

## Supplemental Online Content

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**eMethods.** Information on Covariates in the Study

**eTable 1.** Previous Studies on the Relationship Between Rheumatoid Arthritis (RA) and the Incidence of Depression

**eTable 2.** Disease-Modifying Anti-Rheumatic Drugs Used in the Definition of Diseases

**eTable 3.** The Risk of Depression According to Exposure to Biologic DMARDs (bDMARDs) and Targeted Synthetic DMARDs (tsDMARDs) in Patients With Rheumatoid Arthritis (RA)

**eTable 4.** Stratified Analyses of the Association Between RA Status and Depression Risk by Age and Sex

**eTable 5.** Stratified Analyses of the Association Between RA Status and Depression Risk by Income, Health Behaviors, and Comorbidities

**eFigure 1.** (A) Unadjusted and (B) Adjusted Kaplan–Meier Curve for the Incidence Depression According to the Type of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) Used

This supplemental material has been provided by the authors to give readers additional information about their work.

## eMethods. Information on Covariates in the study

Income level was categorized into quartiles, in which those covered by Medical Aid were merged into the lowest-income quartile group. Information about health-related behavior was obtained using a self-administered questionnaire. Smoking status was categorized as never/ex-smoker or current smoker, and alcohol consumption was classified as non-drinker or drinker (>0 g/day). Regular exercise was defined as performing > 30 minutes of moderate physical activity at least five times per week or > 20 minutes of strenuous physical activity at least three times per week, as used in previous studies.<sup>1-3</sup> Body mass index (BMI) was calculated using the body weight (kg) divided by height in meters squared (m<sup>2</sup>). Comorbidities were defined based on medical claims according to the ICD-10 codes (for hypertension, I10-I13 or I15; for diabetes, E11-E14; for dyslipidemia, E78; and for chronic kidney disease, N18 or N19).

1. Park MJ, Yoo J, Han K, Shin DW, Fava M, Mischoulon D, Jeon HJ. High body weight variability is associated with increased risk of depression: a nationwide cohort study in South Korea. *Psychol Med*. 2023 Jun;53(8):3719-3727.
2. Yook V, Yoo J, Han K, Fava M, Mischoulon D, Park MJ, Kim H, Jeon HJ. Association between pre-pregnancy tobacco smoking and postpartum depression: A nationwide cohort study. *J Affect Disord*. 2022 Nov 1;316:56-62.
3. Kang J, Eun Y, Jang W, Cho MH, Han K, Jung J, Kim Y, Kim GT, Shin DW, Kim H. Rheumatoid Arthritis and Risk of Parkinson Disease in Korea. *JAMA Neurol*. 2023 Jun 1;80(6):634-641.

