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Autoimmune rheumatic disease in Australian Aboriginal and Torres Strait Islander Peoples: What do we know?

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ABSTRACT

Autoimmune rheumatic disease (AIRD) is a collective term, which comprises a group of multisystem inflammatory autoimmune diseases, including connective tissue disease, chronic inflammatory arthritis, sarcoidosis and systemic vasculitis. Some AIRD are prevalent in the general population, and all can cause significant morbidity and reduced quality of life, with some increasing the risk of premature mortality, such as systemic lupus erythematosus (SLE), a connective tissue disease that is more prevalent and severe in Australian Aboriginal and Torres Strait Islander Peoples with high mortality rates. To ensure that management of AIRD can be optimised for all Australians, it is important that we understand the prevalence and potential phenotypic variations of AIRD across the Australian population. However, to date there have been few described cases of AIRD other than SLE in Aboriginal and Torres Strait Islander Peoples. In this review, we summarise what is known about AIRD other than SLE in Aboriginal and Torres Strait Islander Peoples, particularly with regards to prevalence, phenotype and disease outcomes, and highlight the current gaps in knowledge.

- Very little is known about autoimmune rheumatic disease (AIRD) other than systemic lupus erythematosus (SLE) in Australian Aboriginal and Torres Strait Islander Peoples.
- There are no longitudinal studies of AIRD other than SLE in Aboriginal and Torres Strait Islander Peoples.
- Further research into AIRD in Aboriginal and Torres Strait Islander Peoples is needed to ensure that health needs are being met, and to optimise future management strategies.

Introduction

Autoimmune rheumatic disease (AIRD) is a collective term which comprises a heterogenous group of multisystem inflammatory autoimmune diseases, including connective tissue disease (CTD) such as systemic lupus erythematosus (SLE), Sjögren's disease (SD), systemic sclerosis (SSc), idiopathic inflammatory myositis (IIM), mixed connective tissue disease (MCTD) and undifferentiated CTD; as well as chronic inflammatory arthritis including rheumatoid arthritis (RA), psoriatic arthritis (PsA), other spondyloarthropathies and juvenile idiopathic arthritis (JIA); sarcoidosis and systemic vasculitis. Some AIRD are prevalent in the general population and all can cause significant morbidity and mortality [1]. Treatment for some AIRD has improved dramatically over the past thirty years, with multiple targeted

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therapies now approved for use in Australia [2–4]. These therapies have transformed some AIRD from a group of diseases which frequently caused profound disability or rapidly accelerated mortality, to manageable chronic conditions for most patients, although quality of life remains lower and disability and mortality rates remain higher than in the general population [4–6].

In order to ensure that all patients with AIRD can benefit from these advances in treatment, it is important to understand the prevalence and potential phenotypic variations of AIRD across the Australian population. The Aboriginal and Torres Strait Islander Peoples, hereto respectfully referred to as Aboriginal People, are the original inhabitants of Australia, and the traditional owners of Australian land. Aboriginal People have inhabited Australia for approximately 60,000 years [7], and have an incredibly diverse culture, with over 100 self-identified Nations, and over 150 languages actively spoken [8]. In the 2021 Census, just over 800,000 people, or 3.2 % of the Australian population, self-identified as Aboriginal and/or Torres Strait Islander [9]. Unfortunately, Aboriginal People experience poorer outcomes compared to non-Aboriginal Australians across a wide range of health indices, and have a life expectancy at least 8 years lower than the national average [10], although this depends on the area studied. This highlights Aboriginal Health as an important area of focus for health research and healthcare improvement.

The AIRD most frequently described in Aboriginal People is SLE. SLE prevalence is increased in Aboriginal People compared to the general Australian population by 2 to 4-fold [11–13]. Disease severity is also significantly increased, particularly with regards to lupus nephritis, with high rates of progression to end stage renal failure and renal replacement therapy [14,15]. Mortality is considerably higher in Aboriginal People with SLE, with infection being the leading cause of death [11, 15]. The reasons for the increased prevalence and severity of SLE in Aboriginal People are not known, but a complex interplay of socio-economic, environmental and genetic/biological factors likely contribute. This is the scope of another review from our group, providing a more in-depth overview of SLE in Aboriginal People [16].

