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Secular trends in the incidence and prevalence of rheumatoid arthritis within members of an integrated health care delivery system

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Abstract

The study objective was to estimate secular trends in the overall incidence rate (IR) and prevalence rate (PR) of rheumatoid arthritis (RA); and subgroup-specific IR and PR by race, ethnicity, and sex in a multi-ethnic population of a large integrated health care delivery system. An ecological study was conducted within the adult population of Kaiser Permanente Southern California health plan. From January 1995 up to and including December 2014, annual IR and PR were calculated separately by race, ethnicity, sex and pooled overall. Depending on the stationarity of each ecological series, annual percentage change in IR and PR was evaluated using auto-regressive integrated moving average models. Average overall IR was 53 [95% confidence interval (CI) 46, 61] per 100,000 person-years. The overall as well as subgroup-specific annual IR of RA were unchanged from 1995 to 2014. In 1995, the overall PR of RA was 59 (44, 74) per 100,000 person-years which increased by 14% (7%, 21%) annually thereafter. The increase in PR in Caucasians was lower as compared to African American, Asian and other race (13% vs 15%, 15%, and 18%, respectively). Compared to non-Hispanic ethnicity, the increase in PR among Hispanic was higher (17% vs 14%). Over the past 2 decades, while the incidence of RA was unchanged, the prevalence had increased significantly overall as well as within every subgroup of race, ethnicity, and sex.

Keywords Rheumatoid arthritis · Incidence · Prevalence · Secular trends · Box–Jenkins models

Introduction

The National Arthritis Data Workgroup (NADW) had assessed that the prevalence of rheumatoid arthritis (RA) in 1995 was 2.1 million [1]. While the NADW revised its 2005 prevalence estimate downwards to 1.3 million U.S. adults (≥ 18 years of age); another study using the Rochester Epidemiology Project (REP) reports that the prevalence of RA in 2005 was slightly higher at 1.5 million U.S. adults [2]. While these reports suggest that the period prevalence of RA was lower in 2005 compared to 1995, very few studies have quantified the secular trend in the prevalence of RA in recent years [3].

Based on published studies, it is also unclear if the reported decrease in the prevalence rate (PR) is related to changes in the underlying incidence rate (IR) of RA or due to changes in life expectancy/mortality. The past decade has witnessed the introduction of multiple novel anti-rheumatic treatments including biological disease modifying anti-rheumatic drugs (DMARDs). Second, the treatment paradigm for RA has also changed significantly with an emphasis on early and aggressive disease management. Both these technological changes have resulted in increasing life expectancy (without curing RA) and decreasing RA-related mortality. Together this should increase the prevalence of RA [4]. Hence, there remains a need to better understand the long-term trajectory of IR and PR of RA in recent years.

We present contemporary data on the secular trends in the incidence and prevalence of RA to evaluate potential disparities associated with race, ethnicity, and sex. The objective

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of this study was to evaluate the annual percent change in the overall incidence and prevalence of RA in a multi-ethnic population of a large integrated health care delivery system. We also evaluated the annual changes in the IR and PR of RA by subgroups of race, ethnicity and sex.

Methods

Study setting

The Kaiser Permanente Southern California (KPSC) medical care program is a large integrated care organization with over 4.5 million members. Members receive their health care throughout the seven-county region in which KPSC has 15 medical centers and affiliated hospitals, along with 230 medical offices. KPSC members are ethnically diverse; they represent more than 260 different ethnicities and speak about 118 different languages. Additionally, KPSC membership reflects the socioeconomic diversity of the Southern California census population providing valid epidemiologic inferences [5].

One can become KPSC member by choosing KP as the health plan option available from employer-sponsored health plans or purchasing individual plans from the private market or health exchanges or finally opting KP health plan offered by Medicare and Medicaid for those who are eligible for those programs.

Health care at KPSC is coordinated through region-wide electronic medical records (EMR) that capture detailed information on care provided to members at outpatient visits and during inpatient stays, as well as on utilization of pharmacy, immunizations, imaging and laboratory services.

Study design

An ecological study was designed to analyze trends of incidence and prevalence rates. The study period was from January 1, 1995, to December 31, 2014. The incidence rate (IR) and prevalence rate (PR) were calculated on an annual basis from 1995 to 2014. The study population consisted of KPSC members 18 to 100 years of age during the study period.

This study was reviewed and approved by the KPSC Institutional Review Board.

Exposure and outcome measurement

Rheumatoid arthritis case status was defined as a member with *at least two* medical encounters that were separated by 30 days in an outpatient setting, or *one* RA-related hospitalization or emergency department visit. Age was calculated based on the difference between a patient's date of birth and July 1st of each year in the study period for non-RA cases; while for RA cases, age was calculated as of the first RA diagnosis date in that year.

