Incidence and prevalence of rheumatoid arthritis in Denmark from 1998 to 2018: a nationwide register-based study

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Objective: To investigate the incidence and prevalence of rheumatoid arthritis (RA) in the adult Danish population.
Method: In this nationwide register-based cohort study, patients with incident RA between 1998 and the end of 2018 were identified using Danish administrative registries. The age- and sex-standardized incidence rate (IR), incidence proportion (IP), lifetime risk (LR), and point prevalence (PP) of RA were calculated. RA was defined as a first-time RA diagnosis registered in the Danish National Patient Registry combined with a redeemed prescription of a conventional synthetic disease-modifying anti-rheumatic drug in the following year. In addition, three different case definitions of RA were explored.
Results: The overall age- and sex-standardized IR of RA from 1998 to 2018 was 35.5 [95% confidence interval (CI) 35.1–35.9] per 100 000 person-years while the IP was 35.2 (95% CI 34.8–35.5) per 100 000 individuals. The IR was two-fold higher for women than for men. The LR of RA ranged from 2.3% to 3.4% for women and from 1.1% to 1.5% for men, depending on the RA case definition used. The overall PP of RA was 0.6% (95% CI 0.5–0.6%) in 2018: 0.8% (95% CI 0.7–0.8%) for women and 0.3% (95% CI 0.3–0.4%) for men. The prevalence increased about 1.5-fold from 2000 to 2018.
Conclusion: The IR and PP were approximately two-fold higher for women than for men. The prevalence of RA in Denmark increased significantly from 2000 to 2018. The RA case definition had more impact on the results than the choice of denominator.

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by inflammation of the synovial joints, which may lead to irreversible joint damage, deformity, and severe disability. RA is the most common autoimmune joint disease and the incidence rate (IR) has been reported to be approximately 40 per 100 000 people (1, 2). In the southern part of Denmark, the overall IR was 31 per 100 000 person-years (PY) from 1995 to 2001, with twice as high an IR in women as in men; and with a tendency towards an increase over time (3). Studies from other countries have also reported higher IRs in women (1, 2, 4). The influence of the introduction of the 2010 European League Against Rheumatism (EULAR)/American College of Rheumatism (ACR) Rheumatoid Arthritis Classification Criteria on the incidence of RA in Denmark is unknown.

There are regional differences in the prevalence of RA throughout the world, which may be due to differences in genetic disposition and environmental factors (5). The global age-standardized prevalence of RA in 2015 was reported to be 0.47% for women and 0.21% for men, whereas it was 0.61% and 0.26% in the Nordic region and 0.63% and 0.26% in Denmark for women and men, respectively (6). In a Swedish nationwide study covering the period from 2001 to 2007, the prevalence of RA was estimated to 0.70% (7), whereas it had previously been estimated as 0.51% using other methods (8). However, the case definitions of RA used in previous studies have been very heterogeneous, which makes comparison across studies difficult. Thus, some studies have relied on self-reported information on RA, while others have used hospital discharge diagnosis in administrative databases with additional variations in specific criteria, e.g. the number of recorded diagnoses required, the departments from which the diagnosis originated, and/or redeemed prescriptions of medications used in the treatment of RA.

In this nationwide register-based cohort study, we aimed to investigate the incidence and prevalence of RA in Denmark from 1998 to 2018 by calculating IRs, incidence proportions (IPs), lifetime risk (LRs), and point prevalences (PP). Furthermore, we explored the
importance of the RA case definition on the incidence and prevalence estimates obtained.

Method

Study design

We performed a nationwide register-based cohort study. Using data from Danish administrative registers, all RA diagnoses recorded in Denmark from 1998 to 2018 were identified in the Danish National Patient Registry (DNPR) using the unique central personal registry number assigned to all Danish residents at birth or upon immigration (9, 10). This personal identifier allowed for accurate register linkage on an individual level. Individuals migrating to Denmark from 1998 onwards were not part of the study population in incidence estimations but were included in prevalence estimations. Using this approach, we tried to reduce the potential risk of non-true incident cases in incidence estimations. However, individuals immigrating to Denmark before 1998 were part of the study population in both prevalence and incidence calculations.

