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Disparities in rheumatoid arthritis outcomes for North American Indigenous populations

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ABSTRACT

Advances in rheumatoid arthritis (RA) management have significantly improved clinical outcomes of this disease; however, some Indigenous North Americans (INA) with RA have not achieved the high rates of treatment success observed in other populations. We review factors contributing to poor long-term outcomes for INA with RA. We conducted a narrative review of studies evaluating RA in INA supplemented with regional administrative health and clinical cohort data on clinical outcomes and health care utilisation. We discuss factors related to conducting research in INA populations including studies of RA prevention. NA with RA have a high burden of genetic and environmental predisposing risk factors that may impact disease phenotype, delayed or limited access to rheumatology care and advanced therapy. These factors may contribute to the observed increased rates of persistent synovitis, premature end-stage joint damage and mortality. Novel models of care delivery that are culturally sensitive and address challenges associated with providing speciality care to patients residing in remote communities with limited accessibility are needed. Progress in establishing respectful research partnerships with INA communities has created a foundation for ongoing initiatives to address care gaps including those aimed at RA prevention. This review highlights some of the challenges of diagnosing, treating, and ultimately perhaps preventing, RA in INA populations.

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Why study rheumatoid arthritis in first nations people

Rheumatoid arthritis (RA) is a prevalent, immune-mediated, inflammatory disorder affecting 0.5–1% of most populations worldwide. Synovial joints are the primary target organ for this autoimmune disease, and the chronic inflammatory/proliferative process that is established in the synovium of multiple joints results in progressive joint damage and functional loss, if not treated early and effectively [1]. Over the past several decades, through productive collaborations between clinicians, basic scientists, and the pharmaceutical industry, enormous progress has been made in the diagnosis and treatment of RA, where early and sustained remission is now the expected outcome, albeit typically still requiring ongoing pharmacologic therapy. Yet these unprecedented medical successes which have been achieved in a substantial number of RA patients worldwide have not been achieved in all populations, and indeed specific groups continue to experience an excessive burden of the unfavourable outcomes, which were all too prevalent in previous decades. One such population is Indigenous North Americans (INA) a group that includes First Nations (FN), Metis and Inuit peoples [2]. As such, this paper addresses the challenges of diagnosing, treating, and ultimately perhaps preventing, RA in INA populations. These challenges are common to many Indigenous populations, including those of the Circumpolar Region, who are disproportionately affected by preventable chronic diseases [3]. Circumpolar and non-circumpolar Indigenous populations share a need for improved models of health care delivery and evaluation that are culturally sensitive, incorporate the voiced values of Indigenous people [4] and are supported by effective governance structures.

Methods

We conducted a narrative scoping review of studies evaluating RA in North American INA and discuss

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factors related to conducting research in INA populations including studies of RA prevention. We supplemented this review of published work with additional findings from regional administrative health data and data from our clinical cohorts to further describe clinical outcomes and health care access for INA populations. Most of the discussion we present is based on our own work with the Cree, Ojibway and Ojicree People of Central Canada, and to some extent the Tlingit People of Alaska.

Administrative Health Data: Universal health care coverage is provided for 98% of the Manitoba population (approximately 1.2 million). The Manitoba Population Research Data Repository (MPRDR) containing deidentified health claims data was linked to the Canadian Federal Indian Registry file which tracks individuals with INA status. The MPRDR data includes records for nearly all health services used, including date of service, medical provider, diagnosis, vital statistics including date and cause of death, and region of residence (postal code) from 1984 onward. Diagnoses are recorded using the International Classification of Disease (ICD)-9-CM or ICD-10-CA codes. We accessed health records from 1 April 1995 to 31 March 2010. We identified INA in the administrative health data using the Federal Indian Registry File as previously described [5–7]. We identified RA cases using a validated case definition [8]. Age group at first visit (or onset for incident RA) was categorised as 0–18 years, 19–28 years, 29–38 years, 39–48 years, 49–58 years 59–68 years and >69 years. Socioeconomic status was estimated using income quintiles reported separately for urban and rural residence (quintile 1 lowest income, quintile 5 highest income). Income quintiles were based on dissemination area (DA)-level average household income values from public-use census files and postal codes [9]. Comorbidity was determined using a modification of the Charlson Comorbidity Index (mCCI) with scores categorised as 0, 1, 2, 3 or more [10,11]. The presence of any major physical and psychiatric comorbidity was determined using the John Hopkins mental and physical Aggregated Diagnosis Groups® (mADG®, pADG®) [12]. Death, age at death and cause of death (categorised as circulatory, respiratory, infectious, cancer, other) were identified in the prevalent RA cohort. Duration of RA at death was determined for incident RA. Crude all-cause mortality rates for prevalent RA were modelled over time using Poisson regression adjusted to age and sex or to age, sex and last visit mCCI. Differences in comorbidity between groups are reported as odds ratios (OR) with 95% confidence intervals (CI). Age of death and RA disease duration at death were compared between INA and non-INA using Student's t-tests. Cox proportional hazards models evaluated contributors to death in prevalent RA controlling for age, sex, ethnic group, income quintile, and comorbidity (mCCI or ADG) and reported with OR and 95% CI. Administrative data management, programming and analyses were performed using SAS®. See supplemental data files for details of administrative data definitions (supplementary Table S1), and cohorts (supplementary Table S2).