Annual incidence rate (per 100,000 person-years) was calculated as the number of new RA patients divided by the total time of member population at risk within a specified calendar year. Incident RA cases had a $\geq$ 12-month period prior to their first RA diagnosis where they were members of KPSC and did not have any RA diagnosis. Since it is a chronic disease with no cure, once someone had RA, they were assumed to have it going forward unless they died or disenrolled from the health plan. Annual prevalence rate (per 100,000 person-years) was calculated as the total number of RA cases divided by the person-time of active adult KPSC population for each calendar year.

Member enrollment history was used to calculate both the denominators in IR and PR. The denominator was calculated in terms of person-time of adult KPSC population for each calendar year and expressed as per 100,000 person-years. This approach allowed us to incorporate the fact that some adults might have been KPSC members only for a part of the year and not for the full 12 months in that calendar year. It also allowed us to incorporate as much information on each person's enrollment and hence minimize implied assumptions.

Both rates were calculated for the overall population, as well as stratified by race (Caucasian, African American, Asian, and other race), ethnicity (Hispanic and non-Hispanic), and sex (female and male). Race and ethnicity were obtained from Kaiser Permanente's membership and enrollment information maintained by the health plan. All rates were age adjusted to the 2010 U.S. Census population using the direct method. To calculate 95% confidence intervals of annual IR and PR, we assumed that the numbers of incident and prevalent cases followed a Poisson distribution.

Statistical analysis

Modeling of ecological data, also referred to as time series data, to evaluate underlying trends requires an understanding of complex statistical issues that are unique to such data. Coefficient estimates from the predominantly used log-linear models or their equivalent Poisson models rely heavily on the assumption of stationarity of the time series. A time series is considered stationary only if its mean, variance, covariance, and autocorrelation structure are all constant over time. In the absence of stationarity, the variance of the series increases (infinitely) with time, and hence, the standard *t* statistic on the time regressor from the log-linear model may reject the false null hypothesis at an error rate of 60–80% instead of the expected 5% error [6, 7].

We evaluated the stationarity of the time series using the augmented Dickey–Fuller test to check for the presence of unit root. This test determines the suitability of the

log–linear (or Poisson) model over a random walk hypothesis. The random walk hypothesis suggests that using the available time series data, it may not be possible to predict the future prevalence or incidence rate due to irregular growth over time. If the random walk hypothesis holds true, it is better to predict the change that occurs in the series as opposed to the absolute level of the future series. The random walk model predicts the next change which can always be added back to the current incidence/prevalence rate to get the future rate. Random walk, random trend, autoregressive, and exponential smoothing moving average models are all special cases of Auto-Regressive Integrated Moving Average (ARIMA) (or Box–Jenkins) models [8]. These models either add lagged regressors (i.e., auto-regressive) to the differenced series (i.e., integrated) or lagged forecast error (i.e., moving average) to eliminate the auto-correlation over time.

We first assessed the number of differencing required to make the series stationary and then assessed the differenced series for the auto-regressive or moving average signatures using autocorrelation and partial autocorrelation plots, and portmanteau (Q) statistics. Based on these diagnostic procedures, for non-stationary time series, we specified ARIMA (p, d, q) models where 'p' was the number of autocorrelation terms, 'd' was the number of times the series Y_t was differenced (i.e., $Y_t - Y_{t-1}$ with 't' representing time) and 'q' was the number of lagged forecast error terms.

If a series was stationary, we checked for the presence of autocorrelation in the annual incidence and prevalence rates. Presence of autocorrelation was evaluated by Durbin's alternative test and autocorrelation plot. For stationary series, a log–linear time series regression models with the year (1995–2014) as the predictor was specified to estimate longitudinal trends in rates. This regression model allowed for error structure to be heteroskedastic and also controlled for possible autocorrelation up to two lags through Newey–West standard errors.

Results

In 1995, the (age adjusted) overall incidence rate was 34 (95% CI: 23, 45) per 100,000 person-years (Fig. 1 and Supplementary Table (Sup. Table) 1) while the overall prevalence rate was 59 (44, 74) per 100,000 person-years (Fig. 1; Sup. Table 1). By the end of 2 decades in 2014, the overall incidence rate was 57 (42, 72) per 100,000 person-years while prevalence was 890 (831, 948) per 100,000 person-years. In 1995, incidence rate was highest in females [48 (34, 61) per 100,000], non-Hispanic ethnicity [36 (24, 48) per 100,000] (Fig. 2; Sup. Table 1) and Caucasians race [39 (27, 51) per 100,000] (Fig. 3; Sup. Table 1). In 2014, incidence rate in females was 83 (65, 101) per 100,000 person-years while the rate in males was 27 (17, 38) per 100,000 person-years. In 2014, incidence rate in Hispanic ethnicity was 66 (50, 82) per 100,000 person-years, and was higher compared to the incidence rates in non-Hispanic 51 (37, 65).

