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# Is the Incidence of Rheumatoid Arthritis Rising?

## Results From Olmsted County, Minnesota, 1955–2007

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***Objective.*** **To examine trends in the incidence and prevalence of rheumatoid arthritis (RA) from 1995 to 2007.**

***Methods.*** **To augment our preexisting inception cohort of patients with RA (1955–1994), we assembled a population-based incidence cohort of individuals ≥18 years of age who first fulfilled the American College of Rheumatology 1987 criteria for the classification of RA between January 1, 1995 and December 31, 2007 and a cohort of patients with prevalent RA on January 1, 2005. Incidence and prevalence rates were estimated and were age-and sex-adjusted to the white population in the US in 2000. Trends in incidence rates were examined using Poisson regression methods.**

***Results.*** **The 1995–2007 incidence cohort comprised 466 patients (mean age 55.6 years), 69% of whom were female and 66% of whom were rheumatoid factor positive. The overall age- and sex-adjusted annual RA incidence was 40.9/100,000 population. The age-adjusted incidence in women was 53.1/100,000 population (versus 27.7/100,000 population in men). During the period of time from 1995 to 2007, the incidence of RA increased moderately in women ($P = 0.02$) but not in men ($P = 0.74$). The increase was similar among all age groups. The overall age- and sex-adjusted prevalence on January 1, 2005 was 0.72% (95% confidence interval [95% CI] 0.66, 0.77), which is an increase when compared with a prevalence of 0.62% (95% CI 0.55, 0.69) in 1995 ($P < 0.001$). Applying the prevalence on January 1, 2005 to the US population in 2005 showed that an estimated 1.5 million US adults were affected by RA. This is an increase from the previously reported 1.3 million adults with RA in the US.**

***Conclusion.*** **The incidence of RA in women appears to have increased during the period of time from 1995 to 2007. The reasons for this recent increase are unknown, but environmental factors may play a role. A corresponding increase in the prevalence of RA was also observed.**

The incidence and prevalence of rheumatoid arthritis (RA) in populations vary substantially between geographic areas and over time (1–12). The geographic and temporal variability cannot be explained by genetic factors alone. Rather, this variability implicates a combination of environmental exposures and gene–environment interactions. Despite the variability of RA incidence rates in different populations at various time points, the trends of RA incidence in several countries during the past several decades appeared to follow a similar pattern. Indeed, several studies from different countries, including studies from our group, showed declines in the incidence of RA during the second half of the 20th century (2–8,10). The declining incidence, combined with the lack of improvement in survival of patients with RA, resulted in the reported decreases in the prevalence of RA (3,6,11). However, the more recent trends in RA incidence are not as well known. Thus, we sought to extend our studies of RA incidence and prevalence in Olmsted County, Minnesota to include the 1995–2007 period, resulting in a total of >50 years of RA epidemiology data.

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## PATIENTS AND METHODS

The population of Olmsted County, Minnesota represents an optimal source for an investigation of RA epidemiology, because comprehensive medical records for all residents seeking medical care for more than half a century are available. The unique population-based data resources of the Rochester Epidemiology Project (REP) medical record linkage system provide ready access to the medical records from all health care specialists for the local population. These health care providers include the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Group, the Olmsted Community Hospital, local nursing homes, and the few private practitioners. The unique features and potential of the REP medical record linkage system for population-based studies have been described previously (13–15). This system ensures virtually complete ascertainment of all clinically recognized cases of RA among the residents of Olmsted County, Minnesota.

In order to identify all potential incident cases of RA in this population, the computerized diagnostic index was searched for any diagnosis of arthritis (excluding degenerative arthritis or osteoarthritis) made between January 1, 1995 and December 31, 2007 among Olmsted County residents who were ≥18 years of age. Every person in the community ≥18 years of age who qualified during the defined period, regardless of race, ethnicity, or socioeconomic status, was included. The complete (inpatient and outpatient) medical record for each potential case was reviewed by a trained nurse abstractor, using a pretested data collection form. All questionable cases were additionally reviewed by coinvestigators supervised by the principal investigator, and confirmation or rejection of the diagnosis was accomplished based on the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for the classification of RA (16). The incidence date was defined as the earliest date at which the subject fulfilled at least 4 of the ACR criteria for RA. Subjects were allowed to accumulate the criteria over time until fulfillment of the fourth criterion (17).

