Risk of hearing loss in patients with fibromyalgia: A nationwide population-based retrospective cohort study

Thi Phuong Le¹, Ya-Ling Tzeng²,³, Chih-Hsin Muo⁴, Hua Ting⁵,⁶,⁷, Fung-Chang Sung⁸, Shin-Da Lee⁹,¹⁰, Yu-Kuei Teng²,³,*

¹ Nursing Department, Duy Tan University, Da Nang, Vietnam, ² School of Nursing and Graduate Institute of Nursing, China Medical University, Taichung, Taiwan, ³ Department of Nursing, China Medical University Hospital, Taichung, Taiwan, ⁴ Management Office for Health Data, China Medical University Hospital, Taichung, Taiwan, ⁵ Institute of Medicine, Chung-Shan Medical University, Taichung, Taiwan, ⁶ Sleep Medicine Center, Chung Shan Medical University Hospital, Taichung, Taiwan, ⁷ Department of Physical Medicine and Rehabilitation, Chung Shan Medical University Hospital, Taichung, Taiwan, ⁸ Department of Public Health, China Medical University, Taichung, Taiwan, ⁹ Department of Physical Therapy, Graduate Institute of Rehabilitation Science, China Medical University, Taichung, Taiwan, ¹⁰ Department of Healthcare Administration, Asia University, Taichung, Taiwan

* These authors contributed equally to this work.
* tengyk@mail.cmu.edu.tw (YKT); shinda@mail.cmu.edu.tw (SDL)

Abstract

Objectives
Our objectives are to examine whether patients with fibromyalgia (FM) present an increased risk of hearing loss (HL) compared with those without FM and to explore the relationship between comorbidities/drugs and development of HL in patients with FM. Furthermore, we investigated the incidence rate of different types of HL and the joint effects for HL with FM and comorbidities.

Methods
This population-based retrospective cohort study included patients with new-onset FM from 2000 to 2002 (the FM group) and age- and sex-matched randomized patients without FM (the non-FM group) from Taiwan’s National Health Insurance Research Database. Patients were followed up from baseline (3 months after FM diagnosis) until death, withdrawal, HL development, or December 31, 2013. The primary outcome was the risk of HL, which was assessed using Cox proportional-hazards analysis.

Results
The overall HL risk in the FM group was 1.46-fold (95% confidence interval [CI]: 1.38–1.55) higher than that in the non-FM group after adjustment for sex, age, and comorbidities (p < 0.0001). Patients with FM had significantly greater sensorineural HL (adjusted hazard ratio = 1.46, 95% CI: 1.37–1.56) than those without FM. Patients with FM having comorbidities of diabetes, hyperlipidemia, depression, and Meniere’s disease had a higher risk of HL than those without FM.
Conclusion

Our findings support the notion that FM influences HL and is in line with the hypothesis that the FM mechanism is related to a central nervous system abnormality in sensory processing. Health care professionals should provide appropriate screening for the risk of HL and prevention and counseling methods for patients with FM.

Introduction

Fibromyalgia (FM) is a musculoskeletal condition characterized by chronic widespread pain and specific tender points [1]. Its prevalence in the general population is 0.2%–4.7% and increases from the middle age; it is more common in women than in men [2, 3]. Patients with FM often have nonspecific symptoms and are at increased risk of many comorbidities and disorders [4]. Recently, a mechanism underlying FM etiopathology was hypothesized, which led to evidence suggesting that people with FM also may be at risk of hearing loss (HL) [5, 6]. The etiopathogenesis of FM remains clear, but it appears to be complex and multifactorial, involving familial, genetic, environmental, endocrine, and neurological system (both central and peripheral) factors. Dysregulation of the central nervous system (CNS) and peripheral nervous system affects FM development, which might be associated with the activation of nociceptive pathways, further contributing to central sensitization. Central sensitization involves CNS pain amplification and neuroendocrine dysfunctions, including decreased levels of serotonin (which inhibits pain signals) and increased levels of substance P (which propagates pain signals) [7, 8], leading to abnormal pain processing [7]. Thus, FM seems to be closely linked to central sensitivity syndromes, and patients with FM seem to have a nervous system that is overly sensitive to all stimuli [5]. Furthermore, patients with FM might also have brainstem dysfunction, which may cause abnormalities in processing auditory stimuli [5, 6]. Taken together, these findings imply that patients with FM have hypersensitivity toward not only pain but also sensory processing such as hearing.

HL is a leading cause of disability in adults [9] and causes serious communication and psychosocial problems and reduced quality of life. HL may be the result of damage to any part of the peripheral and central auditory systems [9]. Peripheral HL may be conductive (outer or middle ear impairment), sensorineural (cochlear or spiral ganglion dysfunction), or mixed. Neural HL is due to loss or dysfunction of spiral ganglion neurons or of more proximal auditory structures. The etiology of HL includes degenerative processes associated with aging, genetic mutations, exposure to noise, drug-induced adverse effects, and chronic diseases [9]. Studies on HL in people with FM have reported conflicting results [10–15], and long-term population-based cohort studies on the link between HL risk in patients with FM are lacking. Additionally, comorbidities and use of drugs in patients may also relate to HL development [16–22]. However, no study has examined the risk of HL in patients with FM stratified by these comorbidities, HL-inducing drugs, and drugs commonly used in patients with FM, such as antidepressants and pain-relieving drugs. To the best of our knowledge, retrospective cohort studies investigating whether FM influences HL and whether an association exists between comorbidities, drugs, and the risk of HL in patients with FM are scarce.

In this study, we used the Taiwan National Health Insurance Research Database (NHIRD), which has a large sample size. The study hypothesis was that patients with FM had a higher risk of HL than those without FM, after adjustment for sex, age, and comorbidities. More specifically, this study investigated whether people with FM have a significantly higher risk of HL.
than people without FM and whether the common comorbidities and drugs in patients with FM are associated with a risk of HL.

