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Retrospective cohort study on risk of hearing loss in patients with rheumatoid arthritis using claims data

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ABSTRACT

Objectives Population studies on hearing loss (HL) associated with rheumatoid arthritis (RA) are lacking. This study investigated the risk of developing HL in patients with RA using a nationwide population cohort.

Setting The population-based insurance claims data in the Taiwan National Health Insurance Research Database.

Design Retrospective cohort study followed up RA cohort and control cohort without RA frequency matched by sex, age and diagnosis year.

Study population 18 267 patients with RA newly diagnosed in 2000–2006 and 73 068 controls without RA.

Main outcomes Incidences of HL by the end of 2011 and the RA cohort to non-RA cohort HRs after adjusting for sex, age and comorbidities.

Results The HL incidence was higher in the RA cohort than in the non-RA cohort (3.08 vs 1.62 per 1000 person-years), with an adjusted HR (aHR) of 1.91 (95% CI 1.70 to 2.14) for the RA cohort relative to the non-RA cohort after controlling for age, sex and comorbidities. Men and the elderly are at a higher risk. Cardiovascular comorbidities were associated with a further increased HL risk for patients with RA. Medications were associated with reduced HL incidence; patients with RA who used non-steroidal anti-inflammatory drugs (NSAIDs) had an aHR of 0.12 (95% CI 0.07 to 0.20), compared with non-users.

Conclusions This study demonstrates that patients with RA are at an increased risk of developing HL. Findings highlight the need of disease-modifying treatment and scheduled auditory examinations for HL prevention and early detection for patients with RA.

Strengths and limitations of this study

- The strength of this study is the use of a nationwide population-based cohort to identify hearing loss (HL) risk in an Asian population with rheumatoid arthritis (RA). Our findings can be generalised to the general population.
- The inclusion of the Catastrophic Illness Patient Database confirmed the diagnoses of all RA cases with increased reliability of our data; the large sample size reduced the tendency for selection bias, enhanced statistical power and precision of risk appraisal.
- Limitations in this study: information on several suspected risk factors for HL, such as smoking and chronic exposure to occupational and environmental noise, which could be associated with HL in the general population, was not available in the insurance database.
- Information on laboratory test results and HL by severity and sound frequency (high, mid or low frequency) and on RA severity scale, such as disease activity, functional impairment and physical damage, was also unavailable.

INTRODUCTION

Rheumatoid arthritis (RA) is a disease predominantly characterised by chronic joint inflammation and is often accompanied by several peripheral inflammatory manifestations.[1] RA may lead to the destruction of the cartilage and bone due to chronic synovitis and may consequently impair joint function.[2] In addition, patients with RA may have extra-articular manifestations involving other organ systems,[3] such as auditory system alteration, although with a different putative mechanism of damage.[4–6] With respect to the auditory system, previous studies have shown conflicting findings, in both hearing loss (HL) and the RA disease activity and severity.[7–10]

There is a wide variation in the reported prevalence of HL in patients with RA. Sensorineural hearing loss (SNHL) is the most common hearing impairment in patients with RA, ranging from 25% to 72%,[11] whereas conductive HL and mixed HL are less frequently reported.[4 6 12] SNHL could be induced by a direct immune response of either T or B cells against inner ear proteins.[13] Neurovascular inflammation and drugs used for RA treatment could also damage the cochlea.[14] Thus, HL may be a manifestation of systemic vascular involvement in patients with RA and may have a significant effect on the health of patients with RA. However, the risk of developing HL in patients with RA has not been well examined using population data.

Hence, the purpose of this study was to investigate the risk of HL in patients with RA, using representative insurance claims data obtained from the Taiwan National Health Insurance (NHI). The HL risk associated with other comorbidities, such as coronary heart disease, hypertension, stroke, diabetes, hyperlipidaemia, hyperthyroidism, hypothyroidism, chronic renal disease and autoimmune diseases, was also evaluated.

