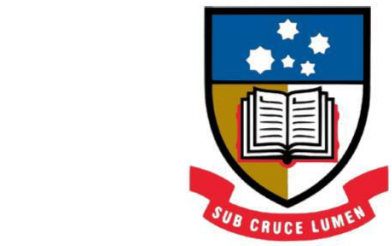

THE UNIVERSITY of ADELAIDE

THE ESTABLISHMENT OF A REGISTRY FOR JUVENILE IDIOPATHIC ARTHRITIS PATIENTS IN SOUTH AUSTRALIA

A thesis submitted in fulfilment for degree of

DOCTOR OF PHILOSOPHY

in

Medicine

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Adelaide Medical School

The University of Adelaide

By

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SUMMARY

Juvenile idiopathic arthritis (JIA) is a complex term that describes inflammatory chronic arthritis that occurs in children and adolescents for unknown reasons. There is still no cure for JIA, though drugs and treatments can control and lessen the disease duration. However, the disease progresses in fluctuation and lifelong effects are experienced by nearly half of the patients and their families. For several patients with JIA, functional ability and psychosocial health are the chief elements of their wellbeing. Despite good control of arthritis and the increasing understanding of patient-centred care, epidemiology and characteristics of JIA patients are indistinct, especially in South Australia (SA). Further, patient-reported data and experiences are increasingly being emphasised in paediatric rheumatology clinical practice worldwide. For these reasons, it is imperative to utilise appropriate measures to draw an overall picture of current clinical practice for the JIA populations in SA. The aim of this thesis was to set up a JIA registry in SA that would enable the evaluation of disease activity, disease outcomes, and the status quo of treatment, and present data from the first phase (Chapter 3). These studies also explored the relationship between routine clinical outcomes and patient-reported outcome and experience measures (PROMs and PREMs) (Chapter 4). To support the accuracy and feasibility of our registry method by verifying the evidence on experiences of living with JIA, a qualitative systematic review including 10 studies and 61 findings was accomplished (Chapter 2). The findings presented in this thesis highlighted the unique characteristics of this cohort in comparison to other published studies (Chapter 2 - 4). The results of these studies also supported that patients and parents still report some negative experiences, despite better clinical-measured scores (Chapter 3 & 4). This picture will be used to direct local clinical practice and, most significantly, guide the development of new strategies to optimise treatment and care in JIA. Further studies are necessary to elucidate the complex relationship between both PROMs and PREMs and clinical outcome measures.

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DETAILS OF PUBLICATIONS

PUBLICATIONS ARISING FROM THIS THESIS

1. **Min M**, Hancock DG, Aromataris E, Crotti T, Boros C. Experiences of living with juvenile idiopathic arthritis: a qualitative systematic review protocol. JBI Evid Synth. 2020 Sep;18(9):2058-2064. doi: 10.11124/JBISRIR-D-19-00301. PMID: 32925420. (Appendix I; Accepted version of manuscript)

2. **Min M**, Hancock DG, Aromataris E, Crotti T, Boros C. Experiences of living with juvenile idiopathic arthritis: a qualitative systematic review. JBI Evid Synth. 2021. *In press*. (Chapter 2; Accepted version of manuscript)

3. **Min M**, Edwards S, Gibson C, Crotti T, Boros C. Juvenile Idiopathic Arthritis in South Australia. *Under review*. (Chapter 3; Submitted)

4. **Min M**, Edwards S, Gibson C, Crotti T, Boros C. Analysis of clinical outcomes and patient-reported data in Juvenile Idiopathic Arthritis: a prospective outcome study. *Under review*. (Chapter 4; Submitted)

CONFERENCE ABSTRACTS AND ORAL PRESENTATIONS

Australian Rheumatology Association 2021 Annual Scientific Meeting

Hybrid Virtual Conference

Abstract accepted *21-23 May 2021*

- Title: Analysis of clinical outcomes and patient-reported data in Juvenile Idiopathic Arthritis: a prospective outcome study

Robinson Research Institute 2020 symposium

Robinson Research Institute, Adelaide

Oral and poster presentation *18 November 2020*

- Title: Analysis of clinical outcomes and patient-reported data in Juvenile Idiopathic Arthritis

Awarded Best Student Poster

14th annual Florey postgraduate research conference

Virtual Conference (Adelaide)

Oral and poster presentation *30 September 2020*

- Title: Epidemiology of Juvenile Idiopathic Arthritis (JIA) in Children and Young People in South Australia

PReS 2020 E-Congress & PReS 2020 YIM

Virtual event due to COVID-19 (Prague)

E-Poster and oral presentation *23-25 September 2020*

- Title: Establishment of a Registry for Juvenile Idiopathic Arthritis Patients in South Australia: Focus on Patient-Reported Outcome and Experience Measures (PROMS/PREMS)

PReS 2020 YIM

Virtual event due to COVID-19 (Prague)

E-Poster presentation *22-23 September 2020*

- Title: Establishment of a Registry for Juvenile Idiopathic Arthritis Patients in South Australia: Focus on Patient-Reported Outcome and Experience Measures (PROMS/PREMS)

ARA 2020 Annual Scientific Meeting

Cancelled due to COVID-19 (Sydney)

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- Title: Establishment of a Registry for Juvenile Idiopathic Arthritis (JIA) Patients in South Australia (SA): Focus on Patient Reported Outcome Measures (PROMs) and Experiences (PREMs)
- Link: https://acrabstracts.org/abstract/establishment-of-a-registry-for-juvenile-idiopathic-arthritis-jia-patients-in-south-australia-sa-focus-on-patient-reported-outcome-measures-proms-and-experiences-prems/
- Number: 074

ARA SA Branch Annual Scientific Meeting 2019

Adelaide Convention Centre, Adelaide

Oral presentation *1 November 2019*

- Title: Updates on the establishment of a registry for Juvenile Idiopathic Arthritis patients in South Australia: Focus on patient reported outcome measures (PROMs) and experiences (PREMs)

ASMR SA 2019

Adelaide Convention Centre, Adelaide

Poster presentation *5 June 2019*

- Title: Children's and parents' experiences of living with juvenile idiopathic arthritis: a qualitative systematic review protocol

DECLARATION

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint-award of this degree.

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I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Signed .....

Date .....09/08/2021.....

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This day has finally come. When I write this section, my days at the University of Adelaide are coming to an end. It started in the golden autumn of 2018 and will end in the gentle spring of 2021.

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Chapter 1. Overview

In the first chapter of this thesis, a background to Juvenile Idiopathic Arthritis (JIA) and its common outcome measures is provided, followed by the methodological basis for this research project including a review of worldwide registries in JIA.

The published systematic review protocol [1] is presented in Appendix I. The systematic review, as accepted in *JBI Evidence Synthesis*, is presented in Chapter 2. The protocol details the methodology of a review project evaluating and synthesising the qualitative evidence to understand the perspectives and experiences of children and families living with JIA. Findings of the review project are detailed in Chapter 2 (Section: Summary of Findings, Review findings, and Discussion), which provides a methodological basis for the follow-up research in Chapter 3 and 4.

In Chapter 3, clinically measured disease activity and patient-reported data are firstly reported for JIA populations in South Australia (SA). Comparisons regarding the discrepancies in priorities between the view of patients and physicians can be found in Chapter 4. In Chapter 5, the discussion of these studies is presented and extended to allow future considerations.

Due to the Thesis by Publication requirements at the University of Adelaide, where Chapter 2, Chapter 3, Chapter 4, and Appendix I represent discrete, standalone manuscript submissions, some repetition of information, for instance introductory content in Chapter 3 and 4, is present and cannot be avoided. Due to individual journal requirements, Chapter 2, Chapter 3, and Chapter 4 are presented in American English spelling and each have a different referencing style and a unique reference list.

1.1 Introduction

JIA is an inflammatory disease occurring in childhood and is characterised by pain and impaired joint function, with a possible occurrence of systemic damage. It is determined by a complex interaction between the environment and genetics, but the cause and

pathogenetic mechanisms of this interaction are unknown. Accordingly, there are no drugs or treatments to cure JIA. Appropriate use of drugs and care can help patients to achieve normal lives, but they cannot be completely cured with current medical practices. JIA symptoms can fluctuate from day to day and month to month. Patients need regular follow-up and imaging investigations even if their arthritis is in remission. Therefore, the establishment of a JIA registry to continuously collect, record and analyse clinical data and patient perspectives, which helps in better understanding the occurrence and the disease course of JIA, and in personalised treatment and care for patients, is warranted.

In this chapter, the current understanding of JIA progression and its clinical perspectives will be introduced in conjunction with a presentation of the various measurements of disease outcomes. Furthermore, registries are extensively used to record patient data and disease information in JIA and/or other inflammatory and autoimmune diseases. This chapter will review the mainstream registries in JIA worldwide, highlighting the importance of formative collection and analysis of registry data for monitoring the disease courses and outcomes of JIA.

1.1.1 JIA Definition and classification

JIA is an umbrella term that is used to describe various kinds of inflammatory arthritis initially occurring in children and adolescents and usually having a fluctuating disease course. 'Juvenile' means the condition initially happens in young people (before the age of 16), while 'Idiopathic' means the cause is unknown [2]. Thus, septic arthritis and arthritis caused by other known conditions like bacterial infections, malignancy or trauma are excluded from the scope of JIA [3].

Joint pain and inflammation are the main symptoms of JIA. Swelling, tenderness and stiffness is common in the affected joints. Any joints can become inflamed and the number of inflamed joints ranges from one to many [4]. This number is considered in the classification of JIA (see below). In general, patients with JIA may feel unwell and fatigued, and present with rashes, ocular inflammation and other complications may occur in some of the patients. A quite distinctive type is systemic JIA, which presents

with a quotidian fever and sometimes with rash, hepatosplenomegaly and serositis [5]. In most patients, the disease course is fluctuating. JIA symptoms can become worse and then silence – these are called flares/relapses and remission [6].The morbidity of JIA can last for a lifetime – with 50% of children still maintaining active disease after entering adult life [4]. In addition, the burden of disease and damage is still high even in patients 18 years after the onset [7].

