Juvenile Idiopathic Arthritis in South Australia

Ming Min (✉ ming.min@adelaide.edu.au)

University of Adelaide Discipline of Paediatrics, Women's and Children's Hospital, South Australia, Australia

<https://orcid.org/0000-0002-6462-7940>

Suzanne Edwards

The University of Adelaide

Catherine Gibson

Women's and Children's Health Network

Tania Crotti

The University of Adelaide Faculty of Health and Medical Sciences

Christina Boros

Women's and Children's Hospital Adelaide

Research article

Keywords: Juvenile Idiopathic Arthritis, Registry, Epidemiology, Comorbidities and complications, Disease activity, Patient-reported data

Posted Date: October 9th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-88109/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License. [Read Full License](#)

Abstract

Background: Juvenile Idiopathic Arthritis (JIA) is a chronic rheumatic disease that shows variation in subtype distribution by geographic regions. The aim of this study was to create a JIA registry, which could describe the epidemiology and characteristics of JIA patients in South Australia (SA).

Methods: Prospectively collected data from JIA patients at the Women's and Children's Hospital in Adelaide, between August 2019 and March 2020 were reported. All children and young people diagnosed with JIA according to the International League of Associations for Rheumatology (ILAR) classification criteria were eligible for inclusion. Data including demographics, complications/comorbidities, medications, disease activity as well as patient-reported data using Childhood Health Assessment Questionnaire (CHAQ) were documented. Non-identified data were extracted from this registry and utilised in descriptive analysis and comparative studies.

Results: There are currently $n=112$ JIA patients in this registry, including $n=11$ incident cases (9.8%), with a predominance of female ($n=75$, 67.0%). The median disease duration was 3.6 years (interquartile range 1.3-7.6). The most common subtype was persistent oligoarthritis ($n=35/112$, 31.3%), followed by rheumatoid factor-negative polyarthritis ($n=32/112$, 28.6%), extended oligoarthritis ($n=23/112$, 20.5%), enthesitis-related arthritis (ERA; $n=12/112$, 10.7%), systemic onset arthritis ($n=5/112$, 4.5%), rheumatoid factor-positive polyarthritis ($n=3/112$, 2.7%) and psoriatic arthritis ($n=2/112$, 1.8%). Complications were documented in $n=40/112$ (35.7%) patients, with $n=21/94$ (22.3%) observed to have uveitis, and musculoskeletal complications observed in $n=10/112$ (8.9%). Methotrexate intolerance was present in $n=10/79$ (12.7%) patients. Forty-nine out of 112 (43.8%) patients had at least one comorbidity, with anxiety/depression ($n=5/112$, 4.5%) and asthma ($n=5/112$, 4.5%) being the most common. Around half of patients ($n=52/112$, 46.4%) had clinically inactive disease at enrolment and most ($n=85/112$, 75.9%) reported no to low functional disability. Non-steroidal anti-inflammatory drugs have been almost universally used ($n=100/112$, 89.3%), and $n=26/112$ (23.2%) have received treatment with biologics.

Conclusions: In this JIA registry study, we found that the JIA cohort in SA is female-dominated with persistent oligoarthritis as the most common subtype, consistent with other studies. Most patients have good disease control and report no or mild disability. Further longitudinal work will add to the current description of our JIA cohort and assist improvement of clinical care.

Background

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in children, which can impact on health status, functional ability and the psychological health of affected patients. Uveitis is the most common extra-articular complication of JIA, affecting approximately 11.6–30% of JIA patients [1]. Other complications include those associated with the musculoskeletal system, such as joint damage and deformity [2, 3], growth retardation, emotional problems such as depression and anxiety, as well as a variety of side effects attributed to treatment and interventions. In addition to these well-known complications, there is an increased incidence and prevalence of comorbidities such as Type 1 Diabetes, celiac disease, autoimmune thyroid diseases, inflammatory bowel disease (IBD) and Crohn's disease in patients with JIA [4].

Epidemiological studies of JIA vary considerably in study methodology, diagnostic criteria, and the age limits of populations included [5]. Population-based registries are important sources for identifying cases for epidemiologic studies accurately [6], as they can assist in improving patient outcomes, as well as providing a normalised platform to researchers which facilitates an interactive and collaborative registry network.

In some countries, many relevant studies and data are available, while in others, data are scarce or non-existent. The prevalence and incidence of JIA have been found to differ in different ethnic groups and regions [5, 7, 8], the knowledge of which is crucial for local and worldwide understanding of disease epidemiology and management. The lowest prevalence (3.43 per 100,000) was reported in Egypt and the highest (196 per 100,000) was reported in South America [9, 10]. In the US, the prevalence of JIA from different published studies has ranged from 1.6 to 86.1 per 100,000 [11, 12]. Studies presented a relatively higher prevalence rate in developed countries, varying from 16 to 150 per 100,000 [13]. However, it should be noted that the current low reported prevalence in developing countries may be related to limited data sources [14]. Published incidence rates for JIA in European countries ranged between 3.5 and 21.7 per 100,000 children under 16 years old [15–19].

In Australia, there are no published studies describing the incidence of JIA. A community-based prevalence study in JIA by Manners et al (1996), reported a prevalence of 400 per 100,000 in a cohort of 2,241 12-year-old children in Perth, Western Australia [20]. The 2004–05 Australian Institute of Health and Welfare (AIHW) reports a prevalence of 100 to 400 per 100,000 Australian children. Moreover, the point prevalence was estimated to exceed 400 per 100,000 among children aged 10–15 years in their data [14]. Both estimates were far higher than found in other published studies [9–13, 15–19].

The only current JIA registry in Australia - The Childhood Arthritis Risk Factor Identification Study (CLARITY) has the primary aim of analysing DNA and environmental data in order to identify risk factors for JIA [21]. An inception cohort study with comprehensive epidemiological data for newly diagnosed JIA patients was performed between 2010 and 2014, to help initial understanding of the demographics, treatment and outcomes of Australian children [22]. Their results have shown a high similarity in patient demographics, disease course and treatment with cohorts in North America and Europe [22].

In this study, we aimed to create the first JIA registry in SA which describes the epidemiology and characteristics of the SA JIA cohort. This population-based registry will help us improve patient care and assist in the development of collaborations with other national and international registries by harmonising datasets, sharing data and identifying shared challenges.

Methods

Study design

The JIA registry in SA is a single-centre, observational and prospective registry with a view to improving the long-term clinical care and patient outcomes. This study reports the baseline characteristics of our SA registry cohort. We conducted our study with the approval of the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/59) and in accordance with the Declaration of Helsinki. Written informed consent was obtained for all participants.

Patient cohort and recruitment

This cross-sectional study has captured and analysed baseline patient data and JIA outcomes in SA, in the period between August 2019 and March 2020. Children and young people with JIA were recruited during a visit to the Paediatric Rheumatology outpatient clinic at the Women's and Children's Hospital (WCH), SA, Australia. The WCH is the major paediatric hospital in SA and provides a state-wide paediatric rheumatology service.