In 1995, prevalence rates were nearly three times higher in females [84 (66, 102) per 100,000] as compared to males [31 (20, 42) per 100,000] and this difference was maintained in 2014 (Fig. 1; Sup. Table 2). Caucasian [69 (53, 85) per 100,000] had the highest prevalence rates among race categories and in 1995, compared to Caucasian, Asian had 41% lower prevalence while African America had 30% lower prevalence. By 2014, the difference in prevalence compared with Caucasian went down to 22% lower in Asian and 9.2% lower in African American. Although in 1995, Hispanic ethnicity had lower prevalence rate compared to non-Hispanic [(44 vs 62) per 100,000], by 2014, this was reversed, and Hispanic ethnicity had much higher prevalence rate [(1018 vs 813) per 100,000] compared to non-Hispanic (Fig. 2; Sup. Table 2).

Longitudinal trends in incidence rate

Secular incidence trends from 1995 to 2014 are exhibited in the first half of Figs. 1, 2 and 3. Based on the Dickey–Fuller test for stationarity, all incidence categories were found to be non-stationary. Thus, all incidence trends were evaluated using ARIMA models. Over the 2 decades from 1995 to 2014, overall incidence rate of RA was steady with 3% average annual change (95% CI − 4%, 10%) (Fig. 4). The annual percent change in incidence rates ranged from 2 to 5% across the subcategories of race, ethnicity and sex; however, none of these estimates were different from the zero null (Fig. 4).

Longitudinal trends in prevalence rates

The annual prevalence trends from 1995 to 2014 are presented in the bottom half of Figs. 1, 2 and 3. Similar to the incidence rates, all prevalence categories were found to be non-stationary; hence, all inferences on longitudinal trends in prevalence rates were also evaluated using ARIMA models.

From 1995 to 2014, overall prevalence rate of RA increased by 14% (95% CI 7%, 21%) annually. During the same interval, the prevalence rate of RA in females increased by 15% (7%, 22%) annually, while in males, this increase was slower by two percentage points 13% (7%, 19%). Amongst those of Hispanic ethnicity, prevalence rates increased by 17% (10%, 24%) annually as compared to 14% (6%, 21%) annual increase observed in non-Hispanic. Annual increase in prevalence rate was lowest in Caucasians 13% (6%, 20%) as compared to other race 18% (2%, 33%) and Asian and African American 15% (6%, 24%) (Fig. 5).