Over the past several decades, the classification of JIA and the commonly used terms to describe it have changed. Since adopted by the International League of Associations for Rheumatology (ILAR) in 2001, the current classification of JIA has incorporated the concept of juvenile chronic arthritis (JCA) and juvenile rheumatoid arthritis (JRA), from the perspective of both terminology and definition [3]. However, researchers and clinicians in the US, in some cases, continue to use 'JRA' as the preferred terminology. This is problematic as there remain differences in diagnostic criteria and subtypes between JIA and JRA [3, 8, 9]. When the term JIA began to replace the term JRA in the mid-1990s, extra subtypes were added, including enthesitis-related arthritis, psoriatic arthritis, and undifferentiated arthritis (see below).

Following the recommendations of ILAR categories [3], JIA can be classified into seven subgroups as follows (Table 1.1.1): systemic arthritis, oligoarthritis, rheumatoid factor positive (RF+) polyarthritis, rheumatoid factor negative (RF-) polyarthritis, psoriatic arthritis (PsA), enthesitis-related arthritis (ERA) and undifferentiated arthritis. The classification of each is based on several rigorous inclusion and exclusion criteria, and those patients that do not satisfy the condition for any subtype, are classified into the subtype of undifferentiated arthritis. Further, oligoarthritis affects four or fewer joints, and can be further classified into persistent oligoarthritis (PO) (the number of affected joints remains stable after 6 months) and extended oligoarthritis (EO) (more than four joints get affected after six months of symptom onset) [10]. These ILAR classification criteria are used throughout this thesis.

Table 1.1.1. Juvenile Idiopathic Arthritis classification according to International

League of Associations for Rheumatology (ILAR), 2001 [3]

Systemic arthritis
Oligoarthritis (persistent [PO] or extended [EO])
Polyarthritis (rheumatoid factor positive)
Polyarthritis (rheumatoid factor negative)
Psoriatic arthritis
Enthesitis-related arthritis
Undifferentiated arthritis

Abbreviations: EO: extended oligoarthritis; PO: persistent oligoarthritis.

Even though ILAR JIA classification criteria has become the international standard, there is growing evidence suggesting that this current classification requires further verification and revision, since some homogeneities exist between subtypes and some categories are present both in children and in adults [11, 12]. This is a cause of confusion. For example, systemic JIA might be re-classified as an auto-inflammatory disease due to its similarity with Still disease in adults; RF-negative polyarthritis and PsA share characteristics of antinuclear antibody (ANA) positivity and early onset. Additionally, the requirement of dermatologist diagnosis can be removed from the criteria of PsA, and the undifferentiated category might be re-defined [3, 11, 12].

Through increasing understanding and comparisons of disease characteristics and internal pathogenetic mechanisms of JIA subtypes, further research would likely improve the revision of current classification criteria, and consequently improve targeted treatment towards subtypes, and further improve disease outcomes. Registries may facilitate this by providing a normalised platform for clinicians and researchers, harmonising datasets, allow for sharing of data and identifying shared challenges.

1.1.2 Epidemiology

JIA is the most common rheumatologic disease of childhood, however studies

investigating JIA, and the extent of available patient data varies considerably between countries and regions. In some countries, relevant data are scarce or unavailable. Therefore, the great regional differences shown in the prevalence and incidence of JIA may be partly attributed to the unbalanced distribution of original data [13-15]. Other paediatric rheumatologic disease includes, but is not limited to, Juvenile Dermatomyositis, Juvenile Ankylosing Spondylitis, Kawasaki Disease and Scleroderma. The prevalence of Kawasaki disease is estimated at 100 /100,000 individuals in Asia, which has a higher risk than Europe and America [16]. Juvenile Dermatomyositis affects approximately 3 per 100,000 children [17, 18].

A review published in 2007 presented the JIA prevalence rate in developed countries as varying from 16 to 150 per 100,000 [4]. This is broadly consistent with more recent data from developed countries as described below. In Europe, the most recent systematic review to describe the overall prevalence and incidence reported a pooled prevalence in Caucasians of 32.6 per 100,000 in 2010 [19]. In the US, the reported prevalence of JIA has ranged from 1.6 to 86.1 per 100,000 [20, 21]. In Australia, such studies or reports are limited; the only available data, according to either a community-based study in 1996 or an official report from the 2004-05 Australian Institute of Health and Welfare (AIHW), suggested that JIA prevalence in Australia was far higher than in other developed regions [22, 23]. This rate was up to 400 per 100,000 Australian children [22, 23]. While in the majority of developing countries, the prevalence of JIA is relatively lower than in developed countries. The lowest prevalence (3.43 per 100,000) was reported in Egypt and the highest (196 per 100,000) was in Brazil [24, 25]. It should be noted, however, that the low rates currently reported by developing countries may be related to limited data sources [23].

In Europe, a pooled incidence of 8.3 per 100,000 Caucasian children was described by the aforesaid systematic review [19]. Other published incidence rates for JIA in European countries are comparable ranging between 3.2 and 21.7 per 100,000 children [26-31]. However, in Australia, there are no published studies describing the incidence of JIA.

Considering the knowledge of prevalence and incidence is key for the understanding of disease epidemiology and optimising management both locally and worldwide, this deficiency in Australia demands added relevant JIA research, especially studies on population-based registries. The establishment of a registry can facilitate a rapid determination of the number of cases and the collection of case information for epidemiological studies and future research on treatment regimens and outcome improvements.

1.1.3 Treatment and interventions

Currently there is no cure for JIA. Treatment of JIA aims to achieve the following: 1) to relieve the symptoms of arthritis, e.g. joint pain and swelling; 2) to alter the disease course; 3) to prevent permanent joint damage and disability; 4) to improve quality of life (QOL) and maintain socioeconomic function for patients and families. Rapid and accurate medication selection is critical and is based on a very complex algorithm. It usually depends on JIA subtypes (see Table 1.1.1) and clinical presentations, such as disease activity, the category of complications and the extent of joint involvement [32]. Throughout the course of JIA, a multidisciplinary team is needed, including a rheumatologist, rheumatology nurse, ophthalmologist, physiotherapist, psychologist, dietician, occupational therapist, and social worker [2]. In the past two decades, the introduction of biologic agents has revolutionised the treatment of JIA [33, 34]. Cumulative evidence has also suggested that early intervention contributes greatly to disease control and disability prevention [35, 36].

Current medications include nonsteroidal anti-inflammatory drugs (NSAIDs), disease modifying anti-rheumatic drugs (DMARDs), corticosteroids, as well as novel biologic agents [37]. NSAIDs have been an effective treatment for almost all subtypes of JIA, by controlling inflammation and providing symptom relief to patients. Methotrexate (MTX), which is one of the most commonly prescribed DMARDs, is a powerful drug that helps decrease joint inflammation in extended oligoarthritis and polyarthritis JIA patients, but is less effective for systemic arthritis [38]. Other common DMARDs include leflunomide

and sulfasalazine. Corticosteroid therapy can be implemented in three ways, intra-articular, oral and intravenous [39]. Intra-articular corticosteroid injections are often used in children who have fewer joints affected and can rapidly relieve joint pain [40], whereas oral and intravenous corticosteroids have greater systemic effects and are used for other JIA subtypes such as systemic JIA.

Of note, both DMARDs and corticosteroids may still have side effects, although a relatively good safety profile has been demonstrated for decades [41]. For instance, systemic corticosteroid therapy may cause growth retardation, whereas intra-articular corticosteroid injection can lead to pain and anxiety. In addition, MTX-associated adverse events include gastrointestinal reaction, anxiety, needle phobia and abnormalities in liver function tests. Treatment with biologic agents was established in the late 1990s and an increasing number of drugs have become available [33]. Potential therapeutic targets include tumour necrosis factor-alpha (TNFα) [37], T-cell [42], and some interleukins (IL), such as IL-1, IL-6 and IL-18 [43]. TNFα inhibitors for JIA include etanercept, infliximab, and adalimumab [44]. They tend to be used in patients who have inadequate responses to MTX or experience MTX intolerance [45]. Other biologic agents such as IL-1 inhibitors and IL-6 inhibitors including anakinra, canakinumab, rilonacept, and tocilizumab, are particularly useful in the treatment of systemic arthritis [46].

Although JIA patients benefit greatly from treatments with biologic agents, risk of infections and other unexpected adverse effects remain nonnegligible in these patients since these agents directly regulate the cytokine pathways or act on autoimmune and autoinflammatory processes as immunosuppressants [47-49]. Most recently, differences in adverse events among different biologic agents were reported by a long-term surveillance of biologic therapies study in Germany [50]. Currently, the association between biologic agents and the incidence of associated adverse events remains unclear. This is partly because there is insufficient relevant data for population-based clinical evaluation. This opinion is also supported by a recent review which suggested such side effects are difficult to detect in small samples [48]. Moreover, there is no such study in

Australia. In this thesis (Chapter 3), we introduce a local registry to help address this issue by providing a data foundation for medication records and potential complications.

Apart from pharmacological medications, non-pharmacological treatments also assist in improving the outcomes of JIA patients, including healthy lifestyle (e.g. reasonable diet, exercise and good sleep), physiotherapies and psychological therapies [51, 52]. Additionally, occupational and physical therapies are recommended to patients with functional limitations, in order to maintain the range of motion in joints and to increase activity participation [53].

Worldwide, a variety of treatment protocols and management standards have been published and reported over recent years, providing guidance for specific practice patterns. For example, in 2011, the American College of Rheumatology (ACR) published recommendations for the treatment of JIA [54]. Subsequently, in 2014, the most recent standards for the management and care of JIA patients were developed in Australia [55]. In 2015, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) published consensus treatment plans for newly diagnosed polyarthritis patients [56]. In 2019, a recommended treatment approach was updated by ACR for patients with polyarthritis, sacroiliitis, and enthesitis [53]. However, the heterogeneity of the disease needs to be considered and any therapy appropriately adapted to individual patients. Personalised treatment goals and strategies should be based on shared decision-making among patients, parents and the paediatric rheumatology team. In addition, regularly assessing disease activity and accordingly adjusting treatment plans can benefit the achievement of treatment goals.