Methods

Data source

In the present population-based cohort study, we used the Longitudinal Health Insurance Database (LHID) 2000, which was retrieved from the NHIRD, Taiwan. Taiwan’s National Health Insurance (NHI) system is a single-payer mandatory program, which covers >99% of Taiwan’s population. The LHID 2000 contains the medical reimbursement claims data of 1 million people randomly sampled from the entire population registered in 2000 and is thus representative of the whole population. The disease diagnoses were encoded in accordance with the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM). For protecting personal privacy, patients’ personal information was encrypted in the released database. Therefore, patient consent is not required to access the NHIRD. This study was approved by the Institutional Review Board of China Medical University (CMUH104-REC2-115[CR-2]). The NHIRD was used for data analysis with the approval of the NHI administration.

Criteria for selecting patients

Fig 1 illustrates the process of identifying patients for this study. We used the diagnostic codes of the ICD-9-codes to identify patients with HL (ICD-9-codes 389, 389.1, and 389.2) and FM (ICD-9-codes 729.0 and 729.1). The ICD-9-codes of subtypes of sensorineural HL include bilateral sensory HL (ICD-9-code 389.11), bilateral neural HL (ICD-9-code 389.12), unilateral neural HL (389.13), and central HL (389.14). We identified an FM cohort and a non-FM cohort from the LHID2000. Patients who were newly diagnosed as having FM for at least 3 months (defined as baseline) between 2000 and 2002 (n = 55,169) were included as the study group (FM group). The date of FM diagnosis was defined as the index date. We excluded those who had HL at baseline and those for whom information on sex or age was missing. Each FM patient in this study was randomly frequency matched with two patients without FM and HL according to age (in 5-year bands), sex, and index year from the LHID2000 to obtain the non-FM group (n = 110,338). Participants were tracked from baseline until development of HL, loss to follow-up, withdrawal from NHI, or December 31, 2013 to examine the risk of HL in patients with FM compared with controls.

Variables of comorbidity and drugs

Baseline comorbidities and diseases considered as potential covariates in the inferring of association between FM and HL included the following: diabetes (ICD-9-code 250), hypertension (ICD-9-codes 401–405), hyperlipidemia (ICD-9-code 272), depression (ICD-9-codes 296.2, 296.3, 300.4, and 311), anxiety (ICD-9-codes 300.01, 300.02, 300.2, 300.3, 308, and 309.81), Meniere’s disease (ICD-9-code 386), insomnia (ICD-9-codes 780.52, 307.40, 307.41, 307.42, 307.43, and 307.44), and autoimmune diseases, including psoriasis (ICD-9-code 696), systemic lupus erythematosus (ICD-9-code 710.0), systemic sclerosis (ICD-9-code 710.1), Sjogren syndrome (ICD-9-code 710.2), dermatomyositis (ICD-9-code 710.3), polymyositis (ICD-9-code 710.4), and vasculitis (ICD-9-codes 446.0, 446.2, 446.4, 446.5, 443.1, 446.7, 446.1, and 136.1).

Pain-relieving drugs comprises dopamine-receptor agonists, serotonin 5-HT3 receptor antagonists, anti-epileptics, and opioid drugs. HL-inducing drugs include antimalarial drugs, aminoglycoside antibiotic drugs, tetracycline antibiotic drugs, other antibiotic drugs,
macrolide antibiotic drugs, phosphodiesterase type 5 inhibitors, aspirin, diuretic drugs, and antitumor drugs/chemotherapeutic agents.

Statistics
SAS software version 9.1 (SAS Institute, Cary, NC, USA) was used to calculate descriptive and inferential statistics. χ² test for categorical data and Student’s t tests for continuous data were used to compare intergroup differences in terms of sex, age, and comorbidities. The incidence rates of HL (per 1000 person-years) and the FM cohort to non-FM cohort hazard ratio (HR) of HL with 95% confidence interval (CI) were calculated using the Cox proportional-hazards analysis. Survival was analyzed with the Kaplan–Meier method, and the cumulative incidence of HL was compared between the FM and non-FM cohorts by using the log-rank test. The statistical significance level was set as P < 0.05.
Results

In this retrospective cohort study, we selected 55,169 patients with FM for the FM group and 110,338 matched patients in sex and age for the non-FM group (1:2 match ratio). In all, 59.4% of the participants were female and 40.6% were male, and the predominant age group was 40–59 years (40.6%; Table 1). The FM group had a higher percentage of comorbidities than the non-FM group, including diabetes, hypertension, hyperlipidemia, depression, anxiety, Meniere’s disease, insomnia, and autoimmune diseases. Patients with FM had a significantly higher prevalence of using antidepressants, pain-relieving drugs, and HL-inducing drugs.

Fig 2 shows that the cumulative HL incidence was higher in the FM group (4.03 per 1000 person-years) than in the non-FM group (2.33 per 1000 person-years; log-rank P < 0.0001) at the end of the follow-up period (Table 2). The overall HL risk in the FM group was 1.46-fold (95% CI: 1.38–1.55) higher than that in the non-FM group after adjustment for sex, age, and comorbidities (p < 0.0001). In general, the incidence of HL was higher in men than in women. The risk of HL in men was 1.45-fold (95% CI: 1.37–1.54, p < 0.0001) higher than that in women.

