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# Association of Tinnitus and Other Cochlear Disorders With a History of Migraines

Juen-Haur Hwang, MD, PhD; Shiang-Jiun Tsai; Tien-Chen Liu, PhD; Yi-Chun Chen, MD; Jen-Tsung Lai, MD

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Supplemental content

**IMPORTANCE** A headache is a symptom of a migraine, but not all patients with migraine have headaches. It is still unclear whether a migraine might increase the risk of cochlear disorders, even though a migraine does not occur concurrently with cochlear disorders.

**OBJECTIVE** To investigate the risk of cochlear disorders for patients with a history of migraines.

**DESIGN, SETTING, AND PARTICIPANTS** This study used claims data from the Taiwan Longitudinal Health Insurance Database 2005 to identify 1056 patients with migraines diagnosed between January 1, 1996, and December 31, 2012. A total of 4224 controls were also identified from the same database based on propensity score matching. Statistical analysis was performed from January 23, 1996, to December 28, 2012.

**MAIN OUTCOMES AND MEASURES** The incidence rate of cochlear disorders (tinnitus, sensorineural hearing impairment, and/or sudden deafness) was compared between the cohorts by use of the Kaplan-Meier method. The Cox proportional hazards regression model was also used to examine the association of cochlear disorders with migraines.

**RESULTS** Of the 1056 patients with migraines, 672 were women and 384 were men, and the mean (SD) age was 36.7 (15.3) years. Compared with the nonmigraine cohort, the crude hazard ratio for cochlear disorders in the migraine cohort was 2.83 (95% CI, 2.01-3.99), and the adjusted hazard ratio was 2.71 (95% CI, 1.86-3.93). The incidence rates of cochlear disorders were 81.4 (95% CI, 81.1-81.8) per 1 million person-years for the migraine cohort and 29.4 (95% CI, 29.2-29.7) per 1 million person-years for the nonmigraine cohort. The cumulative incidence of cochlear disorders in the migraine cohort (12.2%) was significantly higher than that in the matched nonmigraine cohort (5.5%). Subgroup analysis showed that, compared with the nonmigraine cohort, the adjusted hazard ratios in the migraine cohort were 3.30 (95% CI, 2.17-5.00) for tinnitus, 1.03 (95% CI, 0.17-6.41) for sensorineural hearing impairment, and 1.22 (95% CI, 0.53-2.83) for sudden deafness.

**CONCLUSIONS AND RELEVANCE** In this population-based study, the risk of cochlear disorders, especially for tinnitus, was found to be significantly higher among patients with a history of migraines. This finding may support the presence and/or concept of "cochlear migraine."

**Author Affiliations:** Author affiliations are listed at the end of this article.

**Corresponding Author:** Yi-Chun Chen, MD, Department of Nephrology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 2, Minsheng Road, Dalin Township, Chiayi 622, Taiwan (alineycc@gmail.com); Jen-Tsung Lai, MD, Department of Otolaryngology, Kuang-Tien General Hospital, No. 117, Shatian Road, Shalu District, Taichung 433, Taiwan (earlar0401@gmail.com).

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*Migraine* is not a synonym for *headache*. A headache can be a symptom of a migraine, but not all patients with a migraine have headaches. Active migraine symptoms are associated with abnormal sensory perception, including vision, hearing, smell, and somatosensation.[1] The basilar-type migraine aura comprises diplopia, vertigo, tinnitus, bilateral visual symptoms, hyperacusis, ataxia, dysarthria, bilateral paresthesias, and decreased level of consciousness.[2] Intense emotional stimuli and sleep disorders were the most common triggering factors for active migraine symptoms. Also, low socioeconomic status was associated with an increased frequency of migraines.[3]

Dizziness, vertigo, phonophobia, tinnitus, and hearing loss were the most commonly reported symptoms in patients with migraines in one study.[4] In another study, the association between tinnitus and active migraine symptoms was stronger for students with migraines with auras than for those with migraines without auras.[5] The association between active migraine symptoms and sudden deafness was also presented in one case report[6] and a population-based study.[7] In addition, Viirre and Baloh[8] presented 13 cases of individuals with sudden deafness who met the diagnostic criteria for a migraine.