Clinical cohort data: Our clinic has maintained a database since 1990 that includes records for over 10,000 patients and data on diagnoses, demographics, year of disease onset, clinic visit date, and self-reported ethnicity. At each visit, patients completed a modified health assessment score (mHAQ), disease activity visual analogue scales (VAS), and physicians completed joint counts, global VAS, and updated current RA treatment. Comparisons between groups were reported using chi-square tests, Student T tests or Mann–Whitney U tests as indicated and performed using SPSS.

The studies were approved by the local institutional ethics board, the Manitoba Centre for Health Policy, the Heath Information Research Governance Committee (HIRGC) and the Assembly of Manitoba Chiefs (now the First Nations Health and Social Secretariat of Manitoba (FNHSSM))

Prevalence of RA in INA

It is important to point out that the excessive burden of RA, and its unfavourable outcomes, is not universally observed in all INA populations [13,14]. Indeed, this does not seem to be a problem directly related to "indigeneity" itself, as the prevalence of RA differs considerably across multiple INA populations. For example, coastal tribes such as the Haida nations in Canada, and the circumpolar Inuit People have a relatively modest prevalence of RA, which is roughly comparable to most other non-INA populations worldwide [15]. In contrast, INA populations such the Cree/Ojibway First Nations People of Canada, the Pima and Chippewa People of the central US regions, and the Tlingit People of Alaska have an estimated RA prevalence of 2–3%, which are some of the highest worldwide [16–18]. There is a paucity of RA epidemiology data from other circumpolar regions [15]. Thus, as we discuss the challenges of addressing RA in INA, it is important to recognise these geographic differences, which are likely related to complex and unique interactions between genetic, environmental, sociological, and healthcare delivery factors.

Genetic and environmental factors for RA in INA

We examined genetic risk factors for RA in our INA study populations in Central Canada and Alaska [19,20]. Although our study cohorts lacked sufficient power to undertake comprehensive analyses such as genome-wide association studies (GWAS), we found that many of the risk loci identified in other populations were also contributing to the risk of RA in INA [20]. Of these, it is now well established that the strongest genetic risk factor for RA resides in the HLA-DRB1 locus, and the shared epitope (SE) hypothesis remains the best unifying concept for this risk [21]. Amino acids in positions 11 and 13 in the base of this groove also play a key role in disease predisposition [22]. As such, we and others have shown that the primary genetic RA risk factor in INA is HLA-DRB1*1402 (1402), an allele that encodes for SE, and is unique to INA populations [19]. After resolving the crystal structure of 1402, we found that in contrast to other SE alleles such 0401 which readily accommodates citrullinated peptides in its antigen binding P4 pocket, but poorly accommodates the arginine version of the same peptides, 1402 could accommodate both the citrulline and arginine versions of the same peptide by orienting them in opposite directions. These unique antigen presenting properties of 1402 are of unclear significance, although we showed that this allele is strongly associated with the presence of ACPA. The fact that 1402 has a high background frequency in a wide spectrum of INA populations, it can be speculated that it has afforded INA a survival advantage, possibly related to effective immune responses to specific pathogens, but the price of this survival advantage is an increased risk of developing ACPA positive RA.

The evaluation and attribution of specific environmental factors to the risk of developing a multifactorial chronic disease such as RA is a notoriously difficult task. To date, tobacco smoking has been shown to be a key RA risk factor in multiple populations. As an excellent example of gene–environment interactions, smoking is a RA risk factor that is strongly associated with the presence of SE encoding HLA-DRB1 alleles [23]. As such, our Cree, Ojibwe and Oji-Cree INA study population, which is characterised by a high background frequency of predisposing SE alleles, unfortunately, also has a high frequency of smoking [24,25]. In parallel, we explored the role of other environmental factors potentially impacting on RA risk, such as the high prevalence of periodontal disease in the INA population, although the link between this and RA remains unclear [26,27]. Together, these factors are the ingredients of a "perfect storm" for RA development, and likely severity.

Clinical characteristics of RA in INA

Using our own clinical cohorts and administrative datasets available through Manitoba's universal healthcare system, we addressed this question systematically in studies comparing RA in the Manitoba INA population to that seen in the non-INA population. In the context of these studies, we have demonstrated that in addition to the substantially higher RA prevalence previously alluded to, the age of onset is approximately 10 years younger in INA compared to non-NA, with a typical onset in the late-30s for INA [16]. Similar observations regarding the young age of RA onset have been made in other INA populations [13]. This young age of onset would clearly result in a substantial increase in the lifelong burden of the disease, and the accrual of complications.

The sex distribution for RA seems to be similar for Indigenous and non-Indigenous people, with 2–3 times more women than men affected. This female preponderance suggests that hormonal factors play a role in RA development, although the mechanisms are unclear. Furthermore, the improvement in RA symptoms that many women experience during pregnancy and the tendency for symptoms to flare in the postpartum period have led to speculation that pregnancy may influence the risk of developing RA.