Table 1. Distribution of sex, age, and comorbidity between patients with and without fibromyalgia.

| Variable                | Fibromyalgia (N = 55169) | Comparison (N = 110338) | P-value |
|-------------------------|--------------------------|-------------------------|---------|
| Sex                     |                          |                         | 0.99    |
| Female                  | 32756(59.4)              | 65512(59.4)             |         |
| Male                    | 22413(40.6)              | 44826(40.6)             |         |
| Age, year               |                          |                         | 0.99    |
| <40                     | 20557(37.3)              | 41114(37.3)             |         |
| 40–59                   | 22419(40.6)              | 44838(40.6)             |         |
| 60+                     | 12193(22.1)              | 24386(22.1)             |         |
| Mean (SD)               | 45.9(16.9)               | 45.8(17.0)              | 0.56    |
| Comorbidity             |                          |                         |         |
| Diabetes                | 6476(11.7)               | 10062(9.12)             | <0.0001 |
| Hypertension            | 14681(26.6)              | 22656(20.5)             | <0.0001 |
| Hyperlipidemia          | 9928(18.0)               | 12612(11.4)             | <0.0001 |
| Depression              | 2136(3.87)               | 2030(1.84)              | <0.0001 |
| Anxiety                 | 626(1.13)                | 580(0.53)               | <0.0001 |
| Meniere’s disease       | 4180(7.58)               | 3937(3.57)              | <0.0001 |
| Insomnia                | 3961(7.18)               | 3333(3.20)              | <0.0001 |
| Autoimmune diseases b   | 271(0.49)                | 421 (0.38)              | 0.001   |
| Medicine                |                          |                         |         |
| Anti-depression         | 4210(7.63)               | 4099(3.71)              | <0.0001 |
| Pain-relieving drug c   | 3597(6.52)               | 3593(3.26)              | <0.0001 |
| Hearing loss-inducing drug d | 26509(48.1)     | 35985 (32.6)            | <0.0001 |

a Autoimmune disease: psoriasis, systemic lupus erythematosus, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.
b Patients who underwent medical treatment within 1 year before the index date.
c Pain-relieving drugs: dopamine-receptor agonists, serotonin 5-HT3 receptor antagonists, antiepileptics, and opioid analgesics.
d Hearing loss–inducing drugs: antimalarial drugs, aminoglycoside antibiotic drugs, tetracycline antibiotic drugs, other antibiotic drugs, macrolide antibiotic drugs, phosphodiesterase type 5 inhibitors, aspirin, diuretic drugs, and antitumor drugs/chemotherapeutic agents.

https://doi.org/10.1371/journal.pone.0238502.t001
in women after adjustment for sex, age, and comorbidities. Compared with those aged <40 years, the risk of HL was higher in older patients and increased with age. Stratified by comorbidities, the crude HRs indicated that patients with comorbidities had a 1.68–3.53-fold increased risk of HL than patients without comorbidities. After adjustment for FM, sex, age, and drugs, the risk of HL in patients with comorbidities such as diabetes, hyperlipidemia, depression, and Meniere’s disease was significantly higher than that in those without these comorbidities. Stratified by drugs, people taking antidepressants and HL-inducing drugs had higher risks of HL than those who were not taking these drugs.

Results in Table 3 indicated that patients with FM had a significantly increased risk of HL than those without FM with overall (aHR = 1.45, CI: 1.37–1.53, p < 0.0001), conductive (aHR = 1.34, CI: 1.01–1.78, p = 0.044), sensorineural (aHR = 1.46, CI: 1.37–1.56, p < 0.0001), and mixed HL (aHR = 1.56, CI: 1.20–2.02, p = 0.0008) after adjustment for age, sex, comorbidities, and drugs. Among patients with FM with sensorineural HL, the most common type is sensory HL, bilateral (aHR = 1.32, CI: 1.02–1.71, p = 0.03). Patients with FM had a higher risk of sensorineural HL than of conductive HL compared with the non-FM group.

