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Hearing loss associated with rheumatoid arthritis: a nationwide retrospective cohort study

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Running Title: Hearing loss in rheumatoid arthritis

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ABSTRACT

Purposes:

Hearing loss (HL) has been reported as a manifestation of systemic vascular involvement in patients with an autoimmune disease. However, population studies on HL associated with rheumatoid arthritis (RA) are lacking. This study aimed to investigate the risk of developing HL in patients with RA using a nationwide cohort.

Participants:

We used the National Health Insurance Research Database (NHIRD) of Taiwan from 2000 to 2006 and identified 18,267 patients newly diagnosed as having RA and 73,068 subjects without RA who were frequency-matched by sex, age, and index year. We estimated incidence of HL in both cohorts and the RA cohort to non-RA cohort hazard ratios (HRs) adjusted for sex, age, and comorbidities.

Findings to date:

The incidence of HL was higher in the RA cohort than in the non-RA cohort (3.08 versus 1.62 per 1000 person-years), with an adjusted HR of 1.89 (95% confidence interval = 1.68-2.12) for the RA cohort relative to the non-RA cohort after controlling for age, sex, and comorbidities. Men were at a higher risk than women, and the risk

increased with age. Cardiovascular comorbidities were consistently associated with a high HL risk in patients with RA compared with those without RA.

Conclusions:

This nationwide population-based retrospective cohort study demonstrates that patients with RA are at an elevated risk of developing HL. Moreover, cardiovascular comorbidities could increase HL risk.

Keywords: Rheumatoid arthritis, hearing loss, insurance data, retrospective cohort study

Strengths and limitations of this study

1. The strength of this study is the use of a nationwide population-based cohort to identify HL risk in an Asian population with RA. Our findings can be generalized to the general population.
2. 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.
3. In addition, the inclusion of the Catastrophic Illness Patient Database (CIPD) confirmed the diagnoses of all RA cases in the NHIRD database, which increased the reliability of our data.
4. several limitations to the interpretation of our findings should be considered. 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, were not available in the insurance database.
5. Moreover, information on laboratory test results or HL severity was not available in the insurance claims data, and data on RA severity scale, such as disease activity, functional impairment, and physical damage, was also unavailable.

Introduction

Rheumatoid arthritis (RA) is a disease predominantly characterized 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, both as to the types of hearing loss and as to the RA disease activity and severity associated with hearing levels [7-10].

A wide variation in the reported prevalence of different types of hearing loss in patients with RA exists. Sensorineural hearing loss (SNHL) is the most common hearing impairment in patients with RA, ranging from 25 to 72% [11], whereas conductive hearing loss and mixed hearing loss are less frequently reported [12-14]. SNHL could be induced by a direct immune response of either T or B cells against inner ear proteins [15]. Neurovascular inflammation and drugs used for RA treatment could also damage the cochlea [16]. Thus, hearing loss (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 HL incidence in patients with RA. Using representative insurance claims data obtained from the Taiwan National Health Insurance (NHI), the risk of developing HL in patients with RA was examined. The effects of comorbidities, such as coronary heart disease, hypertension, stroke, diabetes, hyperlipidemia, hyperthyroidism, and chronic renal disease, on the risk of developing HL were 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 [17]. We conducted this study using two data sets: the Registry for Catastrophic Illness Patient Database (CIPD) and the Longitudinal Health Insurance Database (LHID2000) from the Taiwan National Health Research Institutes. The registry for CIPD contains health claims data of patients who had major diseases, such as cancer, chronic mental illness, end-stage renal disease, and several autoimmune diseases requiring long-term care, and who were eligible for exemption from making co-payment. The LHID2000 contains the claims data of 1,000,000 people randomly sampled from all populations that registered in 2000 for the insurance coverage. Reimbursement claims data for medical

services from 1996 to 2011 in both data sets were also 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. Diagnosis was coded with the International Classification of Disease Diagnoses, 9th Revision of Clinical Modification (ICD-9-CM). Several studies in Taiwan in the NHIRD demonstrated the high accuracy and validity of ICD-9 diagnosis [18-19]. This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115).

Study participants

Figure 1 shows the flowchart of the subject selection process in this study using a population-based retrospective cohort study design. We identified a RA cohort from the registry for CIPD and a non-RA cohort from the LHID2000. Patients newly diagnosed as having RA (ICD-9-CM 714.0) from 2000 to 2006 and without HL were identified for the RA cohort. The date of diagnosis in the catastrophic illness certificates 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 and were newly diagnosed as having RA and those diagnosed

by rheumatologists were included in the RA cohort [20]. The application for catastrophic illness status was scrutinized by peer review. The patients with RA with a catastrophic illness card can be exempted from paying a co-payment.

For each patient with RA, four insured people without history of RA and HL were randomly selected from the LHID2000 for the non-RA group and were frequency-matched by sex, age (each 5-year span), and index year. Individuals with missing information on age and/or sex and 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 this study.

The principal outcome was the development of HL during the follow-up period. Both cohorts were followed from the index date to the date of HL diagnosis, withdrawal from the NHI system, or the end of 2011. Patients suspected of having HL received comprehensive examinations and, subsequently, treatment when the disorder was confirmed. In the insurance system, HL patients' medical reimbursement and discharge notes are scrutinised by peer review.

Statistical analysis

Distributions of sex and age (20-39, 40-59, and ≥60 years) and baseline comorbidities, including diabetes (ICD-9-CM 250), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401-405), hyperthyroidism (ICD-9-CM 242), ischemic heart

disease (IHD; ICD-9-CM 410-414), stroke (ICD-9-CM 430-438), and chronic kidney disease (CKD; ICD-9-CM 580-589), between the RA and non-RA cohorts were compared. We considered a standardized mean difference of less than 0.1 as a negligible difference between two means or two prevalence rates [21]. The incidence rate of HL was calculated as the number of incident HL identified during the follow-up period divided by the total follow-up person-years for each cohort according to sex, age, and each 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 crude hazard ratio (cHR) and adjusted hazard ratio (aHR) of HL, respectively, and their 95% confidence intervals (CIs). Sex, age, and comorbidities, including diabetes, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, and CKD, 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.

All analyses were conducted using SAS statistical software (version 9.4 for Windows; SAS Institute, Cary, North Carolina, USA), and all statistical tests were

performed at the two-tailed significance level of 0.05.

Results

In this study, we identified 18,267 RA patients newly diagnosed from 2000 to 2006 as the RA cohort and 73,068 persons without RA as the non-RA cohort (Table 1). Distributions of sex, with more women than men (78.4 vs. 21.6%), and age were similar between the RA and non-RA cohorts. Approximately 33.3% of the study population was ≥60 years old. Comorbidities of CKD was more prevalent in patients with RA than in subjects without RA at the baseline.

The cumulative incidence of HL by the end of follow-up, estimated by the Kaplan-Meier method, 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) (Fig. 2). The HL incidence density was approximately two-fold greater in the RA cohort than in the non-RA cohort (3.08 vs. 1.62 per 1000 person-years), with an aHR of 1.89 (95% CI = 1.68-2.12) (Table 2). Men were at a greater risk of HL than women, and the risk increased with age. Compared to 20−39 years old, the aHRs of HL were 2.72 (95% CI =2.08-3.57) and 4.97 (95% CI = 3.77-6.56) for those aged 40-59 and ≥60 years, respectively. The risk of individuals with comorbidities was also elevated.