Little is known about other AIRD in Aboriginal People, and there is significant variation in reported prevalence in the scarce published literature. Some AIRD, including RA, PsA and ankylosing spondylitis (AS), appear to be less prevalent in some studies, although it is unclear whether this low number of published cases reflects a true low prevalence, under-diagnosis or under-reporting. It is important to note that the paucity or lack of published data in many conditions may not reflect true low disease prevalence. Here, we review what is currently known about AIRD other than SLE in Aboriginal People and highlight the current gaps in knowledge where further research is required. A summary of the published studies of AIRD other than SLE in Aboriginal People is shown in Fig. 1, with further details provided in **Supplementary Table 1**.

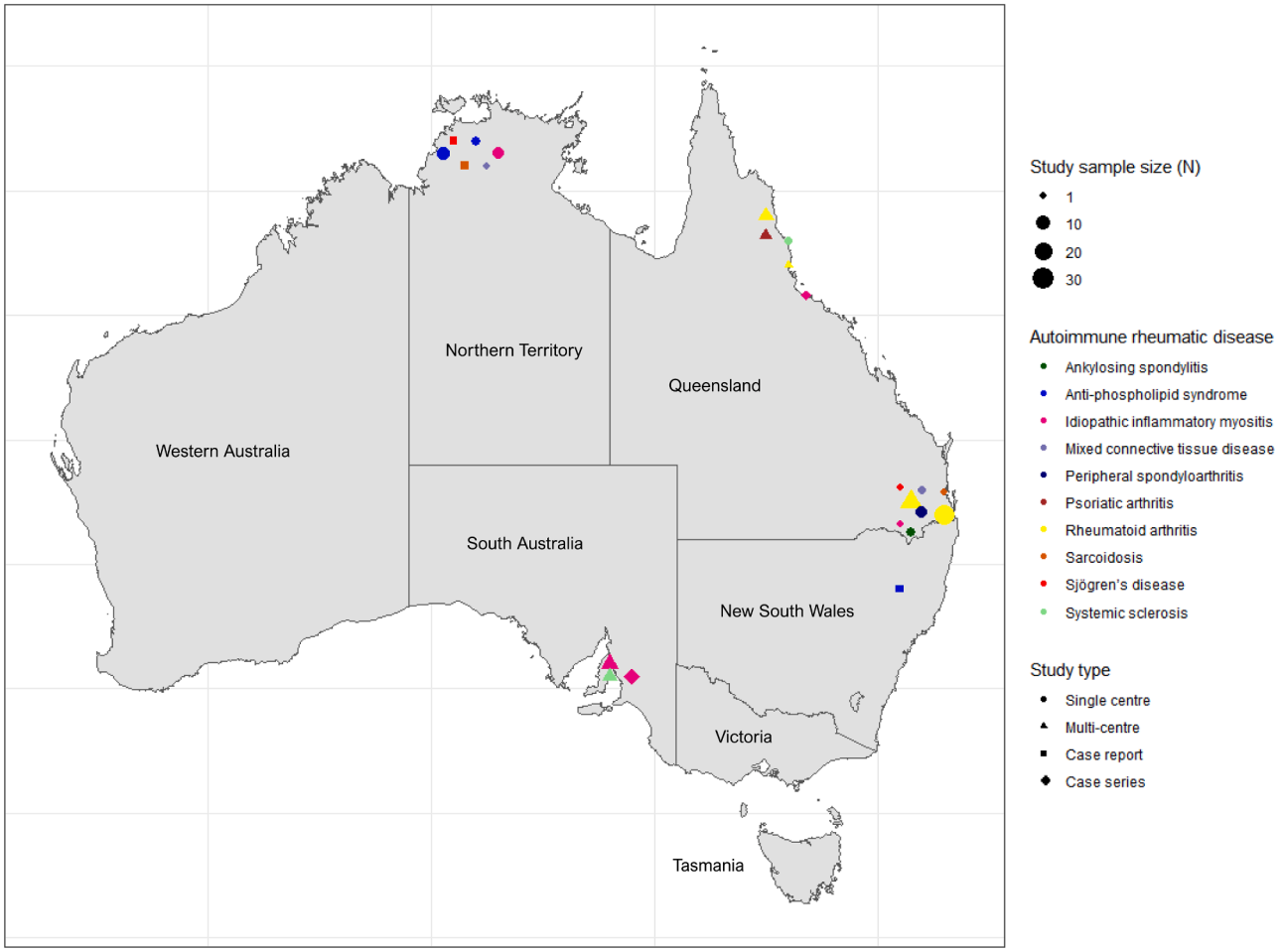

Fig. 1. Overview of studies, case series and case reports on AIRD excluding SLE in Aboriginal and Torres Strait Islander Peoples. All published articles investigating AIRD other than SLE in Aboriginal and Torres Strait Islander Peoples were geolocalised on an Australian map. Each studied AIRD reported in each article was colour-coded. Shapes were used to denote whether the data is from a single (circle) or multi-centre (triangle) study, case series (diamond) or case report (square). The number of patients reported is coded by the size of the shape. Shapes representing different studies in the same region, or different AIRD in the same study, were slightly separated on the map to improve readability. *Abbreviation: CTD: connective tissue disease.*

Methods

Search strategy

A systematic search of databases including MEDLINE and EMBASE was performed, articles were restricted to English Language. No other filters were applied, in order to maximise search results. Search terms used included "Indigenous Australians", "Aboriginal Australians", "Australian Aboriginals", "Australian Aborigines" and "Torres Strait Islander" in combination with the names of the diseases of interest (excluding