However, it is still unclear whether migraines might increase the risk of other cochlear disorders, including tinnitus and/or sensorineural hearing impairment, even though migraines do not occur concurrently with cochlear disorders. Therefore, the aim of this study was to examine the risk of cochlear disorders for patients with a history of migraines.

### Key Points

**Question** Does a history of migraines increase the risk of tinnitus and other cochlear disorders?

**Findings** In this cohort study of claims data among patients in Taiwan, 1056 patients with a history of migraines and 4224 controls were identified. The cumulative incidence of cochlear disorders, especially tinnitus, was found to be significantly higher among patients with history of migraines than those without a history of migraines.

**Meaning** A history of migraines may increase the risk of tinnitus and other cochlear disorders.

## Methods

### Data Source

This retrospective cohort study used claims data from the Longitudinal Health Insurance Database 2005, a subset of the National Health Insurance Research Database of Taiwan, to identify patients with migraines diagnosed between January 1, 1996, and December 31, 2012. The study was approved by the institutional review board of the Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan (No. B10202022). Since the Longitudinal Health Insurance Database 2005 files contain only deidentified secondary data, the review board of Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taiwan, waived the requirement for obtaining informed consent from the patients.

### Study Population

We first identified 996 333 patients who received a diagnosis of migraine based on outpatient claims (**Figure 1**). During this period, we identified 6991 patients with a history of migraines who received a diagnosis twice within 3 months. We excluded patients who had some preexisting diseases before the index date (eTable 1 in the Supplement), as well as patients with a history of migraines who could not be matched with controls. Finally, a total of 1056 patients with a newly diagnosed migraine were identified as the migraine cohort.

