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# The association between Bell's palsy and rheumatoid arthritis
## A longitudinal study

Sang-Yeon Lee, MD[a], Jae-Sung Lim, MD[b], Dong Jun Oh, MD[c], Bumjung Park, MD[d], Il-Seok Park, MD[e], Hyo Geun Choi, MD, PhD[d,*]

## Abstract

This study aimed to evaluate the relationship between Bell's palsy and rheumatoid arthritis in a national sample cohort from Korea.

Data were collected for individuals ≥20 years old from 2002 to 2013 in the Korean National Health Insurance Service-National Sample Cohort. We extracted data for patients with rheumatoid arthritis (n = 7628) and 1:4-matched controls (n = 30,512) and analyzed the occurrence of Bell's palsy in both groups. Matching was performed based on age, sex, income, and region of residence. Rheumatoid arthritis was diagnosed according to International Classification of Disease-10 (ICD-10) codes (M05-M06) and the prescription of biological agents and/or disease-modifying antirheumatic drugs. Bell's palsy patients were diagnosed according to ICD-10 code H912 and treatment ≥2 times with steroids. Adjusted hazard ratios (HRs) were calculated using stratified Cox proportional hazard models for the Charlson comorbidity index and 95% confidence intervals (CIs). Subgroup analyses based on age and sex were also performed.

The rates of Bell's palsy were similar between the rheumatoid arthritis group (0.5% [38/7628]) and the control group, with no significant difference (0.4% [124/30,512], $P = .270$). The adjusted HR for Bell's palsy was 1.12 (95% CI, 0.78–1.62) in the rheumatoid arthritis group ($P = .540$). In the subgroup analyses according to age and sex, the relationship between Bell's palsy and rheumatoid arthritis did not reach statistical significance.

The risk of Bell's palsy was not increased in patients with rheumatoid arthritis.

**Abbreviations:** CCI = Charlson comorbidity index, CIs = confidence intervals, HIRA = Health Insurance Review and Assessment, HR = hazard ratio, ICD-10 = International Classification of Disease-10, NSC = National Sample Cohort.

**Keywords:** Bell's palsy, cohort study, rheumatoid arthritis

## 1. Introduction

Bell's palsy, which is an idiopathic facial neuropathy, exclusively affects the motor branch of the facial nerve.[1] The global annual incidence of Bell's palsy has been reported to range from 13.1 to 53.3 per 100,000 persons.[2–6] The annual incidence of Bell's palsy in Korea is 39.4 per 100,000 persons based on a large population-based case–control study.[7] Several predisposing factors, including diabetes, hypertension, dyslipidemia, and pregnancy, have been identified.[8–10] Various mechanisms, including viral infections, vascular ischemia, and immune-mediated processes, are thought to contribute to Bell's palsy.[11,12] However, the exact pathogenesis of Bell's palsy has not been clearly elucidated in most cases examined to date.

Rheumatoid arthritis, which is a common autoimmune disorder that is characterized by systemic inflammatory polyarthritis, affects approximately 1% of the global population.[13,14] In a Korean population-based case–control study, the overall weighted prevalence of rheumatoid arthritis was 1.5%.[15] Several studies have reported a high prevalence of comorbidities and risk factors, including cardiovascular events, diabetes mellitus, hypertension, and dyslipidemia.[16–18] Rheumatoid arthritis, which may lead to systemic vasculitis, stimulates extra-articular manifestations in other organs, including the central and peripheral nervous systems in rare cases.[19] A recent case-series study described Bell's palsy-associated manifestations, including hemifacial weakness, otalgia, and hemifacial spasm, in a patient with rheumatoid arthritis.[20]