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. Moreover, men had a higher HL incidence than women in both cohorts (i.e., 4.09 per 1000 person-years in men with RA, which was nearly three-fold greater than that in women without RA). Additionally, the HL incidence was greater in patients with each of the comorbidities than without it in both cohorts. The excess rate was generally greater in patients with RA; those with IHD had the highest incident HL, i.e., 5.60 per 1000 person-years. The RA cohort to non-RA cohort hazard ratios (HRs) were generally similar to the overall HR between the RA and non-RA cohorts (Table 2).

Discussion

This retrospective cohort study showed that patients with RA were nearly two-fold more likely to develop HL than the general population (Table 2). In the RA cohort, the patients ≥60 years old had an HL incidence of 4.92 per 1000 person-years, which was greater than that of patients age 20-39 years. The corresponding difference was 2.99 per 1000 person-years in the non-RA cohort, reflecting the natural HL by aging in the general population. The effect of HL associated with RA increased with age. This finding is consistent with that of previous studies of patients with SNHL comorbid with systemic lupus erythematosus [22] and psoriasis [23]. The risk could increase for 50% in patients with psoriasis.

Moreover, we found that, in the RA cohort, men had an incidence of 4.09 per 1000 person-years for HL, which was greater than women had. The corresponding difference was 2.24 per 1000 person-years in the non-RA cohort, indicating a greater HL effect in men with RA. In the entire study population, the overall aHR was 1.39 in men (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 the reasons for this overrepresentation of women are unclear, genetic (X-linked) factors and hormonal aspects are likely involved. Halligan et al. [24] investigated patients with RA and demonstrated that the prevalence of abnormal hearing is significantly greater in males (86% or 12/14) than in females (33% or 5/15) ($p = 0.008$). However, no gender difference in hearing impairment among those without RA was found ($p = 0.715$).

In this study, most baseline comorbidities were more prevalent in the RA cohort than in controls. Factors associated with RA and the related comorbid chronic diseases could be underlying the association between RA and the subsequent development of HL. However, the mechanisms underlying the higher HL risk in patients with RA remain unclear.

Evidence shows that patients with RA are prevalent with comorbid diseases, such as IHD, diabetes, hypertension, and dyslipidemia [25]. The development of RA and the

breakdown of atherosclerotic plaques possibly have common factors contributing to inflammatory cells and proinflammatory cytokines [26]. For example, tumor necrosis factor (TNF)-α, an inflammatory cytokine, is involved in the pathogenesis of both RA and atherosclerosis [27]. It is possible that both RA and HL have a shared mechanism associating with cardiovascular diseases which account for the higher risk of hearing loss in patients with RA. Moreover, in this study, we found that patients with RA with IHD had the highest HL incidence compared with patients with other cardiovascular disorders. Hence, RA and cardiovascular disorders may have a shared contribution to HL risk.

Furthermore, several studies [28,29] have reported elevated plasma renin and angiotensin-converting enzyme (ACE) activities in patients with RA. 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 [29], 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.

The strength of this study is the use of a nationwide population-based cohort to identify HL risk in an Asian population with RA. Our findings can be generalized 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, such as smoking and chronic exposure to occupational and environmental noise, which could be associated with HL in the general population, were not available in the insurance database. Moreover, information on laboratory test results or HL severity was not available in the insurance claims data, and data on RA severity scale, such as disease activity, functional impairment, and physical damage, was also unavailable.

In conclusion, this study provided further evidence of the association between autoimmune disease and the development of HL. RA was significantly associated with an elevated risk of developing HL, and cardiovascular disorders could increase HL risk. Our findings also suggest the need for prompt and early detection of RA for HL prevention. Appropriate and timely medical interventions may improve the prognosis of hearing loss in patients diagnosed as having RA.

Acknowledgments

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Conflict of interest: None.

Footnotes:

Contributors: C-MH and F-CS conceived and designed the study. C-MH wrote the manuscript and revised the important intellectual content. Data were analysed by F-CS and H-JC. F-CS revised important intellectual content and was responsible for the final version of the manuscript. Conception and design summary: C-MH, P-HH, GJT and J-LL. All authors read and approved the final manuscript.

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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Table 1. Distribution of demographic factors and comorbidity between cohorts

	Non-RA cohort N = 73,068		RA cohort N = 18,267		Standardized mean difference
Variable	n	%	n	%	
Sex					
Female	57,288	78.4	14322	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
Hyperlipidemia	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

Abbreviation: RA, rheumatoid arthritis; SD, standard deviation; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

Table 2. Cox model measured hazard ratios and 95% confidence intervals of hearing loss associated with rheumatoid arthritis and covariates

Variables	Event no.	Person-years	IR	HR (95% CI)	
				Univariate	Multivariate‡
RA					
No	927	572031	1.62	1.00	1.00
Yes	429	139085	3.08	1.90 (1.70-2.13)	1.89 (1.68-2.12)
Sex					
Female	977	565205	1.73	1.00	1.00
Male	379	145912	2.60	1.49 (1.33-1.68)	1.39 (1.23-1.56)
Age, years					
20-39	59	123836	0.48	1.00	1.00
40-59	563	368175	1.53	3.21 (2.45-4.19)	2.72 (2.08-3.57)
≥ 60	734	219105	3.35	6.98 (5.35-9.10)	4.97 (3.77-6.56)
Comorbidity†					
No	469	405253	1.16	1.00	1.00
Yes	887	305864	2.90	2.49 (2.23-2.79)	1.66 (1.47-1.87)

Abbreviation: IR, incidence rates per 1000 person-years; HR, hazard ratio; CI, confidence interval; RA, rheumatoid arthritis; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

†Patients with DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, and CKD dermatitis were classified as the comorbidity group.

‡Multivariate Cox proportional hazards regression model, including RA, sex, age, and comorbidity.

Table 3. Incidence rates and hazard ratios 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 no.	Person-years	IR	Event no.	Person-years	IR	Crude	Adjusted[†]
Sex								
Women	663	454249	1.46	314	110956	2.83	1.94 (1.69-2.22)	1.96 (1.71-2.24)
Men	264	117782	2.24	115	28130	4.09	1.82 (1.46-2.27)	1.86 (1.49-2.32)
Age, years								
20-39	40	98817	0.40	19	25020	0.76	1.89 (1.09-3.26)	1.91 (1.10-3.32)
40-59	355	295193	1.20	208	72982	2.85	2.37 (2.00-2.81)	2.33 (1.96-2.76)
≥ 60	532	178021	2.99	202	41084	4.92	1.63 (1.39-1.92)	1.63 (1.38-1.91)
Comorbidity								
DM								
No	765	514262	1.49	362	124722	2.90	1.95 (1.72-2.21)	1.95 (1.72-2.21)
Yes	162	57770	2.80	67	14363	4.66	1.66 (1.25-2.21)	1.75 (1.31-2.33)
Hyperlipidemia								
No	654	464753	1.41	320	113890	2.81	2.00 (1.75-2.28)	1.97 (1.72-2.25)
Yes	273	107279	2.54	109	25195	4.33	1.69 (1.36-2.11)	1.76 (1.41-2.20)
Hypertension								
No	481	402716	1.19	233	97031	2.40	2.01 (1.72-2.35)	1.97 (1.68-2.30)
Yes	446	169316	2.63	196	42054	4.66	1.76 (1.49-2.08)	1.82 (1.54-2.16)
Hyperthyroidism								

No	909	563891	1.61	416	135733	3.06	1.90 (1.69-2.13)	1.93 (1.72-2.17)
Yes	18	8140	2.21	13	3352	3.88	1.76 (0.86-3.58)	1.76 (0.86-3.63)
IHD								
No	671	491566	1.37	316	118909	2.66	1.95 (1.70-2.23)	1.98 (1.73-2.26)
Yes	256	80466	3.18	113	20176	5.60	1.75 (1.40-2.18)	1.75 (1.40-2.19)
Stroke								
No	896	559458	1.60	414	136197	3.04	1.90 (1.69-2.13)	1.91 (1.70-2.15)
Yes	31	12573	2.47	15	2888	5.19	2.10 (1.13-3.89)	2.16 (1.14-4.06)
CKD								
No	835	538065	1.55	369	124534	2.96	1.91 (1.69-2.16)	1.95 (1.73-2.21)
Yes	92	33967	2.71	60	14551	4.12	1.53 (1.11-2.12)	1.73 (1.24-2.41)

Abbreviation: RA, rheumatoid arthritis; IR, incidence rates per 1000 person-years; HR, hazard ratio; CI, confidence interval.