SLE), and their recognised acronyms. A separate search was performed for each disease of interest. Due to a paucity of search results, a separate search was performed on Google Scholar using the same search terms to ensure no relevant articles had been missed. The Australian Institute of Health and Welfare and Australian Bureau of Statistics websites were also searched to ensure that no relevant administrative data was missed. All study types, including case series and case reports, and studies from any year, were included in the review, due to the paucity of published literature. A summary of the search strategy is shown in Fig. 2.

Data visualisation

Data visualisation to geolocalise and represent reported data was carried out using R (Version 4.2.2) and R Studio (Version 2023.03.0 + 386) software [17]. Ozmap R package (Version 0.4.5) was used to visualise data overlayed on an Australian map.

Connective tissue diseases other than SLE

Sjögren's disease

There have only been two cases of SD in Aboriginal People described in the literature [18,19]. One case report described a patient who initially presented with *sicca* symptoms and positive anti-nuclear antibodies (ANA), anti-Ro and anti-La antibodies, and subsequently developed pulmonary amyloidosis [18]. A recent study of patients attending a specialist rheumatology clinic in The Southern Queensland Centre of Excellence in Aboriginal and Torres Strait Islander Primary Health Care also reported one patient with SD, although further clinical details were not provided [19]. Given the increased prevalence of SLE in Aboriginal People, and the significant clinical and biological overlap between SLE and SD, it is surprising that there have been no other cases of SD in Aboriginal People described in the literature, raising the question of under-diagnosis or under-reporting, or misclassification as SLE. High rates of anti-Ro and anti-La antibodies, which are typically seen in patients with SD, are seen in Aboriginal SLE patients, raising the possibility that many of these patients may have concurrent SD [20].