Younger age of onset of RA in Indigenous peoples increases the potential influence of RA on fertility and pregnancy. Age at first pregnancy is much younger in Indigenous compared to non-Indigenous women, with approximately 25% of Indigenous women giving birth before age 20, compared to 6% of non-Indigenous Canadian women [28,29]. Thus, the influence of pregnancy on the risk of RA may be significantly different between the two populations.

An additional important issue relates to the potential effect of multiple pregnancies on the risk of developing RA. We had previously studied the effect of pregnancy on the risk of RA in Indigenous women by comparing women enrolled in two cohort studies [30]. In one study, patients with RA were recruited from a Cree and Ojibway population in Central Canada, and the control group included unaffected 1st or 2nd degree relatives of the RA probands. In the second study, Indigenous RA patients were enrolled along with healthy unrelated Indigenous controls without a personal or family history of RA. A total of 168 Indigenous RA patients and 400 Indigenous controls were included in the study. In a multivariate analysis,

after adjusting for age, smoking status, education and age at menarche, women who had ≥6 births had an OR of 0.43 (95% CI 0.21–0.87) for developing RA compared with women who had 1–2 births; while women who gave birth for the first time after age 20 had an OR of 0.33 (95% CI 0.16–0.66) for developing RA compared with women whose first birth occurred at age 17 or younger. As found in other studies, the odds of developing RA in the first postpartum year were significantly higher than in subsequent years (OR 3.8; 95% CI 1.45–9.93). The complex paradigm of high risk of RA, higher fertility rates, early first births and early RA onset emphasise the need for culturally safe reproductive healthcare for Indigenous women who have RA.

The INA RA clinical and serological phenotype

A key question that arises as we begin to address the potential factors contributing to unfavourable outcomes for RA in INA People is *whether we are dealing with the same disease as that which is seen in White and other non-INA populations*. We sought to determine whether the clinical phenotype of RA differed between INA and non-INA [24]. A key observation is that almost all (>90%) of the clinically classifiable RA in our INA patient population is seropositive for both ACPA and RF. This contrasts starkly with most White RA patient cohorts, where approximately 30% are typically classified as seronegative (at least for ACPA and RF). Seropositive RA is generally regarded as being more severe than seronegative disease, with a higher risk for progressive joint erosions and extraarticular manifestations such as nodulosis and vasculitis. Having said this, it is now well established that the risk of these complications is substantially mitigated by timely and effective therapy for the disease, and early induction of sustained remission.

In addition to the high prevalence of ACPA, RF, and other RA-associated autoantibodies in the INA RA patients, we have also observed a concurrent high prevalence of antinuclear antibodies (ANA) in these patients [24]. The significance of this to the clinical RA phenotype remains unclear, although our anecdotal observations suggest that a proportion of INA patients with classifiable RA do exhibit "overlap" clinical features that are typically seen in other autoimmune diseases such as SLE and scleroderma. We recently demonstrated a high prevalence of ANAs in a longitudinal cohort of the first-degree relatives (FDR) of INA RA patients. Interestingly, despite this high prevalence, in those individuals who ultimately developed seropositive RA, there was a progressive expansion of the ACPA and RF autoantibodies, but not the ANAs [31]. These observations may point to unique immunoregulatory factors that broadly predispose this population to autoreactivity, while other factors determine the specificity of this autoreactivity, and in turn, the clinical manifestations.

Of particular relevance to the unfavourable outcomes of RA in INA is the observation that, compared to White RA patients, there is a substantially higher frequency of large joint involvement, particularly the knees, elbows, shoulders and hips [24]. The impact of inflammation and progressive damage to these large joints on functional capacity is substantial. We showed a strong correlation between the Lansbury articular index [32], which is weighted for joint size, and the modified Health Assessment Questionnaire (HAQ), a widely accepted measure of function. Moreover, and perhaps not unexpectedly, active inflammation in these large joints was also highly correlated with systemic measures of inflammation such as CRP. Together, these observations suggest that the distribution of affected joints in our population of INA RA patients may play a substantial role in determining unfavourable outcomes such as persistent inflammation, functional loss and severe joint damage in this disease.

Healthcare delivery challenges in INA

While biological differences in RA in INA may account for some of this difference in phenotypes, access to and utilisation of primary and speciality care likely plays a larger role in the era of modern therapeutics to clinical outcomes. This is due to a combination of patient-specific and system factors, some of which are not unique to INA and affect other Indigenous and circumpolar populations [3,33]. The historical and ongoing effects of colonisation on INA individuals and families lead to increased rates of low socioeconomic status, geographic isolation, disrupted families and mental health issues including suicidality [34]. These latter factors undoubtedly contribute to lower treatment adherence, particularly among younger patients. System issues include geographic isolation with insufficient and inconsistent primary care that is often not sensitive to the specific issues facing INA patients. This contributes to a lack of trust in the health care system and compounds adherence issues. Travel to specialist appointments is often complicated, may be affected by weather, and not infrequently can require 2–3 days of commitment. INA patients have identified opportunities to enhance rheumatology care delivery that include improved communication between patients and providers that respects patient preferences and cultural practices, greater continuity of care provision to facilitate

and foster mutual relation-building, and increased community education and supports [35]. Outreach clinics that bring RA care closer to the patient and telemedicine are two approaches that can overcome some of these issues. Outreach clinics need to be consistent to establish trust and providers need to provide care remotely between visits if required. Telemedicine has some limitations in assessing disease activity but overall can decrease the need for travel without significant difference in outcome or quality measures [36].