† Model mutually adjusted for sex, age, DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, and CKD in Cox proportional hazards regression.

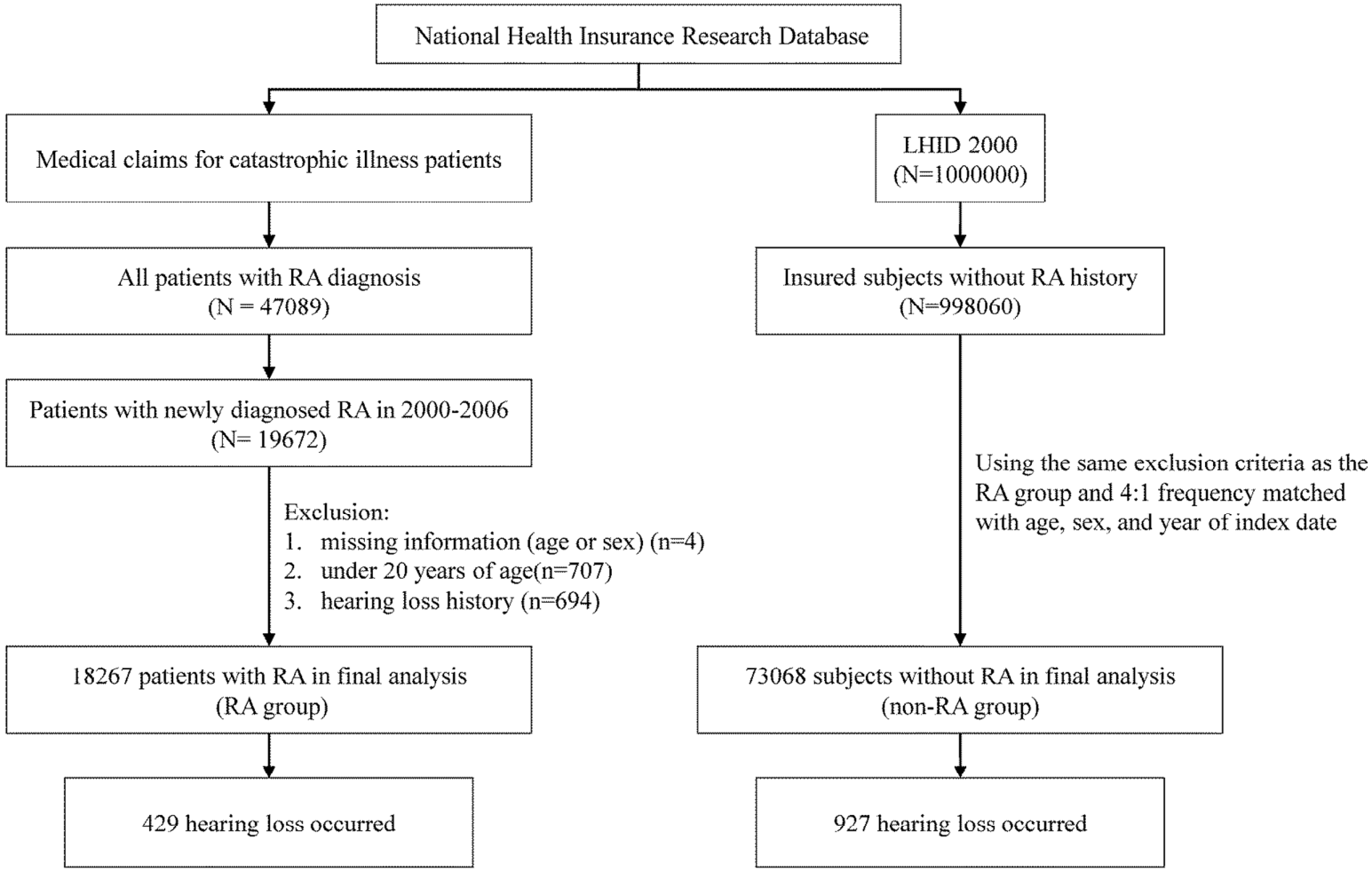
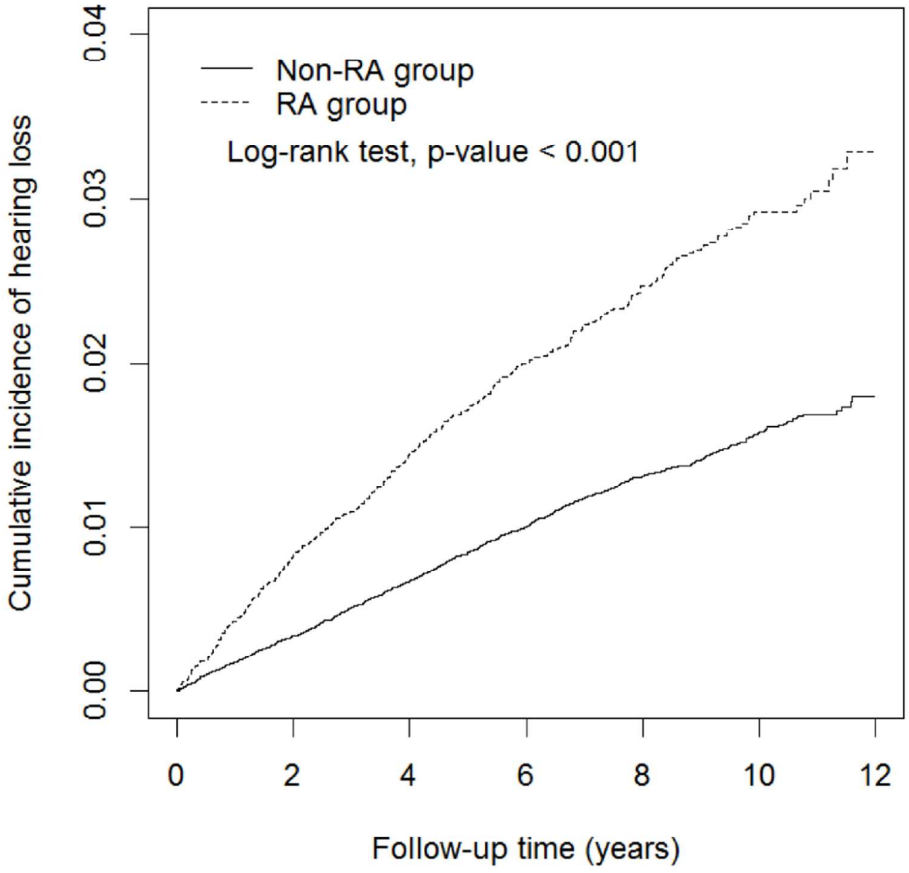


Fig 1. Flowchart showing selection of study cohorts

LHID, Longitudinal Health Insurance Database; RA, rheumatoid arthriti



No. at risk

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

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

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7,8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	26
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	26
		(*e*) Describe any sensitivity analyses	9

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	26
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10,22
		(b) Indicate number of participants with missing data for each variable of interest	26
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10,27
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10,27
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,23
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11,24
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Retrospective Cohort Study on Risk of Hearing Loss in Patients with Rheumatoid Arthritis Using Claims Data

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Secondary Subject Heading:	Epidemiology, Ear, nose and throat/otolaryngology
Keywords:	Rheumatoid arthritis, hearing loss, insurance data,, retrospective cohort study

Retrospective Cohort Study on Risk of Hearing Loss in Patients with Rheumatoid Arthritis Using Claims Data

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Running Title: Hearing loss in rheumatoid arthritis

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Word count: Abstract 247; Strength and limitation 145; Text 2603; 4 Tables; 2 Figures.