Systemic sclerosis

The largest study of SSc in Aboriginal People described six South Australian patients; three with diffuse SSc, two with limited disease and one with mixed disease [21]. Based on data from the South Australian Scleroderma Registry as well as census data, this study suggested that the incidence of SSc was similar in Aboriginal People compared to non-Aboriginal Australians, a finding also supported in a subsequent

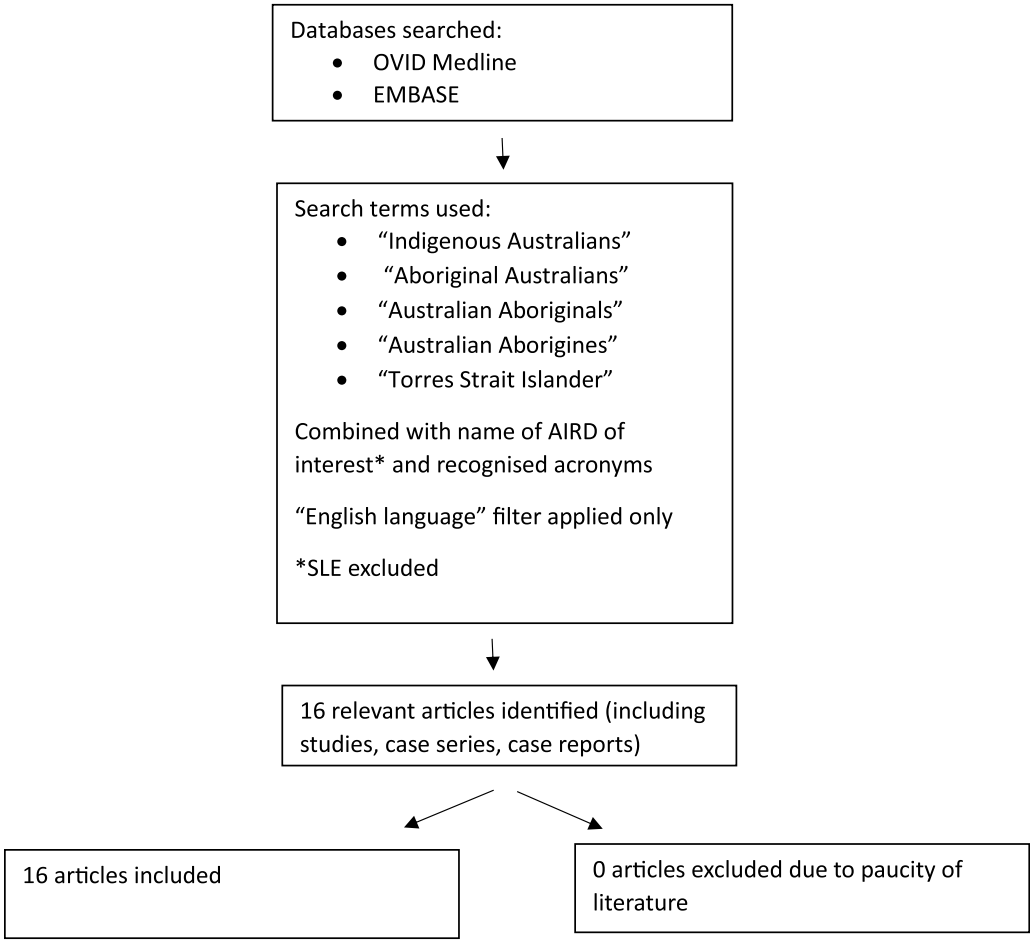

Fig. 2. Summary of search strategy and article selection.

epidemiological study of SSc in South Australia [21,22]. Interestingly, none of these patients, including those with limited disease, had centromere staining ANA [21]. The authors also interrogated laboratory data from the tropical northernmost region of the Northern Territory, known as the 'Top End', and found only two instances of a centromere staining ANA in Aboriginal People, neither of whom had any clinical manifestations of SSc [21]. Limited SSc, particularly associated with centromere staining ANA, might therefore either be less prevalent, under-investigated or under-reported in Aboriginal People. In an observational study of 81 patients with SSc in the extreme northern region of Queensland, known as 'Far North Queensland', 2 % identified as Aboriginal, but further characteristics of their disease were not reported [23]. This is a lower proportion of Aboriginal patients with SSc than expected based on the proportion of Aboriginal People living in this region, raising the possibility of under-diagnosis or under-reporting, or suggesting that SSc might be less prevalent in Aboriginal People living in Far North Queensland, potentially due to protective genetic and/or environmental factors in this population.