In the Women's and Children's Hospital (WCH), SA, JIA patients are treated following the national and international guidelines [55, 57, 58]. Despite this, detailed clinical information in this local cohort is not being tracked clearly and is not easily accessible because of continued paper-based recording. By manually collecting and organising patient data and treatment information, a registry has been established in this site for all patients with JIA in SA. This registry has recorded data of medications and treatments in

detail and would be available for all authorised paediatric rheumatologists and researchers, for both clinical and research purposes.

1.1.4 Complications, comorbidities and adverse events

The course of JIA disease is fluctuating and often accompanied by multiple complications and comorbid diseases, which are also known as 'adverse events' in other literature [59, 60]. Patients who experience complications and comorbidities usually have worse health-related QOL (HRQOL). Therefore, complications and comorbidities should be considered as part of the holistic assessment of JIA.

Common complications of JIA include: ocular, musculoskeletal and emotional problems, growth failure/retardation, macrophage activation syndrome (MAS), and also medication intolerance and side effects [61-66].

The incidence of uveitis, the most common extra-articular complication of JIA, has been reported to range from 5% to 30% and tends to occur more frequently in European and American than in Asian and African countries [67-69]. The lowest rates have been recorded in India and Japan [68, 70]. This partly due to that a relatively small proportion of patients have oligoarthritis and were positive in ANA, both of which are strong risk factors for uveitis [69]. Other ocular problems in JIA patients include uveitis-related glaucoma, cataract and macular oedema [63, 71]. Other complications of JIA include those associated with the musculoskeletal system, such as joint deformity, erosive disease and muscle wasting [72-76]. Common joint deformity includes boutonniere deformity, fixed flexion deformity, and micrognathia in temporomandibular joint (TMJ) arthritis [75]. Furthermore, patients with JIA can experience emotional problems such as depression and anxiety. Psychosocial functioning can be affected and leads to low self-esteem and a distorted self-image [77]. Studies have suggested that depression and anxiety may have a greater impact on QOL than some physical impairments but they have not been widely used to assess disease activities [78].

Treatment and interventions may also directly lead to some complications, called

medication intolerance and side effects. MTX intolerance such as nausea, anxiety, needle phobia and liver function test derangement has been the most studied [64]. Approximately 50% of patients with JIA receiving MTX have MTX intolerance and some children can experience anticipatory symptoms including nausea and vomiting [79, 80]. Interestingly, the incidence of intolerance in JIA patients receiving MTX injection is higher than that of patients receiving oral MTX [80].

Growth retardation is another important complication of JIA and its treatment. Inflammation with systemic arthritis and the use of corticosteroids are considered the major cause [81]. However, additional risk factors should be studied and further identified. An Israeli study suggested that patients with persistent oligoarthritis also have a higher risk of growth retardation [82]. MAS is an established life-threatening complication of JIA patients and can cause severe systemic inflammatory reactions [83]. It mainly occurs in patients with systemic-onset arthritis. Although MAS has not been fully studied because it is rare, the latest advances in physiopathology, diagnosis and treatment have been updated in a recent review [84].

In addition to these well-known complications, an increasing incidence and prevalence of comorbidities such as type 1 diabetes, celiac disease, autoimmune thyroid diseases, inflammatory bowel disease (IBD) and Crohn's disease is observed in patients with JIA [85-87]. Publications systemically reporting on comorbidities of JIA are very limited, except for one review that summarised comorbidities in adult JIA patients [85]. In this review, uveitis was regarded to be the most common comorbid condition because the concepts of complications and comorbidities were jointly referred to as comorbid conditions. Other common comorbidities, such as allergic rhinitis, migraine, and atopic dermatitis have also been reported for adult JIA patients [85].

Type 1 diabetes is a common comorbidity of JIA. A German study found that type 1 diabetes tends to develop manifestations earlier than JIA [88]. Cardiovascular disorders are more common in systemic onset JIA as systemic inflammation can promote atherosclerosis [85, 89]. Obesity is another comorbidity with 18% of JIA patients

classified as obese (BMI ≥ 95th percentile in each age group), according to a study in the USA [90]. Although the relationship between obesity and disease activity remains unclear, a more recent study suggests that obesity can have a negative impact on disease courses and outcomes [91].

1.1.5 Transition to adult services

Similar to other rheumatic diseases, children with JIA will face additional challenges when they enter adulthood. Adults have more autonomy in their lives and in the management of their disease, but the disease is still recurrent and the burden of the disease is cumulative. Even though overall outcomes have improved over the past few decades, the disease can still be associated with significant pain, mood disturbance and even relapses during adulthood [92]. Current research suggests that approximately 50% of youth with JIA will continue to experience active disease into adulthood [93, 94]. These patients require ongoing medical treatment, and many of them may have a significant disability due to prolonged disease activity [95]. It is a great challenge for the young people, their families and the professional team, to manage an adequate and effective transition [96]. If not well managed, the transition may confer a loss of follow-ups and a high risk of developing disease flare or severe complications [97].

Research has illustrated the barriers to providing transition services [98, 99]. For example, it is reported that lack of educational materials appropriate for adolescents, inadequate clinic time, and limited training in dealing with adolescent issues are significant components of barriers [98]. In this thesis (Chapter 2), some of these obstacles are reported as the major challenges for families living with JIA. In addition, a number of NSAIDs demonstrate a better tolerance by children than adults, such as naproxen, ibuprofen, and indomethacin [99]. Thus, it is important to monitor drug responses and switch to medications of high efficacy for youth during the transition. For example, ibuprofen is the most commonly prescribed analgesic in paediatrics, followed by paracetamol. Whilst for adults, they act as the first-line choices [100].

Although high-quality transition is difficult to achieve, transition care providers must be

aware and respect that young adults with JIA present with complex medical, psychosocial and educational needs [97, 101]. Of note, a registry for young JIA patients has potential benefits for adult transition because medical and psychosocial data can be longitudinally followed and thus can help adult rheumatologists grasp the overall condition of the patient.

1.1.6 Long-term considerations

Literature has shown that during the course of JIA disease, disease activity decreases and the frequency of reaching remission increases [97]. Ideally, the ultimate goal of treatment would be clinically inactive disease (CID), also called remission. However, after 10 years of disease, around 50% of patients have achieved a remission off-medication status [94, 102]. Therefore, there is a growing consensus that minimal disease activity (MDA) instead of CID should be a more achievable goal for children and adolescents with JIA [103]. During the last decades, a variety of criteria have been proposed to define these disease activity states in JIA populations, including Wallace's criteria [104], ACR preliminary criteria [6], the juvenile arthritis disease activity score (JADAS) [105] and clinical JADAS (cJADAS) cut-offs [106] (see Section 1.2.1). Of note, CID was defined in detail in all four criteria, while MDA was exclusively defined by JADAS and cJADAS cut-offs. The two most common methods to assess disease activity are: Wallace's criteria and cJADAS, which will be described in detail below (Section 1.2.1). The establishment of a JIA registry will play an increasingly important role in long-term disease activity assessment by longitudinal data recording for an individual patient.

1.2 Outcome measures in JIA

Outcomes in JIA fall into three main categories. 1) Clinical outcomes refer to a series of clinical data such as examination results, quantification of symptoms and data of therapeutic drugs and reactions. 2) Patients' self-reported data of their disease and health conditions, including pain levels, functional abilities, quality of life, activities of daily living and disease activities. 3) Patient-reported experiences of health care and services,

which are recently applied to JIA research and clinical practice. Outcome measures from these three categories have been used to interpret the disease courses and living conditions of JIA patients from various perspectives. The establishment of a JIA registry based on such multi-perspective data in this thesis enables a more comprehensive understanding of JIA and more holistic care through integrated analysis.

1.2.1 Clinical outcomes and measures

The main goal of treatment for JIA patients is to achieve better health outcomes, allowing patients to live a normal life as much as possible. To this end, understanding the full range of disease outcomes is the initial step. Therefore, a registry will play an important role in achieving improvements in understanding and evaluating JIA once it is populated with a full range of pertinent outcomes and corresponding data.

Generally, main outcomes for JIA include disease activity (four criteria), QOL, HRQOL, physical functioning, psychological health, articular manifestations/joint pain, blood biomarkers, complications, and long-term outcomes. These elements of the outcomes are described in more detail in the following.

Disease activity

Disease activity is a group of reversible manifestations of the disease, which can be affected by effective treatment and interventions [107]. Using methods or tools to measure disease activity can monitor the severity of a patient's disease and assess patient's response to treatment from an objective point of view. In JIA, disease activity is usually divided into active disease and inactive disease, which refer to 'flares/relapses and remission' (Section 1.1.1). It includes the signs and symptoms related to inflammation, but not related to functional and structural impairment or damage [108]. Thus, considering that JIA has a comprehensive and multi-angle impact on patients and their families, it further highlights the role of other outcome measures as supplementary measures in the holistic management. The following section will discuss the overview of available disease activity measures in JIA.

a. Wallace's criteria

As proposed by Wallace's criteria, patients who satisfy all the criteria in Table 1.2.1 are considered as CID [104].

Table 1.2.1. Preliminary criteria for clinically inactive disease (CID) in Wallace's criteria [104]

No active synovitis
No fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA
No active uveitis
Normal ESR and/or CRP
Physician’s global assessment of disease activity indicates no active disease

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; JIA: Juvenile Idiopathic Arthritis.

In Wallace's criteria, two types of remission were first proposed to distinguish between different states of CID [104]. These include 1) clinical remission on medication: where the status of CID lasts at least six consecutive months when the patient is receiving medication, and 2) clinical remission off medication: where the status of CID lasts at least 12 continuous months when the patient is off medication.