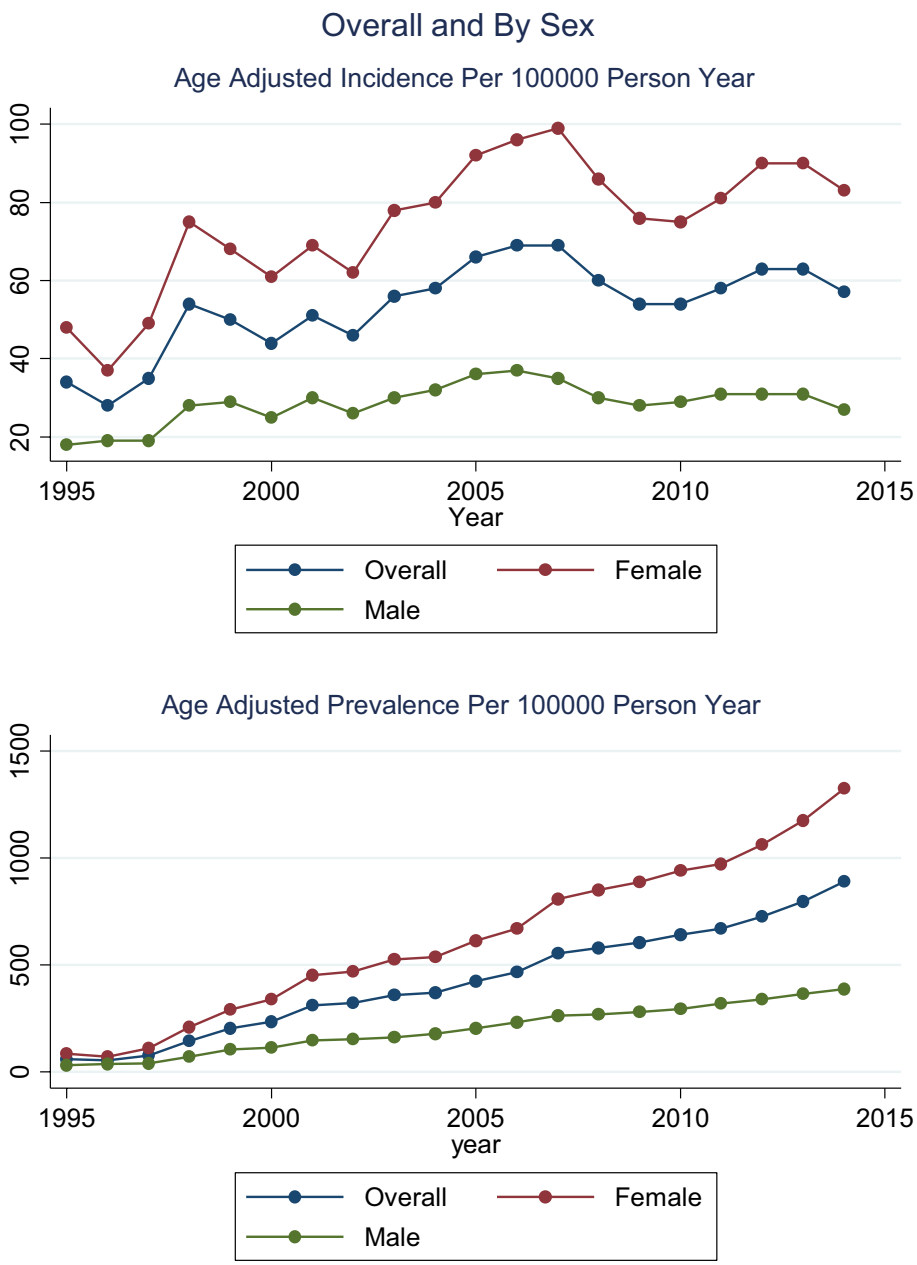

Fig. 1 Age-adjusted incidence and prevalence rate overall and by sex

Discussion

Our study identifies several interesting changes in the occurrence of RA associated with racial/ethnic minorities who may be experiencing disparities in contemporary approaches to screening and management of RA. We also characterize the secular trends in prevalence and incidence in females who are disproportionately affected by RA. Since incidence rate was stable for the past 2 decades while prevalence was increasing, a key insight from our data suggests that the prevalence of RA is driven by increase average disease duration. Increase in disease duration is a result of no cure for the disease and decreased mortality/increased life expectancy, potentially due to better disease modifying anti-rheumatic drugs [4].

From a methodological perspective, we avoid imperfect approaches limited to comparing two-point estimates across time to evaluate secular trends. Such study designs may result in biased estimates of trends with inferences that are heavily dependent on the choice of the time points selected. We also point to the often-missed statistical flaw that if an ecological trend is not statistically stationary, we cannot obtain meaningful sample statistics such as means and variances. Such statistics are useful as descriptors of future behavior only if the series is stationary. Additionally, if the series is consistently increasing over time, the sample mean

