36% (12/33) had abnormal hearing thresholds in at least 1 frequency as baseline	ASA (dosage NR)	HL defined as >20 dB below age-group threshold of Hinchcliffe's presbycusis model.	Baseline then several days following cessation of ASA	75% (9/12) had SNHL (95% CI, 42.8%–94.5%) 25% (3/12) had conductive HL	Subjects were compared to their own baseline	NR	11% (1/9) had Meniere's. 11% (1/9) had acoustic trauma. 75% (9/12) noted hearing worsened after RA onset. Air/bone conduction; impedance, acoustic reflex, Fowler's loudness balance test
Bernstein, 1967 <sup>33</sup>	Prospective cohort (n = 12)	Age 23–68 years with rheumatoid arthritis	ASA 6–8 g daily until patient subjectively reported hearing loss	HL defined as >25 dB on Bekesy tracking	4 days	100% (12/12) had HL that ranged from 25–45 dB. 42% (5/12) had SDS decreased 20%.	Subjects were compared to their	NR	The magnitude of HL appeared to be related to the plasma salicylate level. HL was reversible.

Author, Year	Study Design (sample size)	Patient Description	ASA Regimen Evaluated	Hearing Evaluation	Follow-up Time	ASA Exposure Results	No ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
Young, 1982 <sup>39</sup>	Prospective cohort (n = 5)	Age 22–38 years with normal hearing; 2 females had rheumatoid arthritis; 1 male had tendonitis.	ASA 4 × 2.24 mmol (1.6 g) Q5h × 1 d (n = 2) ASA 3 × 2.24 mmol (1.2 g) Q5h × 1 d (n=1) ASA 3 × 2.24 (1.2 g) mmol Q4h × 1 d (n = 2)	HL defined as a shift in audiometric thresholds	24 h and again within 24 h- 1 week period after first session	SDS decrease with -8dB SNR (16.4% difference from mean pre-ASA condition)	Subjects were compared to their own baseline	NR	Results suggest that aspirin is capable of creating a loss of speech discrimination only when the signal is presented under very adverse listening conditions.

Abbreviations: ASA, aspirin (acetylsalicylic acid); CHL, conductive hearing loss; GI, gastrointestinal; HL, hearing loss; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis; SDS, speech discrimination scores; SGOT, serum glutamic oxaloacetic transaminase; SNHL, sensorineural hearing loss; SNR, signal to noise ratio; SRT, speech reception threshold.

Table 7

Studies Describing the Impact of ASA on Self-reported Hearing Loss in Populations without Inflammatory Conditions.

Author, Year	Study Design (sample size)	Patient Description	ASA Evaluation	Hearing Evaluation	Follow-up Time	ASA Exposure Results	Outcome	Additional Comments
Curhan, 2012 <sup>50</sup>	Prospective observational cohort study (n = 62,261) Nurses Health Study II	Age 31–48 years All women	ASA Frequency of use categorized as < 1, 1.2–3.4, 4–5, or 6 d/w	Self-reported response to survey	Survey every 2 years from 1995 to 2009	Multivariate adjusted analysis RR 1.07 (95% CI, 0.97–1.18) for 2–3 d/w 0.98 (95% CI, 0.87–1.11) for 4–5 d/w 1.00 (95% CI, 0.94–1.07) for >6 d/w	NR	Excluded if tinnitus d/w or malignancy (non-melanoma skin cancer)
Curhan, 2010 <sup>51</sup>	Prospective observational cohort study (n = 26,917) Health Professionals Study	Age 40–74 years All men	ASA Regular use defined as 2 or more times per week.	Self-reported HL in response to survey question.	Survey every 2 years beginning in 1986	Age and multivariable-adjusted HR 1.12 (95% CI, 1.04–1.20) for 2+ times/w	NR	Excluded if malignancy (non-melanoma skin cancer)
Miller, 1978 <sup>52</sup>	Prospective cohort study of consecutive inpatients (n = 35,931) BCOSP	Male and female hospitalized medical patients in 22 hospitals in the US and abroad	Long-acting ASA tablets: 0.09% (32/35,931) Plain ASA tablets: 7.3% (2613/35,931)	“Clinically diagnosed deafness”	Data accumulated 1966–1975, other timeframes NR	Patients with “deafness”: Long-acting ASA: 28% (9/32) Plain ASA: 0.3% (9/2613) Patients without “deafness”: Long acting ASA: 72% (23/32) Plain ASA: 99.7% (2604/2613) Mean daily dose of ASA in patient with deafness was higher than in those without deafness ( $P < .005$ )	NR	Patients who received buffered and enteric-coated ASA tablets were excluded.
Miller, 1977 <sup>53</sup>	Prospective cohort study of consecutive inpatients (n = 26,294) BCOSP	Hospitalized medical patients in 22 sites (US and abroad)	Plain ASA tablets (<0.6–4.8 g/d): 9.1% (2391/26294)	“Clinically diagnosed deafness”	Data from 1966 to 1977, other timeframes NR	0.3% (8/2391) reported deafness 0.8% (20/2391) reported tinnitus	NR	Patients who received buffered and enteric-coated ASA tablets were excluded.
Porter, 1977 <sup>54</sup>	Prospective cohort study of consecutive	Patients in medical wards	ASA	Subjective report of “deafness”	NR	Reported “deafness” in 1.1% (33/2974) exposed to ASA	NR	Duration of “deafness”: 1 permanent, 26 reversible, 5 unknown



