Risk of vestibulocochlear disorders in patients with migraine or non-migraine headache

Sang-Hwa Lee

Chuncheon Sacred Heart Hospital, Hallym University College of Medicine

Jong-Ho Kim

Chuncheon Sacred Heart Hospital, Hallym University College of Medicine

Young-Suk Kwon

Chuncheon Sacred Heart Hospital

Jae-June Lee

Chuncheon Sacred Heart Hospital, Hallym University College of Medicine

Jong-Hee Sohn (✉ deepfoci@hallym.or.kr)

Chuncheon Sacred Heart Hospital, Hallym University College of Medicine <https://orcid.org/0000-0003-2656-9222>

Research article

Keywords: migraine, headache, vestibular disorder, cochlear disorder

Posted Date: October 11th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-958934/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Journal of Personalized Medicine on December 8th, 2021. See the published version at <https://doi.org/10.3390/jpm11121331>.

Abstract

Background Headache, especially migraine, has been associated with various vestibular symptoms and several vestibular syndromes. In addition, cochlear disorders, such as tinnitus and hearing loss, have recently been reported to be more prevalent among migraine patients. However, whether headaches, including migraine or non-migraine headaches, are associated with vestibular and cochlear disorders remains unclear. Thus, the possible associations between headaches, including migraine and non-migraine headaches, and vestibulocochlear disorders were investigated in the present study. **Methods** Clinical data were analyzed from the Smart Clinical Data Warehouse of Hallym University Medical Center from 2011–2021. In patients with migraine and non-migraine headaches, data on Meniere's disease (MD), benign paroxysmal positional vertigo (BPPV), vestibular neuronitis (VN), and cochlear disorders such as sensorineural hearing loss (SNHL) and tinnitus, were collected and compared with clinical data from controls without headache who had health check-ups. In addition, the presence of comorbidities were defined according to the International Classification of Diseases, tenth revision codes in the database and analyzed. **Results** The study included 15,128 participants with migraines and 76,773 with non-migraine headaches. Controls were identified based on propensity score matching (PSM). After PSM, the adjusted odds ratios (ORs) in subjects with migraine versus controls were 2.597 for MD (95% CI, 2.047–3.295; $p < 0.001$), 2.045 for BPPV (95% CI, 1.816–2.302; $p < 0.001$), 2.976 for VN (95% CI, 2.636–3.360; $p < 0.001$), 1.739 for SNHL (95% CI, 1.404–2.156; $p < 0.001$), and 1.970 for tinnitus (95% CI, 1.658–2.341; $p < 0.001$). The adjusted ORs for MD (1.771; 95% CI, 1.560–2.011; $p < 0.001$), BPPV (1.731; 95% CI, 1.637–1.831; $p < 0.001$), VN (2.048; 95% CI, 1.935–2.168; $p < 0.001$), SNHL (1.396; 95% CI, 1.273–1.531; $p < 0.001$), and tinnitus (1.693; 95% CI, 1.569–1.826; $p < 0.001$) in patients with non-migraine headache versus controls were also high after PSM. **Conclusion** The present study findings indicated that migraine and non-migraine headaches are associated with an increased risk of cochlear disorders, such as SNHL and tinnitus, in addition to vestibular disorders.

Background

Dizziness or vertigo is a relatively common symptom in headache patients [1]. Reportedly, more than half of headache patients experience dizziness accompanied by headache. In particular, vestibular symptoms accompanying headache are very common in migraineurs, and the lifetime prevalence of vertigo or dizziness in migraineurs is significantly higher than in controls [2,3]. In addition, in various studies on migraine and tension-type headache (TTH) patients, the frequency of vestibular symptoms such as dizziness, vertigo, imbalance, postural instability, and vestibular disorders was high, and abnormalities in vestibular function tests have been reported [4–9]. Based on the relationship between migraines and vestibular symptoms reported in numerous studies, vestibular migraine (VM) was included in the appendix of the 3rd edition International Classification of Headache Disorders. VM is closely associated with Meniere's disease (MD), and a substantial overlap between VM and MD has been reported [10–14]. In a previous study, patients presented with simultaneous VM and MD signs/symptoms and a new clinical syndrome, VM/MD overlap syndrome, was proposed [15]. Other authors reported a number of

patients who experienced migraine-related symptoms and family histories presenting with long-term, unilateral, fluctuating hearing loss with aural fullness and tinnitus who never develop vertigo or only mild dizziness that did not meet the strict criteria for VM. Therefore, the authors proposed a new concept of cochlear migraine for this condition [16]. Although the pathophysiology of migraine including VM is not well known, the most accepted theories to date are thought to be vascular mechanisms and/or inflammation and neurotransmitter mechanisms. In addition, migraines reportedly damage the cochlea of the inner ear via a neurovascular mechanism [17]. In previous population-based cohort studies, migraines were suggested to increase the risk of tinnitus, sensorineural hearing impairment, and/or sudden deafness [18,19]. In addition, the relationship between headaches and tinnitus or hearing impairment has been described in several clinical studies [20–25]. In cross-sectional studies, several types of headaches, including migraine and TTH, were shown to be associated with tinnitus and hearing impairment [23,20]. In a population-based study, the risk of tinnitus, sensorineural hearing impairment, and sudden deafness were found to be significantly higher in patients with non-migraine headache than in subjects without headache [25]. In other studies, tinnitus was found to be associated with temporomandibular joint and/or cervical dysfunction, or related to pericranial muscle tenderness in patients with headache and craniofacial pain [22,21,24].

However, whether headaches, including migraine and non-migraine headaches, are associated with cochlear disorders such as tinnitus or hearing loss in addition to vestibular disorders remains unclear. Thus, the associations between headaches, including migraine and non-migraine headaches, and vestibulocochlear disorders were investigated in the present study using the Smart Clinical Data Warehouse (CDW) over a period of 10 years.