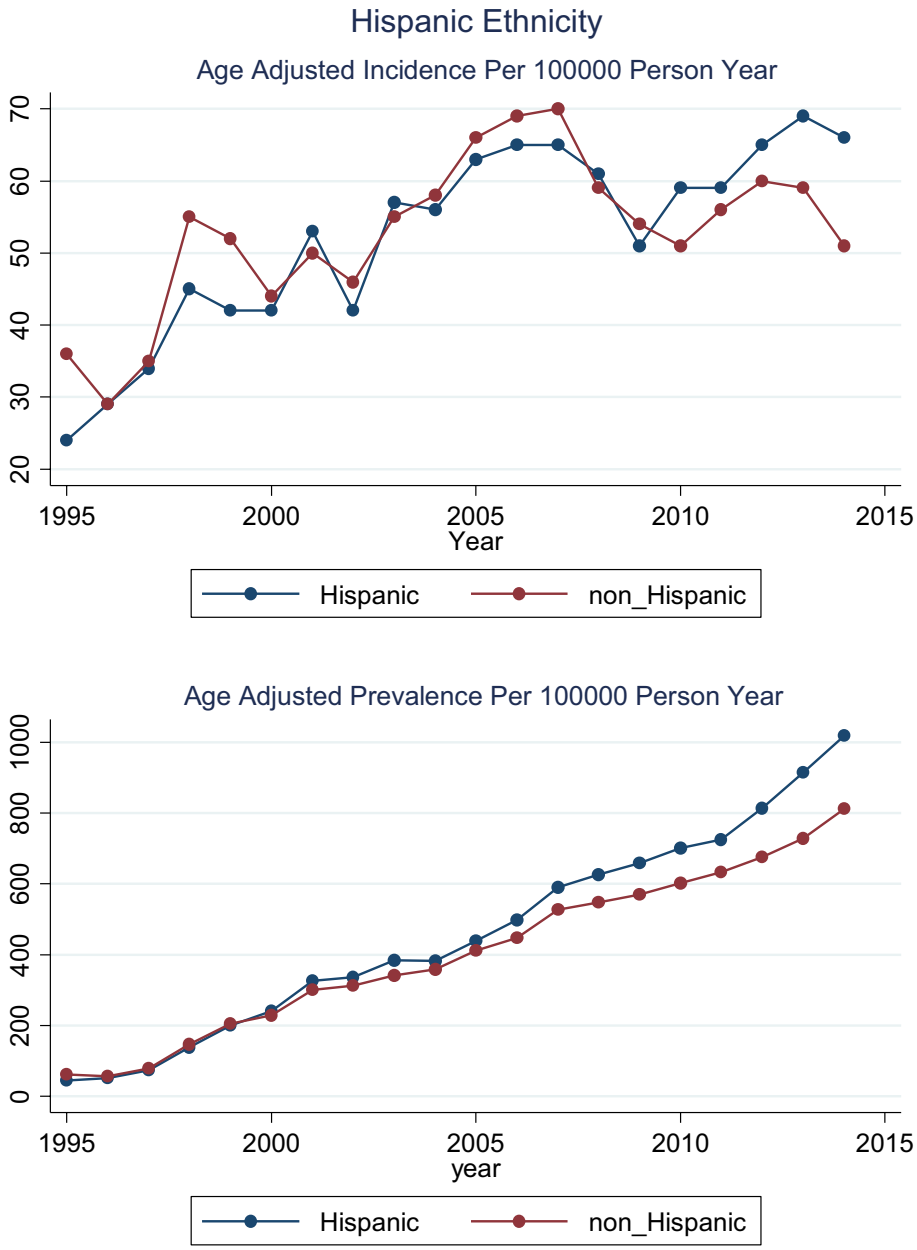

Fig. 2 Age-adjusted incidence and prevalence rate by ethnicity

and variance will grow with the size of the sample, and they will always underestimate the mean and variance in future periods. When the mean and variance are inaccurate, there is no possibility of expecting appropriate results from hypothesis test on difference between two of such estimated means. To avoid the aforementioned issues with non-stationarity of the ecological data, we applied Box–Jenkins models that are robust and well suited for ecological trend analysis. Our approach provides unbiased estimates of ecological trends and thus obtains valid statistical inference to the question whether incidence and prevalence of RA have been changing over time over the past 2 decades. Our approach can be applied by future researchers who are interested in estimating longitudinal epidemiological trends in other diseases.

Our estimates of the secular trends in RA provide valuable information to providers, health plans, policy-makers, as well as private and governmental institutions working in the area of medical technology and population health [9]. For example, these trends could be used for projections of future Medicare and Medicaid costs, social security disability cost associated with RA, planning of future healthcare workforce and changes to office and other facilities to accommodate workers with disability [10].

It is noteworthy that the overall incidence rate of RA has not increased, year over year. This was also true among females who form the majority of RA patients. Similarly, although Caucasians are generally believed to be at much higher risk of developing RA as compared to other races,