The adjusted HRs in women and men were similar in both groups (aHR = 1.50, 95% CI: 1.38–1.63 [women] vs. aHR = 1.41, 95% CI: 1.29–1.54 [men]) after controlling for sex, age, comorbidity, and drugs in Table 4. Stratified by age, the risk of HL in the patients with FM was
| Variable                | Hearing loss no. | Person-years | Rate | Crude        | p       | Adjusted       | P-value   |
|------------------------|------------------|--------------|------|--------------|---------|----------------|-----------|
| Fibromyalgia           |                  |              |      |              |         |                |           |
| No                     | 2186             | 9374718      | 2.33 | Ref.         |         | Ref.           |           |
| Yes                    | 2590             | 6442239      | 4.03 | 1.72 (1.63–1.82) | <0.0001 | 1.46 (1.38–1.55) | <0.0001  |
| Sex                    |                  |              |      |              |         |                |           |
| Female                 | 2454             | 929358       | 2.64 | Ref.         |         | Ref.           |           |
| Male                   | 2322             | 650299       | 3.57 | 1.35 (1.28–1.43) | <0.0001 | 1.45 (1.37–1.54) | <0.0001  |
| Age                    |                  |              |      |              |         |                |           |
| < 40                   | 737              | 636945       | 1.16 | Ref.         |         | Ref.           |           |
| 40–59                  | 1870             | 648135       | 2.89 | 2.50 (2.30–2.72) | <0.0001 | 2.24 (2.06–2.45) | <0.0001  |
| 60+                    | 2169             | 294576       | 7.36 | 6.46 (5.94–7.02) | <0.0001 | 4.71 (4.28–5.17) | <0.0001  |
| Comorbidity            |                  |              |      |              |         |                |           |
| Diabetes               |                  |              |      |              |         |                |           |
| No                     | 3890             | 1442987      | 2.70 | Ref.         |         | Ref.           |           |
| Yes                    | 886              | 136669       | 6.48 | 2.42 (2.25–2.60) | <0.0001 | 1.11 (1.03–1.21) | 0.01     |
| Hypertension           |                  |              |      |              |         |                |           |
| No                     | 2809             | 1263284      | 2.22 | Ref.         |         | Ref.           |           |
| Yes                    | 1967             | 316372       | 6.22 | 2.81 (2.66–2.98) | <0.0001 | 1.06 (0.99–1.14) | 0.11     |
| Hyperlipidemia         |                  |              |      |              |         |                |           |
| No                     | 3550             | 1379315      | 2.57 | Ref.         |         | Ref.           |           |
| Yes                    | 1226             | 200341       | 6.12 | 2.38 (2.23–2.54) | <0.0001 | 1.21 (1.13–1.31) | <0.0001  |
| Depression             |                  |              |      |              |         |                |           |
| No                     | 4536             | 1542623      | 2.94 | Ref.         |         | Ref.           |           |
| Yes                    | 240              | 37034        | 6.48 | 2.21 (1.94–2.52) | <0.0001 | 1.18 (1.02–1.37) | 0.03     |
| Anxiety                |                  |              |      |              |         |                |           |
| No                     | 4721             | 1568726      | 3.01 | Ref.         |         | Ref.           |           |
| Yes                    | 55               | 10930        | 5.03 | 1.68 (1.28–2.18) | 0.0001  | 0.96 (0.73–1.25) | 0.74     |
| Meniere’s disease      |                  |              |      |              |         |                |           |
| No                     | 4108             | 1509853      | 2.72 | Ref.         |         | Ref.           |           |
| Yes                    | 668              | 69804        | 9.57 | 3.53 (3.25–3.83) | <0.0001 | 1.84 (1.68–2.00) | <0.0001  |
| Insomnia               |                  |              |      |              |         |                |           |
| No                     | 4357             | 1514251      | 2.88 | Ref.         |         | Ref.           |           |
| Yes                    | 419              | 65406        | 6.38 | 2.22 (2.01–2.46) | <0.0001 | 1.11 (0.97–1.23) | 0.06     |
| Autoimmune diseases a  |                  |              |      |              |         |                |           |
| No                     | 4754             | 1573486      | 3.02 | Ref.         |         | Ref.           |           |
| Yes                    | 22               | 6171         | 3.57 | 1.18 (0.78–1.80) | 0.43    |                |           |
| Medicine               |                  |              |      |              |         |                |           |
| Anti-depression        |                  |              |      |              |         |                |           |
| No                     | 4295             | 1507950      | 2.85 | Ref.         |         | Ref.           |           |
| Yes                    | 481              | 71706        | 6.71 | 2.36 (2.14–2.59) | <0.0001 | 1.29 (1.16–1.43) | <0.0001  |
| Pain-relieving drug b  |                  |              |      |              |         |                |           |
| No                     | 4425             | 1517824      | 2.92 | Ref.         |         | Ref.           |           |
| Yes                    | 351              | 61832        | 5.68 | 1.95 (1.75–2.17) | <0.0001 | 1.10 (0.98–1.23) | 0.11     |
| Hearing loss-inducing drug c  |          |              |      |              |         |                |           |
| No                     | 2610             | 999496       | 2.61 | Ref.         |         | Ref.           |           |

(Continued)
significantly higher than that in the patients without FM aged <40 (aHR = 1.73, 95% CI: 1.48–2.01, p < 0.0001), 40–59 (aHR = 1.44, 95% CI: 1.31–1.58, p < 0.0001), and ≥60 (aHR = 1.35, 95% CI: 1.23–1.47, p < 0.0001). Patients with FM <40 years old had a higher risk of HL than those without FM in the other age groups.

The incidence rate of HL was higher in patients with comorbidities (diabetes, hypertension, hyperlipidemia, depression, and Meniere’s disease) than in those without comorbidities in both the FM and non-FM groups. Nevertheless, after adjustment for sex, age, comorbidities, and drugs, patients with FM had significantly higher risks of HL than those without FM regardless of whether they had these comorbidities (all p < 0.05). Patients taking antidepressants, pain-relieving drugs, and HL-inducing drugs exhibited increased HL incidence rates in both FM and non-FM groups. However, after adjustment for sex, age, comorbidities, and drugs, patients with FM still had a higher risk of HL than those in the non-FM group irrespective of whether they used these drugs after adjustment for sex, age, comorbidity, and drugs (all p < 0.05).

Regarding the joint effects of various comorbidities on the risk of HL, Table 5 shows the results of regression models adjusted for age, sex, pain-relieving drugs, and HL-inducing drugs. Compared with patients without any comorbidity (reference group), the independent effect of FM on the risk of HL was statistically significant (aHR = 1.63, 95% CI: 1.49–1.78, p < 0.0001). Patients with Meniere’s disease were at the highest risk of HL among patients with only one comorbidity (aHR = 2.80, 95% CI: 2.09–3.76, p < 0.0001). Among patients with FM with one comorbidity, those with Meniere’s disease exhibited the highest risk (aHR = 4.01, 95% CI: 3.27–4.94), followed by those with hyperlipidemia, diabetes, insomnia, hypertension,
Table 4. Incidence and risk of hearing loss stratified by sex, age group, comorbidity, and drug.