The identification of JIA cases was made by three paediatric rheumatologists and the rheumatology nurse in the clinic setting based on the International League of Associations for Rheumatology (ILAR) criteria [23]. Incident cases were defined as those enrolled within six months of initial diagnosis. Prevalent cases older than 18 yrs were excluded, as this is the age of transition to Adult services in our centre.

Once patients were identified as eligible to participate in the registry, they or at least one parent/carer provided written informed consent before the collection of any data. Patients or families unable to provide informed consent were excluded.

Data collection

Upon obtaining consent, treating clinicians were asked to complete a paper-based questionnaire regarding JIA subtype and relevant clinical data. Data including but not limited to demographics, JIA subtype, disease onset, disease duration, complications/comorbidities, medications used as well as investigation results and the clinical Juvenile Arthritis Disease Activity Score (cJADAS) [24] were documented. Patients/carers were asked to complete the paper-based Childhood Health Assessment Questionnaire (CHAQ) [25] at each clinic visit. All data were recorded prospectively in the JIA registry.

Registry development

The registry has been manually curated and stored in a password protected database, accessible only to the principal investigator (MM). Additionally, a newly generated study ID number is applied to each participant so that patient data are kept confidential but re-identifiable. To minimise the potential misclassification of patients, a 6-month period has been provided to ensure an accurate clinical diagnosis, prior to the finalisation of statistical analysis. Furthermore, data-checking has been performed by the principal investigator (MM) to ensure data consistency, and any changes to the stored data are recorded in a log file.

Definitions of disease activity states

The cJADAS has been shown to have good construct validity in clinical practice in the description of disease activity in JIA [26]. In accordance with Consolaro et al. in 2014 [24], children with inactive systemic arthritis, rheumatoid factor negative (RF-) and rheumatoid factor positive (RF+) polyarthritis, or extended oligoarticular onset disease (EO) were included in the functional polyarthritis category. The functional oligoarthritis category included children with persistent oligoarticular onset disease (PO). Children classified in other ILAR subsets were assigned to the functional oligoarthritis or polyarthritis categories based on the number of affected joints (≤ 4 or > 4 joints, respectively) within the first six months of diagnosis.

Complications and comorbidities

Complications and comorbidities were recorded and categorised based on case-note reports. Complications categories included: ocular, musculoskeletal, medication intolerance and side effects, growth failure/retardation, amyloidosis and macrophage activation syndrome [27–32]. Ocular complications included uveitis and uveitis-related complications such as glaucoma, cataract and macular oedema [29, 33]. Musculoskeletal complications included joint deformity (fixed flexion deformity and micrognathia), joint damage, erosive disease and muscle wasting [34–36]. Medication intolerance and side effects included MTX-associated nausea, anxiety, needle phobia and liver function test derangement [30].

Statistical analysis

All analyses were calculated from the extracted data at the first registry visit and were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). In Table 1, categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR), as appropriate. The Shapiro-Wilk test was used to check the assumption of normality for a variable, thus deciding whether the parametric or nonparametric test was correspondingly carried out. The Wilcoxon Rank Sum Test was used to compare the differences between two groups and the Spearman's coefficient was used to explore the correlations between two variables. In Table 2 and Table 3, the outcomes, including disease activity, functional disability and medication exposure,

are reported by frequency and percentage in all patients and within ILAR subtypes. The comparisons with other published data were performed via MedCalc for Windows, version 19.2.6 (MedCalc Software, Ostend, Belgium). Results with p values less than 0.05 were considered as statistically significant.

Results

Patient demographics

Data from $n = 112$ JIA patients was collected in this registry; $n = 75$ (67%) were female (Table 1). The median age at symptom onset in the total group was 5.4 yrs (IQR 2.0–9.7) and the mean $\pm$ SD age at recruitment was 11.7 ± 4.4 yrs. The most common subtype of JIA was PO ($n = 35$, 31.3%), with median onset at age of 2.8 yrs (IQR 1.7–7.0) and predominantly occurring in females ($n = 26/35$, 74.3%). The least common subtype was psoriatic arthritis (PsA) JIA ($n = 2$, 1.8%). The frequencies and percentages for other subtypes were as follows: RF- polyarthritis ($n = 32$, 28.6%), EO ($n = 23$, 20.5%), enthesitis-related arthritis (ERA) ($n = 12$, 10.7%), systemic onset arthritis ($n = 5$, 4.5%), and RF + polyarthritis ($n = 3$, 2.7%). No patients had undifferentiated disease. There were $n = 11$ (9.8%) newly diagnosed JIA cases at enrolment, seven (63.6%) of whom were female. The most common diagnosis was PO ($n = 5/11$, 45.5%), followed by $n = 3/11$ (27.3%) with RF- polyarthritis, $n = 2/11$ (18.2%) with ERA and $n = 1/11$ (9.1%) with RF + polyarthritis. The median age at symptom onset and the median age at recruitment was 13.3 yrs (IQR 2.7–16.3) and 15.8 yrs (IQR 7.3–17.4) for incident cases, and 4.9 yrs (IQR 1.8–9.3) and 11.9 yrs (IQR 8.4–14.9) for prevalent cases.

Disease course

At the time of recruitment, the median active joint count was zero (IQR 0–0.8), the median physician global assessment (PGA) was zero (IQR 0–1.1) and the median patient global evaluation (PGE) was 0.5 (IQR 0–2.4) for all JIA patients (Table 2).

Among $n = 101$ patients with established disease, the median number of active joints was zero (IQR 0–0), with $n = 80/101$ (79.2%) achieving an active joint count of zero at enrolment, with median PGA of zero (IQR 0–1.0). In contrast, $n = 11$ incident patients had a median of one active joint count (IQR 0–2.0), with a higher median PGA of 1.2 (IQR 0–1.9).

Based on the aforementioned cJADAS cut-offs [24], $n = 18$ (16.1%) children had high disease activity at the time of recruitment, with $n = 10$ of them diagnosed with PO and one with EO. Six had RF- polyarthritis and one had RF + polyarthritis. Patients with EO had significantly longer ($p = 0.016$) disease duration [median 7.5 yrs (IQR 3.4–9.9)] than those with PO [median 3.9 yrs (IQR 1.2–6.4)].

The median CHAQ score (disability index) was 0.1 (IQR 0–0.6); most ($n = 61/112$, 54.5%) had no or only mild disability. The distribution of the CHAQ score was highly skewed (mean 0.37) [37]. When the analysis of CHAQ score was limited to those within subtypes, no significant differences were found.