This inception cohort of patients in whom RA was diagnosed during the period of time from 1995 to 2007 augmented the previously assembled cohort of Rochester, Minnesota residents with incident RA from 1955 through 1994. The cohort was also augmented by all Olmsted County, Minnesota residents (including those living outside of Rochester) with incident RA between 1985 and 1994 (5,8). Because the incidence rates based on this larger geographic area were essentially identical to those previously reported for the period of time from 1985 to 1994, this report focuses on the period of time from 1995 to 2007. The demographics and incidence rates based on the augmented cohort were used for comparison in the tables and figure.

The prevalence cohort on January 1, 2005 included persons in the incidence cohort who were still alive and living in Olmsted County, Minnesota on the prevalence date, as well as persons with previously diagnosed RA who moved into Olmsted County. The medical records were reviewed to confirm the diagnosis of RA.

Overall incidence rates were age- and/or sex-adjusted to the population of white persons living in the US in 2000. Age- and sex-specific incidence rates were calculated by using the number of incident cases as the numerator and population estimates based on decennial census counts as the denominator, with linear interpolation used to estimate population size for intercensal years (18). In order to compute 95% confidence intervals (95% CIs) for incidence rates, it was assumed that the number of incident cases followed a Poisson distribution. Trends in incidence rates were examined using Poisson regression methods with smoothing splines for age and calendar year (19). Tests for trends in incidence among women and men were performed using Poisson regression models adjusted for age by fitting a linear calendar-year term to the incidence rates for the 1995–2007 time period. Annual incidence rates were illustrated using a 3-year–centered moving average. Trends in age over time were examined using linear regression models.

Prevalence was calculated on January 1, 1995 and January 1, 2005, using the number of Olmsted County, Minnesota residents ≥18 years of age who fulfilled the ACR 1987 criteria for RA on these dates as the numerator, and the county population on the same date as the denominator. Prevalence estimates for January 1, 1995 and January 1, 2005 were compared using an F test (20). The number of affected US adults was estimated by applying the prevalence rate for each sex and 5-year age group to the US population in 2005, as obtained from the US census report (21).

## RESULTS

We screened the medical records of 1,761 Olmsted County, Minnesota residents ≥18 years of age who had received 1 or more diagnoses of arthritis (excluding degenerative arthritis or osteoarthritis) between January 1, 1995 and December 31, 2007. After comprehensive review of the medical record for each potential case, the diagnosis of RA was confirmed for 466 patients. These patients with RA comprised the final incidence cohort from January 1, 1995 to December 31, 2007. The mean age at incidence of RA was 55.6 years, and 321 of the patients (69%) were female. The median followup was 5.7 years (minimum 0.1 years, maximum 14.0 years). Among those tested, 307 patients (66%) were positive for rheumatoid factor (i.e., at least 1 positive test result during the followup period).

Definite radiographic changes (erosions) during the first year after RA incidence were observed in 92 patients (20%), which is a slight increase from the incidence in the previous decade (33 patients [15%]; $P = 0.08$). The proportion of subjects who underwent radiographic examination also increased (from 92% in 1985–1994 to 97% in 1995–2007), which may explain this change in the proportion of patients with erosions.