Figure 1. Flow Diagram of the Enrollment Process

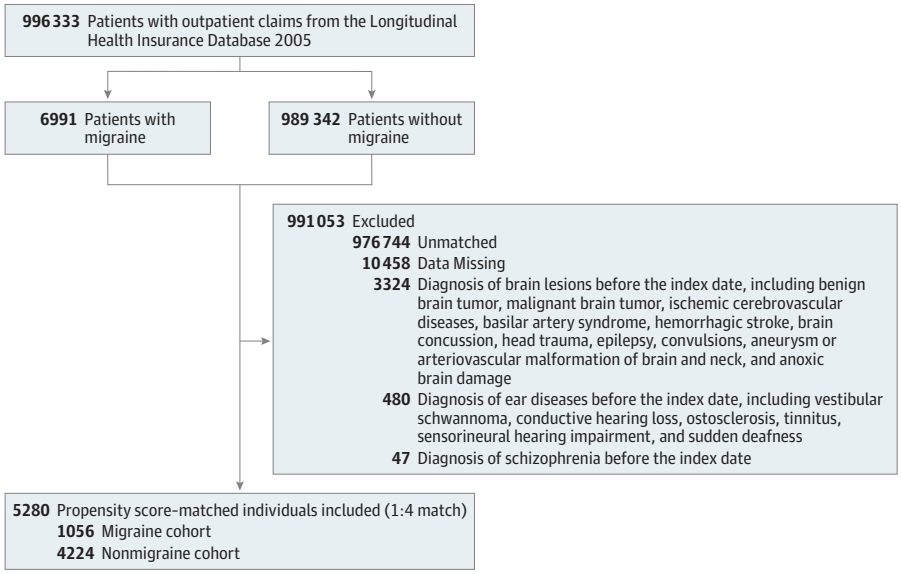


Table 1. Baseline Characteristics of Study Cohort, 1996-2012

| Variable | Patients, No. (%) | |
|---|---|---|
| | Migraine Cohort (n = 1056) | Matched Nonmigraine Cohort (n = 4224) |
| Sex | | |
| Men | 384 (36.4) | 1665 (39.4) |
| Women | 672 (63.6) | 2559 (60.6) |
| Age, mean (SD), y | 36.7 (15.3) | 35.0 (13.7) |
| Comorbidity | | |
| Sleep disorders | 31 (2.9) | 146 (3.5) |
| Heart diseases | 44 (4.2) | 147 (3.5) |
| Hypertension | 68 (6.4) | 179 (4.2) |
| Diabetes | 18 (1.7) | 68 (1.6) |
| Hyperlipidemia | 2 (0.2) | 10 (0.2) |
| Chronic kidney disease | 4 (0.4) | 7 (0.2) |
| Chronic hepatitis | 10 (0.9) | 47 (1.1) |
| Anxiety | 17 (1.6) | 66 (1.6) |
| Depression | 10 (0.9) | 25 (0.6) |
| COPD | 47 (4.5) | 193 (4.6) |
| Pregnancy | 2 (0.2) | 11 (0.3) |
| Menopause | 2 (0.2) | 3 (0.1) |
| Oral contraceptives | 25 (2.4) | 29 (0.7) |
| Geographic region | | |
| Northern | 532 (50.4) | 2240 (53.0) |
| Central | 211 (20.0) | 896 (21.2) |
| Eastern | 16 (1.5) | 111 (2.6) |
| Southern | 297 (28.1) | 977 (23.1) |
| Urbanization level | | |
| Urban | 349 (33.1) | 1233 (29.2) |
| Suburban | 488 (46.2) | 2025 (47.9) |
| Rural | 219 (20.7) | 966 (22.9) |
| Enrollee category | | |
| 1 (Highest) | 611 (57.9) | 1582 (37.5) |
| 2 | 28 (2.7) | 882 (20.9) |
| 3 | 275 (26.0) | 489 (11.6) |
| 4 (Lowest) | 142 (13.4) | 1271 (30.1) |

Abbreviation: COPD, chronic obstructive pulmonary disease.

For each patient in the migraine cohort, 4 individuals were selected from the patients without a history of migraines according to propensity score matching using baseline variables, including age, sex, comorbidities, and year of index date of cases. Finally, the matched nonmigraine cohort included 4224 patients, and the index date was the selected date.

## Main Outcome Measurement

Both cohorts were followed from the index date to the first diagnosis of a cochlear disorder (tinnitus, sensorineural hearing impairment, or sudden deafness), death, or the end of 2012, whichever came first. Death was defined as a withdrawal of a patient from the National Health Insurance program.

## Potential Confounders

We defined the presence of comorbidities according to the presence of *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes in the database before or on the index date, including sleep disorders (*ICD-9* codes 780.50, 780.51, 780.52, 780.53, 780.57, and 307.40), heart diseases (*ICD-9* codes 413.9, 414, 410-429, and 402), hypertension (*ICD-9* codes 401-405), diabetes (*ICD-9* code 250), hyperlipidemia (*ICD-9* code 272), chronic kidney disease (*ICD-9* codes 585 and 586), chronic hepatitis (*ICD-9* codes 070, 571.4, 571, 571.2, 571.5, and 571.6), anxiety (*ICD-9* codes 300.0, 300.00, 300.02, 300.09, 309.21, and 293.84), depression (*ICD-9* codes 296.30, 296.20, 311, and 300.4), pregnancy (*ICD-9* code 633), and menopause (*ICD-9* codes 627.4, 627.8, and 627.9), as well as chronic obstructive pulmonary disease (*ICD-9* codes 490-496) as a proxy for cigarette smoking.[9] Use of oral contraceptives was also considered a possible confounder. Geographic region of residence and urbanization level were included to minimize potential confounding due to differences in urban vs rural location in accessibility to medical care in Taiwan.[10] Also, enrollee category (EC), an indicator for socioeconomic status, was included and was classified as the following 4 subgroups: EC1 (highest socioeconomic status [eg, civil servants or full-time or regularly paid personnel in governmental agencies and public schools]), EC2 (employees of privately owned enterprises or institutions), EC3 (self-employed, other employees or paid personnel, and members of the farmers or fishers associations), and EC4 (lowest socioeconomic status [eg, substitute service draftees, members of low-income families, and veterans]).[10]