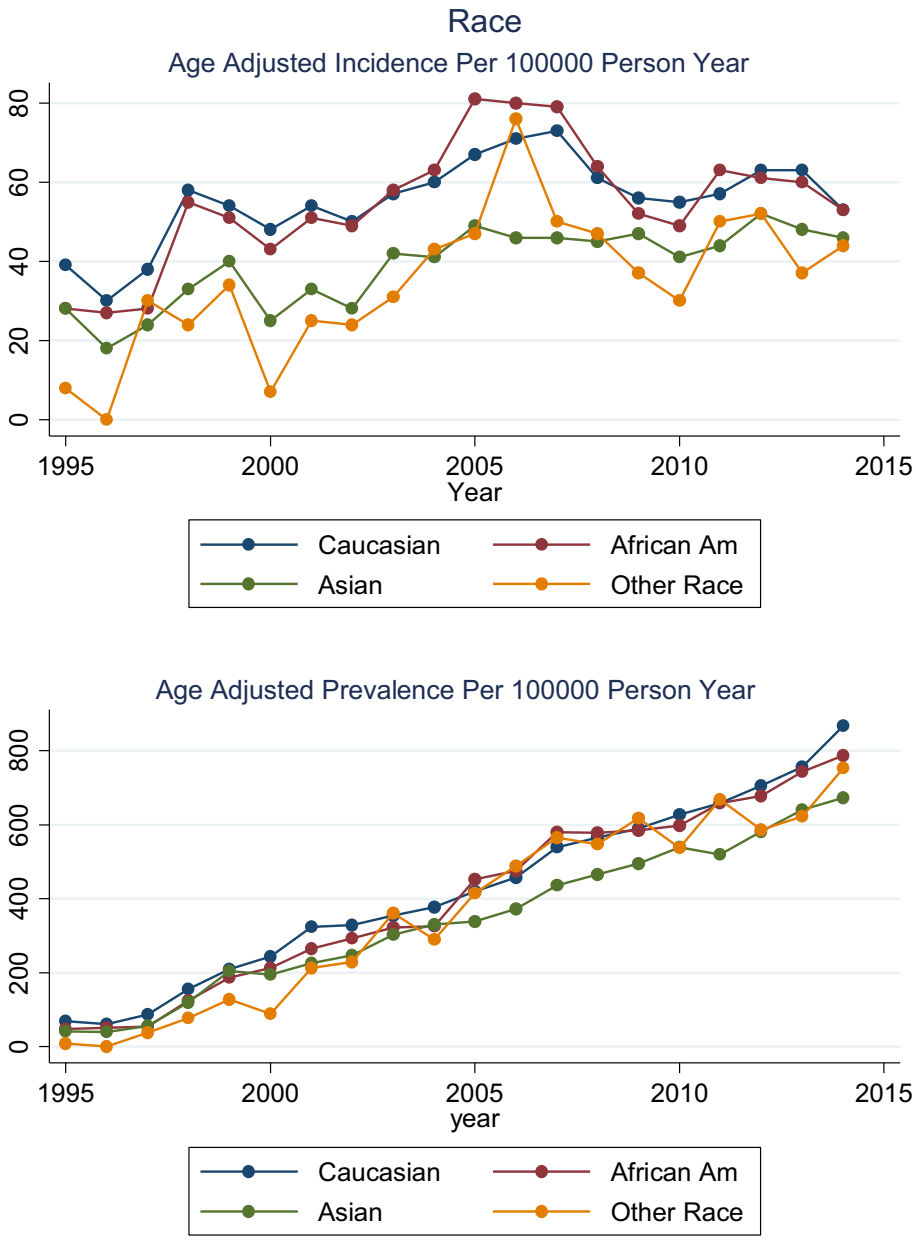

Fig. 3 Age-adjusted incidence and prevalence rate by race

our data suggest that the risk of developing RA remained unchanged for all racial groups including Caucasian race and non-Caucasian race groups. A broad overview of these data suggests that the incidence of RA is stable in those subpopulations which are most likely to develop RA. A recent population-based study from Quebec, Canada, found similar stable RA incidence rate from 2001 to 2015 [3].

In contrast to the stable incidence rate, prevalence rates have been steadily increasing. An aging population adds to the increasing prevalence numbers. Prevalence rates of RA were found to be increasing by nearly 14% each year in the full population and in women. Increases in the prevalence of RA could be partly driven by the non-declining but stable incidence rates. Additionally, increase in prevalence rates can also be explained by the relatively longer survival of RA patients in recent decade resulting from early and aggressive treatment, as well as modern DMARDs including the biological DMARDs that reduce disease activity and improve function [11, 12]. However, compared with expected mortality rates in the general population, RA patients are at an increased risk of mortality and this fact has not changed in the past couple of decades [3, 13]. Excess mortality among RA patients has been largely attributable to cardiovascular disease, but it could also be linked to increased risk from infectious, hematologic, gastrointestinal, and respiratory diseases [13, 14].

With the paradigm change in treatment of RA with DMARDs early on, access to potent DMARD medication