These health care delivery challenges contribute to disparities in general health care and speciality care access for INA in Manitoba [12,37]. To evaluate disparities in health care access between INA and non-INA with RA in Manitoba, we used administrative health records that included 8095 people with RA (1095 INA; 7000 non-INA). We observed that INA with RA had overall more physician visits but fewer rheumatology visits yearly when compared to non-INA with RA (Table 1). Similarly, within our rheumatology clinics, INA with RA were seen less frequently than non-INA with RA (months between clinic visits mean (SD) 8.9 (9.8) vs 7.3 (9.5) $p < 0.001$), and were more likely to be lost to follow-up defined as having more than 12 months between appointments (INA 53% vs non-INA 42% X^2 45 $p < 0.001$). High rates of non-attended appointments also occurred in community outreach clinics (246 missed visits/398 scheduled visits (62%) across three established clinics over 1 year). This observed disparity in attending rheumatology visits indicates that despite having severe RA, INA patients had less access to rheumatologists than non-INA patients. This may contribute to suboptimal disease management.

Limited access to speciality rheumatology care is reflected in differences in RA treatment patterns for INA. Using the same administrative health data from people with diagnosed RA, we observed that compared to non-INA, INA used more steroids, more conventional DMARDs particularly those normally reserved for severe extra-articular manifestations, more combination conventional DMARD use, however, INA used fewer biologics, which at the time of analysis were mainly anti-TNFs and could only be prescribed by rheumatologists. INA also had more interrupted treatment courses (57% vs 37%) Table 1 [38]. Similar findings were observed for 304 RA patients (150 INA and 154 non-INA) followed in our clinic. These INA used more DMARDs over their disease course (5.1 ± 3.2 vs 3.7 ± 2.5; $p < 0.001$), had longer treatment gaps (36 months ±30 vs 25 months ±40; $p = 0.009$), and received more frequent intramuscular steroid injections for flares (21% of INA received 3–5 IMs vs. 12% of non-INA, and 11% received ≥6 IMs vs 3% of non-INA; $p < 0.001$) Table 2 [39]. The observed disparities in RA treatment patterns highlight challenges with consistent access to RA DMARDs for INA and a greater reliance on steroids which are usually reserved for disease flares or disease not controlled by optimal conventional and advanced therapies.

These observed disparities in accessing rheumatology care and treatment may also be due to a greater burden of general health problems that are prioritised over RA care and complicate treatment decisions. Our population-based observations of people with diagnosed RA showed that INA had more comorbidity than non-INA [modified Charlson comorbidity score >0 INA 53% vs non-INA 46% RR 1.4 (1.2,1.5) $p < 0.0001$] and importantly, were more likely to have psychiatric

Table 1. Physician visits and treatment gaps using provincial administrative health records data from January 1990 to December 2010.

	INA (N = 1095)	Non-INA (N = 7000)	RR (p value)[1]
Physician visits- prevalent RA			
All physician visits	109.5 (104.9–114.1)	98.64 (97.21–100.1)	p < 0.0001
Non-specialist visits	86.7 (82.5–91.0)	67.2(66.1–68.3)	p < 0.0001
Rheumatology visits	6.9 (6.4–7.4)	8.2 (8.0–8.4)	p < 0.0001
Treatment pattern – incident RA	INA (N = 566)	Non-INA (N = 3593)	
Corticosteroids – ever	76%	65%	1.2 (p < 0.0001)
DMARDs – ever	74%	65%	1.12 (p < 0.003)
Months to start[2]	8 (6.7–9.5)	6.5 (6–7)	p < 0.03
Duration of use (mean month)[2]	21(22)	25(24)	p < 0.01
Proportion of RA duration on drug[3]	34%	41%	p < 0.0001
Biologics – ever	12%	14%	p = 0.09 NS
Months to start[2]	48 (39–57)	36 (33–38)	p = 0.005
Duration of use (mean month)[2]	17(16)	22(19)	NS
Proportion of RA duration on drug[3]	22%	32%	p = 0.01
Treatment gaps – ever	57%	37%	1.5 (p < 0.0001)

[1]Comparisons between FN and non-FN are reported as rate ratios (RR) with 95% confidence intervals (CI).
[2]Only for incident RA starting drug, mean months (95%CL).
[3]Only for incident RA, mean proportion of disease duration on drug, time to intervention mean days (CI mean), adj = time to intervention adjusted for proportion of time on drug adjusted for modified Charlson comorbidity index.

Table 2. Physician visits and treatment for RA patients followed in the rheumatology clinic. Data are from patients with >1 year and <15 years of disease and serial visits prior to 2015. INA = Indigenous North Americans (Cree, Ojibway and Ojicree people), SD = standard deviation.