## Statistical Analysis

Statistical analysis was performed from January 23, 1996, to December 28, 2012. We calculated the incidence rate of cochlear disorders between the cohorts by using the Kaplan-Meier method and the log-rank test. After ensuring the assumptions of proportional hazards, we used the Cox proportional hazards regression model to examine the association of combined and individual cochlear disorders with migraines, with adjustment for all covariates. We analyzed all data with SAS, version 9.4 (SAS Institute Inc), and SPSS, version 20.0 (IBM Corp), and considered a 2-sided $P < .05$ as statistically significant.

# Results

**Table 1** shows the basic characteristics between the migraine and nonmigraine cohorts. The mean (SD) age of the migraine cohort was 36.7 (15.3) years, and 384 of the 1056 patients (36.4%) were men. The mean (SD) age (36.7 [15.3] years in the migraine group vs 35.0 [13.7] years in the nonmigraine group; $P = .001$), prevalence of hypertension (68 [6.4%] in the migraine group vs 179 [4.2%] in the nonmigraine group; $P = .002$), use of oral contraceptives (25 [2.4%] in the migraine group vs 29 [0.7%] in the nonmigraine group; $P < .001$), geographic region (northern, 532 [50.4%] in the migraine group vs 2240 [53.0] in the nonmigraine group; central, 211 [20.0%] in the migraine group vs 896 [21.2%] in the nonmigraine group; eastern, 16 [1.5%] in the migraine group vs 111 [2.6%] in the nonmigraine group; and southern, 297 [28.1%] in the migraine group vs 977 [23.1%] in the nonmigraine group; $P = .002$),

Table 2. Crude and Adjusted HRs for Combined Cochlear Disorders

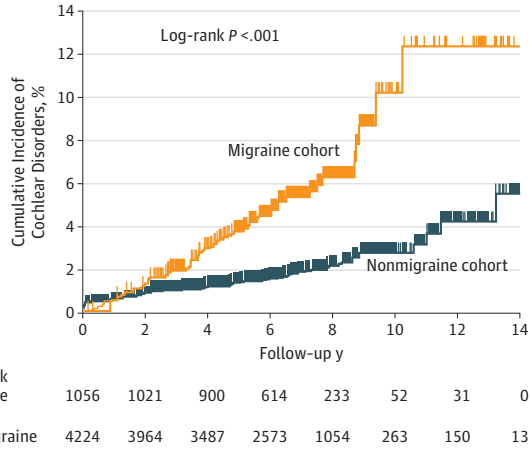
| Variable | Crude HR (95% CI) | Adjusted HR (95% CI)[a] |
|---|---|---|
| Migraine (yes or no) | 2.83 (2.01-3.99) | 2.71 (1.86-3.93) |
| Sex (men or women) | 1.18 (0.83-1.67) | 0.93 (0.64-1.34) |
| Age (per year) | 1.03 (1.02-1.04) | 1.02 (1.01-1.04) |
| Comorbidity (yes or no) | | |
| Sleep disorders | 1.01 (0.44-2.29) | 1.20 (0.52-2.75) |
| Heart diseases | 1.42 (0.72-2.80) | 1.12 (0.53-2.37) |
| Hypertension | 1.45 (0.78-2.70) | 0.71 (0.35-1.45) |
| Diabetes | 4.74 (2.61-8.59) | 3.70 (1.93-7.06) |
| Hyperlipidemia[b] | NA | NA |
| Chronic kidney disease | 2.59 (0.36-18.55) | 1.56 (0.21-11.88) |
| Chronic hepatitis | 2.01 (0.81-4.98) | 1.21 (0.46-3.20) |
| Anxiety | 1.91 (0.84-4.37) | 1.86 (0.81-4.30) |
| Depression | 0.81 (0.11-5.80) | 0.55 (0.08-3.98) |
| COPD | 1.69 (0.97-2.96) | 1.78 (1.01-3.15) |
| Pregnancy[b] | NA | NA |
| Menopause | 6.58 (0.92-47.11) | 4.62 (0.63-33.90) |
| Oral contraceptives | 1.95 (0.62-6.12) | 1.86 (0.58-6.02) |
| Geographic region | | |
| Northern | 1 [Reference] | 1 [Reference] |
| Central | 1.11 (0.71-1.73) | 1.06 (0.64-1.75) |
| Eastern | 0.69 (0.17-2.82) | 0.59 (0.14-2.50) |
| Southern | 1.34 (0.91-2.00) | 1.20 (0.78-1.85) |
| Urbanization level | | |
| Urban | 1 [Reference] | 1 [Reference] |
| Suburban | 0.76 (0.51-1.13) | 0.78 (0.51-1.17) |
| Rural | 1.04 (0.67-1.62) | 1.04 (0.61-1.77) |
| Enrollee category | | |
| 1 | 1 [Reference] | 1 [Reference] |
| 2 | 0.28 (0.12-0.66) | 0.40 (0.17-0.95) |
| 3 | 1.87 (1.22-2.87) | 1.29 (0.81-2.05) |
| 4 | 1.30 (0.86-1.95) | 1.29 (0.83-2.00) |