Other baseline demographics and disease characteristics in the incidence cohort from the 1995–2007 period were not different from those in the 1985–1994 period, except that a lower percentage of men with RA were smokers in the 1995–2007 period (59%) compared

**Table 1.** Characteristics of Olmsted County, Minnesota residents ≥18 years of age with incident rheumatoid arthritis (RA) between January 1, 1985 and December 31, 2007

| Variable | Time period | | *P* |
|---|---|---|---|
| | 1985–1994 | 1995–2007 | |
| Total no. of patients | 240 | 466 | |
| Female sex, no. (%) | 160 (67) | 321 (69) | 0.55 |
| Age at incidence, years | | | |
| Mean, median | 56.6, 55.9 | 55.6, 54.8 | 0.42 |
| Minimum, maximum | 18, 94 | 19, 89 | |
| Rheumatoid factor | | | |
| No. (%) positive of those tested | 165 (69) | 307 (66) | 0.44 |
| % tested* | 100 | 99.7 | |
| No. (%) of patients with erosions on radiographs in first year after RA incidence | 33 (15) | 92 (20) | 0.08 |
| % radiographed | 92 | 97 | |
| Cigarette smoking, former or current, no. (%) | 143 (60) | 233 (50) | 0.02 |
| Women, no. (%) | 81 (51) | 148 (46) | 0.38 |
| Men, no. (%) | 62 (78) | 85 (59) | 0.006 |

* Percentage of patients who had the test performed at least once during the followup period.

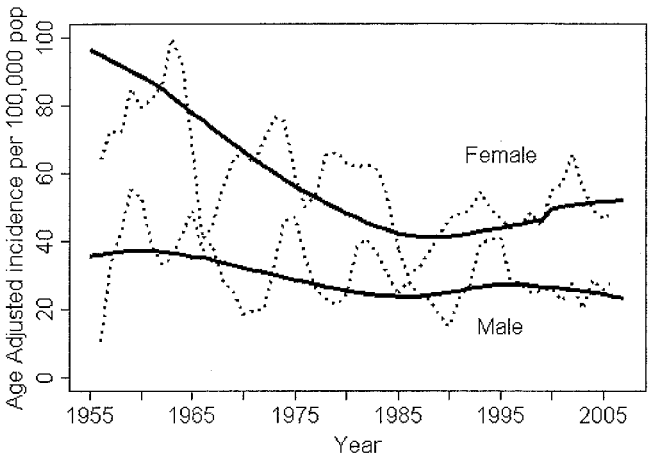


**Figure 1.** Annual incidence of rheumatoid arthritis per 100,000 population in residents of Olmsted County, Minnesota, 1955–2007, according to sex. The broken lines are calculated as a 3-year–centered moving average, and the solid lines are trends in the incidence rates after adjustment for age.

with the 1985–1994 period (78%; $P = 0.006$) (Table 1). During the same period, smoking rates in women remained essentially unchanged from the previous decade (46% versus 51%; $P = 0.38$). For each sex, the changes in smoking status between the decades when current and former smoking were examined separately were similar to those reported for current and former smokers combined (data not shown).

For the 1995–2007 period, the overall age- and sex-adjusted annual RA incidence among Olmsted County residents ≥18 years of age was 40.9/100,000 population (95% CI 37.2, 44.7) (Table 2). The age-adjusted incidence in women was 53.1/100,000 population (95% CI 47.3, 58.9) and in men was 27.7/100,000 population (95% CI 23.1, 32.2). The incidence of RA overall and in both sexes was low in the age group 18–34 years, after which it progressively increased with age, resulting in the maximal incidence in the age group 65–74 years. The incidence of RA declined in persons ages 75 years and older (Table 2).

Figure 1 illustrates the trends in the annual incidence rates of RA per 100,000 population, according to sex, from 1995 to 2007, along with the previously reported data from the 1955–1994 period. The incidence of RA appeared to increase by 2.5% per year from 1995 to 2007 in women (95% CI 0.3%, 4.7% per year [$P = 0.02$]) but not in men (0.5% decrease per year; 95% CI