The study was approved by the North Denmark Region Committee on Health Research Ethics (N-20190031) and the data protection committee of Northern Jutland, Denmark (2019-87).

Data sources

Danish National Patient Registry. The DNPR contains data about all admissions to somatic hospitals since 1977 and all outpatient attendances since 1995 (9, 10). All diagnoses are classified according to the International Classification of Diseases (ICD). The ICD-10 codes followed the ICD-8 codes in 1994 and have been used since.

Danish National Prescription Registry. The Danish National Prescription Registry (NPR) contains information about all prescription drugs dispensed at community pharmacies since 1994 in Denmark, but does not include information about drugs dispensed by hospital pharmacies (11).

Civil Registration System. The Danish Civil Registration System contains information about date of birth, place of residence, vital status, and migration into or out of Denmark since 1968 (12).

Case definitions

The following ICD-10 codes were used for the identification of potential RA patients: M05.x (seropositive RA) and M06.x (other RA), but not including M06.1 (adult-onset Still’s disease), if recorded as a primary or a secondary diagnosis in the DNPR. Subsequently, further requirements were added, and we established four RA case definitions to investigate the importance of different register-based criteria (Table 1).

Our primary case definition, Criterion A, was defined as a first-time RA diagnosis code registered in DNPR combined with a redeemed prescription of a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) in the following year identified by Anatomical Therapeutic Chemical (ATC) codes (Table S1) after linkage to the NPR. Criterion A was based on a validated case definition by Linauskas et al with a positive predictive value (PPV) of 88% for RA (13).

Criterion B was defined as an RA diagnosis recorded twice in the DNPR, with the diagnoses being made within 90 days of each other and with both records originating from a department of rheumatology or general internal medicine. Thus, the first of the two diagnoses could be from a department of rheumatology or general medicine and the second diagnosis from either one of the departments, or both diagnoses could be from the same department. This was based on a validated case definition from another study showing a PPV of 79% (14).

Criterion C was defined as a single RA diagnosis recorded at any time, i.e. not necessarily the first diagnosis as in Criterion A, with a redeemed csDMARD prescription in the year before or after the diagnosis was recorded in the DNPR. This case definition has been used in several other papers from Denmark but has not been validated (15–17).

Criterion D was similar to Criterion A, but with the additional requirement that there were no ICD codes for psoriatic or enteropathic arthropathies (ICD-8: 696.0; ICD-10: M07), systemic connective tissue disorders (ICD-8: 446, 716, 734; ICD-10: M30–M35), inflammatory bowel diseases (ICD-8: 563; ICD-10: K50–K51), or sarcoidosis (ICD-8: 135.99; ICD-10: D86) recorded before the RA diagnosis in the DNPR. Criterion D was an altered case definition first described by Linauskas et al, where cases were excluded if they had ever had a registration with one of the above-mentioned diagnoses. Using this approach, the PPV for RA was 96% (13).

Statistics

We used four different statistical methods to estimate four different epidemiological measures in RA from 1998 to 2018. These measures were the IR, IP, LR, and PP.
### Table 1. Overview of incident and prevalent rheumatoid arthritis (RA) case definitions.

| Case definition | Incident case definition | Prevalent case definition |
|-----------------|--------------------------|---------------------------|
| Criterion A     | Patients with a first-time diagnosis from DNPR and with a redeemed prescription of csDMARD in the following year | All patients fulfilling the incident case definition A in the period from 1994 to the point prevalence year in question and who did not die or emigrate, and in addition patients with a history of RA registered as an ICD-8 code (pre-1994) who did not die or emigrate |
| Criterion B     | Patients with two primary or secondary diagnoses of RA from an inpatient or outpatient contact at a department of rheumatology or general internal medicine within 90 days of each other | All patients fulfilling the incident case definition B in the period from 1994 to the point prevalence year in question and who did not die or emigrate, and in addition patients with a history of RA registered as an ICD-8 code (pre-1994) who did not die |
| Criterion C     | Patients with one diagnosis at any time in the DNPR and with a redeemed prescription of csDMARD in the previous or following year | All patients fulfilling the incident case definition C in the period from 1994 to the point prevalence year in question and who did not die or emigrate, and in addition patients with a history of RA registered as an ICD-8 code (pre-1994) who did not die |
| Criterion D     | Patients with a first-time diagnosis from DNPR, a redeemed prescription of csDMARD in the following year, and with no previous psoriatic or enteropathic arthropathies, systemic connective tissue disorders, inflammatory bowel diseases, or sarcoidosis diagnosis | All patients fulfilling the incident case definition D in the period from 1994 to the point prevalence year in question and who did not die or emigrate, and in addition patients with a history of RA registered as an ICD-8 code (pre-1994) who did not die |