Abbreviations: COPD, chronic obstructive pulmonary disease; HR, hazard ratio; NA, not applicable.

[a] Adjusted for all covariates (age per year, sex, comorbidity, use of oral contraceptives, geographic region, urbanization level, and enrollee category).

[b] Correlated with another independent factor during regression analysis.

Figure 2. Cumulative Incidence of Cochlear Disorders




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Migraine cohort | 1056 | 1021 | 900 | 614 | 233 | 52 | 31 | 0 |
| Nonmigraine cohort | 4224 | 3964 | 3487 | 2573 | 1054 | 263 | 150 | 13 |

The cumulative incidence of cochlear disorders in the migraine cohort (12.2%) was significantly higher than that in the matched nonmigraine cohort (5.5%).

urbanization level (urban, 349 [33.1%] in the migraine group vs 1233 [29.2%] in the nonmigraine group; suburban, 488 [46.2%] in the migraine group vs 2025 [47.9%] in the nonmigraine group; and rural, 219 [20.7%] in the migraine group vs 966 [22.9%] in the nonmigraine group; $P = .04$), and EC (EC1, 611 [57.9%] in the migraine group vs 1582 [37.5%] in the nonmigraine group; EC2, 28 [2.7%] in the migraine group vs 882 [20.9%] in the nonmigraine group; EC3, 275 [26.0%] in the migraine group vs 489 [11.6%] in the nonmigraine group; and EC4, 142 [13.4%] in the migraine group vs 1271 [30.1%] in the nonmigraine group; $P < .001$) were significantly different between the cohorts.

**Table 2** shows the crude hazard ratios (HRs) and adjusted HRs (aHRs) for combined cochlear disorders. Compared with the nonmigraine cohort, the migraine cohort had a crude HR for cochlear disorders of 2.83 (95% CI, 2.01-3.99) and an aHR was for cochlear disorders of 2.71 (95% CI, 1.86-3.93). Age and diabetes were also significantly associated with increased aHRs for cochlear disorders (1.02 [95% CI, 1.01-1.04] for age; and 3.70 [95% CI, 1.93-7.06] for diabetes).

**Table 3** shows the incidence rate of combined cochlear disorders by migraine status. The mean (SD) duration of follow-up was 6.39 (2.34) years for the migraine cohort and 6.52 (2.92) years for the matched nonmigraine cohort. By the end of follow-up, the incidence rate of cochlear disorders was 81.4 (95% CI, 81.1-81.8) per 1 million person-years of follow-up in the migraine cohort and 29.4 (95% CI, 29.2-29.7) per 1 million person-years of follow-up in the nonmigraine matched cohort. Kaplan-Meier estimates showed that the cumulative incidence in the migraine cohort (12.2%) was higher than that in the matched nonmigraine cohort (5.5%) (**Figure 2**).