The median age at onset among patients with functional oligoarthritis ($n = 40$, 35.7%) and patients with functional polyarthritis ($n = 72$, 64.3%) was 3.6 yrs (IQR 1.8–8.9) and 6.2 yrs (IQR 2–9.9), respectively. There was a significant difference in age at recruitment between functional oligoarthritis and polyarthritis categories of JIA ($p = 0.04$). There was no significant difference in age at diagnosis across the two categories ($p = 0.25$). The median time from symptom onset to diagnosis was 0.3 yrs (IQR 0.2–0.9) and there was no significant between-group difference ($p = 0.571$, Mann-Whitney U Test).

Complications and comorbidities

Complications were seen in $n = 40/112$ (35.7%) patients. Over the course of JIA, uveitis was documented in $n = 21/94$ (22.3%) patients and none of them were incident patients. The other $n = 18$ patients had not received ophthalmology screening until the time of recruitment [38]. Most of those with uveitis ($n = 17/21$, 81%) were antinuclear antibody (ANA)

positive, with seven of those (41.2%) having EO, six (35.3%) having RF- polyarthritis and four (23.5%) having PO. Of the remainder who had uveitis but were ANA negative ($n = 4/21$, 19%), three (75%) had EO and one (25%) had RF- polyarthritis. Of those patients with uveitis in our cohort, one had a cataract removed surgically and one had previously developed glaucoma. Patients with systemic onset disease, ERA, PsA and RF + polyarthritis had no uveitis. In this registry, musculoskeletal complications occurred in $n = 10/112$ (8.9%) patients, with the majority ($n = 8/10$, 80%) in the functional polyarthritis category. Musculoskeletal complications in this registry included micrognathia in four, fixed flexion deformity in three, erosive disease in two, joint damage in one, a pars defect in one, and muscle wasting in one patient.

Among $n = 79$ JIA patients having ever used Methotrexate (MTX), liver function test derangement associated with MTX therapy occurred in $n = 2/79$ (2.5%) PO patients. MTX intolerance was present in $n = 10/79$ (12.7%) patients, with anticipatory nausea and anxiety as well as needle phobia included in this category. Subcutaneous atrophy, which resulted from intra-articular steroid injection, was present in $n = 1/35$ (2.9%) PO and $n = 1/23$ (4.3%) EO patient.

Macrophage activation syndrome (MAS) affected $n = 1/5$ (20%) of the systemic onset patients. Growth retardation occurred in $n = 1/5$ (20%) systemic JIA patients due to persistent disease activity and high-dose steroid exposure.

In this registry, $n = 49/112$ (43.8%) patients had at least one comorbidity and $n = 34/49$ (69.4%) of them were in the functional polyarthritis category. Common comorbidities for JIA in our cohort included anxiety and depression ($n = 5$, 4.5%), asthma ($n = 5$, 4.5%), diseases of the skin and subcutaneous tissue (including paronychia, eczema and psoriasis, $n = 4$, 3.6%), autism spectrum disorder ($n = 4$, 3.6%), iron deficiency/anaemia ($n = 4$, 3.6%), developmental delay ($n = 4$, 3.6%), eye disease ($n = 3$, 2.7%), IBD ($n = 2$, 1.8%), coeliac disease ($n = 2$, 1.8%), Type 1 Diabetes ($n = 2$, 1.8%), chondromalacia patellae ($n = 2$, 1.8%), Sinding-Larsen Syndrome ($n = 2$, 1.8%), Epilepsy ($n = 2$, 1.8%) and short stature ($n = 2$, 1.8%). Other comorbidities were also seen in very few patients, including but not limited to Lymphoedema ($n = 1$, 0.9%), Hypothyroidism ($n = 1$, 0.9%), congenital heart disease ($n = 1$, 0.9%), Cardio-facio-cutaneous Syndrome ($n = 1$, 0.9%), Sever's disease ($n = 1$, 0.9%), Kawasaki's disease ($n = 1$, 0.9%), and hypertrichosis ($n = 1$, 0.9%).

Medication

The exposure of the cohort to medications is detailed in Table 3. At enrolment, approximately $n = 29/112$ (25.9%) were no longer taking medication. Non-steroidal anti-inflammatory drugs (NSAIDs) had been used in most patients ($n = 100/112$, 89.3%), followed by non-biologic disease-modifying anti-rheumatic drugs (DMARDs) used in $n = 83/112$ (74.1%). Of these 83 patients, MTX had been used in $n = 79/83$ (95.2%) JIA patients. Sulfasalazine ($n = 8/83$, 9.6%) and Leflunomide ($n = 6/83$, 7.2%) had also been used in treating our patients.

Eighteen out of 23 (78.3%) patients with EO and $n = 25/35$ (71.4%) with PO had received intra-articular steroid therapy, compared to $n = 10/54$ (18.5%) in the other JIA subtypes combined. Use of oral steroids had been more common in systemic onset patients ($n = 5/5$, 100%) and patients with polyarthritis ($n = 2/3$, 66.7% in RF + polyarthritis and $n = 19/32$, 59.4% in RF- polyarthritis).

Biologics had been used in $n = 26/112$ (23.2%) patients, including Adalimumab ($n = 20$, 76.9%), Etanercept ($n = 6$, 23.1%), Tocilizumab ($n = 2$, 7.7%) and Anakinra ($n = 1$, 3.8%). At enrolment, $n = 22/112$ (19.6%) were using biologics. A relatively lower proportion ($n = 1/35$, 2.9%) of children with PO were using or had used biologics, reflecting their least aggressive disease activity.

Associations between disease activity and patient-reported data

There was a significant positive correlation between CHAQ score and cJADAS (Spearman $R = 0.446$, $p < 0.001$), and between patient/carer-reported pain visual analogue scale (VAS) and cJADAS (Spearman $R = 0.700$, $p < 0.001$), which

indicates a consistency of patient- and clinician-assessed disease activity. A negative correlation was also found between disease duration and PGA (Spearman $R=-0.206$, $p=0.029$).

Discussion

In the SA cohort, we have developed a JIA registry and here we describe our cohort in detail. Our findings regarding sex distribution, disease activity and patient-reported data support the data of comparable populations in some geographical regions such as North America and Europe [39–44]. However, there are discrepancies in JIA subtype distribution and complications such as uveitis and MTX intolerance between our cohort and those in other published studies [22, 30, 42, 45, 46].