| Variable           | Fibromyalgia Hearing loss no. | Person-years | Rate  | Comparison Hearing loss no. | Person-years | Rate  | Adjusted HR (95% CI) | p     |
|--------------------|-------------------------------|--------------|-------|-----------------------------|--------------|-------|----------------------|-------|
| Sex                |                               |              |       |                             |              |       |                      |       |
| Female             | 1382                          | 387094       | 3.57  | 1072                        | 542263       | 1.98  | 1.50 (1.38–1.63)     | <0.0001|
| Male               | 1208                          | 255144       | 4.73  | 1114                        | 395154       | 2.82  | 1.41 (1.29–1.54)     | <0.0001|
| Age, year          |                               |              |       |                             |              |       |                      |       |
| < 40               | 414                           | 250440       | 1.65  | 323                         | 386505       | 0.84  | 1.73 (1.48–2.01)     | <0.0001|
| 40–59              | 1046                          | 268150       | 3.90  | 824                         | 379985       | 2.17  | 1.44 (1.31–1.58)     | <0.0001|
| 60+                | 1130                          | 123648       | 9.14  | 1039                        | 170928       | 6.08  | 1.35 (1.23–1.47)     | <0.0001|
| Comorbidity        |                               |              |       |                             |              |       |                      |       |
| Diabetes           |                               |              |       |                             |              |       |                      |       |
| No                 | 2074                          | 573223       | 3.62  | 1816                        | 869764       | 2.09  | 1.48 (1.38–1.58)     | <0.0001|
| Yes                | 516                           | 59015        | 7.48  | 370                         | 67654        | 5.47  | 1.35 (1.18–1.56)     | <0.0001|
| Hypertension       |                               |              |       |                             |              |       |                      |       |
| No                 | 1457                          | 484432       | 3.01  | 1352                        | 778852       | 1.74  | 1.54 (1.42–1.66)     | <0.0001|
| Yes                | 1133                          | 157806       | 7.18  | 834                         | 158566       | 5.26  | 1.31 (1.20–1.44)     | <0.0001|
| Hyperlipidemia     |                               |              |       |                             |              |       |                      |       |
| No                 | 1835                          | 530273       | 3.46  | 1715                        | 849042       | 2.2   | 1.53 (1.43–1.64)     | <0.0001|
| Yes                | 755                           | 111966       | 6.74  | 471                         | 88375        | 5.33  | 1.22 (1.08–1.38)     | 0.001 |
| Depression         |                               |              |       |                             |              |       |                      |       |
| No                 | 2412                          | 618652       | 3.90  | 2124                        | 923970       | 2.30  | 1.45 (1.36–1.54)     | <0.0001|
| Yes                | 178                           | 23586        | 7.55  | 62                          | 13447        | 4.61  | 1.68 (1.24–2.26)     | 0.0007|
| Anxiety            |                               |              |       |                             |              |       |                      |       |
| No                 | 2549                          | 635160       | 4.01  | 2172                        | 933566       | 2.33  | 1.46 (1.37–1.55)     | <0.0001|
| Yes                | 41                            | 7079         | 5.79  | 14                           | 3852         | 3.63  | 1.70 (0.90–3.21)     | 0.10  |
| Meniere's disease  |                               |              |       |                             |              |       |                      |       |
| No                 | 2119                          | 597346       | 3.55  | 1989                        | 912507       | 2.18  | 1.45 (1.36–1.55)     | <0.0001|
| Yes                | 471                           | 44892        | 10.49 | 197                         | 24911        | 7.91  | 1.41 (1.18–1.67)     | 0.0001|
| Insomnia           |                               |              |       |                             |              |       |                      |       |
| No                 | 2296                          | 599029       | 3.83  | 2063                        | 915222       | 2.25  | 1.47 (1.38–1.57)     | <0.0001|
| Yes                | 294                           | 43210        | 6.80  | 123                          | 22196        | 5.54  | 1.23 (0.99–1.53)     | 0.07  |
| Autoimmune diseases a |                           |              |       |                             |              |       |                      |       |
| No                 | 2576                          | 639353       | 4.03  | 2178                        | 934133       | 2.33  | 1.46 (1.37–1.55)     | <0.0001|
| Yes                | 14                            | 2885         | 4.85  | 8                           | 3285         | 2.44  | 1.80 (0.73–4.40)     | 0.20  |
| Medicine           |                               |              |       |                             |              |       |                      |       |
| Anti-depression    |                               |              |       |                             |              |       |                      |       |
| No                 | 2237                          | 596237       | 3.75  | 2058                        | 911714       | 2.26  | 1.44 (1.35–1.53)     | <0.0001|
| Yes                | 353                           | 46002        | 7.67  | 128                         | 25704        | 4.98  | 1.62 (1.31–1.99)     | <0.0001|
| Pain-relieving drug b |                           |              |       |                             |              |       |                      |       |
| No                 | 2343                          | 603160       | 3.88  | 2082                        | 914664       | 2.28  | 1.47 (1.38–1.56)     | <0.0001|
| Yes                | 247                           | 39079        | 6.32  | 104                         | 22753        | 4.57  | 1.31 (1.04–1.66)     | 0.02  |
| Hearing loss-inducing drug c |                     |              |       |                             |              |       |                      |       |
| No                 | 1233                          | 335870       | 3.67  | 1377                        | 663626       | 2.07  | 1.56 (1.44–1.69)     | <0.0001|
| Yes                | 1357                          | 306369       | 4.43  | 809                         | 273791       | 2.95  | 1.33 (1.21–1.45)     | <0.0001|

Manually adjusted for age, sex, diabetes, hypertension, hyperlipidemia, depression, anxiety, Meniere’s disease, insomnia, pain-relieving drug, and hearing loss-inducing drug.

a Autoimmune disease: psoriasis, systemic lupus erythematosus, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis and vasculitis.
b Pain-relieving drugs: dopamine-receptor agonists, serotonin 5-HT3 receptor antagonists, antiepileptics, and opioid analgesics.
c Hearing loss–inducing drugs: antimalarial drugs, aminoglycosides antibiotic drugs, tetracycline antibiotic drugs, other antibiotic drugs, macrolide antibiotic drugs, phosphodiesterase type 5 inhibitors, aspirin, diuretic drugs, and antitumor drugs/chemotherapeutic agents.

https://doi.org/10.1371/journal.pone.0238502.t004
and depression (S1 Appendix). Patients with FM with any five comorbidities exhibited the highest risk of HL (aHR = 3.71, 95% CI: 2.64–5.23, p < 0.0001; Table 5).