	INA (N = 150)	White (N = 154)	*p*
RA disease duration in years (SD)	8 ± 5	9 ± 4 vs years	ns
Female sex (%)	85	79	ns
Time to first DMARD (months), mean ± SD	19.2 ± 26.4	15.3 ± 35.0	ns
Number of DMARD courses, mean ± SD	4.9 ± 2.9	3.6 ± 2.3	<0.001
Months on DMARD, mean ± SD	65.9 ± 43.7	77.6 ± 48.7	0.03
Months off DMARD/Year of disease, mean ± SD	4.6 ± 3.0	3.5 ± 3.0	0.019
Proportion on biologic (ever)	35%	33%	ns
Time to first biologic (months), mean ± SD	57.0 ± 34.5	45.7 ± 44.8	ns
Intramuscular methylprednisolone use (ever)	71%	48%	<0.001
Visits per year	1.6 ± 0.7	1.9 ± 0.5	0.007
Visits missed per year	0.15 ± 0.33	0.04 ± 0.10	<0.001
Distance travelled to clinic (average kilometres)	408 km	73	<0.001

comorbidity (INA 27% vs non-INA 22% RR 1.3 (CI 1.1–1.5) p = 0.0005) (Supplementary Table S2). These population-based estimates likely underestimate the prevalence of clinically significant but undiagnosed mental disease. Psychiatric comorbidity is common in RA and is associated with worse RA clinical outcomes and increased mortality [40–43]. The association of mental health and RA mortality is especially relevant for INA and is potentially amplified by poor socioeconomic status and disparate access to rheumatology care [7].

Are the long-term outcomes of RA unfavourable in INA?

Considering this complex array of biological, sociological, and healthcare delivery considerations, it is important to ask the question: *are the outcomes of RA more unfavourable than those of other populations?* Using clinical data collected from our RA patients over 20 years we have demonstrated worse short-term and long-term outcomes for INA with RA compared to our non-INA patients with RA. Remission rates after 1 year of follow-up were lower for INA than for non-INA patients for both recent onset RA treated within 1 year of symptom onset (proportion in DAS28 remission INA 12% vs non-INA 59% Chi^2 19 p < 0.0001) and for those presenting to the clinic later in their disease course (p < 0.001) [44]. Similar findings have been demonstrated in a multicenter Canadian Early Arthritis cohort [45]. In this national cohort, INA participants (who comprised 5% of the studied cohort) had more poor prognostic indicators at baseline and despite similar baseline disease activity and treatment patterns, were less likely than non-INA to achieve disease remission. Persistent disease activity was partly driven by slower resolution of large joint synovitis and persistent poor patient global scores. Even with the use of advanced therapies and biologics, INA appear to have lower remission rates and more complications [46].

The propensity for persistent synovitis of large joints increases the risk of early end-stage joint damage needing joint replacement surgery. We confirmed this using population-based administrative health data from 4159 people with incident RA (566 INA; 1095 non-INA) seen between 1996 and 2010. Joint replacement surgeries were performed earlier for INA compared to non-INA even after adjusting for treatment [(days to surgery (95% CI) INA vs non-INA and rate ratio for hip replacement 872 (853, 892) vs 1072 (1066, 1078), ratio 0.81 (0.79, 0.83) p < 0.0001; for knee replacement (1424 (1409, 1440) vs 1228 (1222, 1233), ratio 1.2 (1.19, 1.21) p < 0.0001; and for shoulder replacement 734 (697, 774) vs 1248 (1223, 1273), ratio 0.59 (0.56, 0.62) p < 0.0001)]. Although we did not see major differences in overall rates of arthroplasty surgery in INA with RA compared to non-INA with RA, a recent systematic review demonstrated lower rates of elective surgeries, including arthroplasty surgery, and more post-operative complications for INA compared to non-INA, though data were not specific for RA [47]. Overall hospitalisation rates are higher for INA than for non-INA in general [37]. Data from Alaska found INA were three times more likely than non-INA to be hospitalised for RA (odds ratio 3.45 (3.12–3.82)) and had longer hospital stays [48].

Unfortunately, INA continue to have excess and premature mortality compared to non-INA as do INA with RA compared to non-INA with RA [37,49]. In our region, annual mortality rate ratios between 1990 and 2010 were elevated for INA compared to non-INA with and without RA. Even after adjusting for age, sex and comorbidity, INA with RA were 3× more likely to have died and were on average 20 years younger at the time of death (incident RA INA age of death 53 years (46,60) versus non-INA 76 years (46,60)) (age ratio 0.70; (0.66, 0.75) p < 0.0001) (Figure 1). While the most common