Although more objective measures of inflammation are considered in Wallace's criteria and achieving CID is one of the goals in JIA treatment, patient-reported data such as pain, fatigue, and stiffness continue to be important but outside the scope of Wallace's criteria [109, 110].

b. ACR preliminary criteria

From 1997 to 2011, the American College of Rheumatology (ACR) core outcome variables for JIA have developed markedly. The six disease activity core variables include: (1) physician global assessment (PGA) of disease activity, (2) parent/patient

general evaluation (PGE) of overall wellbeing, (3) functional ability measured by CHAQ, (4) number of joints with active arthritis, (5) number of joints with limited range of motion (ROM), and (6) erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) [6, 111, 112].

Criteria for CID are shown in Table 1.2.2 and all the criteria must be met. Compared to Wallace's criteria, ACR preliminary criteria adds an assessment of duration of morning stiffness [113].

Table 1.2.2. Criteria for clinically inactive disease (CID) in the American College of Rheumatology (ACR) preliminary criteria [6]

No joints with active arthritis
No fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA
No active uveitis
Normal ESR and/or CRP
Physician's global assessment of disease activity indicates no active disease
Duration of morning stiffness of ⩽15 minutes

Abbreviations: CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; JIA: Juvenile Idiopathic Arthritis.

In ACR Paediatric 30 response criteria (ACR Pedi 30), improvements in response to treatment are defined as ≥30% improvement in three/six variables with ≤1 remaining variable worsening by ≥30%. Similarly, ACR Pedi 50, 70, and 90 are also used to define the improvement from baseline to each patient. However, the requirement to quantify absolute disease activity and to compare absolute responses between patients has not been met. This led to the development of the JADAS scale to enable the quantification of absolute levels of disease activity.

c. JADAS and cJADAS score

The juvenile arthritis disease activity score (JADAS) consists of four variables: PGA of

overall disease activity, PGE of well-being, count of active joints, and ESR [114]. PGA and PGE are rated by physician and patient VAS, separately. Each of these measures ranges from score 0 to 10. In subsequent studies, however, it was found that ESR has low to moderate inter-correlations with the other three measures [115]. This diminishes the role of the ESR in the calculation of JADAS score. Furthermore, removing the unnecessary tests of acute-phase reactant would enhance the feasibility of JADAS in busy clinic settings, particularly in children with oligoarthritis, which is the most benign JIA subtype and does not require a blood test with every clinic visit [106]. Therefore, cJADAS, the sum of the first three components (omitting ESR) in JADAS, was developed in 2013 [106, 115].

For both JADAS and cJADAS, the achievement of CID is defined as ≤1 (see Table 1.2.3). However, it is unusual for JIA patients to remain in long-lasting remission if all medications stop. As described in the earlier section, the more feasible goal is to achieve a state of MDA. It is an intermediate condition between high disease activity and remission and is exclusively defined by JADAS and cJADAS. Over the decade, different cut-offs have been validated in different populations. In 2012, Consolaro and colleagues [105] put forward a clear definition for MDA for JADAS in oligoarticular and polyarticular course JIA. In 2014, cut-offs for cJADAS were published [103].

Table 1.2.3. Criteria for clinically inactive disease (CID) and minimal disease activity (MDA) in juvenile arthritis disease activity score (JADAS) and clinical JADAS (cJADAS)

Criteria	Requirements for the achievement of CID or MDA	
	CID	MDA
JADAS [105]	JADAS≤1.0	Oligoarticular course: JADAS ≤ 2.0 Polyarticular course: JADAS ≤ 3.8
cJADAS	cJADAS≤1.0	Oligoarticular course: cJADAS ≤ 1.5

[103]	Polyarticular course: cJADAS ≤ 2.5

Abbreviations: CID: clinically inactive disease; cJADAS: clinical juvenile arthritis disease activity score; JADAS: juvenile arthritis disease activity score; MDA: minimal disease activity.

QOL and HRQOL

Overall QOL includes not only the health status but also non-health-related well-being, such as family, friends, jobs and other life and social circumstances [116]. In a more recent study in JIA, QOL includes health status and functional ability of patients with the important inclusion of patient's own perception of the impact of the disease on daily life [117].

When applied in clinical settings and considering only health-related factors, such as physical, functional, emotional and mental well-being, QOL tends to focus on HRQOL [117].

Physical function

Physical function is the ability to perform basic actions and tasks such as walking, reaching, gripping, hearing and vision [117].

Psychological health

Patients with JIA may also experience psychological difficulties, such as depression, anxiety, distorted self-image and low self-esteem [77]. There is a moderate to high association between physical disability and psychological symptoms [118, 119]. However, evidence shows that compared with physical symptoms, emotional difficulties have a greater impact on overall QOL in JIA [78].

Articular manifestations and joint pain

Patterns of joint manifestations in JIA can be different from adult arthritis since younger children may be unable to report joint problems such as tenderness and pain.

Active joint count (AJC) is defined as the number of swollen joints or joints with a

limited ROM accompanied by tenderness and/or pain on motion. Limited joint count (LJC), or restricted/damaged joint count, is defined as the number of joints with deformity, limited ROM, or surgical alterations. Evidence suggests that AJC is more responsive in the assessment of JIA flare than LJC [120].

Blood biomarkers

Some of the most common blood tests for JIA patients include ESR, CRP, ANA, rheumatoid factor (RF) and human leukocyte antigen B27 (HLA-B27).

Complications and comorbidities

Please refer to Section 1.1.4 for details regarding JIA-related complications and comorbidities.

Health status

Health status is an overall or generic outcome to estimate patients' wellbeing in global aspects including physical, psychological as well as social fields [117].

Long-term outcomes such as educational level and employment status

Academic and work achievement represent significant long-term outcomes for JIA. The changes in functional ability, language, memory and version are likely to have adverse impacts on long-term outcomes. In the UK, patients with JIA achieved excellent educational qualifications but the unemployment rate remained high [121, 122]. Nevertheless, a recent German study disagreed that, when children with JIA grow up, those who suffered from longer disease course or have active disease into adulthood have a lower educational level and higher unemployment rate than general populations [123]. This conflict warrants further investigation into long-term outcomes for JIA.

1.2.2 Patient-Reported Outcome Measures (PROMs)

During the past decades, increasing attention has been paid to patient-reported outcome measures (PROMs) and a variety of PROMs have been developed to quantitatively assess these outcomes in children with JIA [124]. PROMs evaluate the QOL, health-related

status, activities of daily living and disease activities from a self-perspective. PROMs show higher accuracy than physicians' interpretation of patients' opinions and can be more persuasive than some observational measures [125]. Patient-centred assessment for the impact of disease and healthcare is increasingly recognised as an important component in assessing health care outcomes in research and practice [126]. Moreover, recording PROMs in a longitude method can provide the treating rheumatologist with a quick reference of a single patient. With a quick scan of the PROMs result before each routine visit, the rheumatologist can obtain a thorough overview of the patient's whole status. This approach helps saving visit time and facilitates more efficient clinical care.

For the use of clinics and research, various PROMs have been developed to evaluate disease activities and clinical interventions. However, high heterogeneity in these outcome measures makes it difficult to compare the data from separate groups using different sets of PROMs. The establishment of registries may solve this by collecting all relevant data and calculate and compare dynamically in more generalisable ways.

In 2016, Hersh et al. [127] summarised existing PROMs relevant to JIA and concluded that the valuable outcome information would be crucial to answering unsolved questions about JIA if combined and compared appropriately. This research is important to assist in understanding and organising JIA-related PROMs in this thesis. A summary of JIA-related PROMs is outlined in Table 1.2.4. We have classified them into two domains to facilitate understanding but it does not imply separation, as these different domains are closely related to each other.

Table 1.2.4. A summary of Juvenile Idiopathic Arthritis-related Patient-Reported Outcome Measures (PROMs)

Domain	Abbreviation	Instrument	Target population/ Respondent	Age range		Number of items	Time to complete
				Self-report	Parent-report		
HRQOL	PedsQL	Paediatric Quality of Life Inventory [128, 129]	Parent and child	5-18	2-18	21-23, depending on age	<4 mins
	CHQ	The Child Health Questionnaire [130, 131]	Parent and child	10-18	5-18	50/28 (parent version), 87/45 (self-report version)	10-15 mins (CF50), 5-10 mins (CF28), 16-25 mins (CF87), <14mins (CF45)
	SF-36	Short Form-36 [132, 133]	Parent and child	N/A	N/A	36	5-10 mins
	JAQQ	Juvenile Arthritis Quality of Life Questionnaire [134, 135]	Parent and child	>9	2-18	74	within 20 mins
	CAPE	The Children's Assessment of Participation and Enjoyment [136, 137]	Children and young people	6-21	n/a	55	30-45 mins

	PRQL	The Paediatric Rheumatology Quality of Life Scale [138]	Parent and child	7-18	2-18	10	~<5 mins
	CASE	Children's Arthritis Self-Efficacy Scale [139]	Child	7-17	n/a	11	~5 mins
Functional ability	CHAQ	Childhood Health Assessment Questionnaire [140, 141]	Parent and child	9-19	1-8	30 (simplified questions), 2 (VAS of pain and overall wellbeing)	<10 mins
	JASI	Juvenile Arthritis Self-Report Index [142]	Child	8-18	n/a	100	30-45 mins
	JAFAS	Juvenile Arthritis Assessment Scale [143]	Child	7-16	n/a	10	10 min
	JAFAR	Juvenile Arthritis Functional Assessment Report [144]	Parent and child	7-18	7-18	23	~10 mins
	ASK	Activities Scale for Kids [145]	Child	5-15	n/a	30	5-9 mins
	JADI	Juvenile Arthritis Damage Index [146]	Parent and child	N/A	N/A	36 (JADI-A), 13 (JADI-E)	5-15 mins (after training)

Measures of HRQOL

Paediatric Quality of Life Inventory (PedsQL)

PedsQL is a validated HRQOL measure in various chronic diseases. There are 23 items in total, 21 of which are for toddlers. These items cover four aspects, i.e. physical, emotional, school and social functioning [147]. Patients aged 2-18 years can respond effectively to this measure, score ranges 0-100 and a higher score means better QOL [128].