Discussion

The incidence rate for HL was higher in patients with FM, which confirms the association between FM and HL. This finding is consistent with that of previous studies and supports the hypothesis that patients with FM are at a higher risk of HL than those without FM [10–12]. Wolfe et al. reported that patients with FM had more sensory symptoms than those with rheumatoid arthritis or osteoarthritis [11]. However, in their study, HL was self-reported by the patients as "hearing difficulties within the last 6 months"; HL was not diagnosed by the physician. Stranden et al. reported that patients with FM showed an increase in subjective HL than those without FM or other musculoskeletal pain disorders [10]. The authors did not adjust for FM measured correctly by the physician, but adjusted for anxiety and depression symptoms, which were self-reported through questionnaires. Gencer et al. demonstrated that the patients with FM had significantly lower air conduction threshold values than the patients without FM at high frequencies [12], but they too did not adjust for other comorbidities and drugs.

The current result showed that sensorineural HL occurred commonly in patients with FM. This finding agrees with the results of Gerster & Hadl-Djilani [23] and Dohrenbusch et al. [24], who reported sensorineural HL in patients with FM in both high and low frequencies. Patients with FM may have sensorineural HL and auditory brainstem response abnormalities because of inner ear or central auditory damage [6]. This relationship may be partly explained by the notion that FM pathomechanism is related to central sensitization, including CNS sensory functions such as hearing. In addition, patients with FM in our cohort had conductive HL. Conductive HL is caused by problems in the outer ear, ear canal, or middle ear structures. Consequently, HL may have been caused by mechanisms involved in the pathogenesis of otoneurologic and systemic signs/symptoms of FM, which may induce abnormal perception of the stimuli from internal or external circumstances. Few patients in our cohort developed

Table 5. Joint effects of comorbidities on hearing loss.

| Variables                     | N     | Hearing loss no. | Person-years | Rate  | Adjusted HR (95% CI) | p       |
|-------------------------------|-------|------------------|--------------|-------|----------------------|---------|
| None                          | 77688 | 1062             | 707150       | 1.50  | Ref.                 |         |
| Only Fibromyalgia             | 32017 | 915              | 385773       | 2.37  | 1.63 (1.49–1.78)     | <0.0001 |
| Only Diabetes                 | 1759  | 42               | 13053        | 3.22  | 1.28 (0.94–1.74)     | 0.12    |
| Only Hypertension             | 10029 | 300              | 74430        | 4.03  | 1.28 (1.12–1.46)     | 0.0003  |
| Only Hyperlipidemia           | 2994  | 74               | 22379        | 3.31  | 1.53 (1.21–1.94)     | 0.0004  |
| Only Depression               | 636   | 14               | 4655         | 3.01  | 1.59 (0.94–2.70)     | 0.09    |
| Only Meniere’s disease        | 1151  | 47               | 8028         | 5.85  | 2.80 (2.09–3.76)     | <0.0001 |
| Only Insomnia                 | 1032  | 24               | 7113         | 3.37  | 1.75 (1.17–2.62)     | 0.007   |
| Fibromyalgia with any one comorbidity | 11577 | 671              | 131845       | 5.09  | 2.03 (1.83–2.24)     | <0.0001 |
| Fibromyalgia with any two comorbidities | 6607  | 536              | 72209        | 7.42  | 2.49 (2.23–2.79)     | <0.0001 |
| Fibromyalgia with any three comorbidities | 3616  | 309              | 38551        | 8.02  | 2.43 (2.13–2.79)     | <0.0001 |
| Fibromyalgia with any four comorbidities | 1072  | 121              | 11073        | 10.93 | 3.03 (2.49–3.69)     | <0.0001 |
| Fibromyalgia with any five comorbidities | 245   | 35               | 2459         | 14.23 | 3.71 (2.64–5.23)     | <0.0001 |
| Fibromyalgia with any all comorbidities | 35    | 3                | 329          | 9.11  | 2.13 (0.68–6.63)     | 0.19    |
| Only comorbidity more than one | 15049 | 623              | 100608       | 6.19  | 1.93 (1.74–2.15)     | <0.0001 |

Adjusted for age, sex, antidepressants, pain-relieving drugs, and hearing loss–inducing drugs.

Comorbidities included diabetes, hypertension, hyperlipidemia, depression, Meniere’s disease, and insomnia.

https://doi.org/10.1371/journal.pone.0238502.t005
neural HL and central HL. Patients with HL had degenerative changes earlier in the central than in the peripheral auditory system [25]. Some studies have stated that patients with FM can report hearing-related complaints but display no objective defect in the audiometry [6, 13]. Similarly, measurement of auditory brainstem responses do not reveal changes in all patients with FM with hearing complaints. This makes it difficult to distinguish between peripheral and central origins in FM patients with hearing complaints.

Women and men with FM had a similar risk of HL compared with the non-FM group, consistent with the finding of Stranden et al. [10]. However, there is a considerably higher number of women with FM than men with FM [3], indicating higher numbers of women with FM who are at risk of HL than men with FM. Accordingly, clinicians should pay attention to the development of HL in women with FM.

In this study, the risk of HL was slightly greater in patients with FM aged ≤40 years than other age groups. By contrast, Stranden et al. demonstrated that the risk of HL increases with age in patients with FM [10]. A possible explanation for this discrepancy might be the high number of younger people in the current study with fewer HL-related comorbidities than their older counterparts, leading to a more pronounced effect of FM on the younger age group.

Some studies have reported results that corroborate the findings with HL-inducing drugs [21, 26, 27]. Our results revealed that patients taking antidepressants and HL-inducing drugs, such as anti-infectives, cancer drugs, loop diuretics, and aspirin, had a clear risk of HL. Moreover, patients taking pain-relieving drugs such as dopamine-receptor agonists, serotonin 5-HT3 receptor antagonists, antiepileptics, and opioid analgesics in this study had higher risks of HL, which was proposed by Oroei et al. and Hamed [28, 29]. The correlation between these drugs and HL development in FM needs further investigation.