MATERIALS AND METHODS

Data source

The Taiwan NHI system is a single-payer compulsory programme with a coverage of over 99% of 23.74 million people.[15] We conducted this study using two data sets: the Registry for Catastrophic Illness Patient Database (CIPD) and the Longitudinal Health Insurance Database (LHID2000), obtained from the Taiwan National Health Research Institutes. Patients with major diseases, such as cancer, chronic mental illness, end-stage renal disease and several autoimmune diseases requiring long-term care, are eligible for the CIPD coverage for exemption from making copayment. The LHID2000 contains the claims data of 1 000 000 people randomly sampled from all populations being registered in 2000 for the insurance coverage. Reimbursement claims data for medical services from 1996 to 2011 in both data sets were used in this study. For privacy protection, all personal identifications were replaced with surrogate identifications suitable for public use and data linkage. The claims data contained information on the demographic status of the insured people, dates of treatment and treatments received, diagnostic codes, prescriptions and costs. Diagnoses of diseases were coded with the International Classification of Disease Diagnoses, Ninth Revision of Clinical Modification (ICD-9-CM). Several studies in Taiwan using the insurance claims data have demonstrated high accuracy and validity of ICD-9 diagnosis.[16 17]

Study population

Figure 1 shows the flow chart for identifying and selecting study population using a population-based retrospective cohort study design. We identified an RA cohort from the registry for CIPD and a non-RA cohort from the LHID2000. Patients newly diagnosed with RA (ICD-9-CM 714.0) from 2000 to 2006 without HL were included in the RA cohort. The date with RA certificated as the catastrophic illness was considered as the index date for the approved patients. Patients who met four or more of the diagnostic criteria based on the 1987 American College of Rheumatology criteria were considered as having RA and those diagnosed by rheumatologists were included in the RA cohort.[18] The application for catastrophic illness status was scrutinised by peer review.

For each patient with RA, four insured people without history of RA and HL were randomly selected from the LHID2000 for the non-RA cohort and were frequency matched by sex, age (each 5-year span) and index year. Individuals with missing information on age and/or sex or with history of HL (ICD-9-CM 388.2, 388.4, 389.00, 389.10, 389.12, 389.2 and 389.9) at baseline were excluded from the non-RA cohort.

Both cohorts were followed from the index date to the date with HL diagnosed, death, withdrawal from the NHI system or the end of 2011. In general, HL was diagnosed based on the audiometry test. To increase the validity of HL diagnosis, only patients with three or more diagnoses in outpatient claims or an inpatient record were included

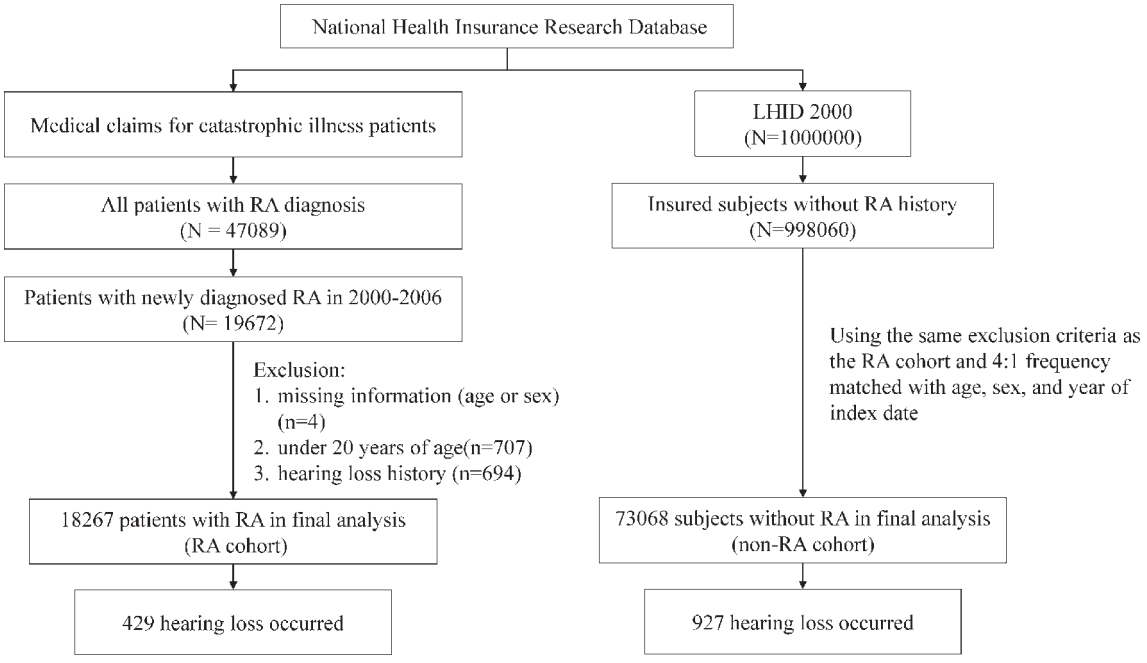


Figure 1 Flow chart showing selection of study cohorts. LHID, Longitudinal Health Insurance Database; RA, rheumatoid arthritis.