DNPR, Danish National Patient Registry; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; ICD-8, International Classification of Diseases, Revision 8.

Annual IRs were calculated as the number of incident RA cases as the numerator and the actual and exact recorded number of person-years in the general population within that year as the denominator. The total Danish population from 1998 to 2018 was used as the reference population for standardization. For each case definition, the overall age- and sex-standardized IR from 1998 to 2018 was calculated as the total number of RA patients divided with the total number of person-years in the study period. To avoid RA cases being mistakenly captured and counted as incident RA in 1998 if a patient had in fact fulfilled the case criteria for RA in previous years, patients fulfilling the case criteria between 1994 and 1997 was identified and excluded.

For the calculation of the IP, the same numerator was used as in the IR calculations, whereas the denominator was derived from annual census count data corresponding to the adult population size in Denmark on 1 January each year stratified by age group (10 year intervals) and sex.

The LR of RA was calculated for men and women separately using the Aalen-Johansen estimator, to take into account the competing risk of death. We used left-truncated data based on the entire population with floating entrance consisting of entry age in 1998 and with the addition of people when they reached 18 years of age. Residents who emigrated were censored. The cumulative risk in percentage at the age of 100 years was interpreted as the LR of RA.

The PP was calculated on 1 January for the years 2000, 2009, 2011, and 2018, with the number of patients aged ≥ 20 years fulfilling the case definition for RA as the numerator but with cases registered back to 1994 instead of 1998; in addition, individuals who had one recorded diagnosis of RA with an ICD-8 code before 1994 were included. The denominator was the Danish population on 1 January in the respective years. The temporal trends in the overall and sex-specific PP were compared for the years 2000 and 2009, and 2011 with 2018, respectively.

Trend in PP over calendar years was investigated using a log-linear Poisson regression with robust sandwich variance estimator. Calendar year was considered continuous when testing for trend and binary when comparing two years. A p-value less than 0.05 was considered significant.

For every estimate, the 95% confidence interval (CI) was calculated. CIs were based on the normal approximation of the logarithm of the rate. The delta method was used to derive the variance of the log rate that was used to derive the CI. For descriptive purposes, demographics and other characteristics of incident patients, including information about region, household income, and selected medications [non-steroidal anti-inflammatory drug (NSAID): ATC code M01A; prednisolone: ATC code H02AB06] and comorbidities, were divided into 7 year intervals.
The statistical software R 3.6.1 was used for analyses, except for the regression analyses, which were conducted in SAS 9.4. We used the popEpi package for R (18).

Results

In total, 31,029 RA patients were identified from 1998 to 2018 when using Criterion A, and patient characteristics according to calendar period are shown in Table 2 (Tables S2–S4 show patient characteristics when using Criteria B, C, and D). Overall, the median age was approximately 60 years throughout the study period, with no major changes across calendar time, and there was a female predominance in all calendar periods. Subjects registered with incident RA from 2012 to 2018 were less likely to use NSAIDs in the year leading up to their RA diagnosis compared to incident RA patients prior to 2012.

The overall IR of RA from 1998 to 2018 based on Criterion A was 35.5 (95% CI 35.1–35.9) per 100,000 PY, with a sex-specific age-standardized IR for women of 47.1 (95% CI 46.5–47.8) per 100,000 PY and 23.6 (95% CI 23.1–24.1) per 100,000 PY for men. The age-standardized IR was higher for women than for men (Figure 1), and this was observed across all age groups. The IR peaked at 70–79 years of age in both men and women.

