Author’s response to reviews

Title: Incidence and Prevalence of Rheumatoid Arthritis in Saskatchewan, Canada: 2001-2014

Authors:

Bindu Nair (bindu.nair@usask.ca)
Regina Taylor-Gjevre (r.gjevre@usask.ca)
Liying Wu (lilywu6721@gmail.com)
Shan Jin (sjin@hqc.sk.ca)
Jacqueline Quail (jquail@hqc.sk.ca)

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Darren Byrne

BMC Rheumatology

http://bmcrheumatol.biomedcentral.com/

Dear Dr. Byrne:

We thank the expert reviewers for their time and guidance in reviewing our manuscript “Incidence and Prevalence of Rheumatoid Arthritis in Saskatchewan, Canada: 2001 – 2014: (BRHM-D-19-00001). We appreciate the opportunity to improve the paper. Please find our responses below:

Reviewer 1:

Thank you for your comment regarding our analysis.
1. The objective was “to determine if the estimates vary across age, gender or population in Saskatchewan.” I did not see any information about population in the report. Should this be removed from the objective?

Yes, you are correct. The phrase ‘or populations in Saskatchewan’ has been removed from the Background, line 98, page 4.

2. The importance of geographic variability for better healthcare services planning is mentioned in both the introduction and the discussion, but this is not the focus of this paper.

The line “Recognition of the time trends of incidence and prevalence of the disease would be important to further advise future healthcare needs for this population.” has been added to the Background, lines 70 - 72, page 3 to reiterate the focus of this paper. The sentence “In contrast a recent study has shown a decreasing prevalence of RA in the United Kingdom and geographic variation within the country has been identified as a possible contributing factor to this result (20)” has been changed to “A recent study in contrast has reported that while the prevalence of RA in the United Kingdom increased from 1990 to 2005, it was noted that from 2005 to 2014 the prevalence of RA had decreased (20)” in Discussion, lines 280 - 283, page 15. The sentence “In Saskatchewan, rural and remote patients with RA have reported concerns with initial access to health care so the influence of geography as a determinant is important for future research (4)” has been removed from Discussion, lines 283-284, page 15.

3. In the discussion on line 302, "be to be" appears to be a typographical error.

Thank you, the word “be” has been removed and is now in Discussion, line 309, page 16.

4. In the discussion, the paragraph on vitamin D does not seem relevant to the paper.

The paragraph on vitamin D has been removed from Discussion, lines 306-314 on page 16 of the initial submitted manuscript.

5. A limitations paragraph should be added to the discussion. It should mention the reliance on administrative codes to define RA incidence and prevalence cases, instead of classification criteria. It should also mention that estimates form this population may not be generalizable to other populations.
A limitations paragraph has been added to Discussion, lines 314-322, pages 16 and 17.

Administrative health databases are valuable for epidemiological studies as they contain a large amount of data that has been systematically collected for a population over a period of time. However these health databases were not designed for the intent of research. We do acknowledge that a limitation of this study is the reliance on a case definition of RA using administrative health database codes rather than using the clinical and serological classification criteria which may cause either overestimation or underestimation of the disease. Thus the estimates of incidence and prevalence that we found for the province of Saskatchewan may not be able to be generalized to other populations.

6. In the figures, the color used for the age 75+ years group does not show up at all when printed in black/white. Perhaps adding different line styles will make this easier for those who may not have color printers.

The format of the figures have been changed as per the suggestion from differing colors to differing black line styles used to characterize specific groups.

Reviewer 2

In the abstract and the Conclusions, the authors state that there was no difference between age adjusted trends in prevalence and incidence for men and women. However, no data on such a comparison are presented.

The sentence has been changed from “While women had higher incidence and prevalence rates compared to men, there was no difference in overall trends of the age adjusted rates for both groups” to “Women were found to have higher incidence and prevalence rates compared to men” in Abstract, lines 53-54, page 2. The sentence “There was no difference between the age adjusted trends for men and women, though women had overall higher incidence and prevalence rates for RA” now reads “Women had overall higher incidence and prevalence rates for RA compared to men” in Discussion, lines 326-327, page 17.