The majority of the population of SA is Caucasian. However, ethnicity data were not recorded in this registry. The main subtype distribution differences between our cohort and other published studies were seen in PsA, RF- polyarthritis and EO (Table 4) [39–41, 46, 47]. In the present study, PO was the most widely distributed subtype ($n=35/112$, 31.3%), which is consistent with the United Kingdom (UK; $n=638/1415$, 45.1%) and four Nordic countries (i.e. Denmark, Finland, Sweden, and Norway, $n=132/440$, 30%) [39, 40, 47]. However, North American, Latin American and South African children are more likely to develop polyarticular onset JIA [42, 46, 48]. PsA, the least common subtype in our study, is very uncommon in all regions, including Asia. Among Asian children, a particularly higher frequency of ERA was observed (around 36%, $p<0.001$) than in other areas [49, 50], whereas around ten percent of patients had ERA: 10.7% in this study, 11.1% in Nordic countries ($p=0.904$ when compared with this study) and 5.4% in the UK ($p=0.0208$ when compared with this study). The frequency of systemic onset JIA was the highest in Asia, North America and Latin America, and had similar frequencies in Australia and Europe (4.5% in this study versus 4.1% in Nordic and 6.8% in the UK). Compared to North America, the rate of functional polyarthritis (as per Consolaro et al. [24]) was significantly lower in our registry ($n=72/112$, 64.3%) versus $n=895/1192$ (75%) in the Childhood Arthritis and Rheumatology Research Alliance registry (CARRA, $p=0.0135$) [42]. The differences in subtype distribution remain unexplained, but may relate partly to small patient numbers in our study to date. Among Australian children, there was a significant difference in the frequency of EO compared with CLARITY data ($p<0.001$) [22]. It can be partly explained by the fact that 13% of patients from the CLARITY cohort had undifferentiated arthritis at enrolment with further classification awaited after 12-month review.

Different sex ratios according to ethnicity and regions have been shown in other epidemiological studies of JIA. Even though there is no clear gender distribution trend in African and Asian patients [8], our data have a similar profile to that of European and North American regions which is predominantly female [39, 40, 42]. Among Australian children, the sex ratio in this study is also comparable with CLARITY data, in which 67% versus 62% of patients were female ($p=0.416$) [22].

In a cross-sectional PRINTO study describing JIA cohorts from various geographic areas, Western Europe, Southern Europe, and North American cohorts were found to have very similar median disease duration of around 4.1 years. In our study, $n=101$ patients with established disease had a similar cJADAS compared to those in Southern Europe and North America ($p=0.4657$ and $p=0.1275$) [41]. However, a significantly higher median cJADAS was observed in the Western European cohort ($p=0.0086$) [41]. Similarly, fewer Western European JIA patients had inactive disease ($p=0.0204$). More Australian children's PGAs were rated as zero by the physician than Western European ($p=0.005$) and North American cohorts ($p=0.013$). However, fewer Australian children/parents reported PGE as zero than did those Southern European ($p<0.001$) or North American ($p=0.001$). In addition, Australian children/parents were more likely to score the pain VAS >0 , compared to those in Southern Europe ($p<0.001$) and North America ($p=0.0418$) [41].

Disease outcomes for newly diagnosed patients in this registry were compared with those in other cohorts. In our cohort, $n=11$ children with newly diagnosed JIA had a median PGA of 1.2, a median PGE of 1.3, a median CHAQ score of 0.4, and a median pain VAS of 3.0. Similar results were assessed in Nordic incident cohorts of 423 patients ($p>0.05$ for all, except $p=0.0291$ for pain VAS) [43]. In comparison with the 295 newly diagnosed JIA patients from the recent CARRA

study, SA incident patients had a similar median joint count ($p = 0.37$) and median CHAQ score ($p = 0.9$), despite small patient numbers [42]. However, a significantly lower PGA was observed in our cohort than in North American children [median 1.2 (IQR 0-1.9) versus median 3 (IQR 1.5–5), $p = 0.0232$]. These data suggest that Australian children with newly diagnosed JIA may have lower disease activity despite similar physical function and Joint-related symptoms than those in North America. Other patient-reported data, such as PGE and pain VAS, were not recorded in the CARRA study. In our study, the median cJADAS for the 11 incident patients was 4.9 (IQR 0.1–10). Our incident cohort had a similar disease activity compared with the Canadian inception cohort study which reported a median cJADAS of 6.5 (IQR 4–10) at enrolment ($p = 0.2707$) [44].

Worldwide, the prevalence of JIA-associated uveitis is reported to be up to 30% [1, 41]. In the SA registry, $n = 21/94$, 22.3% of patients had uveitis, which is similar with Nordic ($n = 89/440$, 20.2%) and significantly higher than German ($n = 406/3271$, 12.4%, $p = 0.0045$) and North American ($n = 94/1175$, 8%, $p < 0.001$) populations [40, 42, 45]. Asian and African populations have significantly lower rates of uveitis, compared with other areas. This may be because fewer patients had oligoarthritis and were positive in ANA, both of which are strong predictors of uveitis [51]. The lowest rates of $n = 19/379$ (5%) and $n = 44/726$ (6%) were recorded in India and Japan ($p < 0.001$ for both, when compared with this registry) [41, 52]. In our SA cohort, Uveitis was detected in $n = 4/31$ (12.9%), $n = 7/27$ (25.9%) and $n = 10/22$ (45.5%) of the PO, RF-polyarthritis and EO populations, respectively. This result is in accord with the highest uveitis risk in EO subtypes in the large cohort study of 3271 patients in Germany [45]. In our study, both active and previous episodes of uveitis were recorded at enrolment.

Musculoskeletal complications occurred in $n = 10/112$ (8.9%) patients in the current study, which included joint deformity, damage, erosive disease and muscle wasting. No comparisons could be made because of the difference in methods of assessment. For example, joint damage rate ranged from 9.7–14.7% in European and North American countries, measured by Juvenile Arthritis Damage Index (JADI)-Articular > 0 [41].

In a recent systemic JIA cohort study in Turkey [27], the frequencies of growth retardation and MAS were 11.3% ($n = 19/168$) and 11.9% ($n = 20/168$), respectively. In the German Biologics JIA Registry (BIKeR), 4.5% of their systemic JIA patients experienced MAS [53]. However, it is difficult to make a comparison with our data because of the comparatively much smaller number of our systemic JIA patients, which included one patient with growth retardation and one patient with MAS. Notably, some common complications in other populations were not found in our cohort. We did not see amyloidosis or hip replacement in the SA population [54, 55].

Among $n = 79$ patients treated with MTX in this study, $n = 10/79$ (12.7%) had MTX intolerance, with $n = 2/79$ (2.5%) patients experiencing MTX-induced liver function test derangement. A higher proportion of MTX intolerance (gastrointestinal and psychological symptoms) and elevated liver enzymes was found in a recent UK study: $n = 151/577$ (26%, $p = 0.0099$) and $n = 56/577$ (10%, $p = 0.0298$), respectively [30]. Selection bias may account for some of this difference because we included all patients treated with MTX regardless of whether or not they were receiving other DMARDs or biologic therapy, whereas the UK study included patients who were treated with MTX alone. However, we found no differences between this study and the German Methotrexate Registry in the frequency of elevated liver enzymes; $n = 2/79$, 2.5% versus $n = 15/411$, 3.6% ($p = 0.6227$) [56]. To our knowledge, comorbidities have not been reported in more recent JIA cohort studies and so no comparisons with our cohort could be made.