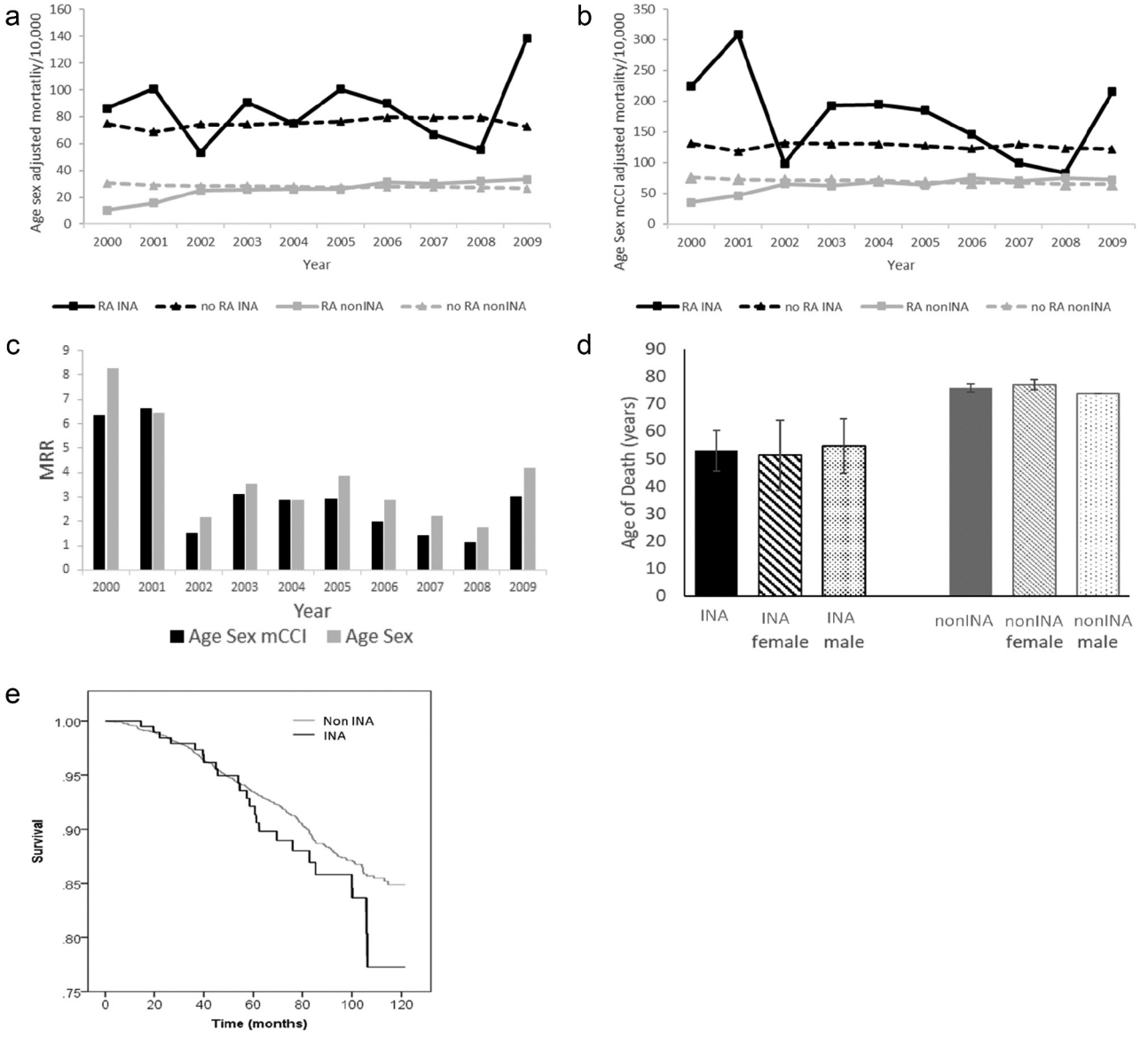

Figure 1. Mortality in Indigenous North Americans and non-Indigenous North Americans with or without rheumatoid arthritis in provincial administrative health records data from January 1990 to December 2010. a) Age and sex-adjusted mortality; b) age sex and mCCI-adjusted mortality; c) mortality rate ratio (MRR) for RA comparing Indigenous North Americans (INA) versus non-Indigenous North Americans (nonINA). d) Age at death for incident rheumatoid arthritis. e) Survival curve (for incident RA). RA = rheumatoid arthritis; mCCI = modified Charlson comorbidity index (modified for use with Manitoba administrative data); INA = Indigenous North Americans; nonINA = non-Indigenous North Americans. Black bars mortality rate ratio adjusted for age, sex and mCCI. Grey bars mortality rate adjusted for age and sex.

cause of death was from circulatory causes for both INA and non-INA (28% of deaths; INA 19% versus non-INA 29%, RR 0.63 (0.4, 1.03) p = 0.06), and rates of death due to respiratory causes (13% of deaths; INA 18% versus non-INA 12%, RR 1.46 (0.88,2.43) p = 0.15) and infection (3% of deaths; RR 2.3 (0.87,6.08) p = 0.09) were similar, INA were less likely to die from malignancy (21% of deaths; INA 10% versus non-INA 22%; RR 0.46 (0.25,0.87) p = 0.02) and more likely to die from other causes (45% of deaths, INA 52% versus non-INA 33%; RR 1.43 (1.05,1.95); p = 0.02). In addition to sex, age and socioeconomic status, the presence of a diagnosed major physical comorbid condition increased the risk of death by 64%, whereas the presence of a mental health comorbid condition increased the risk of death by 56% (Table 3).

Looking forward: development of a RA prevention research agenda for INA

Based on the important considerations discussed above, we propose that the development of an

Table 3. Low socioeconomic state and both physical and mental comorbidity at RA onset contribute to excess mortality in RA in provincial administrative health records data from January 1990 to December 2010.