Subgroup analysis showed that, compared with the nonmigraine cohort, the aHRs in the migraine cohort were 3.30 (95% CI, 2.17-5.00) for tinnitus, 1.03 (95% CI, 0.17-6.41) for sensorineural hearing impairment, and 1.22 (95% CI, 0.53-2.83) for sudden deafness (eTable 2 in the Supplement).

## Discussion

In this large-scale cohort study, we found increased risk of cochlear disorders, especially for tinnitus, among patients with a history of migraines. It could be suggested that the findings do not reflect the cochlea at all and may reflect a central process causing tinnitus. This possibility would need to be investigated further in studies using audiometry; however, it clearly outlines a link between migraine and tinnitus that will be influential.

Vestibular migraine (VM) has been described with recurrent episodic vertigo and migraine-related symptoms.[11] Headache represented the first symptom of VM and was discovered several years before vertigo.[12] Migraine might also be

Table 3. Incidence Rate of Cochlear Disorders by Migraine Status

| Cohort | Mean Follow-up, y[a] | Total Follow-up, Person-years[a] | Cochlear Disorders, No. (%)[b] | Incidence Rate[b,c] |
|---|---|---|---|---|
| Migraine (n = 1056) | 6.39 | 6750 | 55 (5.2) | 81.4 |
| Nonmigraine (n = 4224) | 6.52 | 27 520 | 81 (1.9) | 29.4 |

[a] $P = .15$.

[b] $P < .001$.

[c] Per 1 million person-years.

linked to peripheral and central auditory dysfunctions.[13,14] Subjective hearing loss, aural pressure, and tinnitus were reported in 38% of patients during episodes of VM.[15] Morganti et al[12] also reported that 61.5% of patients with VM had auditory symptoms, with tinnitus the most common. Recently, Lai and Liu[16] proposed a new concept of cochlear migraine (CM) for patients who did not meet the strict criteria for VM. Our study demonstrates that a history of migraines might increase the risk of cochlear disorders. Thus, if CM was really present, we might define migraine-related sequelae in the vestibular system as VM, migraine-related sequelae in the auditory system as CM, and migraine-related sequelae in both the vestibular and auditory systems as cochleovestibular migraine.

Some patients with CM may experience a transformation of their condition to Ménière disease once severe vertigo develops; however, for some patients, their CM and vertigo episodes mimicked Ménière disease, but they had a normal summating potential to action potential ratio on an extratympanic electrocochleogram.

According to Hwang et al,[17] about 21.3% of patients with Ménière disease had a normal summating potential to action potential ratio in the ear with disease. However, Liu et al[18] found bilateral endolymphatic hydrops in a patient with migraine variant without vertigo. Therefore, the association between migraine-related cochleovestibular disorders and Ménière disease may be complex and overlapping.

Migraine and cochlear disorders might share common pathophysiologic characteristics. Sleep disorders, trigeminovascular theory, neuroinflammation, and/or cortical hypersensitivity have been associated with migraine.[2,19] Meanwhile, patients with tinnitus have vagal withdrawal and/or sympathetic overactivity.[20] Sleep disorders, neural inflammation, and/or damage from oxidative stress could increase the risk of tinnitus and age-related hearing impairment.[21-25] That is, these cochleovestibular disorders might result from sleep disorders, migraine-associated vasospasm, cortical hyperexcitability, neural inflammation and/or damage from oxidative stress, or enhanced activation of the sympathetic nervous system in the limbic and autonomous brain regions.