**eTable 1.** Previous studies on the relationship between Rheumatoid arthritis (RA) and the incidence of depression

| Study, country                     | Index period | No. of participants         | Matching   | Range of age | Mean or median age (years)        | Female (%) | Mean or median follow-up (years)  | RA Assessment  | Depression Assessment                         | No. of Outcomes (Incidence rate)                                 | Adjustment   | Adjusted HR (95% CI) |                         |
|------------------------------------|--------------|-----------------------------|--|--------------|-----------------------------------|------------|-----------------------------------|--|---|--|--|----------------------|-------------------------|
| Kim et al (2020), South Korea      | 2002-2013    | RA 7,385<br>Control 29,540  | age, sex, income, region of residence                          | ≥20          | not reported                      | 76.8       | RA 7.25±3.60<br>Control 7.29±3.63 | ICD 10 code: M05, M06 and a prescription for a biologic agent or any DMARD | ICD-10: F31-33, treated 2 or more times       | RA 408 (not reported)<br>Control 1,246 (not reported)            | Charlson comorbidity index (CCI)                                       | Overall              | <b>1.20 (1.07-1.34)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | Age <30              | 0.81 (0.45-1.45)        |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | 30-59                | <b>1.17 (1.01-1.36)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  | Sex  |                      |                         |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | Male                 | 1.26 (0.95-1.67)        |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | Female               | <b>1.19 (1.05-1.35)</b> |
| Marrie et al (2018), Canada        | 1989-2012    | RA 10,206<br>Control 50,960 | age, sex, region of residence                                  | ≥18          | RA 53.7±16                        | 72.2       | RA 9.19<br>Control 9.05           | ICD-9-CM code: 714 /ICD 10 code: M05, M06                                  | ICD-9-CM: 296.2, 296.3 or 311 /ICD-10: F32-34 | not reported   | Number physician visits, follow up duration                            | Overall              | <b>1.46 (1.35-1.58)</b> |
| Drosselmeyer et al (2017), Germany | 2009-2013    | RA 7,301<br>Control 7,301   | age, sex, depression diagnosis in the past, follow-up duration | ≥60          | RA 72.2±7.60<br>Control 72.2±7.60 | 65.1       | RA 3.40±1.20<br>Control 3.40±1.20 | ICD 10 code: M05, M06  | ICD-10: F32 or F33                            | RA 1,606 (not reported)<br>Control 1,044 (not reported)          | Comorbidity <sup>a</sup>   | Overall              | <b>1.55 (1.38-1.74)</b> |
| Lu et al (2016), Taiwan            | 1998-2011    | RA 8,331<br>Control 15,456  | age, sex, index year   | 20-80        | RA 54.6±14.0<br>Control 54.4±14.0 | 67.8       | RA 7.33<br>Control 7.77           | ICD-9-CM code: 714, 3 ambulatory diagnoses or 1 admission diagnosis        | ICD-9-CM: 296.2, 296.3 or 311                 | RA 958 (15.69 per 1,000 PY)<br>Control 1,075 (8.95 per 1,000 PY) | Urbanization level, income, comorbidity <sup>b</sup>                   | Overall              | <b>1.69 (1.51-1.89)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | Sex & Age            |                         |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | Female               |                         |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | ≤40                  | <b>1.73 (1.50-1.84)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | 41-60                | <b>2.14 (1.62-2.69)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | >60                  | <b>1.60 (1.35-1.90)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | Male                 |                         |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | ≤40                  | <b>1.58 (1.37-1.82)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | 41-60                | <b>1.65 (1.33-1.94)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  | >60                  | <b>2.76 (1.83-4.59)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  |                      | <b>1.59 (1.17-2.17)</b> |
|                                    |              |                             |  |              |                                   |            |                                   |  |   |  |  |                      | <b>1.33 (1.01-1.75)</b> |
| Lin et al (2015), Taiwan           | 2000-2004    | RA 3,698<br>Control 7,396   | age, sex, index year   | ≥18          | RA 55.8±15.2<br>Control 55.8±15.2 | 65.8       | RA 9.46<br>Control 9.66           | ICD-9-CM code: 714, 2 ambulatory diagnoses or 1 admission diagnosis        | ICD-9-CM: 296.2, 296.3 or 311                 | RA 413 (11.80 per 1,000 PY)<br>Control 492 (6.89 per 1,000 PY)   | Urbanization level, income, medication usage, comorbidity <sup>c</sup> | Overall              | <b>1.74 (1.48-1.95)</b> |

|                           |           |                            |                      |     |                         |      |                         |                    |  |  |  |         |                         |
|---------------------------|-----------|----------------------------|----------------------|-----|-------------------------|------|-------------------------|--------------------|--|--|--|---------|-------------------------|
| Wang et al (2014), Taiwan | 2000-2008 | RA 3,657<br>Control 14,628 | age, sex, index year | ≥20 | RA 51.0<br>Control 51.0 | 72.8 | RA 4.72<br>Control 4.92 | ICD-9-CM code: 714 | Psychiatrist diagnosed depressive disorder | RA 205 (11.2 per 1,000 PY)<br>Control 384 (5.1 per 1,000 PY) | Urbanization level, income, comorbidity <sup>d</sup> | Overall | <b>2.06 (1.73–2.44)</b> |
|---------------------------|-----------|----------------------------|----------------------|-----|-------------------------|------|-------------------------|--------------------|--|--|--|---------|-------------------------|

RA, Rheumatoid arthritis; PY, person-years; HR, hazard ratio; CI, confidence interval

<sup>a</sup> hypertension, diabetes mellitus, myocardial infarction, coronary heart disease, heart failure, stroke, dementia, cancer, osteoporosis, inflammatory poly arthropathies excluding RA, and osteoarthritis