There was an extreme incidence peak in FY1213. Could this be artificial, and due to factors related to reporting to the database? It is difficult to imagine a biologic reason for this pattern. I would be very hesitant to list a "recent peak in the incidence" as a major conclusion of the study.
The sentence “In Saskatchewan, the overall prevalence of RA is rising while there has been a recent peak in the incidence” is now “In Saskatchewan, the overall prevalence of RA is rising while there has been variability in the incidence” in Abstract, lines 55-56, page 3. We agree it is unlikely a biologic reason and suggest a possibility for this finding: “The periods of heightened incidence may also relate to times when new rheumatologists started their practice in the province and with resulting improvement of patient access to rheumatology subspecialty care. However the Saskatchewan Provincial Health Databases do not distinguish submission of claims by rheumatologists from other internal medicine specialists and therefore we would be unable to determine if the incidence changes relate to difference of case entry over time by different specialties or subspecialties” in Discussion, lines 297-303, page 16. The sentence “In conclusion, we observed that in Saskatchewan, the prevalence of RA is rising and in recent years, there has been an increased incidence of RA during the period from 2011 to 2013” has been changed to “In conclusion, we observed that in Saskatchewan, the prevalence of RA is rising and there has been variability in the incidence of RA” in Conclusions, lines 325-326, page 17.

The authors suggest that the increasing prevalence may be expected in an aging population. However, if the prevalence rates were adjusted for age, how could increased longevity overall be the explanation? By contrast, a reduced rate of premature mortality related to RA could explain the pattern. This should be discussed.

We are currently performing the analysis on mortality rates in this population and since that information is not available yet, we felt it best to remove the statement “The increasing prevalence may be an expected outcome of an aging population” from Discussion, lines 273-274, page 15 of initial submitted manuscript. The sentence “Factors associated with these results may be due to the growing awareness of the need to identify and treat RA cases early in the disease as well as an aging population” is changed to “Factors associated with these results may be due to the growing awareness of the need to identify and treat RA cases early in the disease” from Conclusions, line 327 - 329, page 17.

It is not obvious how changes in treatment strategies for RA would contribute to an increasing prevalence. Do the authors mean that RA is more likely to be recognized and registered in Health Databases because efficient interventions are available? This should be clarified.

The statement “The Treat-to-Target approach has resulted in increased awareness of the importance of early diagnosis and treatment of rheumatoid arthritis to improve clinical outcomes (1) which may contribute to heightened recognition of the disease and need for longitudinal management” in Discussion, lines 277-280, page 15.
It is not clear to this reviewer how limited access to health care in remote areas would explain the observed patterns, unless access may have improved recently, contributing to increased incidence and prevalence.

The statement “In Saskatchewan, rural and remote patients with RA have reported concerns with initial access to health care so the influence of geography as a determinant is important for future research (4)” has been removed from Discussion, lines 280-282, page 15 of the initial submitted manuscript.

Furthermore, it is unclear how vitamin D deficiency is relevant, unless there are data indicating temporal trends in such deficiency.

The paragraph “Vitamin D is a fat soluble vitamin and its role as an immunomodulator has been a source of interest, particularly in regards to the risk of developing RA. Vitamin D deficiency has been demonstrated to be found frequently in North American women (27). In a retrospective study of a Saskatchewan rheumatology outpatient clinic, inadequate vitamin D levels have also been shown to occur in individuals with systemic autoimmune rheumatic disease (28). Vitamin D receptor polymorphisms have been associated with the development of RA and certain receptor polymorphism have also been shown to occur in a Canadian First Nations group (29). These findings contribute to the consideration of Vitamin D’s role in regards to the risk for RA” has been removed from Discussion, lines 306-314, page 16 of the initial submitted manuscript.

The population of Saskatchewan is reported twice - avoid repetition

The sentence “Saskatchewan is one of three Prairie Provinces in Canada, with a population of 1,132,300 in 2015 (15)” is changed to “Saskatchewan is one of three Prairie Provinces in Western Canada” in Methods, line 104, page 5.

Incidence rates in the abstract should be presented per person-years at risk, rather than as %.

The lines ‘The incidence of RA disease demonstrated variation within the study period, ranging from 0.07% to 0.03%. The prevalence of RA increased over time from 0.5% in 2001-2002 to 0.7% in 2014-2015’ has been changed to ‘The incidence of RA disease demonstrated variation within the study period with age and sex adjusted incidence ranging from 33.6 (95% CI 29.9 – 37.6) per 100 000 to 73.1 (95% CI 67.6 – 79.0) per 100 000. The prevalence of RA increased over time from 482 (95% CI 466.7 – 497.7) per 100 000 in 2001-2002 to 683.4 (95 % CI 666.6 – 700.6) per 100 000 in 2014-2015’ in the Abstract, lines 48-52, page 2.
Incident cases and prevalent cases are preferred expressions, rather than “incidence cases”.

The changes are made for the headings in Table 2 in Results, page 14.

Thank you again for your consideration of this manuscript. Please let me know if there are any questions or concerns.

Sincerely yours,

B. Nair, MD, MSc, FRCPC