Author, Year	Study Design (sample size)	Patient Description	ASA Evaluation	Hearing Evaluation	Follow-up Time	ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
	inpatients (n = 32,812)					Dose-dependent response suspected:		
	inpatients (n = 32,812)					<600 mg: 0% (0/312)		
	BCDSP					600–899 mg: 0.13% (3/2273)		
						900–1199mg: 4% (12/269)		
						1200+ mg: 15% (18/120)		

Abbreviations: ASA, aspirin (acetylsalicylic acid); BCDSP, Boston Collaborative Drug Surveillance Program; HL, hearing loss; HR, hazard ratios using Cox proportional hazards regression models; NR, not reported; RR, relative risk.

**Table 8**  
 Studies Describing the Impact of ASA on Self-reported Hearing Loss in Patients with Rheumatoid Arthritis.

Author, Year	Study Design (sample size)	Patient Description	ASA Evaluation	Hearing Evaluation	Follow-up Time	ASA Exposure Results	Time from Exposure to Outcome	Additional Comments
Huskisson, 1974 <sup>74</sup>	Prospective double-blind controlled study (n = 60)	Outpatients with classical or definite RA	ASA 6 g/d: (n = 31) Fenoprofen 2.4 g/d: (n = 29)	Weekly for 4 weeks, monthly up to end of the twenty-fourth week of treatment	Patients assessed for side effects (mild, moderate, severe)	Week 1 : ASA: 66% (19/29) reported tinnitus/deafness Week 24: ASA:41% reported tinnitus/deafness Fenoprofen: 3% (1/29) reported tinnitus/deafness Difference between Fenoprofen and ASA: $\chi^2 = 7.50, P < .01$	1 week	3 patients didn't complete study.
Halla, 1988 <sup>35</sup>	Prospective controlled study (n = 316)	Exposure: ASA/salicylate for RA (n = 134, 20–88 y, mean 58.3) Controls: healthy volunteers (n = 182, 20–61 years, mean 34.3)	“Regular” ASA use for > 1 w prior to study ( 1– 4 g/d) Controls received no ASA.	HL defined as >25 dB HL pure-tone thresholds	NR	ASA: 31% (42/134) had subjective hearing loss Control: 28% (51/182) had subjective hearing loss P = NS, post hoc	NR	Primary goal to determine if hearing symptoms could be used to titrate NSAID doses in RA patients Consecutive NSAID patients

Abbreviations: ASA, aspirin (acetylsalicylic acid); HL, hearing loss; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; RA, rheumatoid arthritis.

**Table 9**

Studies Evaluating Whether Aspirin Potentiates the Effect of Noise on Hearing.