Regardless of which case definition was used, the temporal trend showed a peak in IR in 2010 followed by a plateau until 2016, after which the temporal trends decreased until the end of the study period in 2018 (Figure 2). The temporal trends were parallel for nearly all case definitions, but with different levels of IR.

The overall age- and sex-standardized IR from 1998 to 2018 based on Criterion A was 35.2 (95% CI 34.8–35.5) per 100,000 individuals, and all IP estimates were slightly lower than their corresponding IR calculations: Criterion B IR 40.6 (95% CI 40.2–41.0) per 100,000 individuals versus IR 41.1 (95% CI 40.7–41.5) per 100,000 PY; Criterion C IR 41.3 (95% CI 40.8–41.7) per 100,000 individuals versus IR 41.8 (95% CI 41.3–42.2) per 100,000 PY; and Criterion D IR 29.3 (95% CI 29.0–29.7) per 100,000 individuals versus IR 29.6 (95% CI 29.3–30.0) per 100,000 PY.

The LR for RA in Denmark based on Criterion A was 2.9% (95% CI 2.9–2.9%) for women and 1.4% (95% CI 1.3–1.4%) for men. The cumulative LRs were < 1% before the age of 50 years, corresponding to the small IR of RA under 50 years of age (Figure 3). From 50+ years of age, the LR gradually increased until 80 years, when the curve flattened for both sexes, reflecting the same trends in age- and sex-specific IR.

Table 2. Demographic description of incident rheumatoid arthritis (RA) cases based on Criterion A in Denmark, divided into three calendar periods.

| Calendar period | 1998–2004 | 2005–2011 | 2012–2018 |
|-----------------|-----------|-----------|-----------|
| N               | 8564      | 10,832    | 11,633    |
| Age (years), median (2.5 to 97.5 percentile) | 59.8 (25.8 to 83.5) | 59.8 (26.6 to 84.0) | 62.1 (25.8 to 84.8) |
| Female          | 5983 (69.9) | 7474 (69.0) | 7740 (66.5) |
| Region within Denmark | | | |
| Capital Region | 2577 (30.1) | 2972 (27.4) | 3271 (28.1) |
| Central Region | 1479 (17.3) | 1723 (15.9) | 2425 (20.8) |
| Northern Region | 1101 (12.9) | 1373 (12.7) | 1165 (10.0) |
| Southern Region | 1910 (22.3) | 2880 (26.6) | 2954 (25.4) |
| Zealand Region | 1490 (17.4) | 1845 (17.0) | 1812 (15.6) |
| csDMARD use in previous year | 8539 (99.6) | 10,827 (100.0) | 11,627 (99.9) |
| At least two prednisolone prescriptions in past year | 1879 (21.9) | 2353 (21.7) | 2251 (19.4) |
| NSAID use in previous year | 7032 (82.1) | 7788 (71.9) | 7036 (60.5) |
| Chronic obstructive pulmonary disease | 382 (4.5) | 557 (5.1) | 659 (5.7) |
| Diabetes mellitus | 348 (4.1) | 630 (5.8) | 764 (6.6) |
| Cardiovascular disease | 919 (10.7) | 1343 (12.4) | 1439 (12.4) |
| Previous hip or knee replacement surgery | 293 (3.4) | 672 (6.2) | 982 (8.4) |
| Mean 5 year household income above mean national household (per year), % | 42 | 44 | 42 |

Data are shown as n (%) unless otherwise indicated.
Criterion A was defined as a first-time RA diagnosis code registered in the Danish National Patient Registry combined with a redeemed prescription of a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) in the following year identified through linkage to the Danish National Prescription Registry.
NSAID, non-steroidal anti-inflammatory drug.
Figure 1. Age- and sex-specific incidence rates of rheumatoid arthritis (RA) in Denmark from 1998 to 2018 using four different case definitions.