From a clinical perspective, we have experienced Bell's palsy patients with underlying rheumatoid arthritis. The shared pathogenesis found between rheumatoid arthritis and Bell's palsy is based on a viral infection and a subsequent autoimmune reaction. Because Bell's palsy is associated with rheumatoid arthritis comorbidities,[21] systemic mediators of inflammation, rather than rheumatoid arthritis itself, may be confounding factors for the occurrence of Bell's palsy. Therefore, we hypothesized that this putative association might contribute to an increased incidence of Bell's palsy in patients with rheumatoid arthritis. However, evidence for this association in support of our hypothesis is limited. When we searched the PubMed and EMBASE databases using the keywords "([Rheumatoid arthritis] OR [idiopathic juvenile arthritis] AND ([Bell's palsy] OR [facial nerve palsy] OR [facial weakness])" and limited the results to English language and human-based studies published before March 2018, only 2 publications comprising 4 patients were found that examined this association.[20,22] Given the rarity of reports of Bell's palsy in rheumatoid arthritis, a large cohort study seems to be mandatory to address the risk of the development of Bell's palsy in rheumatoid arthritis patients.

Considering this perspective, an investigation of the association between rheumatoid arthritis and Bell's palsy that minimizes the effects of confounding factors may facilitate better understanding of the treatment and prognosis of such cases. The aim of this study was to elucidate the putative association of Bell's palsy with rheumatoid arthritis using a national Korean population-based sample cohort. We extracted data for patients with rheumatoid arthritis and a 1:4-matched control group and analyzed the occurrence of Bell's palsy in this cohort.

## 2. Materials and methods

### 2.1. Study population and data collection

The ethics committee of Hallym University (2017-I102) approved the use of these data. Written informed consent was exempted by the Institutional Review Board.

This national cohort study relied on data from the Korean Health Insurance Review and Assessment Service-National Sample Cohort (HIRA-NSC). This dataset has been described in detail in our previous studies.[23,24]

### 2.2. Participant selection

For the 1,125,691 cases with 114,369,638 medical claim codes, rheumatoid arthritis was defined according to previous studies that reported the prevalence and incidence of rheumatoid arthritis in Korea.[25,26] Rheumatoid arthritis was selected based on International Classification of Disease-10 (ICD-10) codes (M05 or M06) and the identification of a prescription for a biological agent or any disease-modifying antirheumatic drug (n = 7783).

Bell's palsy was diagnosed as ICD-10 code G510. We included only participants who were treated ≥2 times and who were treated with steroids. Steroid administration included systemic approaches (oral steroids or intravenous dexamethasone injection). From 2002 through 2013, 3996 Bell's palsy participants were selected.

The rheumatoid arthritis group was matched 1:4 with participants (control group) who were not diagnosed with rheumatoid arthritis from 2002 through 2013. The control group

was selected from the total population (n = 1,117,908). Matching was performed for age group, sex, income group, and region of residence. To prevent selection bias when selecting the matched participants, the control participants were sorted using a random number order and then selected from top to bottom. We set the index date as the date of diagnosis of rheumatoid arthritis. To ensure that the matched control participants were involved at the same time as the rheumatoid arthritis participants (index date), control patients who died before the index date were excluded. Participants with a history of Bell's palsy before the index date were excluded from both the rheumatoid arthritis and control groups. In the rheumatoid arthritis group, 14 participants were excluded. Additionally, rheumatoid arthritis patients for whom matching participants could not be identified were excluded (n = 10). We also excluded participants younger than 20 years of age (n = 131). Finally, 1:4 matching resulted in the inclusion of 7628 rheumatoid arthritis patients and 30,512 control participants (Fig. 1).