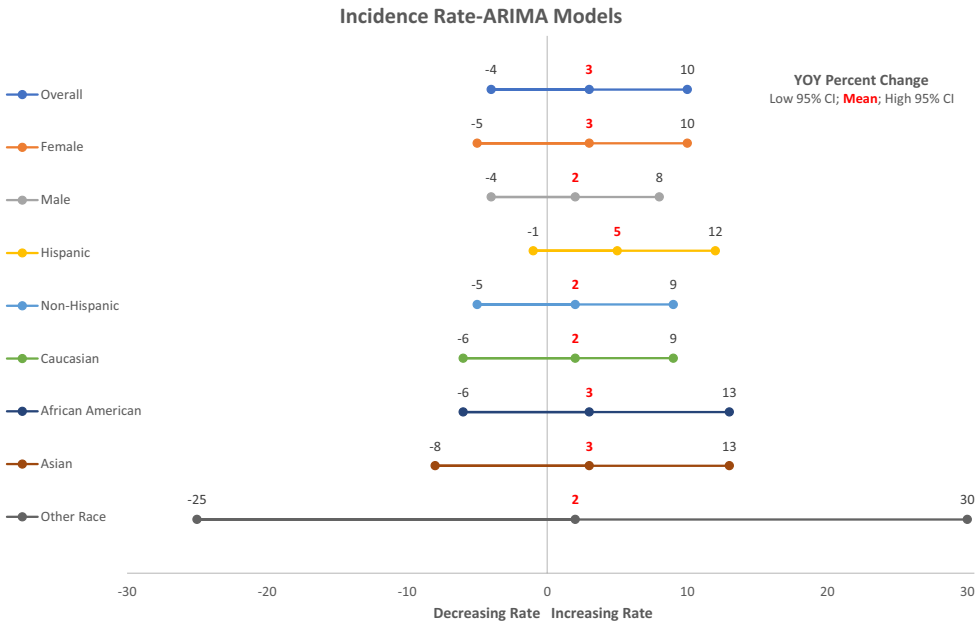

Fig. 4 Annual percentage change in incidence rate

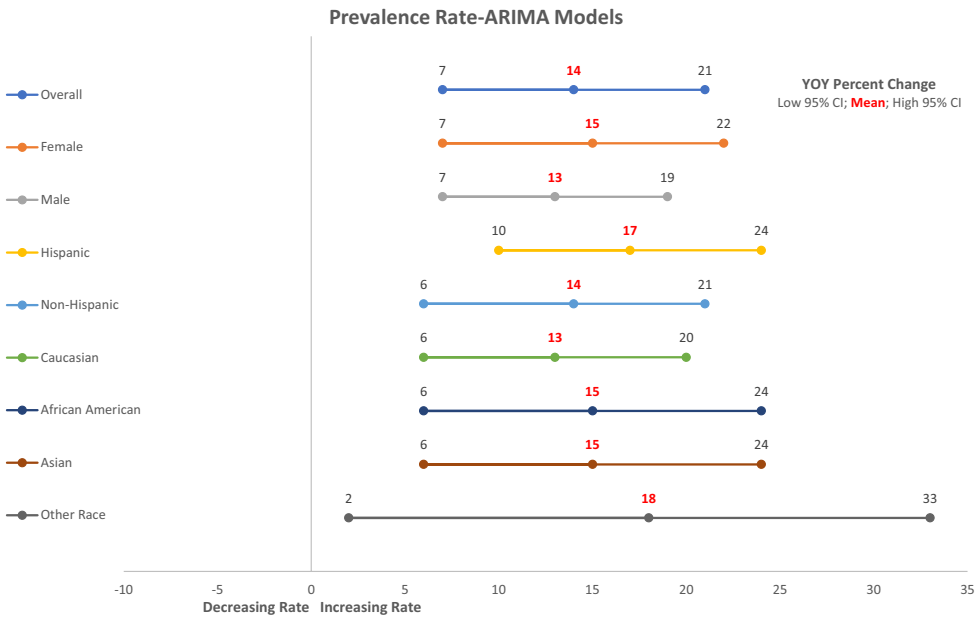

Fig. 5 Annual percentage change in prevalence rate

has changed over time and may be another factor to explain the increasing prevalence. While current clinical goals are to attain remission for all RA patients, there remain large race/ethnic disparities in the uptake of the expensive biologic DMARDs which can help achieve remission [15, 16].

In general, changes in secular trends can be explained by corresponding changes in socio-economic status, demographic structure of population, risk factor's prevalence, as well as changes in prevention, screening, and diagnostic strategies [9]. However, since the etiology of RA is unknown, it is difficult to isolate the exact determinants of the changes in RA incidence and prevalence. Modifiable risk factors that have been associated with RA include reproductive hormonal exposures, tobacco use, dietary factors, and microbial exposures. Myasoedova et al. discuss how some of these risk factors could affect the trends of RA incidence [2]. In their review article, Ezzati and Riboli (2013) summarize the available data on trends in selected behavioral and dietary risk factors for noncommunicable diseases and examine the current and future effects on the health of populations around the world [17]. Additionally, in recent years, the paradigm shift to treat early and aggressively might be one reason why the incidence of RA is stable since early treatment with DMARDs

may delay progression from undifferentiated inflammatory arthritis to classifiable RA [18, 19]. Patients with undifferentiated inflammatory arthritis may have synovitis and a presentation compatible with RA but they do not fulfill all the classification criteria for RA. Lastly, the racial/ethnic disparities observed in the modifiable risk factors of RA could explain the underlying disparities in the secular trends of this disease.