Figure 2. Temporal incidence rates of rheumatoid arthritis (RA) from 1998 to 2018 in Denmark using four different case definitions.
Table 3. Point prevalence (PP) of rheumatoid arthritis in Denmark in the years 2000, 2009, 2011, and 2018.

| Criterion | 2000 (N) | 2009 (N) | 2011 (N) | 2018 (N) |
|-----------|----------|----------|----------|----------|
| **Criterion A** | | | | |
| N total (% women) | 13,478 (71.7) | 17,938 (71.5) | 19,506 (71.4) | 25,106 (70.3) |
| Population | 3,973,297 | 4,167,564 | 4,201,205 | 4,266,374 |
| Overall PP* | 0.36 (0.35–0.36) | 0.43 (0.43–0.44) | 0.46 (0.46–0.47) | 0.55 (0.54–0.56) |
| PP among women† | 0.48 (0.47–0.49) | 0.59 (0.58–0.60) | 0.63 (0.62–0.64) | 0.75 (0.74–0.76) |
| PP among men† | 0.23 (0.23–0.24) | 0.27 (0.26–0.28) | 0.29 (0.28–0.29) | 0.34 (0.33–0.35) |
| **Criterion B** | | | | |
| N total (% women) | 17,219 (72.7) | 22,302 (73.0) | 24,305 (72.9) | 30,739 (72.0) |
| Overall PP* | 0.46 (0.45–0.46) | 0.55 (0.54–0.55) | 0.58 (0.57–0.58) | 0.67 (0.66–0.68) |
| PP among women† | 0.62 (0.61–0.63) | 0.76 (0.75–0.77) | 0.81 (0.80–0.82) | 0.94 (0.93–0.95) |
| PP among men† | 0.28 (0.27–0.29) | 0.32 (0.31–0.33) | 0.34 (0.33–0.34) | 0.39 (0.38–0.40) |
| **Criterion C** | | | | |
| N total (% women) | 16,441 (72.6) | 22,304 (72.8) | 24,244 (72.7) | 30,679 (71.8) |
| Overall PP* | 0.44 (0.43–0.44) | 0.54 (0.53–0.55) | 0.57 (0.56–0.58) | 0.67 (0.66–0.68) |
| PP among women† | 0.59 (0.58–0.61) | 0.75 (0.74–0.77) | 0.80 (0.79–0.82) | 0.93 (0.92–0.95) |
| PP among men† | 0.27 (0.26–0.28) | 0.32 (0.31–0.33) | 0.34 (0.33–0.35) | 0.40 (0.39–0.40) |
| **Criterion D** | | | | |
| N total (% women) | 12,686 (71.6) | 15,495 (71.4) | 16,596 (71.3) | 20,497 (70.3) |
| Overall PP* | 0.34 (0.33–0.34) | 0.38 (0.37–0.38) | 0.39 (0.39–0.40) | 0.45 (0.44–0.46) |
| PP among women† | 0.45 (0.44–0.46) | 0.51 (0.50–0.52) | 0.54 (0.53–0.55) | 0.62 (0.61–0.63) |
| PP among men† | 0.22 (0.21–0.23) | 0.24 (0.23–0.24) | 0.24 (0.24–0.25) | 0.28 (0.27–0.29) |

Data are shown as % (95% confidence interval) unless otherwise indicated.

*Age- and sex-standardized.
†Age-standardized.

Figure 3. Cumulative lifetime risk of rheumatoid arthritis for women and men at various ages in Denmark based on Criterion A.
For other criteria, the LR for women ranged from 2.4% to 3.5% for Criteria D and C, respectively; and for men, the LR ranged from 1.1% for Criterion D to 1.5% for Criteria B and C. Figure S1 displays the LRs for all case definitions.

Depending on the case definition applied, the overall PP in 2018 varied between 0.45% and 0.67% (Table 3). Similar variations were seen for the years 2000, 2009, and 2011. The PP values for women were approximately two-fold higher than for men. The regression models showed a significant increasing trend over time for overall PP, as well as in both women and men across all four RA case definitions (all p-values < 0.0001) (Table S5). Furthermore, there was a significant increasing tendency in PP when comparing the year 2000 to 2009, and the year 2011 to 2018 (all p-values < 0.0001).