The main strength of our study is that we have recruited both newly diagnosed JIA patients as well as those with established disease, which reduces selection bias. Retrospective collection of data from patients with established disease is also important as it provides the ability to document current disease activity as well as disease management. In this study, we have obtained detailed patient data from a retrospective review of the case notes as well as recording real-time data such as physician assessment, patient evaluation, medications and blood test results and prospective data.

Consultation with the treating physicians and strict adherence to the ILAR criteria have enhanced the integrity and validity of our data, which will also facilitate future local and international collaborations.

Compared to the European and North American cohort studies [39–43, 56], our study has a smaller sample size ($n = 112$). This is mainly because of the relatively short period of time since registry inception, with data from a single centre. We will continue to collect prospective data in our registry with ongoing patient recruitment of both newly diagnosed and established cases of JIA. This will assist in ongoing improvement of patient care as well as providing more accurate data to estimate the prevalence and incidence of JIA in South Australia. Another limitation is that the complications and comorbidities were extracted retrospectively from medical records, at times without a clear record date of onset. Some children had therefore already recovered from the complication or comorbidity at the time of recruitment. However, collection of these data are important in the assessment of disease activity and outcomes.

Conclusions

This is the first JIA registry study conducted in SA. The epidemiological data and characteristics of JIA patients, such as subtype distribution, sex distribution, disease course and activity, major complications and comorbidities, medication exposure and patient-reported data were recorded. We found that the JIA cohort in SA is female-dominated with PO as the most common subtype, consistent with other European and Australian studies. Most prevalent patients had good disease control and had no or mild disability. One-third of the patients had complications and comorbidities occurred a greater proportion (43.8%). NSAIDs were used in most patients and biologics are the least-used, which is consistent with our subtype distribution. Patient-reported functional disability and pain were positively correlated with clinical assessment of disease activity. Further longitudinal data collection and comparisons will add to the current description of the SA JIA cohort. The establishment of this registry is a fundamental step in the development and optimisation of the clinical care of our JIA cohort and provides an important resource for collaborative research in Australia and internationally.

List Of Abbreviations

AIHW: Australian Institute of Health and Welfare; ANA: Antinuclear antibodies; BIKeR: German Biologics JIA Registry; CHAQ: Childhood Health Assessment Questionnaire; CHAQ score: CHAQ-disability index score; CI: Confidence intervals; CID: clinically inactive disease; cJADAS: Clinical Juvenile Idiopathic Arthritis Disease Activity Score; CLARITY: Childhood Arthritis Risk Factor Identification Study; DMARDs: Non-biologic disease-modifying anti-rheumatic drugs; EO: extended oligoarticular onset disease; ERA: enthesitis-related arthritis; IA: intra-articular; ILAR: International League of Associations for Rheumatology; IQR: interquartile range; IV: intravenously; JIA: Juvenile idiopathic arthritis; MAS: Macrophage activation syndrome; MTX: Methotrexate; NSAIDs: Non-steroidal anti-inflammatory drugs; PGA: physician global assessment; PGE: patient global evaluation; PO: persistent oligoarticular onset disease; PsA: Psoriatic arthritis; RF: Rheumatoid factor; SA: South Australia; SD: Standard deviation; UK: United Kingdom; VAS: Visual analogue scale; WCH: Women's and Children's Hospital.

Declarations

Ethics approval and consent to participate

This study was approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/59).

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to our privacy policy but are available from the corresponding author on reasonable request.

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

MM was financially supported by the Australian Government Research Training Program (RTP) Scholarship.

Author's contributions

Study conception and design were contributed by CB and TC. MM and CB were involved in the data acquisition. MM conducted the analyses and drafted the work. SE re-performed the data analyses. MM, CB, CG and TC were involved in interpretation of the data. All authors assisted with the substantive revisions, read and approved the final submitted version for publication.

Acknowledgements

We are particularly grateful to the patients and their parents for participating in the present study. We thank Dr Mark Friswell, Dr Geetha Chandran, Hana Connolly, Madeleine Hall, Gabriella Graves and Rheumatology Nurse Consultant Mrs Tracy Rose, for their work in recruitment, obtaining informed consent, as well as data collection and data verification. We also wish to thank the volunteers, Tijana Dejanovic and Saujas Chanana, for their contributions to data entry.

Author details

¹ University of Adelaide Discipline of Paediatrics, Women's and Children's Hospital, South Australia, Australia. ² Adelaide Medical School, Faculty of Health and Medical Sciences, University of Adelaide, South Australia, Australia. ³ Adelaide Health Technology Assessment, University of Adelaide, South Australia, Australia. ⁴ SA Birth Defects Register, Paediatric Rehabilitation Department, Women's and Children's Health Network, South Australia, Australia. ⁵ Women's and Children's Hospital Department of Rheumatology, South Australia, Australia

References

1. Sen ES, Ramanan AV. Juvenile idiopathic arthritis-associated uveitis. *Best Pract Res Clin Rheumatol*. 2017;31(4):517–34.
2. Flato B, Lien G, Smerdel A, Vinje O, Dale K, Johnston V, Sorskaar D, Moum T, Ploski R, Forre O. Prognostic factors in juvenile rheumatoid arthritis: a case-control study revealing early predictors and outcome after 14.9 years. *J Rheumatol*. 2003;30(2):386–93.
3. Sarma PK, Misra R, Aggarwal A. Physical disability, articular, and extra-articular damage in patients with juvenile idiopathic arthritis. *Clin Rheumatol*. 2008;27(10):1261–5.