ABSTRACT

Purposes:

Hearing loss (HL) has been reported as a manifestation of systemic vascular involvement in patients with an autoimmune disease. However, population studies on 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.

Participants:

We used the Taiwan National Health Insurance Research Database to identify 18,267 RA patients newly diagnosed in 2000-2006 and 73,068 controls without RA, frequency-matched by sex, age, and index year. We estimated HL incidences in both cohorts and the RA cohort to non-RA cohort hazard ratios (HRs) after adjusting for sex, age, and comorbidities by the end of 2011.

Findings to date:

The HL incidence was higher in the RA cohort than in the non-RA cohort (3.08 versus 1.62 per 1000 person-years), with an adjusted HR of 1.91 (95% confidence interval = 1.70-2.14) 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 RA patients. Medications were associated with reduced HL incidence; RA patients who used NSAIDs had an aHR of 0.12 (95% CI = 0.07-0.20), compared with non-users.

Conclusions:

This population-based retrospective cohort study demonstrates that patients with RA are at an increased risk of developing HL. Adequate medications should be provided to patients with RA diagnosed and scheduled auditory examinations should be available to enable the early detection of HL.

Keywords: Rheumatoid arthritis, hearing loss, insurance data, retrospective cohort study

Strength and limitation of this study

1. The strength of this study is the use of a nationwide population-based cohort to identify HL risk in an Asian population with RA. Our findings can be generalized to the general population.
2. The inclusion of the Catastrophic Illness Patient Database confirmed the diagnoses of all RA cases with increased the reliability of our data; the large sample size reduced the tendency for selection bias, enhanced statistical power and precision of risk appraisal.
3. Some limitations in this study should be considered. 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, were not available in the insurance database.
4. Information on laboratory test results and HL severity, 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 characterized 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 types of hearing loss, and the RA disease activity and severity [7-10].

There are a wide variations in the reported prevalence of hearing loss 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 hearing loss and mixed hearing loss 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, hearing loss (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, hyperlipidemia, hyperthyroidism, hypothyroidism, chronic renal disease and autoimmune diseases, were 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 co-payment. 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, 9th 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]. This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115).

Study population

Figure 1 shows the flowchart for identifying and selecting study population using a population-based retrospective cohort study design. We identified a 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 and 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 scrutinized 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, 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 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), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401-405), hyperthyroidism (ICD-9-CM 242), ischemic 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 [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 standardized 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 hazard ratio (cHR) and adjusted hazard ratio (aHR) of HL, respectively, and their 95% confidence intervals (CIs). Sex, age, and comorbidities including diabetes,

hyperlipidemia, 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 RA patients by calculating the incidence density and HRs of HL. Medications that had been prescribed for RA treatment during the follow-up period included Nonsteroidal anti-inflammatory drugs (NSAIDs), prednisolone, disease-modifying antirheumatic drugs (DMARDs, including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide), and tumor necrosis factor (TNF, including etanercept and adalimumab).

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

Results

We identified 18,267 RA patients 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) (Fig. 2). The incidence density of HL was approximately two-fold 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 = 1.70-2.14) (Table 2). Men were at a greater risk of HL than women, and the risk increased with age. Compared to 20−39 years old, the aHRs of HL were 2.89 (95% CI =2.21-3.79) and 5.27 (95% CI = 3.99-6.95) for those aged 40-59 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 = 1.07-1.38) and of 1.36 (95% CI = 1.19-1.56), 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 RA patients. RA patients with IHD had the highest incident HL, 5.60 per 1000 person-years.

Table 4 shows that medications were associated with reduced incident HL for RA

patients. Near 99% of RA patients used NSAIDs and users had a HL incidence of 2.98 per 1000 person-years, with an aHR of 0.12 (95% CI = 0.07-0.20) compared with non-users who had an incidence of 30.1 per 1000 person-years for HL. RA patients on medications of TNF (n = 2706) had the lowest HL incidence of 1.17 per 1000 person-years with an aHR of 0.40 (95% CI = 0.27-0.59), compared with non-users who had an incidence of 3.45 per 1000 person-years.

Discussion

This retrospective cohort study showed that patients with RA were nearly two-fold 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 2 age groups in the non-RA cohort, reflecting the natural HL by aging 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 sensorineural hearing loss comorbid with systemic lupus erythematosus [21] and psoriasis [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 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 overrepresentation 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 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], dyslipidemia [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 2 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 interest 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).

The development of RA and the breakdown of atherosclerotic plaques possibly share common factors contributing to inflammatory cells and pro-inflammatory cytokines [25]. Pro-inflammatory cytokines may contribute to the oxidative damage in the inner ear [26]. For example, both tumor necrosis factor (TNF)-α and interleukin (IL)-6 are involved in the pathogenesis of both RA and atherosclerosis [39]. However, Takatsu et al. [6] showed that the pro-inflammatory cytokines (IL-6) and matrix matalloproteinase (MMP) -3 may contribute to harm inner ear cells by an oxidative process. Both RA and HL may have a shared mechanism associating with cardiovascular diseases which account for the higher risk of hearing loss in patients with RA. IHD alone may associate with HL. An earlier study found patients with IHD are prevalent with HL for up to over 30% [40]. 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 HL risk.

Furthermore, several studies [41,42] have reported elevated plasma renin and angiotensin-converting enzyme (ACE) activities in patients with RA. 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 [42], 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 RA patients on medication of NSAID, prednisolone, DMARDs and TNF. Conversely, Halligan et al. [23] described an association between HL and hydroxychloroquine, and Dikici et al. [43] 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, 44]. The inconsistent results may be due to the relatively small study sample sizes, while our study is a nationwide population-based cohort with large sample size. It is likely, the reduced inflammation in patients with RA on medications of NSAID. corticosteroid , DMARDs and TNF could be associated with reduce 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 generalized 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 on laboratory test results, HL severity, and RA severity scale and activity, functional impairment and physical damage of the disease was also unavailable.

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 and early detection of RA for HL prevention. Appropriate and timely medical interventions may improve the prognosis of hearing loss for patients diagnosed with RA.

Acknowledgments

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Conflict of interest: None.

Footnotes:

Contributors: C-MH and F-CS conceived and designed the study. C-MH wrote the manuscript and revised the important intellectual content. Data were analyzed by F-CS and H-JC. F-CS revised important intellectual content and was responsible for the final version of the manuscript. Conception and design summary: C-MH, P-HH, GJT and J-LL. All authors read and approved the final manuscript.

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Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: No additional data are available.