### 2.3. Variables

The age groups were classified using the following 5-year age intervals: 20 to 24, 25 to 29, 30 to 34, . . . , and 85+ years old. A total of 14 age groups were designated. The income groups were initially divided into 41 classes (1 health aid class, 20 self-employment health insurance classes, and 20 employment health insurance classes). These groups were recategorized into 5 classes (class 1 [lowest income]–5 [highest income]). The region of residence was divided into 16 areas according to administrative district. Then, these regions were regrouped into urban (Seoul, Busan, Daegu, Incheon, Gwangju, Daejeon, and Ulsan) and rural (Gyeonggi, Gangwon, Chungcheongbuk, Chungcheongnam, Jeollabuk, Jeollanam, Gyeongsangbuk, Gyeongsangnam, and Jeju) areas. The Charlson comorbidity index (CCI) was used for 16 comorbidities as the continuous variable (0 [no comorbidity] through 28 [multiple comorbidities]) except for rheumatologic diseases.[27]

### 2.4. Statistical Analyses

The Chi-squared test was used to compare the general characteristics between the rheumatoid arthritis and control groups. Stratified Cox proportional hazard models were used to assess hazard ratios (HRs) for rheumatoid arthritis with respect to Bell's palsy. In this analysis, crude (simple) and adjusted (for CCI score) models were used, and 95% confidence intervals (CIs) were calculated. In these analyses, age, sex, income, and region of residence were stratified. Kaplan–Meier analysis and the log-rank test were used.

For the subgroup analyses, we divided the participants by age (<50 years old and ≥50 years old) and sex (men and women). The break point for age was determined as the median value. Two-tailed analyses were conducted, and $P < .05$ were considered significant. The results were statistically analyzed using SPSS v. 21.0 (IBM, Armonk, NY).

## 3. Results

### 3.1. Descriptive data of participants

The rates of Bell's palsy were similar between the rheumatoid arthritis group (0.5% [38/7628]) and the control group (0.4%
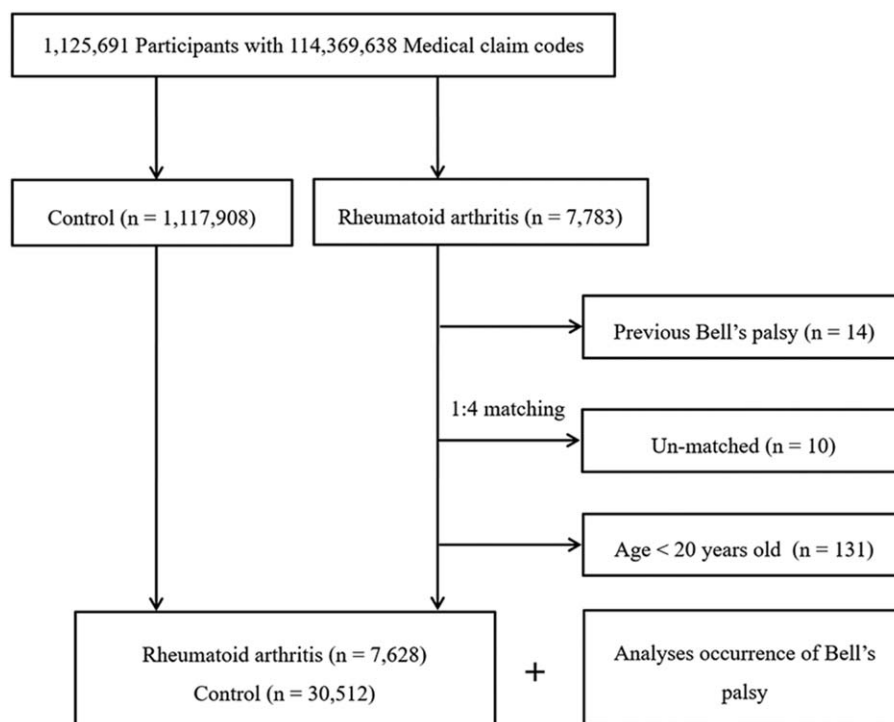
**Figure 1.** A schematic illustration of the participant selection process. Of the total 1,125,691 participants, 7628 rheumatoid arthritis patients were matched with 30,512 control participants with respect to age, group, sex, income group, and region of residence.

[124/30,512]), with no significant differences (P=.270, Table 1). The general characteristics (age, sex, income, and region of residence) of the participants were the same due to the matching procedure (P=1.000).