Methods

Subjects

We retrospectively analyzed clinical data from the Smart CDW of Hallym University Medical Center (HUMC) from January 2011–April 2021. The Smart CDW, based on the QlikView Elite Solution (Qlik, Lund, Sweden), is used at the four hospitals of the HUMC and offers electronic medical record text data analysis and an integrated analysis of fixed data. Patients eligible for the study included those with migraine, 20–80 years of age, diagnosis of migraine by a board-certificated neurologist, and ≥ 2 consecutive visits to the neurology department. Patients with non-migraine headache, 20–80 years of age and a diagnosis determined by the presence of two codes were also eligible. Patients with headache or TTH and subjects with a history of more than one visit for migraine were excluded. The information on comorbidities and migraine medications, such as non-steroid anti-inflammatory drugs (NSAIDs) and triptans, were collected for analysis. Triptan drugs are specifically used to treat migraine; those used at HUMC include almotriptan, frovatriptan, naratriptan sumatriptan, and zolmitriptan. The control group included patients 20–80 years of age who had undergone general health checkups at a health promotion center. Patients with a history of headache or migraine assessed using a basic questionnaire completed prior to the health examination and patients with a history of headache or migraine who visited our

medical center were excluded. This study was approved by the Clinical Research Ethics Committee of Chuncheon Sacred Heart Hospital, Hallym University (IRB No. 2021-06-003). Because only deidentified data were used in this study, the review board waived the requirement for informed consent from all subjects.

Migraine/Non-migraine Headache, Vestibulocochlear Disorders, and Covariates

Among the enrolled groups, the medical records of subjects with a diagnosis of MD, benign paroxysmal positional vertigo (BPPV), vestibular neuronitis (VN), or cochlear disorders such as sensorineural hearing loss (SNHL) and tinnitus, were collected and compared with clinical data from controls without headache who had health check-ups. In addition, the presence of comorbidities was defined according to the presence of International Classification of Diseases, tenth revision (ICD-10) codes in the database and included sleep disorders (ICD-10 codes F51, G258, G47), heart disease (ICD-10 codes I05–09, I21–23, I30–47, I49–52), hypertension (ICD-10 codes I10–15), diabetes mellitus (ICD-10 codes E10–14), dyslipidemia (ICD-10 code E78), renal failure (ICD-10 codes N03, N18–17), chronic hepatitis (ICD-10 codes B18, I85, K70–74), anxiety disorder (ICD-10 code F41), depression (ICD-10 codes F31–34, F412, F432), cerebrovascular diseases (ICD-10 codes G45–46, I60–69), menopause (ICD-10 codes M800, M010, N924, N95), chronic pulmonary disease (ICD-10 codes J40–47), angina (ICD-10 codes I20, I24, I251), and atrial fibrillation (ICD-10 codes I480–482, I489).

Statistical Analysis

Continuous data are presented as means and standard deviations (SDs), and categorical data as frequencies and percentages. A *t*-test was performed to compare the continuous data of patients with migraine or non-migraine headache. Categorical data were analyzed using the chi-square test. First, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for the occurrence of MD, BPPV, VN, SNHL, and tinnitus for each variable using logistic regression. The OR is a measure of the association between an exposure and outcome and, in this study, represents the likelihood of MD, BPPV, VN, SNHL, and tinnitus given a particular exposure compared with the likelihood in its absence. Fully adjusted ORs for MD, BPPV, VN, SNHL, and tinnitus were then calculated for each variable including migraine and non-migraine headache.

Because patients could not be randomized based on the presence of migraine, confounding and selection biases were accounted for using propensity scores. In this study, propensity score matching (PSM) was conducted for normal controls and subjects with migraine or non-migraine headache. Python (version 3.7; Anaconda Inc., Austin, TX, USA) and Pymatch (version 0.3.4; <https://github.com/benmirogllo/pymatch>) were used for PSM. The propensity scores ranged from 0.07–0.87. All matched cases had scores within 0.0001 of each other and the matching ratio was 1:1 (15,128 migraine patients and 15,128 normal controls; 14,606 non-migraine headache patients and 14,606 normal controls).

The ORs for MD, BPPV, VN, SNHL, and tinnitus in migraine and non-migraine headache patients were compared with the normal controls. In the analysis, covariates and propensity scores were used to

calculate adjusted ORs. All p -values were two-sided and a p -value < 0.05 was considered statistically significant. SPSS software (version 24.0; IBM Corp., Armonk, NY, USA) was used for statistical analyses.

Results

Subject Characteristics

The present study included 15,128 patients with migraine and 76,773 patients with non-migraine headache identified between January 2011 and April 2021. A total of 315,330 subjects without migraine or headache were used as controls and selected from the same database. The enrollment process is presented in Figure 1. Among the 15,128 patients with migraine and 76,773 patients with non-migraine headache, 11,247 (74.3%) and 45,148 (58.8%) were female, and the mean (SD) age was 44.0 (14.3) and 49.1 (14.6) years, respectively. In addition, 15,128 and 14,606 controls for migraine and non-migraine headache, respectively, were identified based on PSM (Fig. 1).

Between the migraine and control groups, all the absolute standardized differences were < 0.1 after PSM (Table 1). In addition, significant differences were not observed for any variable after PSM between non-migraine headache and control groups (Table 2). In subgroup analysis, significant difference was not observed between the migraine group taking triptan medication and controls or between the migraine group taking NSAID medication and controls, for any variable after PSM.