Child Health Questionnaire (CHQ)

CHQ is a self-reported outcome measure to study QOL in patients with paediatric rheumatic diseases. It is designed as a multidimensional instrument that can assess various aspects including physical activities, pain, emotional and social components of health status [131]. The CHQ measure has been evaluated and validated in 32 countries, considering its adaptation with CHAQ [148]. The Norwegian version of CHQ was used by the Paediatric Rheumatology International Trials Organisation (PRINTO) study, and CHQ is supported to be a sensitive measure for children with JIA [130].

Short Form-36 (SF-36)

SF-36 questionnaire is a widely used measurement for evaluating HRQOL through eight scales, including physical functioning, social functioning, role limitations caused by physical or emotional problems, mental health, vitality, bodily pain and general health perception. Physical dimensions and mental dimensions are measured separately. The total score is a weighted sum of each question via a special algorithm, ranging from 0-100 [132, 149]. The use of SF-36 is only appropriate for children and adolescents rather than adults.

Juvenile Arthritis Quality of Life Questionnaire (JAQQ)

JAQQ is a disease-specific measurement targeted at children with JIA. It can be completely quickly by children and their parents in about 15 minutes, which ensures it feasible in clinical practice. The measure of JAQQ is composed of four dimensions and

each of them with around 20 items [117]. JAQQ is widely used worldwide; English, French and Dutch versions are available [150].

Children's Assessment of Participation and Enjoyment (CAPE)

CAPE targets children aged between six and 21 years. It uses a questionnaire with 55 items to measure if children with JIA have difficulties participating in physical and leisure activities [136, 137]. CAPE is not commonly used in JIA for the following reasons. First of all, it is a time-consuming questionnaire that usually takes up to 45 minutes to complete. In addition, in view of seasonal differences in leisure activities, the outcome scores are difficult to be inter-compared and the threshold is difficult to be reasonably set. Furthermore, CAPE is not a thorough measurement of HRQOL, with limited considerations about activities participation and enjoyment and ignore other key outcomes such as schooling, physical and emotional issues.

Paediatric Rheumatology Quality of Life Scale (PRQL)

PRQL is a questionnaire with 10 items and focuses on two separate domains associated with HRQOL: physical and psychosocial health [138]. Four-point score criteria are used in each question and a higher score represents worse HRQOL, with zero for 'never', one for 'sometimes', two for 'most of the time', and three for 'all the time'. The limitation is that, in JIA patients, the assessment of physical HRQOL is more accurate than that of psychosocial [138, 151].

Measures of functional ability

Childhood Health Assessment Questionnaire (CHAQ)

Among the existing measurements of functional ability in children with JIA, CHAQ is the most commonly used measurement. CHAQ is specifically developed for the outcome evaluations in children and adolescents with JIA. It includes a set of indicators for disability and pain and has both patient self-report and parent-report versions [152].

Juvenile Arthritis Self-Report Index (JASI)

Respondents to JASI are required to be school-aged children and adolescents with JIA.

Seven point scores represent different difficulty scales [142]. But a great limitation is that it has 100 items and takes patients 30-45 minutes to complete, which totally ignores the inherent difficulty concerning the disease of patients.

Juvenile Arthritis Assessment Scale (JAFAS)

JAFAS was developed in 1989 [143]. It is used for measuring the functional performance in children aged seven to 18 years. It is a short questionnaire with 10 scale items and takes about 10 minutes for children to complete with the assistance of a therapist. JAFAS scores are negatively correlated to disease activity with zero means 'active', one means 'partial remission', and two means 'total remission' [153].

Juvenile Arthritis Functional Assessment Report (JAFAR)

JAFAR measurement has two components, JAFAR-P for parents to complete and JAFAR-C for children age seven to 18 years. The overall score is calculated based on 23 items and ranges from zero to two, zero for 'always', one for 'sometimes' and two for 'never' [144].

Activities Scale for Kids (ASK)

ASK contains 9 domains and 30 items. There are two versions developed from the original ASK, namely ASK-capability (ASKc) and ASK-performance (ASKp). The former focuses on what children 'can' do, the latter measures what children 'actually' do. ASK is designed for the perspective of children (with ages ranging from five to 15) and can be completed by parents/proxies [145]. But it is not a JIA-specific questionnaire.

Juvenile Arthritis Damage Index (JADI)

JADI includes two parts, one for the assessment of articular damage (JADI-A) and another for extra-articular damage (JADI-E). It usually takes patients five to 15 minutes to complete and has proved to be practical to use in clinic settings [146]. JADI covers 36 joints or joint groups (maximum score is 72) and five different organs/systems (maximum score is 17). However, the unbalance between the two parts makes it more accurate for the assessment of articular damage than extra-articular damage.

Measures of other aspects

Other PROMs include measures of pain, fatigue and side effects of medications. For example, the Methotrexate Intolerance Severity Score (MISS) [80] is a validated questionnaire with five specific domains to assess MTX intolerance among children with JIA. As for the measurement of pain and fatigue, the Numeric Rating scale (NRS) or the Global Rating Scale are common choices for most researchers [154]. Furthermore, PedsQL Paediatric Pain Questionnaire (PPQ) [129] and PedsQL Multidimensional Fatigue Scale (PedsQL-Fatigue) [155] are frequently used to measure children's and parents' perspectives of pain and fatigue.

Juvenile Arthritis Multidimensional Assessment Report (JAMAR)

JAMAR is one of the brand new PROMs especially for children with JIA to assess their overall disease states, including overall well-being, HRQOL, functional status, joint pain, extra-articular symptoms, morning stiffness, medication side effects, rating of disease status/course/activities, social problems as well as self-reported satisfaction with disease outcomes [156]. A recent cross-cultural study involving 52 countries across the PRINTO network concluded that JAMAR is a reliable and validated tool for assessing the overall dimensions of disease variables and health states for children with JIA [157]. In addition, the study focusing on the Afrikaans version comes to a similar conclusion, that clinical items in JAMAR discriminate well between healthy controls and JIA patients, and thus JAMAR plays a key role in both clinical research and practice [158]. Although JAMAR performs better than most relevant questionnaires regarding this point, the limitation is a missing measurement of fatigue and consideration of long-term outcomes such as employment.

1.2.3 Patient-Reported Experience Measures (PREMs)

A significant goal of JIA treatment is to improve HRQOL. Patient perceptions about their experience with care and service can reflect HRQOL, especially in terms of psychological and mood issues. Patients' experience about health care or services is

increasingly gaining attention and has been shown to be positively associated with clinical effectiveness and patient safety [159, 160]. Patient-reported experiences include waiting time for consultations, quality of communication with doctors, and involvement in decision-making. Providing feedback via a validated questionnaire after each outpatient visit may help the treating physician to determine what treatment is working well and what areas need improvements. However, limitations and concerns are identified, including that patient-reported experience measures (PREMs) may measure the fulfillment of patient's preconceived expectations, instead of their real experiences [161]. Hence, the key to the success of the application of PREMs is the appropriate selection of the domains in instruments [162, 163].

Currently, we have identified two existing tools capturing patient experiences in rheumatic conditions. Rheumatoid arthritis (RA) PREM is designed for rheumatoid and early inflammatory arthritis [164]. The British Society for Paediatric and Adolescent Rheumatology (BSPAR) PREMs questionnaire is a validated JIA-specific tool, launched and evaluated in the UK paediatric rheumatology clinics [165, 166]. In this thesis, BSPAR PREMs tool is used to capture patient feedback on the quality of care in SA.

1.3 Review of JIA registries

Registries are integrated and organised systems used to collect, store, process, and analyse standardised data of a group of patients with specific diseases. International JIA registries have been in existence for many decades [167-169], but the uneven regional distribution remains a great challenge in addressing worldwide collaborations. In a multinational survey study, information of 18 registries or relevant cohort studies for patients with JIA were reviewed and organised [170]. Among these studies, seven focus on certain treatments or therapies, and the remainders include five inception cohorts and six prevalent cohorts. In the following sections, a brief review and comparative description of worldwide registries in JIA is presented.

1.3.1 International registries

Worldwide, there are various registries for JIA. They focus on national and multi-national cohorts, cover diverse geographic regions, and use different methodologies and JIA classification criteria. There is only one established registry for JIA patients in Victoria, Australia with the initial one-year results reported as an inception cohort study [171, 172]. This registry was established in 2008 and has further been extended to include children in the rest of Australia as well as New Zealand (ANZ-CLARITY); however, no published data are currently available.

A summary of these registries is shown in Table 1.3.1. In addition to routinely collected clinical outcomes, patient-reported outcomes are becoming increasingly important to help understand patients' perspectives about their health status and their experience with receiving care [173]. We find that majority of the registries have included the key data for the evaluation of disease activity (clinical outcomes) but patient-reported outcomes collected in these registries are in different levels. Furthermore, a collection of patient-reported experiences is non-existent.