### 3.2. Outcome data (responding the objectives)

The adjusted HR for Bell's palsy was 1.12 (95% CI=0.78–1.62) in the rheumatoid arthritis group (P=.540, Table 2).

### 3.3. Other secondary analyses

In the subgroup analyses performed according to age and sex, the adjusted HRs for Bell's palsy did not reach statistical significance (each P > .05, Table 3).

### 4. Discussion

This investigation is the first large, population-based, cohort study to investigate the association of Bell's palsy with rheumatoid arthritis. Our results with reference to study objectives indicated that the risk of Bell's palsy was not significantly higher in the rheumatoid arthritis group than in the matched control group. In addition, there was no statistical significance of adjusted HRs for Bell's palsy in the subgroup analyses according to age and sex.

Previous case studies reported the coexistence of Bell's palsy in patients with rheumatoid arthritis, suggesting a potential mechanism by which immunological mediators elicited facial nerve palsy.[20,22] Furthermore, rheumatoid arthritis medications, including nonsteroidal anti-inflammatory drugs, antimalarial agents, and other disease-modifying antirheumatic drugs,

have been shown to alter host immune responses and subsequently induce inflammation.[28,29] Based on this concept, the presence of rheumatoid arthritis might be related to an increased risk of viral infection and a subsequent autoimmune reaction, resulting in Bell's palsy. Nonetheless, evidence for this association is limited on the basis of our large cohort study. Therefore, the pathogenesis of Bell's palsy in rheumatoid arthritis should be considered hypothetical.

A previous study employing the presence of HSV genomic DNA within the sensory ganglion along the facial nerve did not reveal a direct association between viral replication and Bell's palsy.[30] Moreover, a previous study suggested that rheumatoid factor, which is a diagnostic feature of rheumatoid arthritis, may lead to immune complex-mediated vasculitis and eventually result in Bell's palsy due to disruption of the blood supply to the nerve itself.[22] Rheumatoid factor may also be identified in systemic lupus erythematosus, sarcoidosis, and scleroderma[31–33]; however, the evidence presented for the occurrence of Bell's palsy following these autoimmune disorders is limited. In other words, this autoimmune-mediated vasculopathy may yield an increased risk for Bell's palsy in patients with rheumatoid arthritis; however, the impact of autoimmunity on Bell's palsy remains unknown.

As documented by our results, the lack of a relationship between rheumatoid arthritis and Bell's palsy may be attributed to the rheumatoid arthritis-associated comorbidities that may be linked to Bell's palsy. In several previous studies, rheumatoid arthritis showed a strong association with diabetes, hypertension, and hyperlipidemia.[8,12,21] These clinical risk factors, which are associated with a systemic inflammatory profile, are also known to predispose individuals to Bell's palsy. A recent study suggested a causal relationship between hyperlipidemia and Bell's palsy,

### Table 1
**General characteristics of participants.**

| | Total participants | | |
| --- | --- | --- | --- |
| Characteristics | Rheumatoid arthritis (n, %) | Control (n, %) | P |
| Age (years old) | | | 1.000 |
| 20–24 | 182 (2.4) | 728 (2.4) | |
| 25–29 | 297 (3.9) | 1188 (3.9) | |
| 30–34 | 419 (5.5) | 1676 (5.5) | |
| 35–39 | 565 (7.4) | 2260 (7.4) | |
| 40–44 | 723 (9.5) | 2892 (9.5) | |
| 45–49 | 1009 (13.2) | 4036 (13.2) | |
| 50–54 | 1219 (16.0) | 4876 (16.0) | |
| 55–59 | 970 (12.7) | 3880 (12.7) | |
| 60–64 | 879 (11.5) | 3516 (11.5) | |
| 65–69 | 657 (8.6) | 2628 (8.6) | |
| 70–74 | 410 (5.4) | 1640 (5.4) | |
| 75–79 | 219 (2.9) | 876 (2.9) | |
| 80–84 | 68 (0.9) | 272 (0.9) | |
| 85+ | 11 (0.1) | 44 (0.1) | |
| Sex | | | 1.000 |
| Male | 1752 (23.0) | 7008 (23.0) | |
| Income | | | 1.000 |
| 1 (lowest) | 1236 (16.2) | 4944 (16.2) | |
| 2 | 1098 (14.4) | 4392 (14.4) | |
| 3 | 1356 (17.8) | 5424 (17.8) | |
| 4 | 1726 (22.6) | 6904 (22.6) | |
| 5 (highest) | 2212 (29.0) | 8848 (29.0) | |
| Region of residence | | | 1.000 |
| Urban | 3348 (43.9) | 13,392 (43.9) | |
| CCI | | | <.001* |
| 0 | 2027 (26.6) | 12,118 (39.7) | |
| 1 | 670 (8.8) | 3007 (9.9) | |
| 2 | 1094 (14.3) | 3827 (12.5) | |
| ≥3 | 3837 (50.3) | 11,560 (37.9) | |
| Bell's palsy | 38 (0.5) | 124 (0.4) | .270 |