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Table 1. Distribution of demographic factors and comorbidity compared between cohorts

	Non-RA cohort N = 73,068		RA cohort N = 18,267		Standardized mean difference
Variable	n	%	n	%	
Sex					
Female	57288	78.4	14322	78.4	<0.001
Male	15780	21.6	3945	21.6	<0.001
Age, years					
20-39	12224	16.7	3056	16.7	<0.001
40-59	36532	50.0	9133	50.0	<0.001
≥ 60	24312	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
Hyperlipidemia	14078	19.3	3439	18.8	0.011
Hypertension	22844	31.3	5964	32.7	0.030
Hyperthyroidism	1089	1.49	456	2.50	0.072
IHD	10993	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

Abbreviation: RA, rheumatoid arthritis; SD, standard deviation; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

[†]Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.

Table 2. Cox model measured hazard ratios and 95% confidence intervals of hearing loss associated with rheumatoid arthritis and covariates

Variables	Event n	Person-years	Incidence density #	HR (95% CI)	
				Univariate	Multivariate‡
RA					
No	927	572031	1.62	ref	ref
Yes	429	139085	3.08	1.90 (1.70-2.13)	1.91 (1.70-2.14)
Sex					
Female	977	565205	1.73	ref	ref
Male	379	145912	2.60	1.49 (1.33-1.68)	1.40 (1.24-1.58)
Age, years					
20-39	59	123836	0.48	ref	ref
40-59	563	368175	1.53	3.21 (2.45-4.19)	2.89 (2.21-3.79)
≥ 60	734	219105	3.35	6.98 (5.35-9.10)	5.27 (3.99-6.95)
Comorbidity					
DM					
No	1127	638984	1.76	ref	ref
Yes	229	72133	3.17	1.78 (1.55-2.06)	1.14 (0.98-1.33)
Hyperlipidemia					
No	974	578643	1.68	ref	ref
Yes	382	132474	2.88	1.70 (1.51-1.92)	1.10 (0.97-1.26)
Hypertension					
No	714	499747	1.43	ref	ref
Yes	642	211370	3.04	2.11 (1.90-2.35)	1.21 (1.07-1.38)
Hyperthyroidism					
No	1325	699624	1.89	ref	ref
Yes	31	11492	2.70	1.41 (0.99-2.02)	1.33 (0.92-1.92)
IHD					
No	987	610475	1.62	ref	ref
Yes	369	100642	3.67	2.25 (2.00-2.54)	1.36 (1.19-1.56)
Stroke					
No	1310	695656	1.88	ref	ref
Yes	46	15461	2.98	1.55 (1.15-2.07)	0.85 (0.63-1.14)
CKD					
No	1204	662599	1.82	ref	ref
Yes	152	48517	3.13	1.71 (1.45-2.03)	1.06 (0.89-1.26)
Hypothyroidism					
No	1343	706448	1.90	ref	ref

Yes	13	4668	2.78	1.46 (0.85-2.52)	1.15 (0.65-2.01)
Autoimmune diseases[†]					
No	1334	704142	1.89	ref	ref
Yes	22	6975	3.15	1.65 (1.08-2.51)	1.34 (0.88-2.05)

Abbreviation: HR, hazard ratio; CI, confidence interval; RA, rheumatoid arthritis; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

[†]Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.

[#] per 1000 person-years

[‡]Multivariate Cox proportional hazards regression model, including RA, sex, age (categorical), DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism, and autoimmune diseases.

Table 3. Incidence density and RA cohort to non-RA cohort hazard ratios 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 no.	Person-years	Incidence density[#]	Event no.	Person-years	Incidence density[#]	Crude	Adjusted[‡]
Sex								
Women	663	454249	1.46	314	110956	2.83	1.94 (1.69-2.22)	1.95 (1.70-2.23)
Men	264	117782	2.24	115	28130	4.09	1.82 (1.46-2.27)	1.85 (1.48-2.30)
Age, years								
20-39	40	98817	0.40	19	25020	0.76	1.89 (1.09-3.26)	1.80 (1.02-3.16)
40-59	355	295193	1.20	208	72982	2.85	2.37 (2.00-2.81)	2.32 (1.95-2.76)
≥ 60	532	178021	2.99	202	41084	4.92	1.63 (1.39-1.92)	1.62 (1.37-1.90)
Comorbidity								
DM								
No	765	514262	1.49	362	124722	2.90	1.95 (1.72-2.21)	1.94 (1.71-2.20)
Yes	162	57770	2.80	67	14363	4.66	1.66 (1.25-2.21)	1.74 (1.30-2.32)
Hyperlipidemia								
No	654	464753	1.41	320	113890	2.81	2.00 (1.75-2.28)	1.96 (1.72-2.25)
Yes	273	107279	2.54	109	25195	4.33	1.69 (1.36-2.11)	1.74 (1.39-2.18)
Hypertension								
No	481	402716	1.19	233	97031	2.40	2.01 (1.72-2.35)	1.94 (1.66-2.28)
Yes	446	169316	2.63	196	42054	4.66	1.76 (1.49-2.08)	1.82 (1.54-2.16)

Hyperthyroidism								
No	909	563891	1.61	416	135733	3.06	1.90 (1.69-2.13)	1.92 (1.71-2.16)
Yes	18	8140	2.21	13	3352	3.88	1.76 (0.86-3.58)	1.72 (0.84-3.55)
IHD								
No	671	491566	1.37	316	118909	2.66	1.95 (1.70-2.23)	1.96 (1.71-2.24)
Yes	256	80466	3.18	113	20176	5.60	1.75 (1.40-2.18)	1.75 (1.40-2.19)
Stroke								
No	896	559458	1.60	414	136197	3.04	1.90 (1.69-2.13)	1.90 (1.69-2.14)
Yes	31	12573	2.47	15	2888	5.19	2.10 (1.13-3.89)	2.18 (1.16-4.12)
CKD								
No	835	538065	1.55	369	124534	2.96	1.91 (1.69-2.16)	1.94 (1.71-2.19)
Yes	92	33967	2.71	60	14551	4.12	1.53 (1.11-2.12)	1.73 (1.25-2.42)
Hypothyroidism								
No	917	569055	1.61	426	137393	3.10	1.92 (1.71-2.16)	1.94 (1.73-2.18)
Yes	10	2977	3.36	3	1692	1.77	0.53 (0.15-1.93)	0.69 (0.19-2.57)
Autoimmune diseases[†]								
No	916	568956	1.61	418	135186	3.09	1.92 (1.71-2.15)	1.94 (1.73-2.18)
Yes	11	3076	3.58	11	3899	2.82	0.79 (0.34-1.82)	0.89 (0.38-2.07)

Abbreviation: RA, rheumatoid arthritis; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

[†]Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.

[#] per 1000 person-years.

[‡] Model mutually adjusted for sex, age (continuous), DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD,

hypothyroidism, and autoimmune diseases.

Table 4. Incidence density and hazard ratios of hearing loss associated with medication in patients with rheumatoid arthritis

Medicine use	N	Event no.	Person-years	Incidence density[#]	HR (95% CI)	
					Crude	Adjusted[&]
NSAIDs						
No	169	16	532	30.1	ref	ref
Yes	18098	413	138553	2.98	0.11 (0.07-0.18)	0.12 (0.07-0.20)
Prednisolone						
No	1673	60	11529	5.20	ref	ref
Yes	16594	369	127556	2.89	0.56 (0.43-0.74)	0.53 (0.40-0.70)
DMARDs[†]						
No	2723	90	18643	4.83	ref	ref
Yes	15544	339	120443	2.81	0.59 (0.47-0.74)	0.68 (0.53-0.85)
TNF[‡]						
No	15561	403	116876	3.45	ref	ref
Yes	2706	26	22210	1.17	0.34 (0.23-0.51)	0.40 (0.27-0.59)

Abbreviation: HR, hazard ratio; CI, confidence interval RA, rheumatoid arthritis; NSAID, non-steroidal anti-inflammatory drug; DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factor.