4. Raab A, Sengler C, Niewerth M, Klotsche J, Horneff G, Zink A, Girschick H, Weber K, Minden K. Comorbidity profiles among adult patients with juvenile idiopathic arthritis: results of a biologic register. *Clin Exp Rheumatol*. 2013;31(5):796–802.
5. Manners PJ, Bower C. Worldwide prevalence of juvenile arthritis why does it vary so much? *J Rheumatol*. 2002;29(7):1520–30.
6. Harrold LR, Salman C, Shoor S, Curtis JR, Asgari MM, Gelfand JM, Wu JJ, Herrinton LJ. Incidence and prevalence of juvenile idiopathic arthritis among children in a managed care population, 1996–2009. *J Rheumatol*. 2013;40(7):1218–25.
7. Andersson Gare B. Juvenile arthritis—who gets it, where and when? A review of current data on incidence and prevalence. *Clin Exp Rheumatol*. 1999;17(3):367–74.
8. Saurenmann RK, Rose JB, Tyrrell P, Feldman BM, Laxer RM, Schneider R, Silverman ED. Epidemiology of juvenile idiopathic arthritis in a multiethnic cohort: ethnicity as a risk factor. *Arthritis Rheum*. 2007;56(6):1974–84.
9. Schinzel V, da Silva SGL, Terrier MT, Len CA. Prevalence of juvenile idiopathic arthritis in schoolchildren from the city of Sao Paulo, the largest city in Latin America. *Adv Rheumatol*. 2019;59(1):32.
10. Abou El-Soud AM, El-Najjar AR, El-Shahawy EE, Amar HA, Hassan TH, Abd-Allaha SH, Ragab HM. Prevalence of juvenile idiopathic arthritis in Sharkia Governorate, Egypt: epidemiological study. *Rheumatol Int*. 2013;33(9):2315–22.
11. Helmick CG, Felson DT, Lawrence RC, Gabriel S, Hirsch R, Kwoh CK, Liang MH, Kremers HM, Mayes MD, Merkel PA, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States. Part I. *Arthritis Rheum*. 2008;58(1):15–25.
12. Krause ML, Crowson CS, Michet CJ, Mason T, Muskardin TW, Matteson EL. Juvenile Idiopathic Arthritis in Olmsted County, Minnesota, 1960–2013. *Arthritis rheumatology*. 2016;68(1):247–54.
13. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007;369(9563):767–78.
14. Lin CH, Lin CL, Shen TC, Wei CC. Epidemiology and risk of juvenile idiopathic arthritis among children with allergic diseases: a nationwide population-based study. *Pediatr Rheumatol Online J*. 2016;14(1):15.
15. Berthold E, Mansson B, Kahn R. Outcome in juvenile idiopathic arthritis: a population-based study from Sweden. *Arthritis Res Ther*. 2019;21(1):218.
16. Pruunsild C, Uibo K, Liivamagi H, Tarraste S, Talvik T, Pelkonen P. Incidence of juvenile idiopathic arthritis in children in Estonia: a prospective population-based study. *Scand J Rheumatol*. 2007;36(1):7–13.
17. von Koskull S, Truckenbrodt H, Holle R, Hormann A. Incidence and prevalence of juvenile arthritis in an urban population of southern Germany: a prospective study. *Ann Rheum Dis*. 2001;60(10):940–5.
18. Kiessling U, Doring E, Listing J, Meincke J, Schontube M, Strangfeld A, Zink A. Incidence and prevalence of juvenile chronic arthritis in East Berlin 1980–88. *J Rheumatol*. 1998;25(9):1837–43.
19. Berntson L, Andersson Gare B, Fasth A, Herlin T, Kristinsson J, Lahdenne P, Marhaug G, Nielsen S, Pelkonen P, Rygg M, et al. Incidence of juvenile idiopathic arthritis in the Nordic countries. A population based study with special reference to the validity of the ILAR and EULAR criteria. *J Rheumatol*. 2003;30(10):2275–82.
20. Manners PJ, Diepeveen DA. Prevalence of juvenile chronic arthritis in a population of 12-year-old children in urban Australia. *Pediatrics*. 1996;98(1):84–90.
21. Ellis JA, Ponsonby AL, Pezic A, Chavez RA, Allen RC, Akikusa JD, Munro JE. CLARITY - ChiLdhood Arthritis Risk factor Identification sTudY. *Pediatr Rheumatol Online J*. 2012;10(1):37.
22. Tiller G, Buckle J, Allen R, Munro J, Gowdie P, Cox A, Akikusa J. Juvenile idiopathic arthritis managed in the new millennium: one year outcomes of an inception cohort of Australian children. *Pediatr Rheumatol Online J*. 2018;16(1):69.

23. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol.* 2004;31(2):390–2.
24. Consolaro A, Negro G, Chiara Gallo M, Bracciolini G, Ferrari C, Schiappapietra B, Pistorio A, Bovis F, Ruperto N, Martini A, et al. Defining criteria for disease activity states in nonsystemic juvenile idiopathic arthritis based on a three-variable juvenile arthritis disease activity score. *Arthritis Care Res.* 2014;66(11):1703–9.
25. Singh G, Athreya BH, Fries JF, Goldsmith DP. Measurement of health status in children with juvenile rheumatoid arthritis. *Arthritis Rheum.* 1994;37(12):1761–9.
26. McErlane F, Beresford MW, Baildam EM, Chieng SE, Davidson JE, Foster HE, Gardner-Medwin J, Lunt M, Wedderburn LR, Thomson W, et al. Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. *Ann Rheum Dis.* 2013;72(12):1983–8.
27. Barut K, Adrovic A, Sahin S, Tarcin G, Tahaoglu G, Koker O, Yildiz M, Kasapcopur O. Prognosis, complications and treatment response in systemic juvenile idiopathic arthritis patients: A single-center experience. *Int J Rheum Dis.* 2019;22(9):1661–9.
28. Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A, Arico M, Avcin T, Behrens EM, De Benedetti F, et al. 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis: A European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. *Ann Rheum Dis.* 2016;75(3):481–9.
29. Vitale AT, Graham E, de Boer JH. Juvenile idiopathic arthritis-associated uveitis: clinical features and complications, risk factors for severe course, and visual outcome. *Ocul Immunol Inflamm.* 2013;21(6):478–85.
30. Kearsley-Fleet L, Vicente Gonzalez L, Steinke D, Davies R, De Cock D, Baildam E, Beresford MW, Foster HE, Southwood TR, Thomson W, et al. **Methotrexate persistence and adverse drug reactions in patients with juvenile idiopathic arthritis.** *Rheumatology* 2019.
31. Brabnikova Maresova K. Secondary osteoporosis in patients with juvenile idiopathic arthritis. *J Osteoporos.* 2011;2011:569417.
32. Heiligenhaus A, Heinz C, Edelsten C, Kotaniemi K, Minden K. Review for disease of the year: epidemiology of juvenile idiopathic arthritis and its associated uveitis: the probable risk factors. *Ocul Immunol Inflamm.* 2013;21(3):180–91.
33. Angeles-Han S, Yeh S. Prevention and management of cataracts in children with juvenile idiopathic arthritis-associated uveitis. *Curr Rheumatol Rep.* 2012;14(2):142–9.
34. Ording Muller LS, Humphries P, Rosendahl K. The joints in juvenile idiopathic arthritis. *Insights Imaging.* 2015;6(3):275–84.
35. Naz S, Asif M, Naz F, Farooq H, Hamid MH. Spectrum of Joint Deformities in Children with Juvenile Idiopathic Arthritis. *J Coll Physicians Surg Pak.* 2018;28(6):470–3.
36. Walton AG, Welbury RR, Thomason JM, Foster HE. Oral health and juvenile idiopathic arthritis: a review. *Rheumatology.* 2000;39(5):550–5.
37. Lam C, Young N, Marwaha J, McLimont M, Feldman BM. Revised versions of the Childhood Health Assessment Questionnaire (CHAQ) are more sensitive and suffer less from a ceiling effect. *Arthritis Rheum.* 2004;51(6):881–9.
38. Lee JJY, Duffy CM, Guzman J, Oen K, Barrowman N, Rosenberg AM, Shiff NJ, Boire G, Stringer E, Spiegel L, et al. Prospective Determination of the Incidence and Risk Factors of New-Onset Uveitis in Juvenile Idiopathic Arthritis: The Research in Arthritis in Canadian Children Emphasizing Outcomes Cohort. *Arthritis Care Res.* 2019;71(11):1436–43.
39. Hyrich KL, Lal SD, Foster HE, Thornton J, Adib N, Baildam E, Gardner-Medwin J, Wedderburn LR, Chieng A, Davidson J, et al. Disease activity and disability in children with juvenile idiopathic arthritis one year following presentation to paediatric rheumatology. Results from the Childhood Arthritis Prospective Study. *Rheumatology.* 2010;49(1):116–22.