FM has been considered a risk factor for HL [10–12], but no study has evaluated the combined effect of comorbidities in patients with FM on HL. The current study fills this gap and reveals that diabetes, hypertension, hyperlipidemia, depression, and Meniere’s disease increase the risk of HL in patients with FM both independently and jointly with FM. These conditions are often observed in combination with HL [16–19, 30], which is also commonly found in patients with FM [4, 31–33]. Moreover, HL is one of the most prevalent chronic health conditions in older adults [34], and the co-occurrence of two or more chronic conditions is common in older people [35]. The onset of FM is usually in the middle age [3]. Taken together, these data suggest that comorbidities and FM both contribute to HL development, and the joint effect in middle-aged or older adults might worsen the HL.

**Strengths and limitations**

This study has some strengths. First, the FM and non-FM groups were matched for age, sex, and index year, which excludes the effects of these potential confounding variables. Second, the large sample size consolidates power for subgroup stratifications for further statistical analyses, which enabled us to determine the independent and joint effect of FM and comorbidities on HL development. Third, our study minimized the number of patients lost to follow-up because of the high coverage rate of the NHI program throughout the study.

However, this study had a few limitations. We could not control for other behavioral factors of HL risk, such as alcohol drinking, smoking, obesity, and physical activity, which were not obtained from the NHI dataset. Patients with FM and HL were enrolled based on physician diagnosis rather than through research assignment. Other factors not available in the NHIRD such as the stage of FM and neurotransmitter dysfunction could also have influenced the results.
Further research is required to validate the role of HL-related comorbidities/drugs in patients with FM in HL development. Additionally, control of other characteristics related to behavioral factors of HL, such as alcohol drinking, smoking, obesity, and physical activity, must be considered, which may affect the risk of HL in patients with FM. Furthermore, we recommend assessing all disease stages of FM and screening for neurotransmitter dysfunction to elucidate the relationship between HL and FM.

**Conclusion**

The study results evidence that FM and a combination of FM and comorbidities presented a higher risk of HL. Additionally, FM was also found to have a higher incidence of sensorineural HL than other types of HL. These findings contribute to the understanding of the risk of HL in patients with FM and comorbidities and accordingly have several clinical implications. Health care professionals should provide appropriate screening for the risk of HL and prevention and counseling methods for patients with FM.

**Supporting information**

S1 Appendix. Joint effect of comorbidities on hearing loss. (DOCX)

**Author Contributions**

**Conceptualization:** Shin-Da Lee, Yu-Kuei Teng.

**Data curation:** Chih-Hsin Muo, Fung-Chang Sung.

**Formal analysis:** Chih-Hsin Muo.

**Methodology:** Hua Ting, Fung-Chang Sung, Yu-Kuei Teng.

**Resources:** Hua Ting, Fung-Chang Sung.

**Supervision:** Shin-Da Lee, Yu-Kuei Teng.

**Validation:** Ya-Ling Tzeng.

**Writing – original draft:** Thi Phuong Le.

**Writing – review & editing:** Shin-Da Lee, Yu-Kuei Teng.

**References**

1. Wolfe F., et al., The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken), 2010. 62(5): p. 600–10.

2. Marques A.P., et al., Prevalence of fibromyalgia: literature review update. Rev Bras Reumatol Engl Ed, 2017. 57(4): p. 356–363. https://doi.org/10.1016/j.rbre.2017.01.005 PMID: 28743363

3. Walitt B., et al., The Prevalence and Characteristics of Fibromyalgia in the 2012 National Health Interview Survey. PLoS One, 2015. 10(9): p. e0138024. https://doi.org/10.1371/journal.pone.0138024 PMID: 26379048

4. Heidari F., Afshari M., and Moosazadeh M., Prevalence of fibromyalgia in general population and patients, a systematic review and meta-analysis. Rheumatol Int, 2017. 37(9): p. 1527–1539. https://doi.org/10.1007/s00296-017-3725-2 PMID: 28447207

5. Geisser M.E., et al., A psychophysical study of auditory and pressure sensitivity in patients with fibromyalgia and healthy controls. J Pain, 2008. 9(5): p. 417–22. https://doi.org/10.1016/j.jpain.2007.12.006 PMID: 18280211