Table 1.3.1. Summary of international registries in Juvenile Idiopathic Arthritis

Abbreviation	Registry	Country	Start Year	Age Group	Disease	Medication	Website
CARRA Registry	Childhood Arthritis and Rheumatology Research Alliance registry [174]	US and Canada	2009	Children and adolescents	Paediatric rheumatic diseases	No limit	https://carragroup.org/research/carra-registry
Reuma.pt	The Rheumatic Diseases Portuguese Register [175]	Portugal	2008	Adult and children	Rheumatic diseases	No limit	http://reuma.pt/en_UK/Default
BCRD	The Biologics for Children with Rheumatic Diseases Study [168]	UK	2010	Children	JIA	Biologic & MTX	http://www.bcrdstudy.org/
BSPAR-ETN	The British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study [168]	UK	2004	Children and young people	JIA	Etanercept	https://www.rheumatology.org.uk/Knowledge/Registers/Juvenile-Idiopathic-Arthritis-register
PRINTO	The Paediatric Rheumatology International Trials Organisation [167]	Global	1996	Children	Paediatric rheumatic diseases	No limit	https://www.printo.it/

PRCSG	The Pediatric Rheumatology Collaborative Study Group [176]	US, Canada and Puerto Rico	1973	Children	Rheumatic diseases	No limit	https://prcsg.org/
ReACCH-Out	The Research in Arthritis in Canadian Children emphasizing Outcomes study [177]	Canada	2005	Children	JIA	No limit	N/A
CAPS	The Childhood Arthritis Prospective Study [178]	UK	2001	Children	JIA	No limit	https://www.caps-childhoodarthritisprospectivestudy.co.uk/
AID-register	Auto-inflammatory diseases register [179]	Germany	2009	N/A	Auto-inflammatory diseases	No limit	https://aid-register.de
BiKeR	Biologika in der Kinderrheumatologie [169]	Germany and Austria	2001	N/A	Paediatric Rheumatology	Etanercept	http://biker-register.de

Abbreviations: JIA: Juvenile Idiopathic Arthritis; MTX: Methotrexate.

The Childhood Arthritis Prospective Study (CAPS) is an ongoing prospective longitudinal inception cohort study in the UK [180]. The recruitment began in 2001 and aimed to provide information about the long-term outcome of children with inflammatory arthritis for at least five years. The CAPS has advantages due to its prospective cohort study design where the recruitment and follow-up continues [178]. Data recorded by the CAPS includes demographics, diagnosis, disease characteristics, medical history, current medications, and blood test results [180]. However, the CAPS focuses exclusively on newly diagnosed patients and includes limited patient-reported data besides the Childhood Health Assessment Questionnaire (CHAQ).

Similarly, in the UK, two parallel studies/registries which share similar methodologies play important roles in treatment and drug management. The BSPAR Etanercept Cohort Study (BSPAR-ETN) was launched in 2004, with the aims of monitoring long-term effects of a biologic therapy called etanercept to children and young people under the age of 18 [168]. The Biologics for Children with Rheumatic Diseases Study (BCRD) was established in 2010 to collect information regarding children with JIA treated with biologics other than Etanercept [168]. Besides, children and young people receiving treatment of MTX were also recruited in 'Methotrexate-treated group' in both registries. However, the difference in sample size can be a challenge while making comparisons as the number of patients treated with etanercept (in BSPAR-ETN) or other biologic agents (in BCRD) is far fewer than that in 'Methotrexate-treated group'. Moreover, both registries are treatment-based. In other words, they focus on evaluating drug safety or effectiveness. Therefore, these registries may overlook valuable data from the excluded JIA patients and may lead to an incomplete picture of JIA in the UK.

In Germany and Austria, a German etanercept registry (Biologika in der Kinderrheumatologie, or BiKeR) was set up in 2001 to evaluate treatment with etanercept in children with JIA [169]. In 2007, over 1200 JIA patients were registered in BiKeR. In order to monitor the long-term safety and efficacy of etanercept, adverse events and the variables needed to calculate JADAS and ACR core set are collected in

this registry. CHAQ is used to measure patient-reported functional disability [169]. Although patients with all JIA subtypes are recruited, BiKeR is a treatment-based registry and important outcomes such as fatigue, mental health and QOL are ignored. Of note, to solve the loss of follow-ups for age-related reasons, a follow-up registry, juvenile arthritis MTX/biologics long-term observation (JuMBO), has been introduced to follow the adult JIA patients previously included in BiKeR [154].

The CARRA registry shares a similar objective with CAPS, with the purpose of monitoring long-term outcomes for patients with paediatric rheumatic diseases [174]. The CARRA registry started collecting data in 2015 in the United States and Canada, initially limited to JIA. Interestingly, in addition to CHAQ, this registry utilises a new tool, the Patient Reported Outcomes Measurement Information System (PROMIS®), to collect valuable data regarding patient-reported outcome measures [174]. Of note, PROMIS® is a set of measurement tools using large item banks, short forms and computerised adaptive tests (CATs), which aims at precise quantification of patient-reported outcome measures. For example, PROMIS® Paediatric Global Health 7-item (PGH-7) produces a single score to evaluate children's overall physical and mental health. Other outcome measures including PROMIS® pain intensity, physical function and mobility are collected in the CARRA registry.

The Research in Arthritis in Canadian Children emphasizing Outcomes (ReACCh-Out) study was a large inception cohort study of newly diagnosed JIA patients, which provided the opportunity to prospectively ascertain the overall incidence of new-onset in Canada [181]. It included patients in 16 Canadian sites from 2005 to 2010 and the recruitment has now terminated [135]. Key information including clinical and laboratory data, six ACR core outcome measures and treatment were collected regularly to assess the achievement of remission and inactive disease. Additionally, comprehensive PROMs were recorded in this study, including CHAQ, JAQQ and the Quality of My Life (QoML) questionnaire. The limitation is that patients with the established disease were unavailable through this study and patients with extended oligoarthritis were not

differentiated from persistent oligoarthritis.

1.3.2 Australian registries

At present, the Australian Childhood Arthritis Risk Factor Identification Study (CLARITY) is the only registry for JIA patients in Australia [171]. It is a case-control registry set up in 2008, however, data of patients with JIA and their healthy controls are exclusively collected in Victoria. In CLARITY, cross-sectional data regarding early life environment and the environment at disease onset, as well as blood samples for genetic and biomarker analysis are collected [171]. Under the purpose of identifying disease risk factors, several JIA-associated genes and environmental risk factors have been identified by CLARITY through the comparison of case-control data. The group has found that reduced methylation at IL32 in T cells is associated with JIA [182]. Moreover, the associations between JIA and five non-major histocompatibility complex (non-MHC) risk loci have been investigated, including c12orf30, c3orf1, PTPN22, STAT4, and TRAF1-C5 [183]. The majority of these risk loci have been validated in a larger study [184].

More recently, an inception cohort study with comprehensive epidemiological data for newly diagnosed JIA patients (diagnosed between 2010 and 2014) was performed by the CLARITY group to help initial understandings of the demographics, treatment and outcomes of Australian children [172]. Nevertheless, important patient-reported outcomes, such as pain, fatigue and QOL were not included in this study, which serves as a great limitation. Also, disease flare was defined as a joint count of more than zero, without the use of either Wallace criteria or JADAS. This may lead to low comparability with other studies.

In Australia, two new registries are being established to include multicentre data from around Australia, namely the Australian Arthritis and Autoimmune Biobank Collaborative (A3BC, https://a3bc.org.au/) and the Australian and New Zealand Childhood Arthritis Risk Factor Identification Study (ANZ-CLARITY, https://www.mcri.edu.au/clarity, unpublished).

A3BC is a national biobank network initiatively launched in 2016 and aims at identification of causes and cures for a variety of inflammatory arthritis and autoimmune conditions in both children and adults. The A3BC is cooperating with the Australian Rheumatology Association Database (ARAD) to further link internal biological and omics data to patient-reported data [185]. ANZ-CLARITY is an extension of CLARITY and has the same aim as CLARITY and a larger biobank will be established including cross-sectional data from around 6000 children from Australia and New Zealand.

Both registries are going to include information of JIA patients in SA, a local registry that is being established (Chapter 3) will become an important aid to the establishment of both national registries. In addition, the current situation in SA is that patient data are not stored in an easily accessible form, most of which are paper-based rather than electronically recorded. The present SA JIA project presented in this thesis (see Chapter 3) will collect data including, but not limited to, demographics, medications, blood test results, and patient-reported outcome measures, of children and young people with JIA. This is a single-centre registry launched in the WCH, SA. This hospital is the major paediatric hospital in SA and provides a state-wide paediatric rheumatology service. The present registry is expected to have collaborations with ANZ-CLARITY and A3BC in the near future. By these collaborations, the present registry will have an opportunity to contribute to national and international collaborations and thus increase the power of future studies in JIA.

1.4 Thesis objectives

The overall aim of the research presented in this thesis was to evaluate disease activity and improve disease outcomes for JIA patients by setting up a JIA registry in SA.

The thesis specifically addressed the following 4 objectives:

1. To describe the experiences and perspectives of children and carers living with JIA and understand the priorities in their perspectives (Chapter 2).
2. To describe the JIA populations in SA and to compare outcomes with those in

other published studies, in terms of demographics, JIA subtypes, disease onset, complications/comorbidities, medications, disease activity and patient-reported data (Chapter 3).

3. To investigate if PROMs and PREMs are associated with routinely collected clinical outcomes in the South Australian JIA cohort (Chapter 4).
4. To evaluate treatment and clinical care in SA by monitoring disease activities in a longitude manner (Chapter 3 & 4 and Future directions).

Chapter 2. Experiences of living with Juvenile Idiopathic Arthritis: a qualitative systematic review

The following chapter presents the publication 'Experiences of living with Juvenile Idiopathic Arthritis: a qualitative systematic review' (*In press*), submitted to *JBI Evidence Synthesis* on 29 April 2021 and accepted for publication following peer review on 05 July 2020. The only modification to content was the reference to relevant content contained in the appendices presented in this thesis. As per the journal requirements, American English spelling was used in this publication, and in this chapter.

The Authors wish to acknowledge *JBI Evidence Synthesis*. Manuscript ID: JBIES-21-00139. This accepted version is reproduced with permission from *JBI Evidence Synthesis.*

The corresponding methodology paper that preceded this work, 'Experiences of living with Juvenile Idiopathic Arthritis: a qualitative systematic review protocol' is presented in Appendix I. It was submitted to *JBI Evidence Synthesis* on 6 September 2019 and accepted for publication following peer review on 11 December 2019.

The Authors wish to acknowledge *JBI Evidence Synthesis*. DOI: 10.11124/JBISRIR-D-19-00301. The accepted version is reproduced with permission from *JBI Evidence Synthesis*.