Table 1 Distribution of demographic factors and comorbidity compared between cohorts

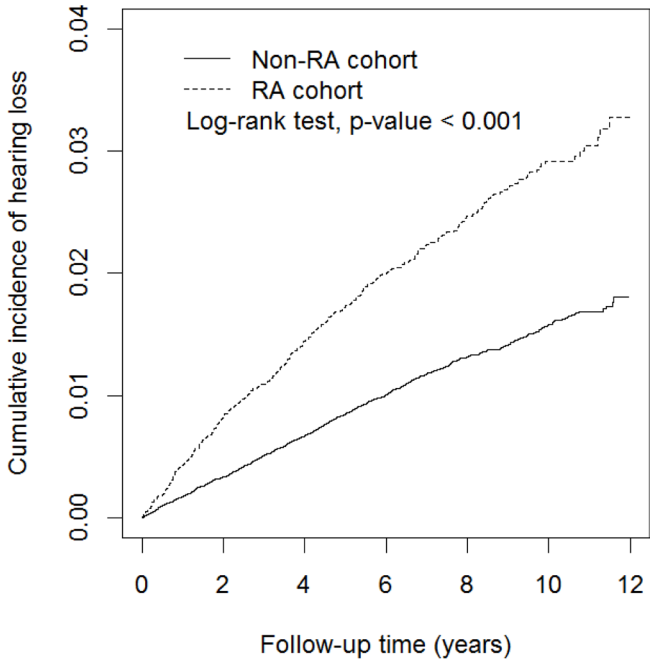
Variable	Non-RA cohort n=73 068		RA cohort n=18 267		Standardised mean difference
	n	%	n	%	
Sex					
Female	57 288	78.4	14 322	78.4	<0.001
Male	15 780	21.6	3945	21.6	<0.001
Age, years					
20–39	12 224	16.7	3056	16.7	<0.001
40–59	36 532	50.0	9133	50.0	<0.001
≥60	24 312	33.3	6078	33.3	<0.001
Means (SD)	53.3	(14.2)	53.6	(13.9)	0.021
Comorbidity					
DM	8102	11.1	2114	11.6	0.015
Hyperlipidaemia	14 078	19.3	3439	18.8	0.011
Hypertension	22 844	31.3	5964	32.7	0.030
Hyperthyroidism	1089	1.49	456	2.50	0.072
IHD	10 993	15.0	2941	16.1	0.029
Stroke	2128	2.91	483	2.64	0.016
CKD	4821	6.60	2061	11.3	0.165
Hypothyroidism	407	0.56	216	1.18	0.067
Autoimmune diseases*	433	0.59	534	2.92	0.178

*Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis and vasculitis.
CKD, chronic kidney disease; DM, diabetes mellitus; IHD, ischaemic heart disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

in the study. Patients who were suspected of having HL received comprehensive examinations and, subsequently, treatment was followed when the disorder was confirmed. In the insurance system, HL patients' medical reimbursement and discharge notes are scrutinised by peer review. The insurance system also randomly reviewed insurance claims to prevent errors and violations. Therefore, diagnoses and codes of HL in the study were highly reliable.[16]