[†] DMARDs including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide.

[‡] TNF including etanercept and adalimumab.

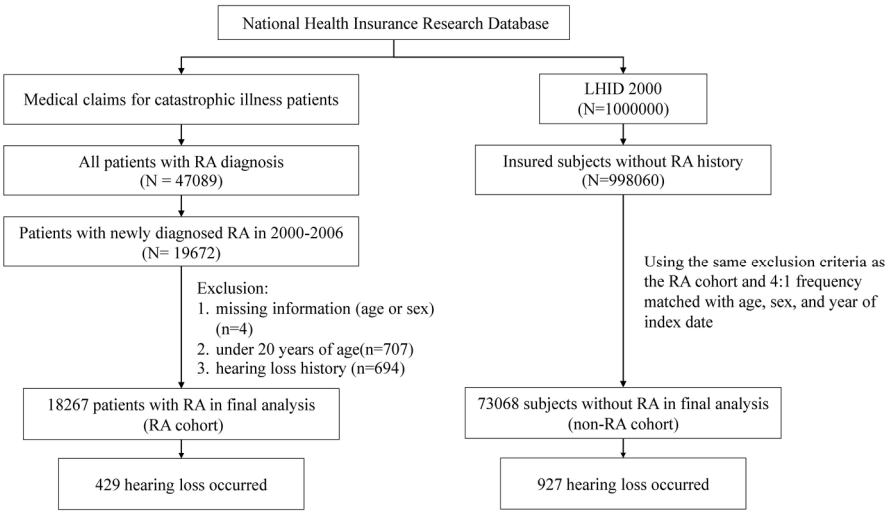
[#] per 1000 person-years.

[&] Model adjusted for sex, age, DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism, and autoimmune diseases.

Fig 1. Flowchart showing selection of study cohorts

LHID, Longitudinal Health Insurance Database; RA, rheumatoid arthritis

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



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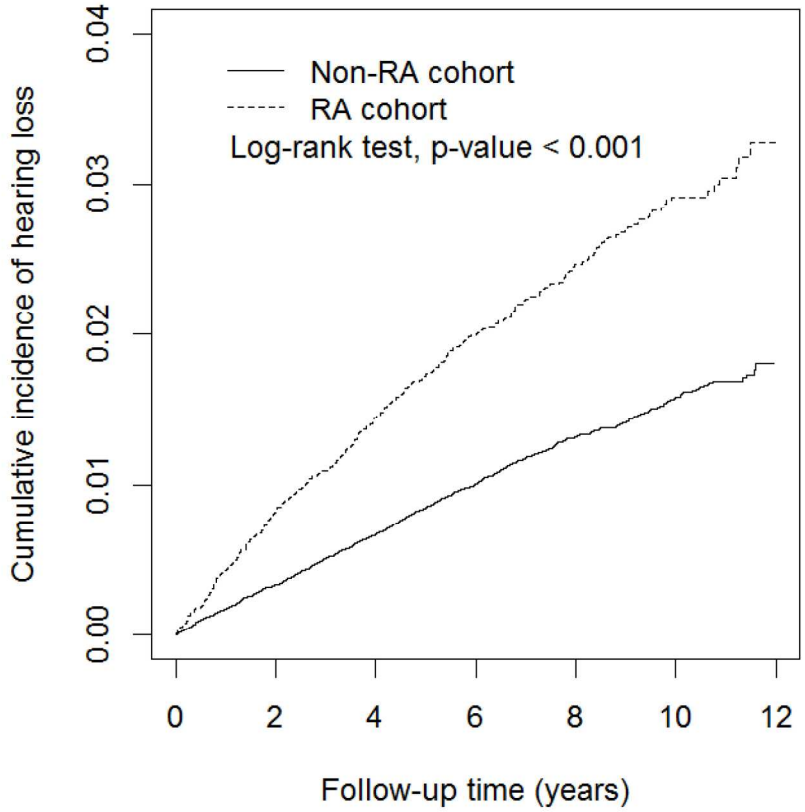

No. at risk

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

199x209mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7,8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	26
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	26
		(*e*) Describe any sensitivity analyses	9

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	26
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10,22
		(b) Indicate number of participants with missing data for each variable of interest	26
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10,27
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10,27
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,23
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11,24
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Retrospective Cohort Study on Risk of Hearing Loss in Patients with Rheumatoid Arthritis Using Claims Data

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Keywords:	Rheumatoid arthritis, hearing loss, insurance data,, retrospective cohort study

Retrospective Cohort Study on Risk of Hearing Loss in Patients with Rheumatoid Arthritis Using Claims Data

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Word count: Abstract 238; Strength and limitation 150; Text 2658; 5 Tables; 2 Figures.

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 RA patients 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 hazard ratios (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 versus 1.62 per 1000 person-years), with an adjusted HR of 1.91 (95% confidence interval = 1.70-2.14) 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 RA

patients. Medications were associated with reduced HL incidence; RA patients who used NSAIDs had an aHR of 0.12 (95% CI = 0.07-0.20), 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 RA patients.

Keywords: Rheumatoid arthritis, hearing loss, insurance data, retrospective cohort study

Strengths and limitations of this study

1. The strength of this study is the use of a nationwide population-based cohort to identify HL risk in an Asian population with RA. Our findings can be generalized to the general population.
2. The inclusion of the Catastrophic Illness Patient Database confirmed the diagnoses of all RA cases with increased the reliability of our data; the large sample size reduced the tendency for selection bias, enhanced statistical power and precision of risk appraisal.
3. 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, were not available in the insurance database.
4. 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 characterized 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 are a wide variations 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, hyperlipidemia, hyperthyroidism, hypothyroidism, chronic renal disease and autoimmune diseases, were 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 co-payment. 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, 9th 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] This study was approved by the Research Ethics Committee of China Medical University and Hospital (CMUH104-REC2-115).

Study population

Figure 1 shows the flowchart for identifying and selecting study population using a population-based retrospective cohort study design. We identified a 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

scrutinized 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 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), hyperlipidemia (ICD-9-CM 272), hypertension (ICD-9-CM 401-405), hyperthyroidism (ICD-9-CM 242), ischemic 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 [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 standardized 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 hazard ratio (cHR) and adjusted hazard ratio (aHR) of HL, respectively, and their 95% confidence intervals (CIs). Sex, age, and comorbidities including diabetes, hyperlipidemia, 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 RA patients by calculating the incidence density and HRs of HL. The HL relating to medications for RA treatment was evaluated, including nonsteroidal anti-inflammatory drugs (NSAIDs), prednisolone, disease-modifying antirheumatic drugs (DMARDs, including hydroxychloroquine, sulfasalazine, methotrexate, and leflunomide), and tumor necrosis factor (TNF, including etanercept and adalimumab). Further analysis evaluated the HL risk by the type of HL: sensorineural, conductive or mixed.