CCI = Charlson comorbidity index except for rheumatologic diseases.
* Chi-squared test or Fisher exact test, significance at P < .05.

indicating that regular statin use exerts protective effects against neural toxicity[10]. Indeed, the present study adjusted for CCI scores and found no significant association between Bell's palsy and rheumatoid arthritis. Considering this perspective, the occurrence of Bell's palsy may have been overestimated in the rheumatoid arthritis group due to associated comorbidities.

The present study had several strengths. The advantages of this study were consistent with those of our previous studies utilizing the HIRA-NSC.[34–36] Notably, in the present study, a diagnostic validity analysis was performed using various algorithms to identify patients with rheumatoid arthritis in the HIRA-NSC. Based on previous studies that employed data in the same

### Table 2
**Crude and adjusted hazard ratios (95% confidence interval) of rheumatoid arthritis for Bell's palsy.**

| | Bell's palsy | | | |
| --- | --- | --- | --- | --- |
| Characteristics | Crude* | P | Adjusted*,† | P |
| Rheumatoid arthritis | 1.23 (0.85–1.76) | .273 | 1.12 (0.78–1.62) | .540 |
| Control | 1.00 | | 1.00 | |

* Stratified model for age, sex, income, and region of residence.
† Adjusted model for Charlson comorbidity index except for rheumatologic diseases.

### Table 3
**Subgroup analysis of crude and adjusted hazard ratios (95% confidence interval) of rheumatoid arthritis for Bell's palsy according to age and sex.**

| | Bell's palsy | | | |
| --- | --- | --- | --- | --- |
| Characteristics | Crude* | P | Adjusted*,† | P |
| Age <50 yrs old (n = 15,975) | | | | |
| Rheumatoid arthritis | 1.64 (0.91–2.93) | .098 | 1.52 (0.84–2.76) | .166 |
| Control | 1.00 | | 1.00 | |
| Age ≥50 yrs old (n = 22,165) | | | | |
| Rheumatoid arthritis | 1.04 (0.65–1.66) | .880 | 0.95 (0.59–1.52) | .814 |
| Control | 1.00 | | 1.00 | |
| Men (n = 8760) | | | | |
| Rheumatoid arthritis | 1.39 (0.65–2.96) | .400 | 1.19 (0.55–2.60) | .661 |
| Control | 1.00 | | 1.00 | |
| Women (n = 29,380) | | | | |
| Rheumatoid arthritis | 1.18 (0.78–1.79) | .427 | 1.10 (0.72–1.67) | .657 |
| Control | 1.00 | | 1.00 | |

* Stratified model for age, sex, income, and region of residence.
† Adjusted model for Charlson comorbidity index except for rheumatologic diseases.