Statistical analysis

Distributions of sex and age (20–39, 40–59 and ≥60 years) and baseline comorbidities, including diabetes (ICD-9-CM 250), hyperlipidaemia (ICD-9-CM 272), hypertension (ICD-9-CM 401–405), hyperthyroidism (ICD-9-CM 242), ischaemic heart disease (IHD; ICD-9-CM 410–414), stroke (ICD-9-CM 430–438), chronic kidney disease (CKD; ICD-9-CM 580–589), hypothyroidism (ICD-9-CM 244) and autoimmune diseases (including psoriasis (ICD-9-CM 696), systemic lupus erythematosus (SLE; ICD-9-CM 710.0), systemic sclerosis (ICD-9-CM 710.1), Sjogren syndrome (ICD-9-CM 710.2), dermatomyositis (ICD-9-CM 710.3), polymyositis (ICD-9-CM 710.4) and vasculitis (ICD-9-CM 446.0, 446.2, 446.4, 446.5, 443.1, 446.7, 446.1 and 136.1), between the RA and non-RA cohorts were compared. A standardised mean difference of less than 0.1 was a negligible difference between two means or two prevalence rates.[19] The incidence density of HL per 1000 person-years was calculated during the follow-up period by sex, age and comorbidity. The Kaplan-Meier method was employed to plot the cumulative incidence of HL for each cohort during the follow-up period, and the log-rank test was used to assess the differences between the two curves. Univariate and multivariate Cox proportional hazards regression analyses were used to measure the RA cohort to non-RA cohort crude HR (cHR) and adjusted HR (aHR) of HL, respectively, and their 95% CIs. Sex, age and comorbidities including diabetes, hyperlipidaemia, hypertension, hyperthyroidism, hypothyroidism, IHD, stroke, CKD and autoimmune diseases were included as covariates in the multivariate Cox regression analysis. To further assess the robustness of our results, we also evaluated the association between RA and HL risk in various subgroups by sex, age and each comorbidity. We further evaluated the treatment effectiveness of medications for patients with RA by calculating the incidence density and HRs of HL. The HL relating to medications for RA treatment was evaluated, including non-steroidal anti-inflammatory drugs (NSAIDs), prednisolone, disease-modifying antirheumatic drugs (DMARDs, including hydroxychloroquine, sulfasalazine, methotrexate and leflunomide), and tumour necrosis factor (TNF, including etanercept and adalimumab). Further analysis evaluated the HL risk by the type of HL: sensorineural, conductive or mixed.



No. at risk

Non-RA cohort	73068	70979	68952	56187	35795	16093
RA cohort	18267	17445	16643	13564	8541	3836

Figure 2 Kaplan-Meier method estimated cumulative incidence curves of hearing loss in the two cohorts. RA, rheumatoid arthritis.

All analyses were conducted using SAS statistical software (V.9.4 for Windows; SAS Institute), and all statistical tests were performed at the two-tailed significance level of 0.05.

RESULTS

We identified 18 267 patients with RA newly diagnosed from 2000 to 2006 for the RA cohort and 73 068 persons without RA for the non-RA cohort as controls (table 1). There were more women than men (78.4 vs 21.6%) in both cohorts. Approximately 66.7% of the study populations were <60 years old. Prevalence rates of CKD and autoimmune diseases were more prevalent in patients with RA than in controls at the baseline.

The Kaplan-Meier method estimated cumulative incidence of HL was 1.5% greater in the RA cohort than in the non-RA cohort (3.3 vs 1.8%; P value <0.001 in the log-rank test; figure 2). The incidence density of HL was approximately twofold greater in the RA cohort than in the non-RA cohort (3.08 vs 1.62 per 1000 person-years), with an aHR of 1.91 (95% CI 1.70 to 2.14; table 2). Men were at a greater risk of HL than women, and the risk increased with age. Compared with 20–39 years old, the aHRs of HL were 2.89 (95% CI 2.21 to 3.79) and 5.27 (95% CI 3.99 to 6.95) for those aged 40–59 years and those aged ≥60 years, respectively. The HL risk for individuals with comorbidities was also elevated. Patients with hypertension and IHD were significantly associated with higher risk of HL compared with their counterparts without the disorder, with aHRs of 1.21 (95% CI 1.07 to 1.38) and of 1.36 (95% CI 1.19 to 1.56), respectively.

Table 3 shows that incidence rates of HL stratified by sex, age and comorbidity were consistently greater in the RA cohort than in the non-RA cohort. Comorbidity was associated with further increased HL risk for patients with RA. Patients with RA with comorbid IHD had the highest incident HL, 5.60 per 1000 person-years.