<sup>b</sup> hypertension, diabetes mellitus, chronic kidney disease, heart disease, stroke, cancer, alcohol dependence syndrome, and tobacco use

<sup>c</sup> hypertension, diabetes mellitus, chronic kidney disease, heart disease, stroke, and cancer

<sup>d</sup> hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, congestive heart failure, cirrhosis, hyperthyroidism, hypothyroidism, cerebrovascular disease, and cancer

**eTable 2.** Disease-Modifying Anti-Rheumatic Drugs Used in the Definition of Diseases.

| Category | Drugs   |
|----------|---|
| csDMARD  | Methotrexate, Hydroxychloroquine, Leflunomide, Sulfasalazine, Tacrolimus, Cyclosporine, D-penicillamine, Bucillamine, Azathioprine, Minocycline, Mizoribine |
| bDMARD   | Adalimumab, Etanercept, Infliximab, Golimumab, Rituximab, Abatacept, Tocilizumab  |
| tsDMARD  | Tofacitinib   |

csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; bDMARD, biologic disease-modifying anti-rheumatic drug; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug

**eTable 3. The risk of Depression According to Exposure to Biologic DMARDs (bDMARDs) and Targeted synthetic DMARDs (tsDMARDs) in Patients with Rheumatoid Arthritis (RA)**

| Subgroup   | N       | Event (N) | Duration (PY) | Incidence rate (per 1,000 PY) | aHR (95% CI)     |
|--|---------|-----------|---------------|-------------------------------|------------------|
| <b>By RA status and bDMARDs and tsDMARDs use</b>         |         |           |               |                               |                  |
| Control  | 192,435 | 20,641    | 841,495.3     | 24.53                         | 1 (Ref.)         |
| RA, bDMARDs or tsDMARDs unexposed                        | 35,439  | 6,020     | 144,646.8     | 41.62                         | 1.69 (1.64-1.74) |
| RA, bDMARDs or tsDMARDs exposed                          | 3,048   | 402       | 13,777.0      | 29.18                         | 1.33 (1.20-1.47) |
| <b>By RA seropositivity and bDMARDs and tsDMARDs use</b> |         |           |               |                               |                  |
| Control  | 192,435 | 20,641    | 841,495.3     | 24.53                         | 1 (Ref.)         |
| SNRA, bDMARDs or tsDMARDs unexposed                      | 11,222  | 1,806     | 44,958.5      | 40.17                         | 1.73 (1.65-1.82) |
| SNRA, bDMARDs or tsDMARDs exposed                        | 423     | 40        | 1,818.0       | 22.00                         | 1.48 (1.08-2.02) |
| SPRA, bDMARDs or tsDMARDs unexposed                      | 24,217  | 4,214     | 99,688.3      | 42.27                         | 1.67 (1.62-1.73) |
| SPRA, bDMARDs or tsDMARDs exposed                        | 2,625   | 362       | 11,959.0      | 30.27                         | 1.32 (1.19-1.46) |

RA, Rheumatoid arthritis; PY, person-years; aHR, adjusted hazard ratio; CI, confidence interval; SNRA, seronegative RA; SPRA, seropositive RA

aHRs were adjusted for age, sex, smoking, alcohol drinking, physical activity, income, body mass index, diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease.