2.1 Abstract

Objective: The objective of this review was to investigate the available qualitative evidence to enhance understanding of the experiences of children, young adults and their carers living with Juvenile Idiopathic Arthritis (JIA) in any setting.

Introduction: JIA is the most common chronic rheumatic disease in childhood. Despite the availability of effective treatments, persistent pain, growth retardation, physical disability, and psychological problems can occur. This may reduce the quality of life for JIA patients by negatively affecting their family, educational, and social well-being.

Patient-centered management and care for JIA requires increasing attention to their self-reported quality of life and experiences, in addition to clinically measured disease activity. Furthermore, taking care of children with JIA may have negative impacts on the lives of their carers and families. The experiences of carers have been poorly understood and studied. This review describes experiences and perspectives from patients and carers in order to inform the needs of families throughout their JIA journey.

Inclusion criteria: Studies describing the experiences of patients aged <21 years who have been diagnosed with JIA according to the International League of Associations for Rheumatology criteria, as well as the experiences of their carers, have been considered.

Methods: A comprehensive search using PubMed, CINAHL, Embase, PsycINFO, Web of Science, and Google Scholar, as well as relevant conference proceedings of the American College of Rheumatology (ACR; 2018–2019), the European Pediatric Rheumatology Congress (PReS) 2018, the European League Against Rheumatism (EULAR; 2018–2019), and the Asia Pacific League of Associations for Rheumatology (APLAR; 2018–2019), was undertaken in December 2020 to identify pertinent published and unpublished studies. Studies published in English from 2001 to 2020 were included. The JBI approach to study selection, critical appraisal, data extraction, and data synthesis was used.

Results: Ten studies were included in this review. A total of 61 findings were extracted and aggregated to form 12 categories. From the 12 categories, five synthesized findings were developed: i) Self-management of JIA requires pain management, medication management, and the acquisition of knowledge and professional support; ii) A promising relationship with healthcare professionals but unbalanced access to services; iii) Parental financial burden and their adjustment to maintain family happiness; iv) Patients and parents support the web-based approach to communicate and develop self-management skills and acknowledge the importance of clinical trials; v) Desire to live a normal life without prejudice from school, social settings, and the workplace.

Conclusions: This review has provided a comprehensive overview of experiences and

perceptions of JIA patients and their parents. It is important to understand what they need to know and understand about the disease. This review also highlights the importance of appropriate web-based programs, career counseling, infrastructures, and school facilities. Findings in this review can guide future policy and practice in order to improve care for families and children with JIA. Further research is required to develop management strategies for medication intolerance and evaluate the longitudinal benefits of relevant JIA programs.

Systematic review registration number in PROSPERO: CRD42019133165

Keywords: children; experience; Juvenile Idiopathic Arthritis; parents; young people.

2.1.1 Summary of Findings

Experiences of living with Juvenile Idiopathic Arthritis: a qualitative systematic review					
Bibliography: Min M, Hancock DG, Aromataris E, Crotti T, Boros C. Experiences of living with juvenile idiopathic arthritis: a qualitative systematic review. JBI Evid Synth. 2021.					
Synthesized finding	**Type of research**	**Dependability**	**Credibility**	**ConQual score**	**Comments**
Self-management of JIA requires pain management, medication management, and the acquisition of knowledge and professional support	Qualitative	High (No downgrading)	Moderate (Downgrade one level)	Moderate	Dependability: Half of studies (4/8) scored 4 and 5 for the questions relating to appropriateness of the conduct of the research. Credibility: Downgraded one level due to mix of unequivocal (U) and credible (C) findings. U=19, C=3
A promising relationship with	Qualitative	Moderate	Moderate	Low	Dependability: Majority of studies (3/5) scored 2 and 3 for

healthcare professionals but unbalanced access to services		(Downgrade one level)	(Downgrade one level)		the questions relating to appropriateness of the conduct of the research. Credibility: Downgraded one level due to mix of unequivocal (U) and credible (C) findings. U=5, C=1
Parental financial burden and their adjustment to maintain family happiness	Qualitative	High (No downgrading)	Moderate (Downgrade one level)	Moderate	Dependability: Half of studies (1/2) scored 4 and 5 for the questions relating to appropriateness of the conduct of the research. Credibility: Downgraded one level due to mix of unequivocal (U) and credible (C) findings. U=3, C=1
Patients and parents support the web-based approach to communicate and develop self-management skills and	Qualitative	High (No downgrading)	Moderate (Downgrade one level)	Moderate	Dependability: Half of studies (2/4) scored 4 and 5 for the questions relating to appropriateness of the conduct of the research. Credibility: Downgraded one level due to mix of

acknowledge the importance of clinical trials					unequivocal (U) and credible (C) findings. U=6, C=3
Desire to live a normal life without prejudice from school, social settings, and the workplace	Qualitative	High (No downgrading)	Moderate (Downgrade one level)	Moderate	Dependability: Majority of studies (5/8) scored 4 and 5 for the questions relating to appropriateness of the conduct of the research. Credibility: Downgraded one level due to mix of unequivocal (U) and credible (C) findings. U=20, C=3
U: unequivocal; C: credible; JIA, Juvenile Idiopathic Arthritis					

2.2 Statement of Authorship

Statement of Authorship

Title of Paper	Experiences of living with juvenile idiopathic arthritis: a qualitative systematic review
Publication Status	☐ Published ☐ Accepted for Publication ☒ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Submitted for publication to JBI Evidence Synthesis. Currently under view.

Principal Author

Name of Principal Author (Candidate)	Ming Min		
Contribution to the Paper	First author and main contributor. Study conception and design, investigation, project administration, data collection, analysis and interpretation of results, formulation of draft and reviewing and incorporating co-author comments and suggestions.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	14/05/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	David G. Hancock		
Contribution to the Paper	Co-reviewer. Investigation, methodology, data collection, interpretation of results and review of the manuscript.		
Signature		Date	14/05/2021

Name of Co-Author	Edoardo Aromataris		
Contribution to the Paper	Concept and methodological design, methodology, planning and supervision of the work, review of the manuscript.		
Signature		Date	17/5/21

Please cut and paste additional co-author panels here as required.

Name of Co-Author	Tania Crotti		
Contribution to the Paper	Methodology, data collection and interpretation, supervision of the work and review of the manuscript.		
Signature		Date	14/05/21

Name of Co-Author	Christina Boros		
Contribution to the Paper	Conceptualisation, Investigation, methodology, data collection, planning and supervision of the work, review of the manuscript. Due to illness Dr Christina is on long term leave. A/Prof has signed on her behalf		
Signature		Date	14/05/21

Name of Co-Author			
Contribution to the Paper			
Signature		Date	

2.3 Introduction

Juvenile Idiopathic Arthritis (JIA) is the most common rheumatic disease of childhood. It is defined as arthritis of unknown cause with onset before 16 years old with persistent symptoms for at least six weeks and is associated with major morbidity and impacts on quality of life (QOL).[1, 2] There are seven different subtypes according to the International League of Associations for Rheumatology (ILAR) classification criteria, which were designed to minimize the heterogeneity within subtypes and facilitate the internationally accepted subtype-specific disease management.[1] Symptoms include joint pain, swelling, stiffness, fatigue, and sometimes fever and skin rash, which lead to negative experiences of living with JIA. The goal of treatment is to reduce symptoms, relieve pain, avoid damage and complications, as well as maintain function and increase QOL.

Although major advances have been made in the treatment of JIA with the introduction of biologic agents, patients can still experience a reduced health-related QOL (HRQOL) even when arthritis is well controlled from a clinical perspective.[3] For instance, in a cohort study, children with JIA report more fatigue than healthy peers regardless of disease activity states.[3] Thus, the subjective experiences and feelings of living with JIA need to be considered in the holistic management of these patients. Physical damage and functional disability have been identified as the main contributors to poor outcomes in JIA patients.[4] Joint-related complications include fixed flexion deformity, erosive disease, bony overgrowth, and osteopenia.[5] Patients with poorly controlled or very active disease are at higher risk of experiencing permanent joint damage. Around 50% of children with JIA maintain active disease as adults.[4, 5] Extra-articular complications such as uveitis, glaucoma, cataract, and macular oedema, also impact upon lifestyle and wellbeing. Uveitis, which is the most common ocular complication of JIA, affects approximately 10% of all patients and, if untreated, can lead to blindness and, thus, a long-term reduction in QOL.[6]

The use of biologic agents, has improved the outcomes of JIA patients. However, in most countries, non-steroidal anti-inflammatory drugs (NSAIDs) and traditional disease-

modifying anti-rheumatic drugs (DMARDs) remain the first-line treatment for most subtypes of JIA.[7, 8] Additionally, traditional DMARDs like methotrexate (MTX), in addition to biologic agents, need to be prescribed throughout the treatment period for some patients to optimize treatment effects.[9] Generally, patients with more severe or systemic disease require more intensive treatment and may be more likely to experience medication side effects.[10] Around 50% of JIA patients treated with MTX experience medication intolerance, including anticipatory nausea, anxiety, and needle phobia.[11] Medication side effects can affect JIA patients negatively in their day-to-day lives and may delay the achievement of inactive disease due to reduced adherence.[12]

Reduced QOL in JIA patients is not only attributed to chronic and recurrent symptoms, but also because of the resulting restriction in daily activities, such as sports and social events. Children with JIA may also be absent from school frequently.[13] Participation in school and in sports is significantly negatively associated with disease activity and functional disability, and can increase after a long-term disease course.[14] In addition, studies have reported that JIA patients with high disease activity reported fewer leisure activities, even with family members, when compared to those with milder disease.[15] This has an impact on the establishment of friendships and causes delays in psychosocial development for JIA patients.[16] When JIA patients grow up, they may experience higher unemployment rates,[17] despite the equivalent educational achievement as healthy children.[18]

Patients with JIA may also experience emotional difficulties, such as depression, anxiety, distorted self-image, and low self-esteem.[19] There is a moderate to high association between physical disability and psychological symptoms[20, 21]; however, evidence shows that, compared with physical symptoms, emotional difficulties have a greater impact on overall QOL for children with JIA.[22]

There is evidence that parent/family characteristics are closely related to the physical or psychosocial functioning of children with chronic pain,[23] which may also be a case in JIA where chronic pain is common. It was also reported in a recent study that increased

parental depression is associated with poor physical functioning in children with JIA, and this may contribute to poor disease outcomes.[24] Several studies have investigated the experiences of carers who are caring for children with JIA.[25-29] Managing a child with JIA can be challenging for both the carers and their families. Apart from monitoring disease activity, administering medications, and communicating with healthcare professionals, carers also have a crucial role in maintaining some balance between family and disease, shared medical decision-making, and support and care for the child. Moreover, carers' lives are also affected, including work, financial, and social aspects. This suggests the need for additional understanding about the concerns of parents and carers, which may directly or indirectly help improve treatment adherence and satisfaction, and ensure optimized health outcomes.