### Limitations

There were some limitations to this study. All diagnoses were based on *ICD-9-CM* codes in the database. The definition of a migraine used in this study (the presence of 2 *ICD-9-CM* diagnosis codes of migraine within 3 months) might contribute to bias. We had considered alternatives; however, we believed that including patients with a single diagnosis of a migraine might increase the rate of false-positive diagnoses in the migraine group, and 3 or more diagnoses might increase the rate of false-negative diagnoses in the nonmigraine group. We had explored alternative definitions of the migraine cohort and found similar results if we included patients with 2 or more diagnoses of a migraine within the entire study period. Risk of sudden deafness was increased, in addition to tinnitus (eTables 3 and 4 in the Supplement). Nevertheless, it is possible that the outcomes of this study apply to patients with more severe migraines and may not represent the general population of patients with migraines in Taiwan. Furthermore, there may be unmeasured variables, such as use of medical services, noise exposure, or medication use, that could confound the results of this study.

## Conclusions

In this large-scale cohort study, we found that patients with a history of migraine had a tendency to develop cochlear disorders, especially tinnitus. The results of this study supported the new concept and/or presence of CM.

ARTICLE INFORMATION

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**Author Affiliations:** Department of Otolaryngology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Dalin, Chiayi, Taiwan (Hwang); School of Medicine, Tzu Chi University, Hualien, Taiwan (Hwang, Chen); Department of Medical Research, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Dalin, Chiayi, Taiwan (Tsai); Department of Otolaryngology, National Taiwan University Hospital, Taipei, Taiwan (Liu); Department of Nephrology, Dalin Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Dalin, Chiayi, Taiwan (Chen); Department of Otolaryngology, Kuang-Tien General Hospital, Shalu, Taichung, Taiwan (Lai).

**Author Contributions:** Drs Hwang and Chen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Hwang and Tsai contributed to this manuscript equally.
*Concept and design:* Hwang, Tsai, Liu, Lai.
*Acquisition, analysis, or interpretation of data:* Hwang, Tsai, Chen.
*Drafting of the manuscript:* Hwang, Tsai, Chen.
*Critical revision of the manuscript for important intellectual content:* All authors.
*Statistical analysis:* Hwang, Tsai, Chen.
*Administrative, technical, or material support:* Hwang, Chen.
*Supervision:* Liu, Chen, Lai.

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Invited Commentary

# The Role of Migraine in Hearing and Balance Symptoms

Harrison W. Lin, MD; Hamid R. Djalilian, MD

**Episodic dizziness** is a highly prevalent symptom that has historically been a challenge for primary care physicians, neurologists, and otolaryngologists to accurately diagnosis and properly treat. With an array of diagnoses to consider, including benign positional vertigo, vestibular migraine, Ménière disease, vertebrobasilar syndrome, and vestibular schwannoma, among others, considerable effort has been placed by otolaryngology and neurology societies to carefully examine the literature and generate clinical criteria and guidelines to aid the clinician and to standardize diagnostic algorithms and treatment protocols. In recent decades, Ménière disease has been intensely investigated in both clinical and histopathologic studies and has been among the more frequent diagnoses given to patients with episodic dizziness. Even more recently, many studies have reported substantial overlap between the symptoms of vestibular migraine and those of Ménière disease, and, consequently, distinguishing between these 2 disease entities can be difficult.[1] To this end, the presence of sensorineural hearing loss has notably been suggested to be the primary finding to differentiate Ménière disease from vestibular migraine, highlighting the previously held and popular notion that migraine activity will seldom have a negative influence on the auditory pathways and generate cochlear symptoms, such as hearing loss and tinnitus.[2] As Hwang and colleagues[3] eloquently discuss in this issue of *JAMA Otolaryngology–Head & Neck Surgery*, there is a growing body of evidence of both the association and causal relationship between migraine and the development of cochlear symptoms.

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In this report, the authors sought to determine whether patients with a diagnosis of migraine are at increased risk of experiencing tinnitus, sensorineural hearing loss, and sudden hearing loss. Using a national database of nearly 1 million patients tracked longitudinally for a 16-year period, Hwang and associates[3] applied a strict set of inclusion and exclusion criteria to extract a cohort of patients with isolated migraine, and ultimately identified 1056 patients with migraine to examine. This group was compared with 4224 controls without migraine who were selected based on demographic and