40. Nordal E, Zak M, Aalto K, Berntson L, Fasth A, Herlin T, Lahdenne P, Nielsen S, Straume B, Rygg M, et al. Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. *Arthritis Rheum.* 2011;63(9):2809–18.
41. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, Bovis F, De Inocencio J, Demirkaya E, Flato B, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: an observational cohort study. *Lancet Child Adolesc Health.* 2019;3(4):255–63.
42. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, Best B, Jones J, Schanberg LE, Investigators CR. The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. *Pediatr Rheumatol Online J.* 2017;15(1):30.
43. Rypdal V, Arnstad ED, Aalto K, Berntson L, Ekelund M, Fasth A, Glerup M, Herlin T, Nielsen S, Peltoniemi S, et al. Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study. *Arthritis Res Ther.* 2018;20(1):91.
44. Batthish M, Berard R, Cabral D, Bolaria R, Chedeville G, Duffy C, Gerhold K, Gerschman T, Huber A, Proulx-Gauthier JP, et al: **A new Canadian inception cohort for juvenile idiopathic arthritis: The Canadian Alliance of Pediatric Rheumatology Investigators Registry.** *Rheumatology* 2020.
45. Heiligenhaus A, Niewerth M, Ganser G, Heinz C, Minden K. German Uveitis in Childhood Study G: **Prevalence and complications of uveitis in juvenile idiopathic arthritis in a population-based nation-wide study in Germany: suggested modification of the current screening guidelines.** *Rheumatology.* 2007;46(6):1015–9.
46. Gutierrez-Suarez R, Pistorio A, Cespedes Cruz A, Norambuena X, Flato B, Rumba I, Harjacek M, Nielsen S, Susic G, Mihaylova D, et al. Health-related quality of life of patients with juvenile idiopathic arthritis coming from 3 different geographic areas. The PRINTO multinational quality of life cohort study. *Rheumatology.* 2007;46(2):314–20.
47. Shoop-Worrall SJW, Verstappen SMM, Baidam E, Chieng A, Davidson J, Foster H, Ioannou Y, McErlane F, Wedderburn LR, Thomson W, et al. How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition. *Ann Rheum Dis.* 2017;76(8):1381–8.
48. Weakley K, Esser M, Scott C. Juvenile idiopathic arthritis in two tertiary centres in the Western Cape, South Africa. *Pediatr Rheumatol Online J.* 2012;10(1):35.
49. Shen CC, Yeh KW, Ou LS, Yao TC, Chen LC, Huang JL: **Clinical features of children with juvenile idiopathic arthritis using the ILAR classification criteria: a community-based cohort study in Taiwan.** *Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi* 2013, **46**(4):288–294.
50. Kunjir V, Venugopalan A, Chopra A. Profile of Indian patients with juvenile onset chronic inflammatory joint disease using the ILAR classification criteria for JIA: a community-based cohort study. *J Rheumatol.* 2010;37(8):1756–62.
51. Carvounis PE, Herman DC, Cha S, Burke JP. Incidence and outcomes of uveitis in juvenile rheumatoid arthritis, a synthesis of the literature. *Graefe's archive for clinical experimental ophthalmology = Albrecht von Graefes Archiv fur klinische experimentelle Ophthalmologie.* 2006;244(3):281–90.
52. Yasumura J, Yashiro M, Okamoto N, Shabana K, Umabayashi H, Iwata N, Okura Y, Kubota T, Shimizu M, Tomiita M, et al. Clinical features and characteristics of uveitis associated with juvenile idiopathic arthritis in Japan: first report of the pediatric rheumatology association of Japan (PRAJ). *Pediatr Rheumatol Online J.* 2019;17(1):15.
53. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, Trauzeddel R, Ganser G, Weller-Heinemann F, Haas JP. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. *Arthritis Res Ther.* 2017;19(1):256.
54. Chantarogh S, Vilaiyuk S, Tim-Aroon T, Worawichawong S. Clinical improvement of renal amyloidosis in a patient with systemic-onset juvenile idiopathic arthritis who received tocilizumab treatment: a case report and literature review. *BMC Nephrol.* 2017;18(1):159.

55. Marino A, Pontikaki I, Truzzi M, Menon A, Artusi C, Di Marco M, Randelli PS, Cimaz R, Vigano R: **Early joint replacement in juvenile idiopathic arthritis (JIA): trend over time and factors influencing implant survival.** *Arthritis care & research* 2020.
56. Klein A, Kaul I, Foeldvari I, Ganser G, Urban A, Horneff G. Efficacy and safety of oral and parenteral methotrexate therapy in children with juvenile idiopathic arthritis: an observational study with patients from the German Methotrexate Registry. *Arthritis Care Res.* 2012;64(9):1349–56.

Tables

Table 1
Characteristics of 112 children with juvenile idiopathic arthritis.

Female sex, n (%)	75 (67%)
Prevalent cases, n (%)	101 (90.2%)
JIA subtype, ILAR criteria, n (%)	
Persistent oligoarthritis	35 (31.3%)
Extended oligoarthritis	23 (20.5%)
RF- Polyarthritis	32 (28.6%)
RF + Polyarthritis	3 (2.7%)
Enthesitis-related arthritis	12 (10.7%)
Psoriatic arthritis	2 (1.8%)
Systemic onset arthritis	5 (4.5%)
Age at onset, median (IQR), years	5.4 (2.0-9.7)
Age at diagnosis, median (IQR), years	6.2 (2.6–10.7)
Age at recruitment, mean $\pm$ SD, years	11.7 $\pm$ 4.4
Disease duration, median (IQR), years	3.6 (1.3–7.6)
Abbreviations: ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JIA: juvenile idiopathic arthritis; RF: rheumatoid factor; SD: standard deviation.	

Table 2

Disease activity and patient-reported outcomes in South Australian cohort by juvenile idiopathic arthritis subtypes, at recruitment.