**Table 2.** Annual incidence of rheumatoid arthritis in Olmsted County, Minnesota residents ≥18 years of age, 1995–2007, by sex and age group*

| Age group | Male | | Female | | Total | |
|---|---|---|---|---|---|---|
| | No. of patients | Rate | No. of patients | Rate | No. of patients | Rate |
| 18–34 years | 7 | 3.6 | 27 | 13.8 | 34 | 8.7 |
| 35–44 years | 26 | 19.1 | 73 | 55.0 | 99 | 36.2 |
| 45–54 years | 30 | 26.9 | 72 | 62.4 | 102 | 44.9 |
| 55–64 years | 36 | 51.7 | 55 | 74.2 | 91 | 63.3 |
| 65–74 years | 31 | 72.4 | 51 | 104.4 | 82 | 89.4 |
| 75–84 years | 13 | 52.3 | 30 | 81.1 | 43 | 69.5 |
| ≥85 years | 2 | 26.1 | 13 | 63.7 | 15 | 53.5 |
| Total (95% CI) | 145 | 27.7 (23.1, 32.2)† | 321 | 53.1 (47.3, 58.9)† | 466 | 40.9 (37.2, 44.7)‡ |

* Values are the annual incidence rate (95% confidence interval [95% CI]) per 100,000 population.
† Age-adjusted to the 2000 US white population.
‡ Age- and sex-adjusted to the 2000 US white population.

**Table 3.** Prevalence of rheumatoid arthritis in Olmsted County, Minnesota residents ≥18 years of age on January 1, 1995 and January 1, 2005*

| | Time point | |
|---|---|---|
| | January 1, 1995 | January 1, 2005 |
| Men | 0.44 (0.34, 0.53) | 0.41 (0.35, 0.48) |
| Women | 0.77 (0.66, 0.87) | 0.98 (0.90, 1.07)† |
| Total | 0.62 (0.55, 0.69) | 0.72 (0.66, 0.77)† |

* Values are the percent (95% confidence interval) per 100,000 population. Values were age-adjusted (men and women) and age- and sex-adjusted (total) to the 2000 US white population.
† $P < 0.001$ versus previous decade.

−3.6%, 2.7% [$P = 0.74$]). There was no apparent difference in the trend for RF-positive patients compared with RF-negative patients ($P = 0.26$ for women and $P = 0.70$ for men).

We then examined whether age at RA incidence has changed over time. The distribution of age at RA incidence was stable from 1980 to 2007 ($P = 0.32$). Furthermore, the increases in incidence rates from the 1985–1994 period to the 1995–2007 period for each sex were proportional to the incidence rates in each age category. In other words, there were no disproportionate increases in RA incidence in particular age groups over time.

The overall age- and sex-adjusted prevalence of RA among individuals who were 18 years of age or older on January 1, 2005 was 0.72%, which represents an increase from the estimate of 0.62% on January 1, 1995 ($P < 0.001$) (Table 3). Compared with January 1, 1995, the prevalence of RA in women increased significantly, from 0.77% to 0.98% on January 1, 2005 ($P < 0.001$); the prevalence of RA in men on January 1, 2005 was unchanged ($P = 0.18$). Applying the prevalence of RA on January 1, 2005 to the US population in 2005 showed that an estimated 1.5 million US adults were affected by RA. This is an increase from the 1.3 million reported previously (11).

## DISCUSSION

Here, we report the most recent trends in RA incidence in a population-based US cohort. We observed a modest increase in the incidence of RA among women during the period of time from 1995 to 2007. This increase followed the sharp decline in the incidence of RA that was observed over the previous 4 decades. As expected, the increased incidence was accompanied by an increase in the prevalence of RA.

From the middle of the 20th century, the occurrence of RA has been widely studied in multiple centers, predominantly in the US and Western Europe (1–8,10–12,22). Despite the variable disease frequency reported for different populations, all of these studies (including our own) showed a compelling decline in RA incidence during the period of time from 1955 to 1994. Very few epidemiologic studies have shown secular trends in the incidence of RA after 1995. Pedersen et al demonstrated an increasing incidence of RA from 1995 to 2001, particularly among women (23). These findings are consistent with our own. Kaipiainen-Seppänen et al compared the incidence of RA in 1980, 1985, 1990, 1995, and 2000 (10), verifying the previously observed declining trend observed in our cohort (5,8). The observed declines in that study were less apparent among patients older than 64 years, in whom a modest increase in incidence was shown from 1980 to 2000 (10). This increasing trend in RA incidence is concordant with our data. However, unlike these other reports, we did not observe a difference in increased RA incidence among different age groups.