Table 4 shows that medications were associated with reduced incident HL for patients with RA. Near 99% of patients with RA used NSAIDs, and users had an HL incidence of 2.98 per 1000 person-years, with an aHR of 0.12 (95% CI 0.07 to 0.20) compared with non-users who had an incidence of 30.1 per 1000 person-years for HL. Patients with RA on medications of adalimumab (n=950) had the lowest HL incidence of 0.64 per 1000 person-years with an aHR of 0.23 (95% CI 0.10 to 0.55), compared with non-users who had an incidence of 3.23 per 1000 person-years.

Further evaluation on the subtype HL showed that patients with RA had only few cases of conductive HL, but were at increased risk of sensorineural HL and mixed HL with aHRs of 2.35 (95% CI 1.91 to 2.89) and 1.77 (95% CI 1.54 to 2.03), respectively (table 5).

DISCUSSION

This retrospective cohort study showed that patients with RA were nearly twofold more likely to develop HL than those without RA. The risk of HL associated with RA increased with age. In the RA cohort, those ≥60 years old had an HL incidence of 4.92 per 1000 person-years, which was 4.16 per 1000 person-year greater than that of patients aged 20–39 years. The corresponding difference was 2.49 per 1000 person-years between the two age groups in the non-RA cohort, reflecting the natural HL by ageing in the non-RA cohort. Similar to reports in other studies, HL is age dependent in patients and control subjects.[6 14 20] This finding is also consistent with previous studies for patients with sudden SNHL comorbid with SLE and psoriasis.[21 22] The excess HL risk could be 50% in patients with psoriasis.

We also found that, in the RA cohort, men had an incidence of 4.09 per 1000 person-years for HL, which was 1.26 per 1000 person-years greater than women had. The corresponding difference was 0.78 per 1000 person-years in the non-RA cohort, indicating that the relationship between RA and HL risk may be slightly greater for men. In the entire study population, the overall aHR was 1.40 for men compared with women (table 2). There is a remarkable imbalance between the number of males and females with autoimmune diseases, with females representing the majority of cases. Although reasons for this over-representation of women are unclear, genetic (X-linked) factors and hormonal aspects are likely involved. Halligan *et al*[23] investigated patients with RA and also demonstrated that the prevalence of abnormal

Table 2 Cox model measured HRs and 95% CIs of hearing loss associated with RA and covariates

Variable	Event (n)	Person-years	Incidence density†	HR (95% CI) Univariate	HR (95% CI) Multivariate‡
RA					
No	927	572 031	1.62	Ref	Ref
Yes	429	139 085	3.08	1.90 (1.70 to 2.13)***	1.91 (1.70 to 2.14) ***
Sex					
Female	977	565 205	1.73	Ref	Ref
Male	379	145 912	2.60	1.49 (1.33 to 1.68)***	1.40 (1.24 to 1.58)***
Age, years					
20 – 39	59	123 836	0.48	Ref	Ref
40 – 59	563	368 175	1.53	3.21 (2.45 to 4.19)***	2.89 (2.21 to 3.79)***
≥ 60	734	219 105	3.35	6.98 (5.35 to 9.10)***	5.27 (3.99 to 6.95)***
Comorbidity					
DM					
No	1127	638 984	1.76	Ref	Ref
Yes	229	72 133	3.17	1.78 (1.55 to 2.06)***	1.14 (0.98 to 1.33)
Hyperlipidaemia					
No	974	578 643	1.68	Ref	Ref
Yes	382	132 474	2.88	1.70 (1.51 to 1.92)***	1.10 (0.97 to 1.26)
Hypertension					
No	714	499 747	1.43	Ref	Ref
Yes	642	211 370	3.04	2.11 (1.90 to 2.35)***	1.21 (1.07 to 1.38)*
Hyperthyroidism					
No	1325	699 624	1.89	Ref	Ref
Yes	31	11 492	2.70	1.41 (0.99 to 2.02)	1.33 (0.92 to 1.92)
IHD					
No	987	610 475	1.62	Ref	Ref
Yes	369	100 642	3.67	2.25 (2.00 to 2.54)***	1.36 (1.19 to 1.56)***
Stroke					
No	1310	695 656	1.88	Ref	Ref
Yes	46	15 461	2.98	1.55 (1.15 to 2.07)**	0.85 (0.63 to 1.14)
CKD					
No	1204	662 599	1.82	Ref	Ref
Yes	152	48 517	3.13	1.71 (1.45 to 2.03)***	1.06 (0.89 to 1.26)
Hypothyroidism					
No	1343	706 448	1.90	Ref	Ref
Yes	13	4668	2.78	1.46 (0.85 to 2.52)	1.15 (0.65 to 2.01)
Autoimmune diseases§					
No	1334	704 142	1.89	Ref	Ref
Yes	22	6975	3.15	1.65 (1.08 to 2.51)*	1.34 (0.88 to 2.05)