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

RESULTS

We identified 18,267 RA patients 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) (Fig. 2). The incidence density of HL was approximately two-fold 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 = 1.70-2.14) (Table 2). Men were at a greater risk of HL than women, and the risk increased with age. Compared to 20−39 years old, the aHRs of HL were 2.89 (95% CI =2.21-3.79) and 5.27 (95% CI = 3.99-6.95) for those aged 40-59 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 = 1.07-1.38) and of 1.36 (95% CI = 1.19-1.56), 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 RA patients. RA patients 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 RA patients. Near 99% of RA patients used NSAIDs and users had a HL incidence of 2.98 per 1000 person-years, with an aHR of 0.12 (95% CI = 0.07-0.20) compared with non-users who had an incidence of 30.1 per 1000 person-years for HL. RA patients 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 = 0.10-0.55), compared with non-users who had an incidence of 3.23 per 1000 person-years.

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

DISCUSSION

This retrospective cohort study showed that patients with RA were nearly two-fold 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 2 age groups in the non-RA cohort, reflecting the natural HL by aging 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 sensorineural hearing loss comorbid with systemic lupus erythematosus 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 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 overrepresentation 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 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], dyslipidemia[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 2 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 interest 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 sensorineural hearing loss 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 pro-inflammatory cytokines.[25] Pro-inflammatory cytokines may contribute to the oxidative damage in the inner ear.[26] For example, both tumor necrosis factor (TNF)- α and interleukin (IL)-6 are involved in the pathogenesis of both RA and atherosclerosis.[40] However, Takatsu et al. showed that the pro-inflammatory cytokines (IL-6) and matrix matalloproteinase (MMP) -3 may contribute to harm 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 hearing loss in patients with RA. IHD alone may associate with HL. An earlier study found 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 angiotensin-converting enzyme (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 RA patients 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 to the relatively small study sample sizes, while our study is a nationwide population-based cohort with large sample size. It is likely, 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 generalized 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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Table 1. Distribution of demographic factors and comorbidity compared between cohorts

	Non-RA cohort N = 73,068		RA cohort N = 18,267		Standardized mean difference
Variable	n	%	n	%	
Sex					
Female	57288	78.4	14322	78.4	<0.001
Male	15780	21.6	3945	21.6	<0.001
Age, years					
20-39	12224	16.7	3056	16.7	<0.001
40-59	36532	50.0	9133	50.0	<0.001
≥ 60	24312	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
Hyperlipidemia	14078	19.3	3439	18.8	0.011
Hypertension	22844	31.3	5964	32.7	0.030
Hyperthyroidism	1089	1.49	456	2.50	0.072
IHD	10993	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

Abbreviation: RA, rheumatoid arthritis; SD, standard deviation; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

†Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.

Table 2. Cox model measured hazard ratios and 95% confidence intervals of hearing loss associated with rheumatoid arthritis and covariates

Variables	Event n	Person-years	Incidence density #	HR (95% CI)	
				Univariate	Multivariate‡
RA					
No	927	572031	1.62	ref	ref
Yes	429	139085	3.08	1.90 (1.70-2.13)***	1.91 (1.70-2.14)***
Sex					
Female	977	565205	1.73	ref	ref
Male	379	145912	2.60	1.49 (1.33-1.68)***	1.40 (1.24-1.58)***
Age, years					
20-39	59	123836	0.48	ref	ref
40-59	563	368175	1.53	3.21 (2.45-4.19)***	2.89 (2.21-3.79)***
≥ 60	734	219105	3.35	6.98 (5.35-9.10)***	5.27 (3.99-6.95)***
Comorbidity					
DM					
No	1127	638984	1.76	ref	ref
Yes	229	72133	3.17	1.78 (1.55-2.06)***	1.14 (0.98-1.33)
Hyperlipidemia					
No	974	578643	1.68	ref	ref
Yes	382	132474	2.88	1.70 (1.51-1.92)***	1.10 (0.97-1.26)
Hypertension					
No	714	499747	1.43	ref	ref
Yes	642	211370	3.04	2.11 (1.90-2.35)***	1.21 (1.07-1.38)**
Hyperthyroidism					
No	1325	699624	1.89	ref	ref
Yes	31	11492	2.70	1.41 (0.99-2.02)	1.33 (0.92-1.92)
IHD					
No	987	610475	1.62	ref	ref
Yes	369	100642	3.67	2.25 (2.00-2.54)***	1.36 (1.19-1.56)***
Stroke					
No	1310	695656	1.88	ref	ref
Yes	46	15461	2.98	1.55 (1.15-2.07)**	0.85 (0.63-1.14)
CKD					
No	1204	662599	1.82	ref	ref
Yes	152	48517	3.13	1.71 (1.45-2.03)***	1.06 (0.89-1.26)
Hypothyroidism					
No	1343	706448	1.90	ref	ref

Yes	13	4668	2.78	1.46 (0.85-2.52)	1.15 (0.65-2.01)
Autoimmune diseases[†]					
No	1334	704142	1.89	ref	ref
Yes	22	6975	3.15	1.65 (1.08-2.51)*	1.34 (0.88-2.05)

Abbreviation: HR, hazard ratio; CI, confidence interval; RA, rheumatoid arthritis; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

[†]Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.

[#] per 1000 person-years

[‡]Multivariate Cox proportional hazards regression model, including RA, sex, age (categorical), DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism, and autoimmune diseases.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$

Table 3. Incidence density and RA cohort to non-RA cohort hazard ratios 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 no.	Person-years	Incidence density[#]	Event no.	Person-years	Incidence density[#]	Crude	Adjusted[‡]
Sex								
Women	663	454249	1.46	314	110956	2.83	1.94 (1.69-2.22)***	1.95 (1.70-2.23)***
Men	264	117782	2.24	115	28130	4.09	1.82 (1.46-2.27)***	1.85 (1.48-2.30)***
Age, years								
20-39	40	98817	0.40	19	25020	0.76	1.89 (1.09-3.26)*	1.80 (1.02-3.16)*
40-59	355	295193	1.20	208	72982	2.85	2.37 (2.00-2.81)***	2.32 (1.95-2.76)***
≥ 60	532	178021	2.99	202	41084	4.92	1.63 (1.39-1.92)***	1.62 (1.37-1.90)***
Comorbidity								
DM								
No	765	514262	1.49	362	124722	2.90	1.95 (1.72-2.21)***	1.94 (1.71-2.20)***
Yes	162	57770	2.80	67	14363	4.66	1.66 (1.25-2.21)***	1.74 (1.30-2.32)***
Hyperlipidemia								
No	654	464753	1.41	320	113890	2.81	2.00 (1.75-2.28)***	1.96 (1.72-2.25)***
Yes	273	107279	2.54	109	25195	4.33	1.69 (1.36-2.11)***	1.74 (1.39-2.18)***
Hypertension								
No	481	402716	1.19	233	97031	2.40	2.01 (1.72-2.35)***	1.94 (1.66-2.28)***
Yes	446	169316	2.63	196	42054	4.66	1.76 (1.49-2.08)***	1.82 (1.54-2.16)***

Hyperthyroidism								
No	909	563891	1.61	416	135733	3.06	1.90 (1.69-2.13)***	1.92 (1.71-2.16)***
Yes	18	8140	2.21	13	3352	3.88	1.76 (0.86-3.58)	1.72 (0.84-3.55)
IHD								
No	671	491566	1.37	316	118909	2.66	1.95 (1.70-2.23)***	1.96 (1.71-2.24)***
Yes	256	80466	3.18	113	20176	5.60	1.75 (1.40-2.18)***	1.75 (1.40-2.19)***
Stroke								
No	896	559458	1.60	414	136197	3.04	1.90 (1.69-2.13)***	1.90 (1.69-2.14)***
Yes	31	12573	2.47	15	2888	5.19	2.10 (1.13-3.89)*	2.18 (1.16-4.12)*
CKD								
No	835	538065	1.55	369	124534	2.96	1.91 (1.69-2.16)***	1.94 (1.71-2.19)***
Yes	92	33967	2.71	60	14551	4.12	1.53 (1.11-2.12)*	1.73 (1.25-2.42)**
Hypothyroidism								
No	917	569055	1.61	426	137393	3.10	1.92 (1.71-2.16)***	1.94 (1.73-2.18)***
Yes	10	2977	3.36	3	1692	1.77	0.53 (0.15-1.93)	0.69 (0.19-2.57)
Autoimmune diseases[†]								
No	916	568956	1.61	418	135186	3.09	1.92 (1.71-2.15)***	1.94 (1.73-2.18)***
Yes	11	3076	3.58	11	3899	2.82	0.79 (0.34-1.82)	0.89 (0.38-2.07)

Abbreviation: RA, rheumatoid arthritis; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus; IHD, ischemic heart disease; CKD, chronic kidney disease.