Author, Year	Study Design (sample size)	Patient Description	NSAID Evaluated	Hearing Evaluation	Follow-up Time	NSAID Exposure Results	No NSAID Exposure Results	Time from Exposure to Outcome	Additional Comments
Lindgren, 1986 <sup>56</sup>	Prospective cohort (n = 8)	Age mean 19.3 years, male normal hearing (250 Hz–8 kHz) at the outset, exposed to noise (one-third octave band filtered noise with 2 kHz CF at 105 dB SPL for 10 min)	ASA 1 g 1 h prior to noise exposure in 5 sessions Control: no ASA	2–8 kHz Bekeasy sweep frequency audiometry	Baseline, 1 minute after noise exposure	TTS reduced in the fourth session only. Over all sessions, ASA had no effect on the TTS.	Subjects compared to their own baseline.	NR	Originally 10 subjects; 1 subject withdrew, 1 subject's data lost to computer failure
McFadden, 1984 <sup>75</sup>	Prospective crossover study (n = 11)	11 males, 19–23 years old with normal hearing	ASA 3.9 g/d × 4d All sessions with intensity necessary for 10 min 2500 Hz tone to produce ~12 dB of TTS	>5 dB shift in audiometric thresholds, as measured by a 2-interval forced choice method	4 days	ASA with exposure to intense noise produced HL ~10–15 dB greater than that produced by exposure to the intense sound alone.	Subjects were compared to their own baseline and performance in other drug regimens	2.8 min	Moderate doses of ASA may increase risk of noise-induced hearing loss.
McFadden, 1983 <sup>57</sup>	Prospective cohort (n = 4)	4 volunteers (age, gender unspecified) exposed to 10 min 2500 Hz tone at intensity necessary to produce 14 dB TTS at baseline	ASA 1.95 or 3.9 g/d × 0.5–2.75 d	Adaptive psychophysical method with interval forced choice	Baseline, during, and 2 d after exposure	Exposures that ordinarily produce 14 dB TTS produce 18–27 dB instead; effect is dose and duration dependent	Subjects were compared to their own baseline	0–48 h	All hearing losses were reversed at 24–48 h after the exposure

Abbreviations: ASA, aspirin (acetylsalicylic acid); CF, center frequency; HL, hearing loss; NR, not reported; NSAID, nonsteroidal anti-inflammatory drugs; SPL, sound pressure level; TTS, temporary threshold shift.

**Table 10**  
 Studies with Audiometric Data Showing ASA Confers Protection from Gentamicin-Associated Hearing Loss.

Author, Year	Study Design (sample size)	Patient Description	NSAID Evaluated	Hearing Evaluation	Follow-up Time	ASA Results	Placebo Results	Time from Exposure to Outcome	Additional Comments
Sha, 2006 <sup>59</sup> ; Chen, 2007 <sup>60</sup>	Randomized double-blind placebo-controlled trial (n = 195)	ASA: 76 males and 13 females Placebo: 95 males and 11 females scheduled for gentamicin 80–160 mg intravenous twice per day	ASA 1 g Q8h x14 d	Pure-tone audiograms; HL defined as 15 dB or more at 6 and 8k Hz	Day 1 of treatment, day of discharge, and 5–7 w after beginning treatment	3% (3/89) had HL 15 dB at 6000 Hz and at 8000 Hz <i>P</i> = .013	13% (14/106) had HL 15 dB at 6000 Hz and at 8000 Hz	Not further specified	Severity of illness requiring gentamicin may have been a theoretical confounder.
Behnoud, 2009 <sup>58</sup>	Randomized double-blind controlled trial (n = 60)	Age > 18 years, scheduled gentamicin 80 mg 3 times intravenous per day Exclusion criteria: preexisting HL, systemic disease, and pregnant	Experimental group: ASA 1.5 g/d x 7 d Control group: given placebo	PTA and SDS; HL defined as threshold shift of > 15 dB at 6 and 8 kHz	Baseline, 8, and 15 days after beginning treatment	3% (1/30) had HL 15 dB at 4000 Hz ( <i>P</i> = .001) 3% (1/30) had HL 15 dB at 8000 Hz ( <i>P</i> = .0014)	36% (11/30) had HL 15 dB at 4000 Hz ( <i>P</i> = .001) 20% (6/30) had HL 15 dB at 8000 Hz ( <i>P</i> = .0014)	8, 15 days	ASA was also associated with better PTAs in other frequencies. Patients had similar gender, age, weight, at baseline.