Variable	Hazzard ratio	95% CI	P value
INA	1.3	0.8–2.1	0.26
Male sex	1.3	1.0–1.6	0.04
Age group (years)	ref	ref	-0.67
<18	1.7	0.2–18.6	0.47
19–28	2,2	0.3–18.3	0.24
29–38	3.3	0.4–25.2	0.04
39–48	7.8	1.1–56.9	0.005
49–58	16.8	2.3–121.9	<0.0001
59–68	52.6	7.3–377.3	
>69			
Income quintile[1]	1.8	1.2–2.0	0.004
Q1	1.3	0.88–1.99	0.18
Q2	1.4	0.92–2.1	0.11
Q3	1.2	0.77–1.83	0.43
Q4	ref	ref	-
Q5			
Comorbidity onset[2]	1.64	1.29–2.08	0.001
Physical ADG	1.56	1.19–2.04	0.004
Mental ADG			

[1]Income quintile based on dissemination area level average household income values from public-use census files and postal codes. Higher quintile represents higher income [9].
[2]ADG = Aggregated Diagnosis Groups® (mental ADG®, physical ADG ®) created using the John Hopkins ACG® Case-Mix System Version 8. The mADG and pADG have been previously used in the Manitoba Provincial Registry Database [12].

effective, cost-effective, culturally acceptable, ethical, prevention strategy for RA in INA has the potential to substantially impact on the unfavourable outcomes we have documented. As such, we have participated in a major international consortium focused on a research agenda aiming to develop such prevention strategies for RA [50]. In developing a RA prevention research strategy that is appropriate and specific for INA people, there are key considerations relating both to the conduct of research in general, and to unique aspects that are specific to RA prevention research.

Indigenous people have been exploited and harmed through their involvement in research to the point where there has been a collective resistance to research through multiple generations of Indigenous peoples [51–55]. Over the past 30 years, with an increasing number of Indigenous scholars, an incredible amount of work has gone into the design and implementation of research ethics guidelines and frameworks for research involving Indigenous peoples [53,54]. This has resulted in a major shift in ways of doing research. No longer can researchers make decisions in the absence of consultation, discussion, negotiation, and agreement with Indigenous individuals, communities and nations involved in the research. The focus now is on building meaningful research relationships that address power imbalances within research and honour Indigenous knowledge.

The importance of research agreements

The recognition and implementation of agreements for respectful, Indigenous-led research relationships has been central to this evolvement of research practice. We now commonly see terms such as research agreements, community agreements, sharing agreements, and partnership agreements with the understanding that the collaboration of research partners and the establishment of agreements between partners comes first before any research decisions are finalised by the researcher. While it is important to note that each community and nation is unique and carries their own needs and desires, the baseline of establishing respectful, meaningful, and beneficial to community research partnerships is central to the notion of Indigenous research ethics [51].

Several frameworks, guidelines, and protocols for Indigenous research discuss the importance of, and the processes for, the development and signing of formal research agreements [52]. The signing of research agreements is often seen as the foundation for the establishment of collaborative and respectful researcher partnerships between academic researchers and Indigenous peoples and communities. As an example of an agreement, Alcock et al. [54] note that "an MOU (Memorandum of Understanding) is both a process and a tool for collaborative research. It is an active, living document used between research partners to develop,

discuss and physically outline the ethical, moral and practical guidelines and protocols that will be used throughout the research project". The establishment of research agreements signifies a commitment to moving away from colonial-based research practices and towards research practices that honour and value Indigenous peoples, knowledge, and ways of understanding the world [54]. It is a practice towards the reclamation of the power of Indigenous knowledge, where Indigenous knowledge is seen as valid and the explanation of phenomena through an Indigenous worldview becomes desirable. Through research agreements, Indigenous partners hold power to make research decisions, control more aspects of the research, and advocate for outcomes that are meaningful and beneficial to Indigenous peoples, communities and nations [52,54].

Positive outcomes of respectful research partnership and agreements

The benefits of collaborative research partnerships extend far beyond the ability to conduct and complete research. Research structured around ethical guidelines for research involving Indigenous peoples promotes the development of trust and cooperation between research partners, mutual learning and capacity-building opportunities for all partners, increased ability to understand and meet the needs of Indigenous peoples involved in the research, and the achievement of relevant and meaningful outcomes for Indigenous peoples [51,53,54].

RA prevention in INA

The stage prior to the onset of RA, termed pre-clinical RA, has revolutionised our understanding of how RA begins from a clinically quiescent state. Autoantibodies such as ACPA develop during this time, typically years before disease onset. These biomarkers are highly predictive for the development of future RA in both INA and non-INA populations [25,56] Strategies to identify individuals who are most likely to benefit from RA prevention strategies continue to evolve; and in turn, the initiation of several international clinical trials to delay or prevent the onset of RA is being completed [56,57]. This represents an exciting and entirely new field of rheumatic disease research. Despite this momentum, prevention trials have not been undertaken in communities facing health disparities, though from the view of a risk-benefit profile, prevention of chronic diseases is most beneficial in populations facing challenges with access to care and higher prevalence of disease. Importantly, the lifetime health care cost of an RA patient continues to increase, particularly due to more expensive targeted treatments [58], although these cost calculations have not been performed specifically in INA populations. Despite these potential benefits, RA prevention also poses a new set of challenges for physicians and researchers, all of which need to be considered for INA populations.