manner, the diagnostic yield for rheumatoid arthritis had a high sensitivity, positive predictive value, and accuracy of 96.46%, 92.35%, and 90.33%, respectively.[25,26] We enrolled only participants who were treated more than once and who were treated with steroids to increase the validity of the Bell's palsy diagnosis. For treatment of Bell's palsy, early treatment with steroids significantly improves the chances of complete recovery, whereas there is no evidence of a benefit for administration of acyclovir alone or an additional benefit for administration of acyclovir in combination with steroids.[37] Although a variety of treatments have emerged for recovery of Bell's palsy to date, steroid administration is considered the only proven treatment. Given that the prognosis of Korean patients with Bell's palsy is worse than that of global Bell's palsy patients, defining Bell's palsy, including steroid therapy, in a Korean cohort could be appropriate.[38] We examined a very large, representative, and nationwide population. Because National Health Insurance Service data cover all Korean citizens without exception, no participants were lost during follow-up. The control group was randomly selected and matched based on age, sex, income, and region of residence to decrease any confounding effects. In this study, the annual incidence of Bell's palsy was 40.3 per 100,000 persons, which was similar to previously reported rates ranging from 13.1 to 83.2 per 100,000 persons.[2–6] In accordance with previous results, the occurrence of Bell's palsy did not significantly differ according to age and sex in the present subgroup analysis.[39,40]

Nevertheless, this study had limitations that need to be noted. First, although this study used a representative large population and was matched and adjusted for possible confounders, confounders were still present, including Ramsay Hunt syndrome, HIV infection, and Lyme disease.[41] Second, information on additional suspected risk factors for Bell's palsy, including alcohol, smoking, obesity, and diet, was not available in the insurance database.[9,42] Since our investigation was a national cohort study using medical claim records, we could not identify the characteristics of rheumatoid arthritis and Bell's palsy. In other words, without data from individual medical records, such as serologic results and specific treatments, adjusted analyses to

identify potential risk factors for the development of Bell's palsy in patients with rheumatoid arthritis appear to be beyond the scope of a large population-based study such as this study. Likewise, it is difficult to elicit the causative relationship of Bell's palsy in response to rhumatoid arthritis treatment using claim data information alone. Third, a substantial number of patients with Bell's palsy may not have been included in the present study because the patients may have recovered on their own without specific therapy[43]; this possibility may have confounded our results. Fourth, clinic visits for rheumatoid arthritis can lead to an increased possibility of detecting Bell's palsy; thereby, we performed an additional analysis regarding the risk of rheumatoid arthritis for Bell's palsy 6 months after the index date. The results of this analysis were consistent with our findings (adjusted HR for Bell's palsy = 1.28, 95% CI = 0.88–1.87, $P$ = .199, Table S1, http://links.lww.com/MD/D971). Given the limitations presented here, our results that show no association of Bell's palsy with rheumatoid arthritis should be cautiously interpreted.

## 5. Conclusion

Taken together, the risk of Bell's palsy was not significantly increased in patients with rheumatoid arthritis compared with that of matched control participants, despite the hypothetical link.

## Author contributions

**Conceptualization:** Bumjung Park, Il-Seok Park, Hyo Geun Choi.
**Data curation:** Bumjung Park, Il-Seok Park.
**Formal analysis:** Bumjung Park, Il-Seok Park.
**Funding acquisition:** Hyo Geun Choi.
**Investigation:** Jae-Sung Lim, Dong Jun Oh, Bumjung Park, Il-Seok Park, Hyo Geun Choi.
**Methodology:** Jae-Sung Lim, Dong Jun Oh, Bumjung Park, Il-Seok Park, Hyo Geun Choi.
**Software:** Il-Seok Park.
**Supervision:** Jae-Sung Lim, Dong Jun Oh.
**Validation:** Hyo Geun Choi.
**Visualization:** Sang-Yeon Lee.
**Writing – original draft:** Sang-Yeon Lee.
**Writing – review & editing:** Sang-Yeon Lee, Jae-Sung Lim, Dong Jun Oh, Hyo Geun Choi.
Hyo Geun Choi orcid: 0000-0003-1655-9549.

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