Abbreviations: ASA, aspirin (acetylsalicylic acid); HL, hearing loss; NSAID, nonsteroidal anti-inflammatory drugs; PTA, pure-tone average; SDS, speech discrimination scores.

**Table 11**

Study Designs: Audiometric and Self-reported Outcomes.

Author, Year	Randomized	Prospective	Blinding of Participants	Blinding of Assessors/Outcome Measurement	Hearing Is the Primary Outcome
Pure-tone threshold audiometry and speech discrimination scores associated with aspirin in subjects without inflammatory conditions					
Abdala, 2005 <sup>23</sup>	—	x	—	—	x
Day, 1989 <sup>25</sup>	—	x	x	x	x
Bonding, 1979 <sup>24</sup>	—	x	—	—	x
Johnsen, 1982 <sup>26</sup>	—	x	—	—	x
Pure-tone threshold audiometry and speech discrimination scores associated with aspirin in subjects with rheumatoid arthritis and connective tissue diseases					
Jardini, 1978 <sup>37</sup>	x	x	x	x	x
Halla, 1988 <sup>35</sup>	—	x	—	—	x
Davis, 1979 <sup>34</sup>	—	x	x	x	—
Myers, 1965 <sup>38</sup>	—	x	—	—	x
Heyworth, 1972 <sup>36</sup>	—	x	—	—	x
Bernstein, 1967 <sup>33</sup>	—	x	—	—	x
Young, 1982 <sup>39</sup>	—	x	—	—	x
Self-reported evaluation of hearing results associated with aspirin in populations without inflammatory conditions					
Curhan, 2012 <sup>50</sup>	—	x	—	—	x
Curhan, 2010 <sup>51</sup>	—	x	—	—	x
Miller, 1978 <sup>52</sup>	—	x	—	—	x
Miller, 1977 <sup>53</sup>	—	x	—	—	x
Porter, 1977 <sup>54</sup>	—	x	—	—	—
Self-reported evaluation of hearing results associated with aspirin in patients with rheumatoid arthritis					
Huskisson, 1974 <sup>74</sup>	—	x	x	x	—
Halla, 1988 <sup>35</sup>	—	x	—	—	x
Impact of aspirin on hearing changes after noise exposures					
Lindgren, 1986 <sup>56</sup>	—	x	—	—	x
McFadden, 1984 <sup>75</sup>	—	x	—	—	x
McFadden, 1983 <sup>57</sup>	—	x	—	—	x
Protective effects of aspirin when co-administered with aminoglycoside therapy					

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Author, Year	Randomized	Prospective	Blinding of Participants	Blinding of Assessors/Outcome Measurement	Hearing Is the Primary Outcome
Sha, 2006 <sup>59</sup> ; Chen, 2007 <sup>60</sup>	x	x	x	x	x
Behnoud, 2009 <sup>38</sup>	x	x	x	x	x

**Table 12**

Study Designs: Otoacoustic Emissions and Psychophysical Measurements.

Author, Year	Randomized	Prospective	Blinding of Participants	Blinding of Assessors/Outcome Measurement	Hearing Is the Primary Outcome
Otoacoustic emissions associated with aspirin					
Brown, 1993 <sup>76</sup>	—	x	x	x	x
Abdala, 2005 <sup>23</sup>	—	x	—	—	x
Parazzini, 2005 <sup>41</sup>	—	x	—	—	—
McFadden, 1984 <sup>46</sup>	—	x	—	—	—
Long, 1988 <sup>42</sup>	—	x	—	—	—
Rao, 2011 <sup>43</sup>	—	x	—	—	—
Wier, 1989 <sup>44</sup>	—	x	—	—	—
Hall, 2001 <sup>45</sup>	—	x	—	—	—
Psychophysical measurements associated with aspirin					
Beveridge, 1996 <sup>49</sup>	—	x	x	x	x
Carlyon, 1993 <sup>48</sup>	—	x	x	x	x
McFadden, 1984 <sup>75</sup>	—	x	—	—	x
Bonding, 1979 <sup>24</sup>	—	x	—	—	x
McFadden, 1984 <sup>46</sup>	—	x	—	—	x