ORs for Vestibulocochlear Disorders in Migraineurs

Before PSM, the unadjusted ORs in subjects with migraine *versus* controls were 2.519 (95% CI, 1.988–3.192; $p < 0.001$) for MD, 1.941 (95% CI, 1.728–2.182; $p < 0.001$) for BPPV, 2.838 (95% CI, 2.518–3.200; $p < 0.001$) for VN, 1.647 (95% CI, 1.331–2.038; $p < 0.001$) for SNHL, and 1.869 (95% CI, 1.574–2.215; $p < 0.001$) for tinnitus. The ORs for MD (OR, 2.597; 95% CI, 2.047–3.295; $p < 0.001$), BPPV (OR, 2.045; 95% CI, 1.816–2.302; $p < 0.001$), VN (OR, 2.976; 95% CI, 2.636–3.360; $p < 0.001$), SNHL (OR, 1.739; 95% CI, 1.404–2.156; $p < 0.001$), and tinnitus (OR, 1.970; 95% CI, 1.658–2.341; $p < 0.001$) in patients with migraine were also high after PSM (Table 3). Subgroup analysis showed the ORs in the migraine group taking triptans were 2.928 (95% CI, 2.038–4.206; $p < 0.001$) for MD, 2.359 (95% CI, 1.960–2.838; $p < 0.001$), 2.882 (95% CI, 2.385–3.483; $p < 0.001$), for 1.812 (95% CI, 1.291–2.543; $p < 0.001$) for SNHL, and 1.862 (95% CI, 1.446–2.399; $p < 0.001$) for tinnitus after PSM. The ORs for MD (OR, 1.809; 95% CI, 1.360–2.408; $p < 0.001$), BPPV (OR, 2.433; 95% CI, 2.095–2.826; $p < 0.001$), VN (OR, 3.365; 95% CI, 2.887–3.921; $p < 0.001$), SNHL (OR, 1.649; 95% CI, 1.274–2.133; $p < 0.001$), and tinnitus (OR, 1.941; 95% CI, 1.566–2.405; $p < 0.001$) in the migraine group using NSAIDs were also high after PSM (Table 4).

ORs for Vestibulocochlear Disorders in Non-migraine headaches

Table 5 shows the ORs for development of vestibular and cochlear disorders in non-migraine headache patients. The unadjusted and adjusted ORs for MD, BPPV, VN, SNHL and tinnitus were lower in non-migraine headache patients than in migraine patients. After PSM, the adjusted ORs in subjects with non-

migraine headache *versus* controls were 1.771 (95% CI, 1.560–2.011; $p < 0.001$) for MD, 1.731 (95% CI, 1.637–1.831; $p < 0.001$) for BPPV, 2.048 (95% CI, 1.935–2.168; $p < 0.001$) for VN, 1.396 (95% CI, 1.273–1.531; $p < 0.001$) for SNHL, and 1.693 (95% CI, 1.569–1.826; $p < 0.001$) for tinnitus (Table 5).

Discussion

In the present study, the risk of cochlear disorders in patients with migraine or non-migraine headache, in addition to vestibular disorders, was investigated based on data from the Smart CDW of HUMC over a 10-year period. The study included 15,128 patients with migraines, 76,773 patients with non-migraine headache, and 315,330 non-headache controls. After PSM, patients with migraine or non-migraine headache were at significantly greater risk of MD, BPPV, VN, SNHL, and tinnitus than control subjects without headache.

Migraine is associated with various vestibular symptoms and several vestibular syndromes [26]. In addition, several vestibular laboratory abnormalities in migraineurs have been identified in previous studies [27]. VM is a common cause of recurrent episodic vertigo, accompanied by migraine-related symptoms [28]. VM is closely associated with MD and a significant overlap between these two diseases has been reported [11,12,14,10,13]. In a previous report, patients presenting simultaneously with VM and MD sign/symptoms was proposed as a new clinical syndrome and termed VM/MD overlap syndrome [15]. In other studies, a number of patients who experienced migraine-related symptoms and family histories presenting with long-term, unilateral, fluctuating hearing loss with aural fullness and tinnitus but without vertigo or only mild dizziness that did not meet the strict criteria for VM were reported. Therefore, the authors proposed a new concept of cochlear migraine [16]. In previous epidemiological studies, vestibulocochlear signs and symptoms were shown to be common in patients with migraine. Similar to the results of previous studies, our results showed that the ORs for vestibulocochlear disorders, including MD, BPPV, VN, SNHL, and tinnitus, were significantly higher in migraine patients compared with controls. The non-migraine headache group also showed similar results to the migraine group. The ORs showed a significantly greater risk of vestibular and cochlear disorders in non-migraine headache patients, although each OR was lower in non-migraine headache patients than in migraine patients. The non-migraine cohort in the present study included patients with codes having TTH or non-specific headache and excluded all types of migraines. Thus, the non-migraine headache cohort mainly included patients with TTH.

In several studies targeting patients with TTH, the frequency of vestibular signs/symptoms was high, and abnormalities were reported in vestibular function tests [6,4]. Furthermore, in several cross-sectional studies, various types of headache were shown to be associated with tinnitus and hearing impairment, including TTH, mixed headache, and headache combined with cervical muscle tenderness [20,21,23]. In population-based cohort studies from Taiwan, a relationship was observed between primary headache mainly in patients with TTH and cochlear disorders [25,29]. In one study, the non-migraine headache cohort was associated with the risk of tinnitus, sensorineural hearing impairment, and sudden deafness [25], whereas in another study, an association was observed between TTH and sudden sensorineural