Alamanos et al. (2006) have reported substantial variation in the incidence and prevalence of RA across various studies and also across time periods within the studies [20]. In general, a substantial decline in RA incidence over time, with a shift toward a more elderly age of onset, was a consistent finding across several studies in the U.S. and other western countries [13, 21–25]. Our results mirror secular trends observed in these studies that have been conducted in a variety of geographically and ethnically diverse populations. However, contrasting findings have been reported from the REP data which suggest that the incidence of RA (at least in women) appears to be rising after 4 decades of decline [2, 13].

Using data from the REP, Myasoedova et al. report that the age-adjusted incidence in women was nearly twice of that observed in men and during the 1995–2007 period, incidence increased in women but not in men [2]. A corresponding increase in the prevalence of RA was also observed. Aside from women, the number of elderly patients with RA was increasing in the REP. The difference in the trajectory of incidence estimates between the REP and our study may arise from differences in the populations of Rochester and Southern California, differences in statistical modeling and slightly different time periods in the two studies.

Outside of the REP and within the U.S., very little is known about the trends in incidence and prevalence of RA. Costenbader et al. report that compared to those in the Western parts of U.S., women in New England had a 37–45% elevated risk of RA. They attribute the geographic variation in risk of RA to regional variation in behavioral factors, climate, environmental exposures, RA diagnosis, or genetic factors [21]. Akushevich and colleagues evaluated the secular trends of age-adjusted incidence rates of 19 aging-related diseases for the period from 1992 to 2005 using the National Long-Term Care Survey (NLTCS) and the Surveillance, Epidemiology and End Results (SEER) registry which represent estimates at the national level [9]. With a log-linear model, they found no statistical difference in the average annual percent change of incidence of rheumatoid arthritis in the elderly. Although the NLTCS and SEER-Medicare data can provide national level estimates, they still are limited to the elderly Medicare enrollees, and inferences cannot be drawn for younger age groups. These datasets may also have much smaller cell counts to be able to stratify by age, sex, or race in a disease with low prevalence such as RA [26].

Comparing trend studies conducted in the European population during a period similar to our study period reveals mixed results in trends in incidence and prevalence of RA [27]. Englund et al. evaluated the incidence and prevalence of RA in southern Sweden and report no decrease in incidence between 2003 and 2008 [28]. They reported that the incidence of RA in south Sweden was 50/100,000 while prevalence was 0.66%. Using the Swedish National Health Service data, another study reported RA incidence estimate of 41/100,000 but with variation in incidence that was dependent on population density [29]. Pedersen et al. estimated the incidence of RA in the southern part of Denmark at 32/100,000 person-years and found an increase in RA incidence from 1995 to 2001 [23, 24]. Although with little or no overlap in time period with our study, a Norwegian cohort study reported no change in incidence of RA between 1988 and 1993, while a Finnish study reported decrease in incidence of rheumatoid factor-positive RA between 1980 and 2000 [22, 30].

The strengths of this study include a combination of an ecological trend design paired with ARIMA (Box–Jenkins) models. We estimate the parameters for the Box–Jenkins models by numerically approximating the solutions of nonlinear equations using nonlinear least squares. In contrast, most published studies on secular trends in RA have reported estimates from log-linear models or their equivalent Poisson models. Although these models rely heavily on the assumption of stationarity of the secular trend, the validity of this assumption has not been reported. In the absence of stationarity, the variance of the series increases infinitely with time. Had we ignored the stationarity issue and chose log-linear models instead, we would have wrongly inferred that incidence rate was increasing (see Sup. Figure 1) over the past 2 decades and average disease duration was not the only contributor to increasing prevalence.

Limitations

Some potential limitations may apply to our study that may affect inferences. Although our data afford rich diversity and volume in terms of race and ethnicity of RA cases, our estimates may be less generalizable outside of California to states with homogenous racial distribution and higher fee-for-service health plan penetration. Additionally, as compared to some published studies that have chart-confirmed RA case status, given the large size of our cohort, we were unable to chart confirm all RA cases. Another potential limitation is the short time series available for the study, and longer follow-up would provide more robust estimates.

Conclusion

We present contemporary data on the secular trends in the incidence and prevalence of RA that identify moderate disparities associated with race, ethnicity, and sex. While incidence of RA is stable in those sub-populations which are most likely to develop RA, prevalence of this disease continues to rise. These results should prove valuable for the development of screening and prevention strategies, determining rheumatology workforce, predicting future medical expenditures and disability cost associated with RA.

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Compliance with ethical standards

Conflict of interest Aniket A. Kawatkar, Sherine E. Gabriel, and Steven J. Jacobsen have no direct conflict of interests. Dr. Kawatkar reports grants from Medac Pharma, grants from Bristol-Myers Squibb, outside the submitted work.

Ethical approval The study was approved by the Kaiser Permanente Southern California Institutional Review Board.

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