6. Rosenhall U., Johansson G., and Ormdahl G., Otoneurologic and audiologic findings in fibromyalgia. Scand J Rehabil Med, 1996. 28(4): p. 225–32. PMID: 9122651
7. Bellato E., et al., Fibromyalgia syndrome: etiology, pathogenesis, diagnosis, and treatment. Pain Res Treat, 2012. 2012: p. 426130.
8. Clauw D.J., Fibromyalgia: a clinical review. Jama, 2014. 311(15): p. 1547–1555. https://doi.org/10.1001/jama.2014.3266 PMID: 24737367
9. Cunningham L.L and Tucci D.L., Hearing Loss in Adults. N Engl J Med, 2017. 377(25): p. 2465–2473. https://doi.org/10.1056/NEJMa1616601 PMID: 29262274
10. Stranden M., et al., Are persons with fibromyalgia or other musculoskeletal pain more likely to report hearing loss? A HUNT study. BMC Musculoskelet Disord, 2016. 17(1): p. 477. https://doi.org/10.1186/s12891-016-1331-1 PMID: 27852259
11. Wolfe F., Rasker J.J., and Hausser W., Hearing loss in fibromyalgia? Somatic sensory and non-sensory symptoms in patients with fibromyalgia and other rheumatic disorders. Clin Exp Rheumatol, 2012. 30(6 Suppl 74): p. 88–93. PMID: 23137751
12. Kapusuz Gencer Z., et al., Does fibromyalgia have an effect on hearing loss in women? Turk J Med Sci, 2017. 47(6): p. 1699–1702. https://doi.org/10.3906/sag-1511-25 PMID: 29306226
13. Bayazit Y.A., et al., Neurological manifestations of the fibromyalgia syndrome. J Neurol Sci, 2002. 196 (1–2): p. 77–80. https://doi.org/10.1016/s0022-510x(02)00032-1 PMID: 11959160
14. Yilmaz M., et al., Assessment of the ear and otoacoustic emission findings in fibromyalgia syndrome. Clin Exp Rheumatol, 2005. 23(5): p. 701–3. PMID: 16173251
15. Ikuni F., et al., Why do patients with fibromyalgia complain of ear-related symptoms? Ear-related symptoms and otological findings in patients with fibromyalgia. Clin Rheumatol, 2013. 32(10): p. 1437–41. https://doi.org/10.1007/s10067-013-2287-2 PMID: 23700040
16. Besser J., et al., Comorbidities of hearing loss and the implications of multimorbidity for audiological care. Hear Res, 2018. 369: p. 3–14. https://doi.org/10.1016/j.heares.2018.06.008 PMID: 29941312
17. Doosti A., Lotfi Y., and Bakhshi E., Effects of Hyperlipidemia on Noise Induced Hearing Loss (NIHL). Indian J Otolaryngol Head Neck Surg, 2016. 68(2): p. 211–3. https://doi.org/10.1007/s12070-015-0855-2 PMID: 27340639
18. Havia M., Kentala E., and Pyykko I., Hearing loss and tinnitus in Meniere’s disease. Auris Nasus Larynx, 2002. 29(2): p. 115–9. https://doi.org/10.1016/s0385-8146(01)00142-0 PMID: 11893444
19. Lim H.M., et al., Insomnia and hearing impairment among occupational noise exposed male workers. Ann Occup Environ Med, 2017. 29: p. 36. https://doi.org/10.1186/s40557-017-0195-7 PMID: 28824813
20. Rossi B.A.A., et al., Sudden Sensorineural Hearing Loss and Autoimmune Systemic Diseases. Int Arch Otorhinolaryngol, 2017. 21(3): p. 213–223. https://doi.org/10.1055/s-0036-1586162 PMID: 28680488
21. International., P., Drug-induced hearing loss. Prescrire Int, 2014. 23(155): p. 290–4. PMID: 25629145
22. Häusser W., et al., Review of pharmacological therapies in fibromyalgia syndrome. Arthritis Res Ther, 2014. 16(1): p. 201. https://doi.org/10.1186/ar4441 PMID: 24433463
23. Gerster J.C. and Hadj-Djilani A., Hearing and vestibular abnormalities in primary fibrositis syndrome. J Rheumatol, 1984. 11(5): p. 678–80. PMID: 6595407
24. Dohrenbusch R., et al., Fibromyalgia as a disorder of perceptual organization? An analysis of acoustic stimulus processing in patients with widespread pain. Z Rheumatol, 1997. 56(6): p. 334–41. https://doi.org/10.1007/s003930050047 PMID: 9487649
25. Hwang J.H., et al., Aging effects on the activation of the auditory cortex during binaural speech listening in white noise: an fMRI study. Audiol Neurootol, 2007. 12(5): p. 285–94. https://doi.org/10.1159/000103209 PMID: 17536391
26. Curhan S.G., et al., Analgesic use and the risk of hearing loss in men. Am J Med, 2010. 123(3): p. 231–7. https://doi.org/10.1016/j.amjmed.2009.08.006 PMID: 20198381
27. Curhan S.G., et al., Analgesic use and the risk of hearing loss in women. Am J Epidemiol, 2012. 176 (6): p. 544–54. https://doi.org/10.1093/aje/kws146 PMID: 22933387
28. Hamed S.A., The auditory and vestibular toxicities induced by antiepileptic drugs. Expert Opin Drug Saf, 2017. 16(11): p. 1281–1294. https://doi.org/10.1080/14740338.2017.1372420 PMID: 28938247
29. Oroei M., Peyvandi A.A., and Mokhtarinejad F., Opioid Drugs and Sensorineural Hearing Loss. Addict Health, 2018. 10(1): p. 64–66. https://doi.org/10.22122/ahj.1011.560 PMID: 30627386
30. Chung S.D., et al., Association between sudden sensorineural hearing loss and anxiety disorder: a population-based study. Eur Arch Otorhinolaryngol, 2015. 272(10): p. 2673–8. https://doi.org/10.1007/s00405-014-3235-8 PMID: 25115314
31. Su C.H., et al., Increased Risk of Coronary Heart Disease in Patients with Primary Fibromyalgia and Those with Concomitant Comorbidity—A Taiwanese Population-Based Cohort Study. PLoS One, 2015. 10(9): p. e0137137. https://doi.org/10.1371/journal.pone.0137137 PMID: 26966998
32. Santos Dde M., et al., The association of major depressive episode and personality traits in patients with fibromyalgia. Clinics (Sao Paulo), 2011. 66(6): p. 973–8.

33. Soriano-Maldonado A., et al., Association of different levels of depressive symptoms with symptomatology, overall disease severity, and quality of life in women with fibromyalgia. Qual Life Res, 2015. 24 (12): p. 2951–7. https://doi.org/10.1007/s11136-015-1045-0 PMID: 26071756

34. Stevens G., et al., Global and regional hearing impairment prevalence: an analysis of 42 studies in 29 countries. Eur J Public Health, 2013. 23(1): p. 146–52. https://doi.org/10.1093/eurpub/ckr176 PMID: 22197756

35. Wolff J.L., Starfield B., and Anderson G., Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch Intern Med, 2002. 162(20): p. 2269–76. https://doi.org/10.1001/archinte.162.20.2269 PMID: 12418941