hearing loss [29]. In particular, tinnitus, defined as the perception of sound in absence of a corresponding sound source, can be present in patients with or without hearing loss and its cause may be multifactorial. In previous studies, the specific subtypes of tinnitus, such as somatosensory and cervicogenic somatic tinnitus, were shown to be associated with increased pericranial and cervical muscle tenderness in patients with migraine, TTH, myogenous pain, and arthrogenous temporomandibular joint disorders [23,22,21,24]. The authors suggested that tinnitus was associated with increased pericranial and cervical muscle tenderness and not any particular form of headache in patients with headache and craniofacial pain [21]. In patients with migraine and TTH, both episodic and chronic, are combined with pericranial and cervical muscle tenderness. In particular, prior study results support the pathogenetic importance of muscular and stress factors in TTH [30–35]. In another study, headache laterality was significantly associated with tinnitus laterality, and in the majority of patients, fluctuations in symptom severity of tinnitus and headache were interrelated [33]. Thus, tinnitus and TTH may have common pathophysiological mechanisms. Vascular insufficiency has been proposed as the main pathogenesis of SNHL because many vascular events are associated with SNHL. In a prior study, the sympathetic response to stress was hypothesized to cause vasoconstriction, hemoconcentration, and microcirculation occlusion in the inner ear, which could occur afterwards, ultimately leading to SNHL [37]. In another cohort study, acutely increased neutrophil counts and IL-6 level and a decrease in natural killer cell activity were associated with severe hearing loss and poor prognosis. These results indicate that inflammatory biomarkers and stress are involved in the pathophysiology of SNHL [38]. Thus, the relationship between SNHL and TTH could share pathophysiological mechanisms due to stress-induced inflammatory activities.

In addition, the ORs for each cochlear disorder in migraine and non-migraine headache patients were lower than for vestibular disorders in the present study. The ORs for each vestibulocochlear disorder were higher in migraine than in non-migraine headache patients. In most prior studies, the association between migraine or each headache group and vestibular or cochlear disorder was investigated; the association between various headache groups and vestibulocochlear disorders have been simultaneously compared in only a few studies. In a large cross-sectional study among students, the adjusted ORs of tinnitus were 1.77 for migraine and 1.38 for non-migraine headache, somewhat lower than in the present study. In the previous study, stronger association was found for migraine with aura and no significant association for non-migraine headache after adjustment [39]. Furthermore, vestibular symptoms were shown to be more common in subjects considered to have definite migraine than in subjects considered to have definite TTH [40,41]. Even in younger patients presenting with a primary headache disorder, the presence of vestibular symptoms helps differentiate migraine from TTH [41]. To date, the association between migraine and vestibular disorder has been generally established; therefore, VM has been included in the appendix criteria of the International Classification of Headache Disorders-3. More recently, because reports of the association between cochlear disorder and migraine are increasing, a new concept of “cochlear migraine” or “vestibulocochlear migraine” should be considered. In addition, associations between non-migraine headaches and vestibular or cochlear disorders have been reported; thus, additional studies on the association with non-migraine headaches are needed.

Vestibulocochlear signs and symptoms have been reported to be common in patients with migraine as well as with other types of primary headache. However, the pathogenesis of these signs and symptoms is unclear. In previous studies, multiple potential interactions between the trigeminal and vestibular systems at various levels were reported. In migraine patients, stimulation of the trigeminal nuclei produced spontaneous nystagmus [42]. Conversely, vestibular nuclei receive both serotonergic inputs from the dorsal raphe nucleus and noradrenergic inputs from the locus coeruleus, and activation of these pain structures during migraine can affect central vestibular processing [27]. These reciprocal connections between the vestibular nuclei and trigeminal nucleus caudalis may include a mechanism in which vestibular signals influence the trigeminovascular pathway and trigeminal information processing during migraine attacks [43]. Furthermore, vestibular and cranial nociceptive pathways possess similarities in neurochemical milieu and express serotonin receptor subtypes that are targets for anti-migraine drugs, such as triptans. The serotonergic 5-HT_{1B} and 5-HT_{1D} receptors are expressed prominently in the inner ear of rats and monkeys [44]. All vestibular and considerable numbers of trigeminal ganglia show positive 5-HT_{1F} receptor immunoreactivity in monkeys. In addition, similar findings in cochlear inner hair cell afferents were observed and these results are applicable to migraine-related tinnitus [45]. In other previous experimental studies, the trigeminal ganglion was shown to innervate the cochlear nucleus and superior olivary complex in guinea pigs. This projection may be associated with integration mechanisms involving the auditory end organ and its central targets [46]. In clinical studies, histopathological findings indicate that sudden deafness in migraine patients resulted from ischemia [17], and ischemia was most likely to be due to migraine-associated vasospasm of the cochlear vasculature [17,47]. In the electrophysiologic study for monitoring cochlear status, subclinical dysfunction of cochlear and cochlear efferents were observed in migraine patients [48]. Additional experimental studies are needed to elucidate the various potential interactions between the trigeminal nociceptive pathway and vestibular or cochlear systems.

The present study had several limitations. The study was retrospective in design, thus, unmeasured confounders may not have been accounted for. In addition, data were used from subjects who visited one university medical center with four hospitals. Therefore, generalizing the results to the general population is difficult and the possibility of selection bias must be considered. In addition, detailed clinical information regarding headache characteristics was not collected. Future prospective, population-based studies are needed to investigate further the association between headache and vestibulocochlear disorders.

Conclusions

The results of the present study indicate that patients with migraine and non-migraine headache are at an increased risk of cochlear disorders, such as SNHL and tinnitus, in addition to vestibular disorders. Furthermore, the ORs for each vestibulocochlear disorder were higher in migraine than in non-migraine headache patients. Thus, we propose the concept of “cochlear migraine” or “vestibulocochlear migraine”. Additional experimental studies to elucidate the potential interactions between the trigeminal nociceptive

pathway and vestibular or cochlear systems and prospective, population-based studies to investigate the association between headache and vestibulocochlear disorders are needed.