*P<0.05, **P<0.01, ***P<0.001.
†Per 1000 person-years.
‡Multivariate Cox proportional hazards regression model, including RA, sex, age (categorical), DM, hyperlipidaemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism and autoimmune diseases.
§Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis and vasculitis.
CKD, chronic kidney disease; DM, diabetes mellitus; IHD, ischaemic heart disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

Table 3 Incidence density and RA cohort to non-RA cohort HRs of hearing loss by sex, age and comorbidity in the two cohorts

	Non-RA cohort			RA cohort			RA cohort to non-RA cohort HR (95% CI)	
Variables	Event (n)	Person-years	Incidence density†	Event (n)	Person-years	Incidence density†	Crude	Adjusted‡
Sex								
Women	663	454249	1.46	314	110956	2.83	1.94 (1.69 to 2.22)***	1.95 (1.70 to 2.23)***
Men	264	117782	2.24	115	28130	4.09	1.82 (1.46 to 2.27)***	1.85 (1.48 to 2.30)***
Age, years								
20–39	40	98817	0.40	19	25020	0.76	1.89 (1.09 to 3.26)*	1.80 (1.02 to 3.16)*
40–59	355	295193	1.20	208	72982	2.85	2.37 (2.00 to 2.81)***	2.32 (1.95 to 2.76)***
≥60	532	178021	2.99	202	41084	4.92	1.63 (1.39 to 1.92)***	1.62 (1.37 to 1.90)***
Comorbidity								
DM								
No	765	514262	1.49	362	124722	2.90	1.95 (1.72 to 2.21)***	1.94 (1.71 to 2.20)***
Yes	162	57770	2.80	67	14363	4.66	1.66 (1.25 to 2.21)***	1.74 (1.30 to 2.32)***
Hyperlipidaemia								
No	654	464753	1.41	320	113890	2.81	2.00 (1.75 to 2.28)***	1.96 (1.72 to 2.25)***
Yes	273	107279	2.54	109	25195	4.33	1.69 (1.36 to 2.11)***	1.74 (1.39 to 2.18)***
Hypertension								
No	481	402716	1.19	233	97031	2.40	2.01 (1.72 to 2.35)***	1.94 (1.66 to 2.28)***
Yes	446	169316	2.63	196	42054	4.66	1.76 (1.49 to 2.08)***	1.82 (1.54 to 2.16)***
Hyperthyroidism								
No	909	563891	1.61	416	135733	3.06	1.90 (1.69 to 2.13)***	1.92 (1.71 to 2.16)***
Yes	18	8140	2.21	13	3352	3.88	1.76 (0.86 to 3.58)	1.72 (0.84 to 3.55)
IHD								
No	671	491566	1.37	316	118909	2.66	1.95 (1.70 to 2.23)***	1.96 (1.71 to 2.24)***
Yes	256	80466	3.18	113	20176	5.60	1.75 (1.40 to 2.18)***	1.75 (1.40 to 2.19)***
Stroke								
No	896	559458	1.60	414	136197	3.04	1.90 (1.69 to 2.13)***	1.90 (1.69 to 2.14)***
Yes	31	12573	2.47	15	2888	5.19	2.10 (1.13 to 3.89)*	2.18 (1.16 to 4.12)*
CKD								
No	835	538065	1.55	369	124534	2.96	1.91 (1.69 to 2.16)***	1.94 (1.71 to 2.19)***
Yes	92	33967	2.71	60	14551	4.12	1.53 (1.11 to 2.12)*	1.73 (1.25 to 2.42)**