Recruitment has become a major endeavour for prevention studies, with the goal of identifying participants that are most likely to benefit from preventative interventions [59]. A multi-pronged approach to find participants typically involves finding individuals with RA autoantibodies, with or without joint pain. Recruitment is thus undertaken by screening First-Degree Relatives of RA patients or community-wide antibody testing. Some participants may be identified by primary care physicians or be directly recruited from longitudinal studies of at-risk. The remote location of many INA communities creates a major barrier for screening, given the challenges associated with acquiring, shipping and storing biospecimens such as serum. To further complicate recruitment, INA and other minority groups have a higher prevalence of other chronic conditions such as diabetes and cardiovascular disease [60]. This impacts on eligibility to safely enrol into a clinical trial, and the inclusion/exclusion criteria need to be carefully evaluated by weighing safety and generalisability. Remote location also increases the burden on study participants if they must travel for study visits. This raises the possibility that study visits may be conducted within remote communities, which could reduce study burden and enhance enrolment. However, isolating biological samples such as PBMCs, RNA and serum requires infrastructure and methodological considerations to ensure experimental reproducibility and sample viability in the context of a clinical trial.

Careful consideration of the tools used to assess and follow clinical RA disease activity are also needed as most available tools were not developed or validated for use with Indigenous populations. Clinical disease patterns are likely best assessed by tools that reflect joint distribution, such as the Lansbury articular index. Patient reported measures of overall disease activity and physical function should be evaluated in INA populations to ensure cultural relevance and acceptability.

Selection of an intervention may be the most challenging consideration for RA prevention trial design, and specific considerations must be applied to studies recruiting INA participants [61]. Proposed regimens have historically been limited to repurposing of typical RA therapy. Many of these medications are both expensive and associated with serious side effects. A balance between the selected intervention and the individuals

perceived risk of future RA needs to be achieved for efficient uptake and recruitment. For many individuals facing health care disparities, this balance is likely much more challenging to achieve, given that it hinges on numerous factors which include cultural considerations, education level and socioeconomic status, all of which uniquely impact disparate communities. More research is needed to better understand the INA perspective on participating in preventative clinical research studies. For example, there may be a desire to integrate Indigenous healing practices into prevention strategies. Indeed, in patients with established RA, qualitative studies suggest there is a preference towards a holisitic approach to treatment, and that acceptance of pharmacologic interventions hinges primarily on patient-provider trust [62]. Qualitative studies may also serve to optimise our understanding of the risk-benefit profile of at-risk INAs, which would help tailor interventions to enhance recruitment and trial success. Preclinical symptoms such as joint pain are a major motivator to accept medications for prevention but further restrict efficient recruitment by expanding the inclusion criteria [59]. It was recently shown in a non-INA population that a perceived risk of future RA of less than 60% was a major barrier accepting an intervention for individuals who were eligible for inclusion in prevention trials [61]. Defining this threshold in INA and other minority populations will be crucial for the design and completion of successful prevention trials. Despite the challenges laid out, the potential benefits of preventing RA in INA persons clearly warrant a widened breadth of investigation to better understand the uniqueness of these challenges, and how to best address them.

Conclusions

Collectively, these observations suggest that multiple factors contribute to poor long-term outcomes for INA with RA including high population prevalence of genetic and environmental risk factors, delayed or limited access to rheumatology care and advanced therapy, disease features and comorbidity. The observed increased rates of persistent synovitis, end-stage joint damage and early mortality highlight the need for improved health care delivery that incorporates indigenous-focused models of health care. Ongoing initiatives conducted in respectful partnership with Indigenous communities that address RA prevention have the potential to significantly reduce the burden of RA in INA population as well as inform prevention strategies for non-INA population. Adapting models of health care provision that incorporate voiced key values of circumpolar indigenous peoples, address core social determinants of health, and are supported by effective and culturally relevant governance systems have potential to improve the health outcomes of chronic diseases including RA.

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Article highlights

- . Indigenous North American people are predisposed to severe rheumatoid arthritis due to a high prevalence of genetic and environmental risk factors.
- . Disparities in clinical outcomes for INA with RA exist and are likely impacted by complex factors relating to disease and rheumatology care delivery.
- . Community focused, culturally appropriate strategies will best inform initiatives to improve outcomes for INA with rheumatic disease.

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Authors contribution

Hitchon: Conceptualisation; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Visualisation; Roles/Writing – original draft; Writing – review & editing.

Liam O;Neil: Conceptualisation; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation;

Visualisation; Roles/Writing – original draft; Writing – review & editing.

Peschken: Data curation; Formal analysis, Roles/Writing – original draft; Writing – review & editing.

Robinson: Data curation, Roles/Writing – original draft; Writing – review & editing.

Fowler-Woods: Roles/Writing – original draft; Writing – review & editing.

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