Idiopathic inflammatory myopathies

There are several studies and case series describing IIM in Aboriginal People. A retrospective study describing the off-label use of rituximab in the Northern Territory included six Aboriginal patients with IIM, three of whom were classified as having polymyositis, one as statin-induced myositis, and two who were not further classified [24]. Five of the six patients had biopsy-proven myositis, with antibodies including anti-Ku, anti-Ro52, anti-Jo1, anti-Mi2 and anti-RNP. Each of these patients, except for the patient with statin-induced myositis, had responded well to rituximab [24]. Given this cohort of patients was identified as part of an audit on the use of rituximab in the Northern Territory, meaning that all patients included in the study would most likely have had severe disease, it is not possible to comment on the severity of IIM in Aboriginal People compared to the general population based on this data. Several other studies have reported one to two Aboriginal patients with IIM as part of a larger cohort, but have not provided further clinical details [19,25].

A South Australian case series reported fifteen Aboriginal patients with severe statin-induced myositis, with a mean serum creatinine kinase level of 50,000. Of the eight patients who had a muscle biopsy performed, five had necrotizing myositis [26]. HMG-CoA reductase antibody status was not reported in this cohort. Outcomes were poor, with three patients requiring prolonged mechanical ventilation due to respiratory muscle failure, three deaths and two patients with significant permanent disability, despite immunosuppressive treatment [26]. Another South Australian study on immune-mediated necrotizing myositis (IMNM) ($N = 55$, including ten Aboriginal patients) reported Aboriginal patients presenting at a younger age and with a more severe clinical and histological phenotype, with significantly higher peak CK levels, significantly higher rates of dysphagia and significantly higher necrosis grades on muscle biopsy [27]. Another case series described four Aboriginal patients with statin-induced necrotizing autoimmune myositis in Far North Queensland [28]. Two of these patients were HMG-CoA reductase antibody positive. All had slow recovery with immunosuppression, and a prolonged inpatient admission, with a mean length of stay of 54 days [28]. Further research is warranted to explore whether Aboriginal People have a propensity to develop more severe and refractory statin-induced myositis than non-Aboriginal Australians, and to identify factors which may contribute to this.

Anti-phospholipid syndrome

There have been two cases of probable primary catastrophic anti-phospholipid syndrome (APLS) in Aboriginal People reported in the literature [24,29]. Interestingly, one of these patients was also diagnosed with relapsing polychondritis [29]. There have been several other published cases of secondary APLS, including catastrophic APLS, in Aboriginal People, all in the setting of SLE [24,30]. Given the increased prevalence of SLE in Aboriginal People, it is surprising that there have been very few cases of APLS described in the literature, once again raising the question of under-diagnosis or under-reporting.

Mixed and undifferentiated connective tissue disease

There have only been two published cases of MCTD in Aboriginal patients, although no further clinical details on these patients were provided [19]. In addition, one of the patients with polymyositis described above was reported to have a MCTD phenotype [24]. In light of the high rates of anti-RNP autoantibodies seen in Aboriginal patients with SLE, one could speculate that MCTD may be more prevalent in Aboriginal People than currently reported [13,30]. There are no published cases of undifferentiated connective tissue disease in Aboriginal People.