Continued

Table 3 Continued

Variables	Non-RA cohort			RA cohort			RA cohort to non-RA cohort	
	Event (n)	Person-years	Incidence density†	Event (n)	Person-years	Incidence density†	HR (95% CI) Crude	Adjusted‡
Hypothyroidism								
No	917	569055	1.61	426	137393	3.10	1.92 (1.71 to 2.16)***	1.94 (1.73 to 2.18)***
Yes	10	2977	3.36	3	1692	1.77	0.53 (0.15 to 1.93)	0.69 (0.19 to 2.57)
Autoimmune diseases§								
No	916	568956	1.61	418	135186	3.09	1.92 (1.71 to 2.15)***	1.94 (1.73 to 2.18)***
Yes	11	3076	3.58	11	3899	2.82	0.79 (0.34 to 1.82)	0.89 (0.38 to 2.07)

*P<0.05, **P<0.01, ***P<0.001.
†Per 1000 person-years.
‡Model mutually adjusted for sex, age (continuous), DM, hyperlipidaemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism and autoimmune diseases.
§Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis and vasculitis.
CKD, chronic kidney disease; DM, diabetes mellitus; IHD, ischaemic heart disease; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

hearing is significantly greater in males (86% or 12/14) than in females (33% or 5/15) (P=0.008). However, no significant gender difference in HL among those without RA was found (P=0.715).

Evidences have shown that patients with RA are prevalent with comorbidities, such as IHD,[24–26] stroke,[27] hypertension,[28 29] diabetes,[30–32] dyslipidaemia,[27 33] CKD[34 35] and thyroid disorders.[36–38] In this study, the study populations in both cohorts were young. The baseline prevalence rates of most comorbidities between the two cohorts were not significantly different, except that CKD and autoimmune diseases were more prevalent in patients with RA than in controls without RA at the baseline (table 1). However, it is interesting to note that most of the comorbidities are associated with further increased incidence of HL, greater for the RA cohort than for the non-RA cohort, except hypothyroidism, and autoimmune diseases (table 3). Autoimmune disease is a possible pathology associated with SNHL because of the destruction of the cochlear hair cells.[39] Our study failed to prove this relationship.

The development of RA and the breakdown of atherosclerotic plaques possibly share common factors contributing to inflammatory cells and proinflammatory cytokines.[25] Proinflammatory cytokines may contribute to the oxidative damage in the inner ear.[26] For example, both TNF-α and interleukin (IL)-6 are involved in the pathogenesis of both RA and atherosclerosis.[40] However, Takatsu *et al* showed that the proinflammatory cytokines (IL-6) and matrix matalloproteinase-3 may contribute to harm in inner ear cells by an oxidative process.[6] Both RA and HL may have a shared mechanism associating with cardiovascular diseases which account for the higher risk of HL in patients with RA. IHD alone may associate with HL. An earlier study found that patients with IHD are prevalent with HL for up to over 30%.[41] Moreover, in this study, we found that patients with RA with IHD had the highest HL incidence among patients with cardiovascular disorders. Hence, RA and cardiovascular disorders may have a shared contribution to the HL risk.

Furthermore, several studies have reported elevated plasma renin and ACE activities in patients with RA.[42 43] Poor blood pressure control could induce changes in the renin–angiotensin system. Higher oxidative stress in patients with RA could also impair the vasodilatory mechanism of the endothelium,[43] which could be associated with the higher HL risk in patients with RA. Hence, hypertension is likely another risk factor contributing to HL. The findings in our study further demonstrate the association between autoimmune disease and HL risk.

After adjustment for sex, age and comorbidity, we found reduced HL risk for patients with RA on medication of NSAID, prednisolone, DMARDs and TNF. Conversely, Halligan *et al*[23] described an association between HL and hydroxychloroquine, and Dikici *et al*[44] observed a dose relation between HL using methotrexate. On the other hand, some studies found no relationship between HL and RA treatment using NSAID, corticosteroid and DMARDs.[6 9 20 45] The inconsistent results may be due

Table 4 Incidence density and HRs of hearing loss associated with medication in patients with RA