Discussion

In this nationwide register-based cohort study, we found an overall IR of RA from 1998 to 2018 in Denmark of 35.5 per 100 000 PY, while the IP was 35.2 per 100 000 individuals and the overall PP in 2018 was 0.6% when defined according to our primary case definition of RA. We observed an approximately two-fold higher incidence and prevalence of RA in women compared to men, and an increasing trend in both parameters over time. Our outcomes of interest varied according to the case definition of RA used. However, temporal analysis showed that regardless of the case definition used, there was a peak of IR in 2010 and a decrease after 2016. We believe that the observed peak in 2010 was probably due to the introduction of the 2010 EULAR/ACR Rheumatoid Arthritis Classification Criteria. On the other hand, we suspect that the decrease in incidence seen in 2017 and 2018 may be due to delayed and suboptimal registration of diagnoses in DNPR after the introduction of a new health-care information technology system in the Capital and Zealand Regions of Denmark, but we have no data to support this. Using case Criterion C for estimating the IR could be considered controversial, when the criteria did not require that it be the first ever RA diagnosis that was preceded or followed by redemption of a csDMARD. However, as this case definition has been used in several previous studies (15–17), we wanted to see whether this would provide different RA population sizes with different temporal IR patterns, but we found that Criterion C generated more or less the same results, with the same temporal patterns in IR.

We found that the IR was highest in 70–79-year-old individuals in both sexes, which is similar to what has been reported from Sweden (1). The IR observed in our study was slightly higher than the IR of 31 per 100 000 PY based on analyses conducted in another study from the southern part of Denmark during 1995–2001 (3). The higher IR observed in our study might be explained by the new classification criteria in 2010 and better registration, but, conversely, Pedersen et al also included cases from rheumatologists in private practice whose patients are not registered in DNPR, meaning that our IR is likely to be an underestimation (3). Previous studies from other European countries, including Sweden, Norway, and the UK, have also reported an approximately two-fold higher risk of RA in women compared with men (1, 3, 4, 19).

A systematic literature review investigating the trend in incidence of RA over time reported conflicting results (20). Based on the 1987 ACR criteria, Myasoedova et al showed a stable incidence of overall RA from 2005 to 2014 in a US population compared with the previous decade (1995–2004) (2).

The incidence of RA varies among countries and areas of the world and caution should be applied because of geographic variations and differences in statistical methods, case definitions, and registration. Nevertheless, our IRs are consistent with those reported from Sweden when we used Criteria B and C, whereas the calculated IRs when using Criteria A and D were lower than those observed in the Swedish population (1).

Compared to the IR estimate for Criterion A, the relative difference in overall IR ranged from +18 (Criterion C) to −17% (Criterion D). Eriksson et al previously showed that the definition of cases can affect the incidence estimate (1). Our results support this and emphasize the importance of case definitions used in register-based calculations of incidence, which need to be taken into account when comparing estimates across studies. Our results showed that the choice of RA case definition had a larger influence than the choice of denominator on the incidence estimates.

The LR for RA in Denmark was between 2.3% and 3.4% for women and between 1.1% and 1.5% for men, depending on the RA case definition used. Crowson et al studied the LR for RA in the adult population of Olmsted County, Minnesota, USA (21). They found LRs of 3.6% for women and 1.7% for men, estimated with a decennial census count and a different statistical approach, using a hypothetical cohort of 100 000 people and age- and sex-specific IRs and mortality rates (21). The LR estimates were slightly higher than the LR estimates that we found; nevertheless, we think that the results are comparable and both showed a higher LR for women than for men (21). To our knowledge, no previous study has reported the LR of RA in Denmark.

Our PP estimates were in line with previous results from other Scandinavian register-based cohort studies, showing
a higher prevalence in women than in men (6, 22, 23). As is the case with IRs, comparisons of prevalence estimates across time and countries should be made with caution. The PP of RA in Sweden was higher in 2008 than the PP in Denmark in 2009, regardless of which case definition applied (22). Comparison of the previously reported PP of 0.26% in the southern part of Denmark in 2004 to the values reported here should be done with caution owing to the different methodological approaches (23). With a less restrictive case definition than ours, a non-significant increase in the age-standardized prevalence of RA from 1990 to 2015 in both sexes in Denmark, a non-significant decrease globally and in the Nordic region for men, and a significant decrease for women was found (6). In the UK, an overall increase in the prevalence has been reported; however, the prevalence increased per year from 1990 to 2005 followed by a decrease per year from 2005 to 2014 (19). Our PP estimates showed a significant increasing trend in prevalence from 2000 to 2018 regardless of the case definition used. Differences seen in the increase in incidence and prevalence, with a magnified increase in prevalence, may be due to better registration of RA cases, with more registered cases from around 2000 onwards, as well as an improved prognosis for RA patients.