Chronic inflammatory arthritis

Rheumatoid arthritis

There is no reported evidence of chronic inflammatory arthritis in Aboriginal People prior to European settlement based on paleopathological and ethnographical studies [31]. To the best of our knowledge, only one small case series described the phenotype of seven Aboriginal People with confirmed RA, in which five out of six patients with data available had erosive disease and three out of six had rheumatoid nodules [32]. This is at the higher end of what is classically described in the literature, potentially suggesting a more severe disease phenotype in Aboriginal People [33,34]. A subsequent publication by the same group identified an additional 18 Aboriginal patients with RA, but did not report further details regarding their disease characteristics [35]. More recently, a study of an Aboriginal rheumatology clinic in Southern Queensland reported 26 patients with RA, 17 of whom were seropositive, although no other clinical details were reported [19]. Larger studies are needed to further explore disease phenotype and severity in Aboriginal People with RA.

In a study investigating musculoskeletal conditions in 847 Aboriginal People in Far North Queensland, no cases of RA were identified [36]. However, it is important to note that this study involved patient self-reporting of musculoskeletal symptoms and conditions via a survey administered by health workers in a single community, and most patients who reported no symptoms or musculoskeletal diagnosis did not go on to be assessed by a study clinician. This represents a significant limitation, particularly in a population with limited health literacy. In an earlier study of 288 Aboriginal People in Far North Queensland, only one definite case of RA was identified [37]. Despite the limitations of these studies, the rate of RA in both studies was lower than what would generally be expected, given the size of the study populations. A possible explanation for the lower rates of RA observed in Aboriginal People in some studies is that the prevalence of the shared epitope, which confers genetic predisposition to RA, appears very low in this population [38,39]. Absence of the shared epitope has also been documented in other populations without reported cases of RA, including a rural Nigerian population [40]. It is worth noting, however, that the two studies examining the shared epitope in Aboriginal People are over 25 years old; therefore, studies using current and state of the art technology are required to confirm the previously reported low prevalence of the shared epitope in this group.

Rheumatoid factor (RF), an autoantibody which is commonly associated with RA [41], was positive in 53 % of healthy Aboriginal People in one study [35], compared to only 1.3–4 % of healthy people of European ethnicity in other studies [41]. This potentially suggests RA rates may be under-reported in Aboriginal People, or that there may be other factors, such as infection, driving RF elevation. However, it is also

important to note that larger and more up to date studies are required to confirm the finding of prevalent RF positivity in Aboriginal People.

In contrast to the low rates of RA observed in these above-mentioned studies, a report issued by the Australian Institute of Health and Welfare (AIHW) documented a higher rate of RA in Aboriginal People (2 %), compared to the general Australian population (1 %), based on a comparison between the AIHW National Hospital Morbidity Database and the 2004–05 National Aboriginal and Torres Strait Islander Health Survey, in which patients were required to answer whether they had "doctor-diagnosed" RA [42]. However, this study was limited by the self-reported nature of the survey, as well as the fact that no data was collected from Aboriginal People living in remote areas, thus excluding an important sub-group of the Aboriginal population [42].

The conflicting nature of the above results highlights the need for further research to determine the true prevalence, phenotype and outcomes of RA in the Aboriginal Australian population.

Psoriatic arthritis

Similar to RA, there is a scarcity of published literature regarding PsA in Aboriginal People. In the aforementioned study investigating musculoskeletal conditions *via* a survey of 847 Aboriginal People in Far North Queensland, four cases of PsA were described, all in patients with concomitant psoriasis, although no further details on the characteristics of these patients were reported [36]. This would equate to a PsA prevalence of 0.5 %, which falls within the estimated prevalence range for the general population [43]. Psoriasis appears to be uncommon in Aboriginal People [44], although a Western Australian study of 104 Aboriginal patients attending public hospital dermatology clinics reported five patients with psoriasis [45]. To our knowledge, there have been no other published cases of PsA or psoriasis in Aboriginal People.