Abbreviations

TTH, tension-type headache; VM, vestibular migraine; MD, Meniere`s disease; CDW, Clinical Data Warehouse; HUMC, Hallym University Medical Center; NSAIDs, non-steroid anti-inflammatory drugs; BPPV, benign paroxysmal positional vertigo; SNHL, sensorineural hearing loss; ICD, International Classification of Diseases; SD, standard deviation; OR, odds ratio; CI, confidence interval; PSM, propensity score matching

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Clinical Research Ethics Committee of Chuncheon Sacred Heart Hospital, Hallym University (IRB No. 2021-06-003). Because this study uses only deidentified data, the review board waived the requirement for obtaining informed consent form all subjects.

Consent for publication:

Not applicable

Availability of data and materials

Available as supplementary data

Competing interests

The authors have no competing interests to declare.

Funding

This research was supported by the Basic Science Research Program through the NRF of Korea funded by the Ministry of Education (NRF-2018R1D1A1B07045645) and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR21C0198). The role of funding was in the design of the study and collection, analysis, and interpretation of data. No other financial relationships relevant to this publication were disclosed.

Author Contributions

Conception and design of the work, JHS; Acquisition of data for the work, SHL JHK and JHS; Analysis and interpretation of data for the work, JHK, YSK and JHS; Writing the manuscript, original draft preparation-SHL and JHS, review and editing-SHL, JHK, YKL, JKL and JHS. All authors have read and agreed to the published version of the manuscript.

References

1. Bisdorff A, Andree C, Vaillant M, Sándor PS (2010) Headache-associated dizziness in a headache population: prevalence and impact. *Cephalalgia* 30 (7):815-820. doi:10.1177/0333102409353617
2. Akdal G OA, Ergor G (2013) The prevalence of vestibular symptoms in migraine or tension-type headache. *J Vestib Res* 23 (2):101-106. doi:10.3233/ves-2011-0423
3. Vuković V, Plavec D, Galinović I, Lovrenčić-Huzjan A, Budisić M, Demarin V (2007) Prevalence of vertigo, dizziness, and migrainous vertigo in patients with migraine. *Headache* 47 (10):1427-1435. doi:10.1111/j.1526-4610.2007.00939.x
4. Ishizaki K, Mori N, Takeshima T, Fukuhara Y, Ijiri T, Kusumi M, Yasui K, Kowa H, Nakashima K (2002) Static stabilometry in patients with migraine and tension-type headache during a headache-free period. *Psychiatry Clin Neurosci* 56 (1):85-90. doi:10.1046/j.1440-1819.2002.00933.x
5. Lee H, Sohn SI, Jung DK, Cho YW, Lim JG, Yi SD, Yi HA (2002) Migraine and isolated recurrent vertigo of unknown cause. *Neurol Res* 24 (7):663-665. doi:10.1179/016164102101200726
6. Asai M, Aoki M, Hayashi H, Yamada N, Mizuta K, Ito Y (2009) Subclinical deviation of the subjective visual vertical in patients affected by a primary headache. *Acta Otolaryngol* 129 (1):30-35. doi:10.1080/00016480802032785
7. von Brevern M, Neuhauser H (2011) Epidemiological evidence for a link between vertigo and migraine. *J Vestib Res* 21 (6):299-304. doi:10.3233/ves-2011-0423
8. Boldingh MI, Ljøstad U, Mygland Å, Monstad P (2013) Comparison of interictal vestibular function in vestibular migraine vs migraine without vertigo. *Headache* 53 (7):1123-1133. doi:10.1111/head.12129
9. Bisdorff A (2014) Migraine and dizziness. *Curr Opin Neurol* 27 (1):105-110. doi:10.1097/wco.0000000000000061
10. Wang Y, Diao T, Zhao Y, Yu L (2018) The clinical characteristics and audiogram in 103 Meniere's disease patients with and without vestibular migraine. *Clini Otolaryngol* 43 (1):343-347. doi:10.1111/coa.12946
11. Shin CH, Kim Y, Yoo MH, Kim TS, Park JW, Kang BC, Park HJ (2019) Management of Ménière's Disease: How Does the Coexistence of Vestibular Migraine Affect Outcomes? *Otol Neurotol* 40 (5):666-673. doi:10.1097/mao.0000000000002176

12. Pyykkö I, Manchaiah V, Färkkilä M, Kentala E, Zou J (2019) Association between Ménière's disease and vestibular migraine. *Auris Nasus Larynx* 46 (5):724-733. doi:10.1016/j.anl.2019.02.002
13. Ghavami Y, Mahboubi H, Yau AY, Maducdoc M, Djalilian HR (2016) Migraine features in patients with Meniere's disease. *Laryngoscope* 126 (1):163-168. doi:10.1002/lary.25344
14. Abouzari M, Abiri A, Djalilian HR (2019) Successful treatment of a child with definite Meniere's disease with the migraine regimen. *Am J Otolaryngol* 40 (3):440-442. doi:10.1016/j.amjoto.2019.02.004
15. Murofushi T, Tsubota M, Kitao K, Yoshimura E (2018) Simultaneous Presentation of Definite Vestibular Migraine and Definite Ménière's Disease: Overlapping Syndrome of Two Diseases. *Front Neurol* 9:749. doi:10.3389/fneur.2018.00749
16. Lai JT, Liu TC (2018) Proposal for a New Diagnosis for Cochlear Migraine. *JAMA otolaryngol Head Neck Surg* 144 (3):185-186. doi:10.1001/jamaoto.2017.2427
17. Lee H, Lopez I, Ishiyama A, Baloh RW (2000) Can migraine damage the inner ear? *Arch Neurol* 57 (11):1631-1634. doi:10.1001/archneur.57.11.1631
18. Hwang JH, Tsai SJ, Liu TC, Chen YC, Lai JT (2018) Association of Tinnitus and Other Cochlear Disorders With a History of Migraines. *JAMA Otolaryngol Head Neck Surg* 144 (8):712-717. doi:10.1001/jamaoto.2018.0939
19. Chu CH, Liu CJ, Fuh JL, Shiao AS, Chen TJ, Wang SJ (2013) Migraine is a risk factor for sudden sensorineural hearing loss: a nationwide population-based study. *Cephalalgia* 3 (2):80-86. doi:10.1177/0333102412468671
20. Farri A, Enrico A, Lacilla M, Sartoris A (1999) Tinnitus during headache: clinical-instrumental evaluation. *Acta Otorhinolaryngol Ital* 19 (2):70-75. doi: 10.14639/0392-100X-1342
21. Pezzoli M, Ugolini A, Rota E, Ferrero L, Milani C, Pezzoli L, Pecorari G, Mongini F (2015) Tinnitus and its relationship with muscle tenderness in patients with headache and facial pain. *J Laryngol and Otol* 129 (7):638-643. doi:10.1017/s0022215115001425
22. Ralli M, Altissimi G, Turchetta R, Mazzei F, Salviati M, Cianfrone F, Orlando MP, Testugini V, Cianfrone G (2016) Somatosensory Tinnitus: Correlation between Cranio-Cervico-Mandibular Disorder History and Somatic Modulation. *Audiol Neurotol* 21 (6):372-382. doi:10.1159/000452472
23. Langguth B, Hund V, Landgrebe M, Schecklmann M (2017) Tinnitus Patients with Comorbid Headaches: The Influence of Headache Type and Laterality on Tinnitus Characteristics. *Front Neurol* 8:440. doi:10.3389/fneur.2017.00440
24. Michiels S, Van de Heyning P, Truijen S, Hallemans A, De Hertogh W (2017) Prognostic indicators for decrease in tinnitus severity after cervical physical therapy in patients with cervicogenic somatic tinnitus.