We can speculate on possible explanations for the modest increase in RA incidence observed in our study. Oral contraceptives (OCs) have been clearly shown to be associated with a dose-dependent protective effect against the development of RA in women (1,24–29). Modern OCs contain significantly lower doses of synthetic estrogens as compared with the OCs used decades ago (30,31). Because these lower doses of synthetic estrogens confer less protection against the development of RA than higher doses, it is almost certain that the protective effect of OCs has diminished over time. Thus, this exposure may contribute to the observed increase in RA incidence among women.

Breastfeeding is another sex-specific factor reported to have a dose-dependent protective effect against the development of RA (32,33). Moreover, the rates of breastfeeding in the US have been increasing in recent years (34). However, this protective effect is limited to the population of parous women who choose breastfeeding, and the effects are most significant among those who choose long-term (>24 months) breastfeeding, which is an even smaller number. Therefore, this factor is unlikely to have a major impact on RA incidence.

Cigarette smoking is perhaps the strongest environmental risk factor that is clearly associated with the development of RA in both sexes (35–42). Although smoking has become less prevalent in the US in general, smoking rates are declining at a significantly slower pace among women compared with men. Thus, the gap in the

proportion of male and female smokers has significantly and progressively narrowed since 1965 (43). The slower decline in the smoking rate among women can, in part, explain the lack of decline in the RA incidence rate among women.

Several lines of evidence suggest that vitamin D deficiency may be associated with the development of RA (44–50). In addition, the incidence of vitamin D deficiency has been demonstrated to be increasing over the previous decades, particularly in women (44). Thus, vitamin D deficiency may also contribute to the observed trends in the incidence of RA.

Other environmental factors postulated to play a role in the incidence of RA, especially in women, may also be implicated in the observed trends. These include infections, immunizations, obesity, and socioeconomic status (51–56).

Although the findings described above are speculative, when taken together they suggest that the cumulative effect of multiple environmental factors (each of which is associated with either an increase in risk or a loss of protection, particularly in women) could explain the observed increase in the incidence of RA during the study period. Besides the risk factors mentioned, the effect of other, as-yet-unknown risk factors on the changes in RA incidence over time cannot be excluded.

Our study has several important strengths, including its longitudinal population-based design and the use of a systematic and standardized approach to case identification. Limitations of this study include the possibility of an increased awareness of RA in recent years, potentially including awareness of the ACR 1987 criteria for RA. The increase in the incidence of RA in women without changes in the incidence in men and the lack of differences in the incidence of RF-positive and RF-negative RA provide evidence against ascertainment bias. The small sample size and the resulting lack of statistical power could be responsible for our inability to detect a change in the incidence in men. Although it is possible that the observed increase in the incidence of RA in women represents merely a lack of decline, we believe this is unlikely, because the increase was observed across several years. Furthermore, there is a possibility of underascertainment of cases in studies involving medical record review. However, the comprehensive and standardized approach to case ascertainment described in Patients and Methods makes selection bias unlikely. Finally, the population of Olmsted County, Minnesota is 90% white, suggesting that the results of our study may not be generalizable to other, more racially diverse populations. Furthermore, the demographic characteristics of the residents of Olmsted County (including survival rates, aging, race, percent of emigrants) have not changed substantially over recent years and were thus unlikely to influence the observed epidemiologic trends.

In conclusion, we observed that the incidence of RA appeared to increase during the period from 1995 to 2007. This rise in incidence followed a 4-decade period of time during which the incidence declined, and it appeared to be limited to women. The reasons for this increase in incidence are unknown, but environmental factors likely play a role.

## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Gabriel had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Myasoedova, Maradit Kremers, Gabriel.
**Acquisition of data.** Myasoedova, Gabriel.
**Analysis and interpretation of data.** Myasoedova, Crowson, Maradit Kremers, Therneau, Gabriel.

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