Other spondyloarthropathies

A recent study of patients attending the specialist rheumatology clinic in The Southern Queensland Centre of Excellence in Aboriginal and Torres Strait Islander Primary Health Care reported three patients with AS, one of whom was human leukocyte antigen (HLA) B27 positive [19]. This study reported a further six patients with peripheral spondyloarthritis, two of whom were HLA-B27 positive [19]. Further clinical details regarding these patients were not reported. To our knowledge, there are no other published cases of confirmed AS, or other types of spondyloarthritis (i.e., non-radiographic axial spondyloarthritis, enteropathic spondyloarthritis or reactive spondyloarthritis) in Aboriginal People. The survey in Far North Queensland did include a question regarding AS, but did not yield any cases [36]. The low reported frequency of AS in Aboriginal People is thought to be due to the rarity of the HLA-B27 allele in this population [35]. Although the HLA-B27 allele is reportedly present in approximately 8 % of the Australian population, and in 80–90 % and 20–40 % in patients with AS and PsA respectively [46–49], in a study of 186 healthy Aboriginal People in Central Australia, none had a positive HLA-B27 allele [50]. It is worth noting, however, that this study was performed in 1975, and that newer, more advanced genotyping technology may enable identification of HLA-B27 sub-alleles, which could confer risk for spondyloarthritis in the Aboriginal population. Therefore, further studies are required in this area.

Anterior uveitis, which is also associated with HLA-B27 positivity, has been reported in 4 out of 1881 Aboriginal patients recruited to the Central Australian Ocular Health Study, *via* remote clinics in Central Australia, although most of these cases were attributed to infection or trauma rather than autoimmune disease [51]. A number of other studies have reported anterior uveitis in Aboriginal People associated with infections, especially Human T-Lymphotrophic Virus Type-1 (HTLV1) [52, 53]. One published case of a HLA-B27 positive Aboriginal patient with acute anterior uveitis has been described in Central Australia, although this patient had no other systemic features of HLA-B27 associated disease [54].

Inflammatory bowel disease (IBD), which is also associated with the HLA-B27 allele (although less strongly than AS), was described in 250 Aboriginal patients in a large cross-sectional study, with 123 having a diagnosis of Crohn's disease, and 121 having a diagnosis of ulcerative colitis [55]. This resulted in an estimated prevalence of IBD of 337 per 100,000 in Aboriginal People, approximately half that of the non-Aboriginal study population [55]. While HLA-B27 testing in this study was not reported, it would be interesting to know the rate of HLA-B27 positivity among Aboriginal People with IBD in this study population.

Juvenile idiopathic arthritis

There have been no published studies or case reports of JIA in Aboriginal People. One study on rheumatic fever reported a 9 year old Aboriginal child who had initially been diagnosed with JIA, but subsequently re-presented with rheumatic heart disease, and it was felt that his initial presentation had been more in keeping with acute rheumatic fever [56].

Sarcoidosis

There have been two published cases describing sarcoidosis in Aboriginal People [19,57]. One patient presented with mild pulmonary sarcoidosis and hilar lymph node enlargement [57], the other patient had no further clinical details described [19].

Systemic vasculitis

To our knowledge there are no published studies or case reports of confirmed ANCA-associated vasculitis (AAV) in Aboriginal People, although the authors of a review on immune dysfunction in Aboriginal People alluded to several Aboriginal AAV patients they had cared for [31]. Furthermore, there are no published studies or case reports of giant cell arteritis, Takayasu's arteritis or polyarteritis nodosa reported in Aboriginal People. There are also no published studies or case reports of polymyalgia rheumatica in this population.

Conclusion

There have been relatively few published studies, case series and case reports describing AIRD other than SLE in Aboriginal People, with no longitudinal or population studies. While SLE appears to be more prevalent and severe in Aboriginal People, certain AIRD, such as AS, might be less prevalent, although larger, well-designed studies are needed to confirm this. Further research into the prevalence, phenotype and disease outcomes of AIRD in Aboriginal People is needed to ensure that their healthcare needs are optimally met.

Author contributions

LEE wrote the first draft with assistance from FBV; FBV reviewed and edited all subsequent versions of the draft. All co-authors reviewed, edited and approved the final draft for submission.

Ethics approval and consent to participate

N/A.

Availability of data

N/A.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152354.

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