25. Chen YC, Tsai SJ, Chen JC, Hwang JH (2019) Risks of tinnitus, sensorineural hearing impairment, and sudden deafness in patients with non-migraine headache. PLoS One 14 (9):e0222041. doi:10.1371/journal.pone.0222041
26. Neuhauser HK, Radtke A, von Brevern M, Feldmann M, Lezius F, Ziese T, Lempert T (2006) Migrainous vertigo: prevalence and impact on quality of life. Neurology 67 (6):1028-1033. doi:10.1212/01.wnl.0000237539.09942.06
27. Furman JM, Marcus DA, Balaban CD (2003) Migrainous vertigo: development of a pathogenetic model and structured diagnostic interview. Curr Opin Neurol 16:5-13. doi:10.1097/01.wco.0000053582.70044.e2 [doi] M1 - Journal Article
28. Dieterich M, Obermann M, Celebisoy N (2016) Vestibular migraine: the most frequent entity of episodic vertigo. J Neurol 263 Suppl 1:S82-89. doi:10.1007/s00415-015-7905-2
29. Hsiao PC, Hu HY, Yang TH, Lee FP, Huang HM (2015) Sudden sensorineural hearing loss associated with tension-type headache: a population-based study. Audiol Neurotol 20 (2):122-127. doi:10.1159/000370301
30. Watson DH, Drummond PD (2012) Head pain referral during examination of the neck in migraine and tension-type headache. Headache 52 (8):1226-1235. doi:10.1111/j.1526-4610.2012.02169.x
31. Mongini F, Ciccone G, Deregibus A, Ferrero L, Mongini T (2004) Muscle tenderness in different headache types and its relation to anxiety and depression. Pain 112 (1-2):59-64. doi:10.1016/j.pain.2004.07.025
32. Jensen R, Rasmussen BK, Pedersen B, Olesen J (1993) Muscle tenderness and pressure pain thresholds in headache. A population study. Pain 52 (2):193-199. doi:10.1016/0304-3959(93)90131-8
33. Raja SN, Meyer RA, Campbell JN: Peripheral mechanisms of somatic pain. Anesthesiology 1988; 68: 571–590.
34. Nakamura-Craig M, Smith TW: Substance P and peripheral inflammatory hyperalgesia. Pain 1989; 38: 91–98.
35. Ge HY, Fernandez-de-las-Penas C, Arendt-Nielsen L: Sympathetic facilitation of hyperalgesia evoked from myofascial tender and trigger points in patients with unilateral shoulder pain. Clin Neurophysiol 2006; 117: 1545–1550.
36. Langguth B, Hund V, Busch V, Jürgens TP, Lainez JM, Landgrebe M, Schecklmann M (2015) Tinnitus and Headache. BioMed Res Int 2015:797416. doi:10.1155/2015/797416