JIA subtype, ILAR criteria, n	cJADAS, median (IQR)	Reached CID as per cJADAS, n (% of subtype)	PGA, median (IQR)	PGE, median (IQR)	CHAQ score, median (IQR)	None to low disability as per CHAQ score, n (% of subtype)	Pain VAS, median (IQR)
Persistent oligoarthritis (n = 35)	1.0 (0.0-5.7)	18 (51.4%)	0.0 (0.0-0.9)	0.5 (0.0-2.6)	0.1 (0.0-0.8)	26 (74.3%)	0.8 (0.0-3.0)
Extended oligoarthritis (n = 23)	2.2 (0.3-5.5)	10 (43.5%)	0.0 (0.0-1.1)	1.2 (0.1-3.0)	0.3 (0.0-0.8)	17 (73.9%)	1.5 (0.1-3.4)
RF-Polyarthritis (n = 32)	1.6 (0.0-5.1)	13 (40.6%)	0.1 (0.0-1.7)	0.5 (0.0-2.3)	0.0 (0.0-0.8)	23 (71.9%)	0.3 (0.0-2.8)
RF + Polyarthritis (n = 3)	4.9 (4.6-*)	0 (0.0%)	1.8 (0.0-*)	4.6 (2.0-*)	0.3 (0.0-*)	3 (100.0%)	3.8 (0.0-*)
Enthesitis-related arthritis (n = 12)	0.3 (0.0-2.7)	8 (66.7%)	0.0 (0.0-0.8)	0.1 (0.0-1.6)	0.1 (0.0-0.5)	11 (91.7%)	0.8 (0.1-3.9)
Psoriatic arthritis (n = 2)	1.2 (0.2-*)	1 (50.0%)	0.6 (0.0-*)	0.6 (0.2-*)	0.2 (0.0-*)	2 (100.0%)	0.7 (0.5-*)
Systemic onset arthritis (n = 5)	1.3 (0.1-5.5)	2 (40.0%)	0.0 (0.0-1.1)	0.2 (0.1-5.0)	0.4 (0.1-0.9)	3 (60.0%)	0.3 (0.1-4.3)
Overall (n = 112)	1.3 (0.1-5.0)	52 (46.4%)	0.0 (0.0-1.1)	0.5 (0.0-2.4)	0.1 (0.0-0.6)	85 (75.9%)	0.8 (0.0-3.0)
Abbreviations: CHAQ: Childhood Health Assessment Questionnaire; CHAQ score: CHAQ-disability index score; CID: clinically inactive disease; cJADAS: clinical Juvenile Arthritis Disease Activity Score; ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JIA: juvenile idiopathic arthritis; None to low disability: none-mild disability with CHAQ score = 0-0.13 and mild-moderate disability with CHAQ score = 0.131-0.63; PGA: physician global assessment; PGE: patient global evaluation; RF: rheumatoid factor; VAS: visual analogue scale. * not defined							

Table 3
Medication exposure by juvenile idiopathic arthritis subtypes [ever used, n(%)].

JIA subtype, ILAR criteria, n	Any	NSAIDs	DMARDs	Biologics	Steroids IV	Steroids oral	Steroids IA
Persistent oligoarthritis (n = 35)	35 (100%)	30 (86%)	13 (37%)	1 (3%)	0 (0%)	2 (6%)	25 (71%)
Extended oligoarthritis (n = 23)	23 (100%)	22 (96%)	20 (87%)	6 (26%)	0 (0%)	9 (39%)	18 (78%)
RF- Polyarthritis (n = 32)	32 (100%)	30 (94%)	31 (97%)	10 (31%)	7 (22%)	19 (59%)	8 (25%)
RF + Polyarthritis (n = 3)	3 (100%)	2 (67%)	3 (100%)	1 (33%)	1 (33%)	2 (67%)	1 (33%)
Enthesitis-related arthritis (n = 12)	12 (100%)	10 (83%)	9 (75%)	5 (42%)	2 (17%)	5 (42%)	0 (0%)
Psoriatic arthritis (n = 2)	2 (100%)	2 (100%)	2 (100%)	1 (50%)	0 (0%)	1 (50%)	1 (50%)
Systemic onset arthritis (n = 5)	5 (100%)	4 (80%)	5 (100%)	2 (40%)	4 (80%)	5 (100%)	0 (0%)
Overall (n = 112)	112 (100%)	100 (89%)	83 (74%)	26 (23%)	14 (13%)	43 (38%)	53 (47%)
Abbreviations: Biologics: i.e. Adalimumab, Anakinra, Etanercept and Tocilizumab; DMARDs: non-biologic disease-modifying anti-rheumatic drugs, including Methotrexate, Leflunomide and Sulfasalazine; IA: intra-articular; IV: intravenously; ILAR: International League of Associations for Rheumatology; JIA: juvenile idiopathic arthritis; NSAIDs: non-steroidal anti-inflammatory drugs; RF: rheumatoid factor.							

Table 4
Comparison of juvenile idiopathic arthritis subtype distribution among different geographical regions.

JIA subtype, ILAR criteria, n (%)	South Australia <i>n</i> = 112	CLARITY, Victoria [22] <i>n</i> = 134	Nordic countries [40] <i>n</i> = 440	United Kingdom [47] <i>n</i> = 1415	North America [42] <i>n</i> = 1192	Taiwan, China [49] <i>n</i> = 195	India [50] <i>n</i> = 235
Persistent oligoarthritis	35 (31.3%)	45 (33.6%)	132 (30.0%)	638 (45.1%)**	152 (12.8%)***	32 (16.4%)**	39 (16.6%)**
Extended oligoarthritis	23 (20.5%)	3 (2.2%)***	78 (17.7%)	69 (4.9%)***	102 (8.6%)***	13 (6.7%)***	10 (4.3%)***
RF- Polyarthritis	32 (28.6%)	34 (25.4%)	80 (18.2%)*	292 (20.6%)*	510 (42.8%)**	23 (11.8%)***	41 (17.4%)*
RF + Polyarthritis	3 (2.7%)	3 (2.2%)	3 (0.7%)	49 (3.5%)	101 (8.5%)*	9 (4.6%)	28 (11.9%)**
Enthesitis-related arthritis	12 (10.7%)	13 (9.7%)	49 (11.1%)	77 (5.4%) *	104 (8.7%)	73 (37.4%)***	84 (35.7%)***
Psoriatic arthritis	2 (1.8%)	9 (6.7%)	14 (3.2%)	97 (6.9%)*	57 (4.8%)	2 (1.5%)	3 (1.3%)
Systemic onset arthritis	5 (4.5%)	10 (7.5%)	18 (4.1%)	96 (6.8%)	154 (12.9%)**	37 (19.0%)***	19 (8.1%)
Undifferentiated arthritis	0 (0.0%)	17 (12.7%)***	66 (15.0%)***	97 (6.9%)**	12 (1.0%)	5 (2.6%)	11 (4.7%)*
* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$ when compared with South Australia.							
Abbreviations: CLARITY: Childhood Arthritis Risk Factor Identification Study; ILAR: International League of Associations for Rheumatology; JIA: juvenile idiopathic arthritis; Nordic countries: i.e. Denmark, Finland, Sweden, and Norway; RF: rheumatoid factor.							