**eTable 4. Stratified analyses of the association Between RA Status and Depression Risk by Age and Sex**

| Subgroup   | RA      | N       | Event (N) | Duration (PY) | Incidence rate (per 1,000 PY) | aHR (95% CI)     | <i>P</i> for interaction | Difference in RMST <sup>a</sup> (95% CI), day | <i>P</i> value |
|------------|---------|---------|-----------|---------------|-------------------------------|------------------|--------------------------|---|----------------|
| <b>Age</b> |         |         |           |               |                               |                  |                          |   |                |
| 20-39      | Control | 19,625  | 1,003     | 90,734.8      | 11.05                         | 1 (Ref.)         | 0.81                     | Ref.  | <.0001         |
|            | RA      | 3,925   | 333       | 17,609.3      | 18.91                         | 1.70 (1.50-1.93) |                          | -91.8 (-123.5, -60.2)                         |                |
| 40-59      | Control | 106,035 | 9,583     | 477,341.6     | 20.08                         | 1 (Ref.)         |                          | Ref.  | <.0001         |
|            | RA      | 21,207  | 3,074     | 91,073.5      | 33.75                         | 1.67 (1.61-1.74) |                          | -142.3 (-161.5, -123.2)                       |                |
| ≥60        | Control | 66,775  | 10,055    | 273,418.8     | 36.78                         | 1 (Ref.)         |                          | Ref.  | <.0001         |
|            | RA      | 13,355  | 3,015     | 49,740.9      | 60.61                         | 1.65 (1.58-1.72) |                          | -274.0 (-306.6, -241.5)                       |                |
| <b>Sex</b> |         |         |           |               |                               |                  |                          |   |                |
| Male       | Control | 55,830  | 4,943     | 23,6410.4     | 20.91                         | 1 (Ref.)         | 0.13                     | Ref.  | <.0001         |
|            | RA      | 11,166  | 1,587     | 44,312.9      | 35.81                         | 1.73 (1.63-1.83) |                          | -192.5 (-219.2, -165.8)                       |                |
| Female     | Control | 136,605 | 15,698    | 605,084.8     | 25.94                         | 1 (Ref.)         |                          | Ref.  | <.0001         |
|            | RA      | 27,321  | 4,835     | 114,110.9     | 42.37                         | 1.64 (1.59-1.69) |                          | -171.5 (-190.7, -152.4)                       |                |

RA, Rheumatoid arthritis; PY, person-years; aHR, adjusted hazard ratio; CI, confidence interval; RMST, restricted mean survival time

aHRs were adjusted for age, sex, smoking, alcohol drinking, physical activity, income, body mass index, diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease.

<sup>a</sup> Truncated time was 8 years.

**eTable 5. Stratified analyses of the association Between RA Status and Depression Risk by Income, Health Behaviors, and Comorbidities**