37. Miguel A. Lopez-Gonzalez CL-L, Antonio Abrante, Pedro Benaixa, Francisco Esteban (2009) Sudden Deafness Caused by Lifestyle Stress: Pathophysiological Mechanisms and New Therapeutic Perspectives. *The Open Otorhinolaryngology Journal* 3:1-4. doi:10.2174/18744281003010001
38. Masuda M, Kanzaki S, Minami S, Kikuchi J, Kanzaki J, Sato H, Ogawa K (2012) Correlations of inflammatory biomarkers with the onset and prognosis of idiopathic sudden sensorineural hearing loss. *Otol Neurotol* 33 (7):1142-1150. doi:10.1097/MAO.0b013e3182635417
39. Guichard E, Montagni I, Tzourio C, Kurth T (2016) Association Between Headaches and Tinnitus in Young Adults: Cross-Sectional Study. *Headache* 56 (6):987-994. doi:10.1111/head.12845
40. Akdal G, Özge A, Ergör G (2015) Vestibular symptoms are more frequent in migraine than in tension type headache patients. *J Neurol Sci* 357 (1-2):295-296. doi:10.1016/j.jns.2015.06.059
41. Akdal G, Ozge A, Ergör G (2013) The prevalence of vestibular symptoms in migraine or tension-type headache. *J Vestibu Res* 23 (2):101-106. doi:10.3233/ves-130477
42. Marano E, Marcelli V, Di Stasio E, Bonuso S, Vacca G, Manganelli F, Marciano E, Perretti A (2005) Trigeminal stimulation elicits a peripheral vestibular imbalance in migraine patients. *Headache* 45 (4):325-331. doi:10.1111/j.1526-4610.2005.05069.x
43. Buisseret-Delmas C, Compoin C, Delfini C, Buisseret P (1999) Organisation of reciprocal connections between trigeminal and vestibular nuclei in the rat. *J Comp Neurol* 409 (1):153-168. doi:10.1002/(SICI)1096-9861(19990621)409:1<153::AID-CNE11>3.0.CO;2-# [pii] M1 - Journal Article
44. Ahn SK, Balaban CD (2010) Distribution of 5-HT1B and 5-HT1D receptors in the inner ear. *Brain Res* 1346:92-101. doi:10.1016/j.brainres.2010.05.057
45. Usman HO, Balaban CD (2016) Distribution of 5-HT(1F) Receptors in Monkey Vestibular and Trigeminal Ganglion Cells. *Front Neurol* 7:173. doi:10.3389/fneur.2016.00173
46. Shore SE, Vass Z, Wys NL, Altschuler RA (2000) Trigeminal ganglion innervates the auditory brainstem. *J Comp Neurol* 419 (3):271-285. doi:10.1002/(sici)1096-9861(20000410)419:3<271::aid-cne1>3.0.co;2-m
47. Viirre ES, Baloh RW (1996) Migraine as a cause of sudden hearing loss. *Headache* 36 (1):24-28. doi:10.1046/j.1526-4610.1996.3601024.x
48. Bolay H, Bayazit YA, Gündüz B, Ugur AK, Akçali D, Altunyay S, Ilica S, Babacan A (2008) Subclinical dysfunction of cochlea and cochlear efferents in migraine: an otoacoustic emission study. *Cephalalgia* 28 (4):309-317. doi:10.1111/j.1468-2982.2008.01534.x

Tables

Table 1. Characteristics of the migraine and control groups before and after PSM

	Before PSM		ASD	After PSM		
	Migraine (n = 15,128)	Control (n = 315,330)		Migraine (n = 15,128)	Control (n = 15,128)	ASD
Age, years (min, SD)	44.0 (14.3)	46.6 (15.4)	0.18	44 (14.3)	45 (14.6)	0.04
Female (n, %)	11,247 (74.3)	150,593 (47.8)	0.61	11,247 (74.3)	11,243 (74.3)	< 0.01
DM (n, %)	686 (4.5)	17,655 (5.6)	0.05	686 (4.5)	690 (4.6)	< 0.01
HTN (n, %)	1,657 (11)	26,579 (8.4)	0.08	1,657 (11)	1,703 (11.3)	< 0.01
Dyslipidemia (n, %)	959 (6.3)	19,032 (6)	0.01	959 (6.3)	923 (6.1)	< 0.01
Angina (n, %)	726 (4.8)	10,792 (3.4)	0.06	726 (4.8)	717 (4.7)	< 0.01
AF (n, %)	9 (4.6)	3,346 (1.1)	0.06	94 (0.6)	82 (0.5)	0.01
Heart disease (n, %)	518 (3.4)	9,202 (2.9)	0.03	518 (3.4)	497 (3.3)	< 0.01
Cerebrovascular disease (n, %)	1,756 (11.6)	14,888 (4.7)	0.21	1,756 (11.6)	1,840 (12.2)	0.02
Chronic pulmonary disease (n, %)	1,075 (7.1)	17,797 (5.6)	0.06	1,075 (7.1)	1,097 (7.3)	< 0.01
Renal failure (n, %)	145 (1)	4,355 (1.4)	0.04	145 (1)	142 (0.9)	< 0.01
Chronic hepatitis (n, %)	583 (3.9)	17,223 (5.5)	0.08	583 (3.9)	559 (3.7)	< 0.01
Anxiety (n, %)	641 (4.2)	3,607 (1.1)	0.15	641 (4.2)	636 (4.2)	< 0.01
Depression (n, %)	1,874 (12.4)	7,581 (2.4)	0.3	1,874 (12.4)	1,931 (12.8)	0.01
Sleep disorder (n, %)	912 (6)	5,230 (1.7)	0.18	912 (6)	907 (6)	< 0.01
Menopause (n, %)	584 (3.9)	7,128 (2.3)	0.08	584 (3.9)	590 (3.9)	< 0.01

PSM, propensity score matching; ASD, absolute standardized difference; SD, standard deviation; DM, diabetes mellitus; HTN, hypertension; AF, atrial fibrillation

Table 2. Characteristics of the non-migraine headache and control groups before and after PSM