Medicine use	N	Event (n)	Person-years	Incidence density†	HR (95% CI) Crude‡	HR (95% CI) Adjusted‡
NSAIDs						
No	169	16	532	30.1	Ref	Ref
Yes	18098	413	138553	2.98	0.11 (0.07 to 0.18)***	0.12 (0.07 to 0.20)***
Prednisolone						
No	1673	60	11529	5.20	Ref	Ref
Yes	16594	369	127556	2.89	0.56 (0.43 to 0.74)***	0.53 (0.40 to 0.70)***
DMARDs						
Hydroxychloroquine						
No	12200	309	91284	3.39	Ref	Ref
Yes	6067	120	47801	2.51	0.75 (0.60 to 0.92)**	0.77 (0.62 to 0.95)*
Sulfasalazine						
No	5141	148	36176	4.09	Ref	Ref
Yes	13126	281	102909	2.73	0.68 (0.56 to 0.83)***	0.74 (0.61 to 0.91)**
Methotrexate						
No	9261	268	67188	3.99	Ref	Ref
Yes	9006	161	71897	2.24	0.57 (0.47 to 0.69)***	0.65 (0.53 to 0.79)***
Leflunomide						
No	15393	405	116118	3.49	Ref	Ref
Yes	2874	24	22967	1.04	0.30 (0.20 to 0.45)***	0.33 (0.22 to 0.50)***
TNF						
Etanercept						
No	16259	408	122506	3.33	Ref	Ref
Yes	2008	21	16579	1.27	0.39 (0.25 to 0.60)***	0.44 (0.28 to 0.68)***
Adalimumab						
No	17317	424	131303	3.23	Ref	Ref
Yes	950	5	7783	0.64	0.20 (0.08 to 0.48)***	0.23 (0.10 to 0.55)**

*P<0.05, **P<0.01, ***P<0.001.
†Per 1000 person-years.
‡Model adjusted for sex, age, DM, hyperlipidaemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism and autoimmune diseases.
CKD, chronic kidney disease; DM, diabetes mellitus; DMARD, disease-modifying antirheumatic drug; IHD, ischaemic heart disease; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

Table 5 Incidence density and HRs for subtypes of HL according to RA status

	RA				Compared with non-RA group	
	No		Yes		HR (95% CI)	
Types of HL	Event (n)	Incidence density*	Event (n)	Incidence density*	Crude	Adjusted†
Sensorineural	249	0.44	144	1.04	2.38 (1.94 to 2.92)***	2.35 (1.91 to 2.89)***
Conductive	10	0.02	1	0.01	0.41 (0.05 to 3.21)	0.41 (0.05 to 3.23)
Mixed	668	1.17	284	2.04	1.75 (1.52 to 2.01)***	1.77 (1.54 to 2.03)***

ICD-9-CM: sensorineural, 389.10 and 389.12; conductive, 389.00; mixed, 388.2, 388.4, 389.2 and 389.9.
*Per 1000 person-years.
†Model adjusted for sex, age (continuous), DM, hyperlipidaemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism and autoimmune diseases.
***P<0.001.
CKD, chronic kidney disease; DM, diabetes mellitus; HL, hearing loss; ICD-9-CM, International Classification of Disease Diagnoses, Ninth Revision of Clinical Modification; IHD, ischaemic heart disease; RA, rheumatoid arthritis.

to the relatively small study sample sizes, whereas our study is a nationwide population-based cohort with large sample size. It is likely that the reduced inflammation in patients with RA on medications of NSAID, corticosteroid, DMARDs and TNF could be associated with reducing the HL risk.

The strength of this study is the use of a nationwide population-based cohort to evaluate HL risk in an Asian population with RA. Our findings can be generalised to the general population. The large sample size allowed the identification of risk factors associated with the development of HL in Taiwan with a minimal tendency for selection bias and enhanced the statistical power and precision of risk appraisal. In addition, the inclusion of the CIPD confirmed the diagnoses of all RA cases in the NHIRD database, which increased the reliability of our data.

However, several limitations to the interpretation of our findings should be considered. Information on several suspected risk factors for HL was unavailable, such as smoking and chronic exposure to occupational and environmental noise, which could be associated with HL for both cohorts. Moreover, information was also unavailable on laboratory test results, HL severity and RA severity scale and activity, functional impairment and physical damage of the disease. Hearing impairments by specific sound frequency were not measured to differentiate high, mid or low frequency HL.

In conclusion, this study demonstrated that patients with RA are at an elevated risk of developing HL. Our findings also suggest the need for prompt treatment and early detection of RA for HL prevention. Appropriate and timely medical interventions may improve the prognosis of HL for patients diagnosed with RA.

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