| Subgroup                   | RA      | N       | Event (N) | Duration (PY) | Incidence rate (per 1,000 PY) | aHR (95% CI)     | P for interaction |
|----------------------------|---------|---------|-----------|---------------|-------------------------------|------------------|-------------------|
| <b>Income</b>              |         |         |           |               |                               |                  |                   |
| Low 25% + Medicaid group   | Control | 149,230 | 15,780    | 653,380.4     | 24.15                         | 1 (Ref.)         | 0.60              |
|                            | RA      | 30,109  | 4,976     | 124,693.8     | 39.91                         | 1.65 (1.60-1.71) |                   |
| Above 25%                  | Control | 43,205  | 4,861     | 188,114.8     | 25.84                         | 1 (Ref.)         |                   |
|                            | RA      | 8,378   | 1,446     | 33,729.9      | 42.87                         | 1.68 (1.59-1.79) |                   |
| <b>Smoking</b>             |         |         |           |               |                               |                  |                   |
| Nonsmoker                  | Control | 167,750 | 18,373    | 735,017.4     | 25.00                         | 1 (Ref.)         | 0.28              |
|                            | RA      | 33,599  | 5,675     | 138,742.5     | 40.90                         | 1.65 (1.60-1.70) |                   |
| Current smoker             | Control | 24,685  | 2,268     | 106,477.9     | 21.30                         | 1 (Ref.)         |                   |
|                            | RA      | 4,888   | 747       | 19,681.2      | 37.96                         | 1.73 (1.60-1.88) |                   |
| <b>Alcohol consumption</b> |         |         |           |               |                               |                  |                   |
| Nondrinker                 | Control | 125,642 | 15,150    | 552,967.2     | 27.40                         | 1 (Ref.)         | <.001             |
|                            | RA      | 27,331  | 4,881     | 113,043.4     | 43.18                         | 1.61 (1.56-1.67) |                   |
| Drinker                    | Control | 66,793  | 5,491     | 288,528.0     | 19.03                         | 1 (Ref.)         |                   |
|                            | RA      | 11,156  | 1,541     | 45,380.3      | 33.96                         | 1.82 (1.72-1.93) |                   |
| <b>Physical activity</b>   |         |         |           |               |                               |                  |                   |
| None                       | Control | 153,906 | 16,652    | 675,793.1     | 24.64                         | 1 (Ref.)         | 0.76              |
|                            | RA      | 31,636  | 5,321     | 130,719.3     | 40.71                         | 1.66 (1.61-1.72) |                   |
| Regular                    | Control | 38,529  | 3,989     | 165,702.2     | 24.07                         | 1 (Ref.)         |                   |
|                            | RA      | 6,851   | 1,101     | 27,704.5      | 39.74                         | 1.64 (1.54-1.76) |                   |
| <b>Body mass index</b>     |         |         |           |               |                               |                  |                   |
| <25                        | Control | 130,665 | 13,863    | 574,280.8     | 24.14                         | 1 (Ref.)         | 0.09              |
|                            | RA      | 27,547  | 4,507     | 114,399.8     | 39.40                         | 1.63 (1.58-1.69) |                   |
| ≥25                        | Control | 61,770  | 6,778     | 267,214.5     | 25.37                         | 1 (Ref.)         |                   |
|                            | RA      | 10,940  | 1,915     | 44,023.9      | 43.50                         | 1.72 (1.64-1.81) |                   |
| <b>Diabetes</b>            |         |         |           |               |                               |                  |                   |
| No                         | Control | 171,079 | 17,644    | 754,098.6     | 23.40                         | 1 (Ref.)         | 0.72              |
|                            | RA      | 34,405  | 5,557     | 143,376.7     | 38.76                         | 1.66 (1.61-1.71) |                   |
| Yes                        | Control | 21,356  | 2,997     | 87,396.6      | 34.29                         | 1 (Ref.)         |                   |
|                            | RA      | 4,082   | 865       | 15,047.1      | 57.49                         | 1.68 (1.56-1.81) |                   |
| <b>Hypertension</b>        |         |         |           |               |                               |                  |                   |
| No                         | Control | 130,650 | 12,256    | 577,829.8     | 21.21                         | 1 (Ref.)         | 0.08              |
|                            | RA      | 25,026  | 3,619     | 105,523.0     | 34.30                         | 1.62 (1.57-1.69) |                   |
| Yes                        | Control | 61,785  | 8,385     | 263,665.4     | 31.80                         | 1 (Ref.)         |                   |
|                            | RA      | 13,461  | 2,803     | 52,900.7      | 52.99                         | 1.71 (1.64-1.79) |                   |
| <b>Dyslipidemia</b>        |         |         |           |               |                               |                  |                   |
| No                         | Control | 139,775 | 14,019    | 625,783.2     | 22.40                         | 1 (Ref.)         | 0.40              |



|                               |         |         |        |           |       |                  |  |
|-------------------------------|---------|---------|--------|-----------|-------|------------------|--|
| Yes                           | RA      | 28,081  | 4,390  | 118,770.3 | 36.96 | 1.65 (1.59-1.70) |  |
|                               | Control | 52,660  | 6,622  | 215,712.0 | 30.70 | 1 (Ref.)         |  |
|                               | RA      | 10,406  | 2,032  | 39,653.4  | 51.24 | 1.69 (1.61-1.78) |  |
| <b>Chronic kidney disease</b> |         |         |        |           |       |                  |  |
| No                            | Control | 182,165 | 18,943 | 795,715.6 | 23.81 | 1 (Ref.)         |  |
|                               | RA      | 35,786  | 5,855  | 147,589.4 | 39.67 | 1.68 (1.63-1.73) |  |
| Yes                           | Control | 10,270  | 1,698  | 45,779.6  | 37.09 | 1 (Ref.)         |  |
|                               | RA      | 2,701   | 567    | 10,834.3  | 52.33 | 1.50 (1.36-1.65) |  |

RA, Rheumatoid arthritis; PY, person-years; aHR, adjusted hazard ratio; CI, confidence interval

aHRs were adjusted for age, sex, smoking, alcohol drinking, physical activity, income, body mass index, diabetes mellitus, hypertension, hyperlipidemia, and chronic kidney disease.

eFigure 1. (A) Unadjusted and (B) adjusted Kaplan–Meier curve for the incidence depression according to the type of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) used