This study had some limitations that need to be mentioned. In register-based studies, there is a risk of misclassification bias, which we tried to reduce and explore by including four different case definitions of RA. Criteria A, B, and D are based on validated case definitions, while Criterion C has not been validated; however, Criterion C has been used in several previous register-based studies. By solely focusing on redeemed csDMARD prescriptions, we may have missed patients initiating a biological disease-modifying anti-rheumatic drug (bDMARD) and not receiving a concomitant csDMARD. However, since the introduction of the first tumour necrosis factor inhibitors in 2000, Danish treatment guidelines for RA have highlighted that csDMARDs, and methotrexate in particular, remain the first choice and are the mainstay in the treatment of patients with RA. This has been one of the main messages of all national guidelines published during the study period. Thus, using csDMARDs as part of the case criteria rather than both csDMARDs and bDMARDs is not very likely to have influenced our results. There is a risk that our results may have underestimated the true estimates of RA as patients with RA followed by privately practising rheumatologists in primary care are not captured unless they are transferred to or come into contact with a hospital because of RA or for other reasons. Another limitation to the present study is that we did not have access to laboratory data on anti-cyclic citrullinated peptide and only had information on immunoglobulin M–rheumatoid factor for the last part of the study period, thus preventing visualization of temporal patterns in seropositive versus seronegative RA.

Our study also had strengths, including the large nationwide register-based cohort of patients with RA. In Denmark, the nationwide registers allow us to follow up a dynamic cohort, accounting for migrations and deaths, with highly valid individual-level-based information. We accounted for demographic changes by weighting and standardizing calculations; to account for population changes, growth rates were calculated, and to account for temporal trends in the sex and age composition of the population, we standardized all results. Using a strict RA case definition with information obtained from national registers, the risk of misclassification bias was reduced. On the other hand, a very strict case definition such as Criterion D increases the risk of false-negative misclassification and thereby an underestimation of the true numbers (24).

Conclusion

In summary, there was a peak in the IR of RA in 2010 and a significant increasing trend in the PP over time irrespective of case definition. Women had approximately two-fold higher IR, LR, and PP of RA compared to men. We confirmed and emphasize the importance of the case definition of RA used in register-based studies.

Acknowledgements

A patient research partner was included in the development of the protocol and had the opportunity to submit comments to the protocol. The authors thank the patient research partner for her contribution.

Disclosure statement

Dr. Soussi reports grants from The Danish Rheumatism Association, grant from Aase and Ejnar Danielsens Foundation, during the conduct of the study. Dr. Cordt has nothing to disclose. Dr. Kristensen has nothing to disclose. Dr. Bork has nothing to disclose. Dr. Christensen has nothing to disclose. Dr. Schmidt has nothing to disclose. Dr. Torp-Pedersen reports grants from Bayer, grants from Novo Nordisk, outside the submitted work. Dr. Prieto-Alhambra reports grants and other from AMGEN, grants, non-financial support and other from UCB Biopharma, grants from Les Laboratoires Servier, outside the submitted work; and Janssen, on behalf of IMI-funded EHDEN and EMIF consortiums, and Synapse Management Partners have supported training programmes organised by DPA’s department and open for external participants. Dr. Dreyer reports grants from BMS, other from Galderma, other from Eli Lilly, outside the submitted work.

Funding

This work was supported by the Aase og Ejnar Danielsens Fond [19-10-0295]; Danish Rheumatism Association [R172-A6090,R175-A6091,R186-A6573].
Rheumatoid arthritis in Denmark

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Supplementary material

Supplemental data for this article can be accessed here.