[†]Autoimmune diseases including psoriasis, SLE, systemic sclerosis, Sjogren syndrome, dermatomyositis, polymyositis, and vasculitis.

[#] per 1000 person-years.

[‡] Model mutually adjusted for sex, age (continuous), DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism, and

autoimmune diseases.

* p<0.05, ** p<0.01, *** p<0.001

Table 4. Incidence density and hazard ratios of hearing loss associated with medication in patients with rheumatoid arthritis

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

Abbreviation: HR, hazard ratio; CI, confidence interval RA, rheumatoid arthritis; NSAID, non-steroidal anti-inflammatory drug; DMARDs, disease-modifying antirheumatic drugs; TNF, tumor necrosis factor.

[#] per 1000 person-years.

[†] Model adjusted for sex, age, DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism, and autoimmune diseases.

* p<0.05, ** p<0.01, *** p<0.001

Table 5. Incidence density and hazard ratios for subtypes of hearing loss according to rheumatoid arthritis status

	Rheumatoid arthritis				Compared to non-TTH group	
	No		Yes		HR (95% CI)	
Types of hearing loss	Event no.	Incidence density[#]	Event no.	Incidence density[#]	Crude	Adjusted[†]
Sensorineural	249	0.44	144	1.04	2.38 (1.94-2.92)***	2.35 (1.91-2.89)***
Conductive	10	0.02	1	0.01	0.41 (0.05-3.21)	0.41 (0.05-3.23)
Mixed	668	1.17	284	2.04	1.75 (1.52-2.01)***	1.77 (1.54-2.03)***

ICD-9-CM: sensorineural, 389.10 and 389.12; conductive, 389.00; mixed, 388.2, 388.4, 389.2, and 389.9.

Abbreviation: HR, hazard ratio; CI, confidence interval; TTH,.

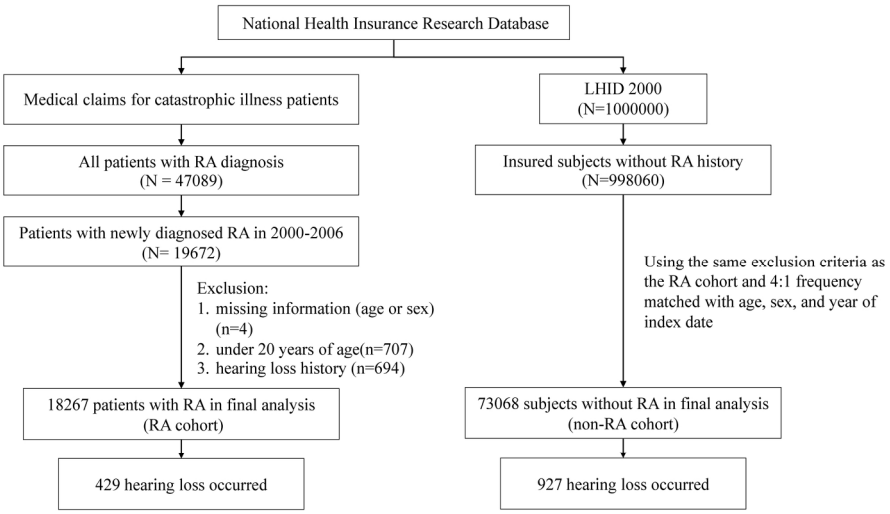
[#] per 1000 person-years.

[†] Model adjusted for sex, age (continuous), DM, hyperlipidemia, hypertension, hyperthyroidism, IHD, stroke, CKD, hypothyroidism, and autoimmune diseases.

*** $p<0.001$.

Fig 1. Flowchart showing selection of study cohorts
LHID, Longitudinal Health Insurance Database; RA, rheumatoid arthritis

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



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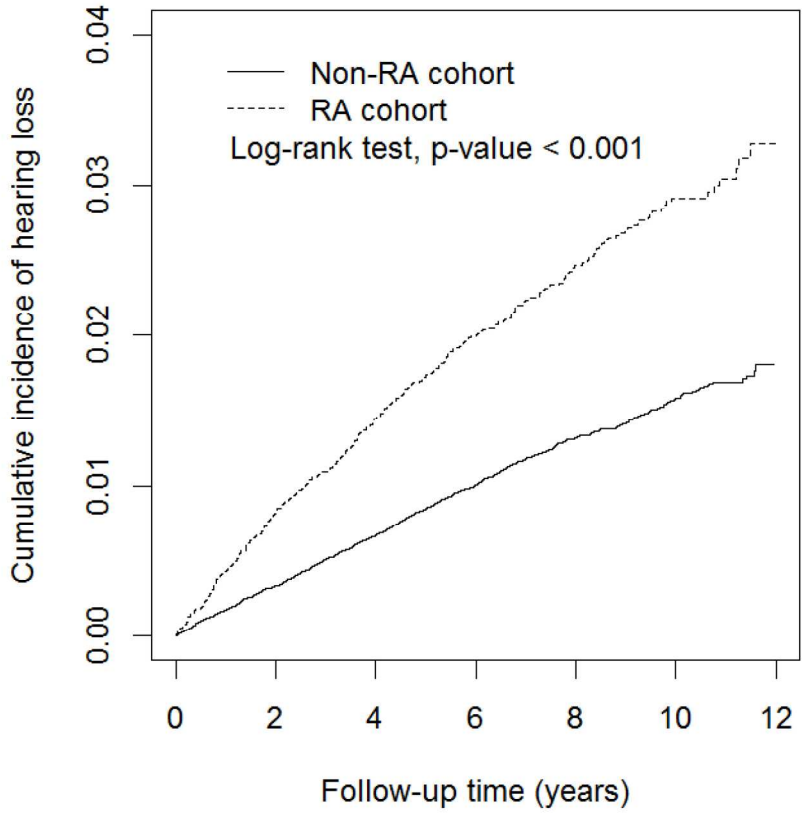

No. at risk

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

199x209mm (300 x 300 DPI)

STROBE Statement

Checklist of items that should be included in reports of observational studies

Section/Topic	Item No	Recommendation	Reported on Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6,7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7,8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	7,8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7,8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8,9
		(*b*) Describe any methods used to examine subgroups and interactions	8,9
		(*c*) Explain how missing data were addressed	26
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	26
		(*e*) Describe any sensitivity analyses	9

Section/Topic	Item No	Recommendation	Reported on Page No
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	26
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10,22
		(b) Indicate number of participants with missing data for each variable of interest	26
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	10,27
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10,27
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10,23
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,11,24
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	13,14
Other Information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

**Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.*

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.