	Before PSM		ASD	After PSM		
	NMH (n = 76,773)	Control (n = 315,330)		NMH (n = 14,606)	Control (n = 14,606)	ASD
Age, years (min, SD)	49.1 (14.6)	46.6 (15.4)	0.17	49 (14.6)	50 (14.9)	0.03
Female (n, %)	45,148 (58.8)	150,593 (47.8)	0.22	45,148 (58.8)	44,649 (58.2)	0.01
DM (n, %)	4,471 (5.8)	17,655 (5.6)	<0.01	4,471 (5.8)	4,700 (6.1)	0.01
HTN (n, %)	9,737 (12.7)	26,579 (8.4)	0.13	9,737 (12.7)	10,361 (13.5)	0.02
Dyslipidemia (n, %)	5,622 (7.3)	19,032 (6)	0.05	5,622 (7.3)	5,865 (7.6)	0.01
Angina (n, %)	4,394 (5.7)	10,792 (3.4)	0.1	4,394 (5.7)	4,393 (5.7)	< 0.01
AF (n, %)	911 (1.2)	3,346 (1.1)	0.01	911 (1.2)	914 (1.2)	< 0.01
Heart disease (n, %)	3,014 (3.9)	9,202 (2.9)	0.05	3,014 (3.9)	3,104 (4)	< 0.01
Cerebrovascular disease (n, %)	9,743 (12.7)	14,888 (4.7)	0.24	9,743 (12.7)	9,739 (12.7)	< 0.01
Chronic pulmonary disease (n, %)	5,871 (7.6)	17,797 (5.6)	0.08	5,871 (7.6)	6,085 (7.9)	0.01
Renal failure (n, %)	1,070 (1.4)	4,355 (1.4)	<0.01	1,070 (1.4)	1,095 (1.4)	< 0.01
Chronic hepatitis (n, %)	3,523 (4.6)	17,223 (5.5)	0.04	3,523 (4.6)	3,488 (4.5)	< 0.01
Anxiety (n, %)	2,679 (3.5)	3,607 (1.1)	0.13	2,679 (3.5)	2,502 (3.3)	0.01
Depression (n, %)	4,497 (5.9)	7,581 (2.4)	0.15	4,497 (5.9)	4,636 (6)	< 0.01
Sleep disorder (n, %)	2,700 (3.5)	5,230 (1.7)	0.1	2,700 (3.5)	2,782 (3.6)	< 0.01
Menopause (n, %)	2,602 (3.4)	7,128 (2.3)	0.06	2,602 (3.4)	2,549 (3.3)	< 0.01

NMH, non-migraine headache; PSM, propensity score matching; ASD, absolute standardized difference; SD, standard deviation; DM, diabetes mellitus; HTN, hypertension; AF, atrial fibrillation

Table 3. ORs for vestibular and cochlear disorders in migraine patients after PSM

	OR (95% CI)				
	MD	BPPV	VN	SNHL	Tinnitus
UA	2.519 (1.988–3.192)	1.941 (1.728–2.182)	2.838 (2.518–3.200)	1.647 (1.331–2.038)	1.867 (1.574–2.215)
AVA	2.597 (2.047–3.295)	2.045 (1.816–2.302)	2.976 (2.636–3.360)	1.740 (1.404–2.156)	1.972 (1.659–2.343)
AVPA	2.597 (2.047–3.295)	2.045 (1.816–2.302)	2.976 (2.636–3.360)	1.739 (1.404–2.155)	1.970 (1.658–2.341)

All *p*-values were *p* < 0.001. SPSS UA, unadjusted; AVA, all variables adjusted; AVPA, all variables plus propensity score adjusted; MD, Meniere’s disease; BPPV, benign paroxysmal positional vertigo; VN, vestibular neuronitis; SNHL, sensorineural hearing loss; OR, odds ratio; CI, confidence interval

Table 4. ORs for vestibular and cochlear disorders in migraine subgroups after PSM

ORs in the migraine group taking triptans (95% CI)					
	MD	BPPV	VN	SNHL	Tinnitus
UA	2.781 (1.943–3.960)	2.222 (1.853–2.664)	2.683 (2.228–3.230)	1.749 (1.250–2.448)	1.732 (1.350–2.224)
AVA	2.930 (2.040–4.209)	2.365 (1.965–2.845)	2.883 (2.385–3.484)	1.821 (1.298–2.556)	1.859 (1.443–2.394)
AVPA	2.928 (2.038–4.206)	2.359 (1.960–2.838)	2.882 (2.385–3.483)	1.812 (1.291–2.543)	1.862 (1.446–2.399)
ORs in the migraine group using NSAIDs (95% CI)					
	MD	BPPV	VN	SNHL	Tinnitus
UA	1.746 (1.315–2.318)	2.314 (1.997–2.683)	3.190 (2.743–3.711)	1.568 (1.228–2.048)	1.841 (1.490–2.275)
AVA	1.809 (1.360–2.408)	2.434 (2.095–2.827)	3.364 (2.887–3.921)	1.649 (1.275–2.134)	1.984 (1.572–2.414)
AVPA	1.809 (1.360–2.408)	2.433 (2.095–2.826)	3.365 (2.887–3.921)	1.649 (1.274–2.133)	1.941 (1.566–2.405)

All *p*-values were *p* < 0.001. SPSS UA, unadjusted; AVA, all variables adjusted; AVPA, all variables plus propensity score adjusted; MD, Meniere's disease; BPPV, benign paroxysmal positional vertigo; VN, vestibular neuronitis; SNHL, sensorineural hearing loss; NSAIDs, non-steroid anti-inflammatory drugs; OR, odds ratio; CI, confidence interval

Table 5. ORs for vestibular and cochlear disorders in non-migraine headache patients after PSM

OR (95% CI)					
	MD	BPPV	VN	SNHL	tinnitus
UA	1.749 (1.541–1.984)	1.681 (1.590–1.777)	1.990 (1.881–2.105)	1.339 (1.222–1.468)	1.640 (1.521–1.768)
AVA	1.774 (1.562–2.014)	1.731 (1.637–1.831)	2.048 (1.935–2.168)	1.395 (1.272–1.530)	1.693 (1.569–1.827)
AVPA	1.771 (1.560–2.011)	1.731 (1.637–1.831)	2.048 (1.935–2.168)	1.396 (1.273–1.531)	1.693 (1.569–1.826)

All *p*-values were *p* < 0.001. SPSS UA, unadjusted; AVA, all variables adjusted; AVPA, all variables plus propensity score adjusted; MD, Meniere’s disease; BPPV, benign paroxysmal positional vertigo; VN, vestibular neuronitis; SNHL, sensorineural hearing loss; OR, odds ratio; CI, confidence interval

Figures

Figure 1

Flow chart of the enrollment process

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [supplementarymaterialdata.xlsx](#)