Within the context of patient-centered care, carers can play an active role in managing the disease.[30] Patient-related tools, such as patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), can be used to capture subjective assessment from patients' and carers' perspectives.[31] These, in combination with clinical approaches, will help a thorough analysis of treatment outcomes and facilitate better management of the disease. Some research has explored the efficacy of PROMs, but few studies so far have focused on PREMs. The incorporation of PROMs and PREMs both clinically and in research has been demanded by many authors.[31, 32] This review may help appropriate selection of comprehensive PROMS tools by understanding what patients and carers actually care about.

A search of MEDLINE, PROSPERO, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports was conducted. Two systematic reviews that have reported qualitative experiences of JIA were located. Tong et al.[33] conducted a qualitative systematic review in 2012 describing JIA patients' experiences, however experiences of their parents/carers were ignored. Additionally, multiple diagnostic criteria were considered in this review, however, it failed to focus on the experiences of patients who have been diagnosed with JIA according to the

standardized ILAR criteria.[33] The other literature review and meta-analysis by Bourdier et al.[34] analyzed physical activity and sedentary behaviors in patients with JIA or inflammatory bowel disease (IBD), compared to healthy children. Although physical experiences of JIA patients were included, an appraisal and synthesis tool, which is a formal approach for a qualitative systematic review, was not used to analyze the qualitative results. To conclude, although the findings of the afore-mentioned reviews have provided a significant overview and knowledge base regarding the lived experiences of JIA patients, a number of gaps exist as stated. Carers' experiences were rarely explored.

The objective of this systematic review was to synthesize the existing evidence on JIA patients' and carers' experiences of living with JIA.

Review question(s)

i). What are the experiences of children and young adults living with JIA?

ii). What are the experiences of their carers?

Inclusion criteria

Participants

The review considered studies that included patients aged <21 years who were diagnosed with JIA according to the 2001 ILAR criteria.[1] Studies including carers, including family members, who manage JIA in children and young adults were also considered. In the results, no other family members were included other than parents.

Phenomena of interest

The review considered studies exploring the experiences of JIA patients and those of their carers. These experiences were broadly defined and included, physical and/or psychosocial experiences, physical manifestations, psychological reactions, financial burden, and disease complications. In addition, studies describing patients'/carers' ability to manage disease, school, and social activities, as well as met and unmet needs were included. Carers' interpretation of the JIA patient's experience was in the scope of this

review.

Context

Studies conducted in any country were included in the review. All experiences of living with JIA were considered, independent of the location of the primary study's participants (e.g. home, clinics, hospitals, and community settings).

Types of studies

The review considered empirical qualitative studies including, but not limited to, designs based on phenomenology, grounded theory, and ethnography. Descriptive qualitative studies were also considered. Studies were limited to those published in English (full papers) as the meaning of qualitative data can be lost or modified by translation.[35] Editorials, non-research articles and observational epidemiologic studies were ineligible.

2.4 Methods

This qualitative systematic review was conducted in accordance with the JBI methodology for systematic reviews of qualitative evidence.[36] This review was conducted according to a *priori* published protocol.[37] The protocol was registered in PROSPERO with the registration number: CRD42019133165.

Search strategy

The search strategy aimed to find both published and unpublished studies. A three-step search strategy was applied in this review. First, an initial limited search of MEDLINE (PubMed) and Embase (Elsevier) was undertaken to identify articles on the topic, followed by an analysis of text words contained in the title and abstract, and of the index terms used to describe the articles. A second search using all identified keywords and index terms was then undertaken across each included database (see below). Searches were developed and combined using broad search terms, key-words, Medical Subject Headings (MeSH) / Emtree, and filters. The search strategy was adapted for each source database, including all identified keywords and corresponding index terms. The full search strategies performed on 9th December 2020, are presented in Appendix I.

Consistent with the publication of the revised ILAR JIA classification criteria, the search was limited to studies published after 2001.[1] Finally, the reference lists of all eligible studies were screened for additional potentially eligible studies.

Information sources

The databases searched include: MEDLINE (PubMed), Embase (Elsevier), Web of Science (Clarivate), CINAHL (EBSCO) and PsycINFO (Ovid).

Sources of unpublished studies and gray literature searched included Google Scholar and conference proceedings of the American College of Rheumatology (ACR; 2018–2019), the European Pediatric Rheumatology Congress (PReS) 2018, the European League Against Rheumatism (EULAR; 2018–2019), and the Asia Pacific League of Associations for Rheumatology (APLAR; 2018–2019), with the keyword of "JIA AND (qualitative OR experience)". Reference lists and bibliographies of all full text papers identified as meeting the inclusion criteria were also searched for eligible studies.

Study selection

Following the search, all identified citations were collated and uploaded into Endnote X8.2 (Clarivate Analytics, PA, USA) and duplicates removed. Article selection was conducted in three steps. The first step was preliminary citation screening, in which the titles and abstracts were screened by one reviewer (MM) for assessment against the inclusion criteria. In the second step, the titles and abstracts of records identified as potentially relevant during the preliminary screen were screened by two independent reviewers (MM, DH). In the final step, potentially relevant studies were retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI; JBI, Adelaide, Australia).[36] Following retrieval, studies were again screened independently for eligibility by two reviewers (MM, DH). Any disagreements that arose between the reviewers at any phase of the selection process were resolved through discussion, or with a third reviewer (CB, EA). We contacted the authors of 21 conference abstracts to request the full text.

Assessment of methodological quality

Methodological quality of all eligible studies was critically assessed by two reviewers (MM & DH) using the JBI Critical Appraisal Checklist for Qualitative Research.[38] The critical appraisal process involved analyzing each individual paper and allocating a response of "Yes", "No" or "Unclear" to each of the 10 questions on the JBI critical appraisal tool. Where there were discrepancies, consensus was achieved by discussion between three reviewers (MM, DH, CB). Studies that rated a "No" or "Unclear" for three or more of the 10 criteria (30% or greater) on the critical appraisal tool were excluded.

Data extraction

Data were extracted from included studies by two reviewers (MM, DH), using the standardized JBI data extraction tool integrated in JBI SUMARI.[36] The data extracted included details about the populations, context, geographical location, culture, phenomena of interest, study methods, and findings of significance to the review question and objectives. Findings were identified by repeatedly reading the results sections of each paper. A finding in this review was considered to be a verbatim extract of the author's analytic interpretation, accompanied by either a direct quotation or participant voice, fieldwork observation, or other data.[36] Findings were extracted by only one reviewer (MM) to ensure consistency. The independently extracted findings were then checked by the second reviewer (DH) to ensure congruency. Findings were extracted at a theme and sub-theme level for some papers if subthemes were presented. Findings, and their illustrations, were extracted and assigned one of three levels of credibility: unequivocal (U), credible (C), or not supported (NS).[39]

Data synthesis

Meta-aggregation was conducted using JBI SUMARI software to synthesize the extracted findings and present the main findings of this systematic review.[38] This involved the aggregation or synthesis of findings to generate a set of statements that represented that aggregation, through assembling the findings rated according to their credibility (level 1 findings), and categorizing these findings on the basis of similarity in

meaning (level 2 findings). These categories were then subjected to a meta-synthesis to produce a single comprehensive set of synthesized findings (level 3 findings) that could be used as a basis for evidence-based practice. The extracted findings were read repeatedly (MM) to iteratively develop the sets of categories and synthesized findings; these were in turn iteratively discussed and agreed on (DH).

Assessing confidence in the findings

The ConQual approach was applied to transparently determine confidence of each synthesized finding.[39] Qualitative studies were initially ranked as high and then moved up or down according to their dependability and credibility score. Dependability was established based on five specific questions from the critical appraisal scores. Four to five ‘‘Yes’’ responses meant the study remained unchanged as high ranking, two to three ‘‘Yes’’ responses meant the study moved down one level, and zero to one ‘‘Yes’’ responses meant the study moved down two levels. Credibility of each synthesized finding was also assessed by cross-checking how many findings of each type were included in each synthesized finding.[36] All unequivocal findings remain unchanged, a mix of unequivocal/credible findings was downgraded one (-1) level and a mix of credible/not supported findings was downgraded three (-3) levels.

Included in the Summary of Findings were the title, population, phenomena of interest and context. Each synthesized finding from the review was presented, along with the type of research informing it, the score for dependability and credibility, and the overall ConQual score. Each synthesized statement was initially assumed to be of high quality and then downgraded for any credibility and/or dependability rating less than high.

2.5 Results

2.5.1 Study inclusion

As shown in Figure 1, 5945 records were identified following the detailed search strategy. An additional six records were identified through hand searching of unpublished studies and gray literature. Following removal of 1988 duplicates, titles and abstracts of 3963

papers were screened for eligibility. Ultimately, 3865 records were excluded for not meeting the inclusion criteria; 98 papers were selected for retrieval and, after reviewing the full text, 86 were excluded for not meeting the inclusion criteria (see Figure 1). Following correspondence with 21 authors, four abstracts were confirmed as having been published as corresponding studies, six had no corresponding study published, and 11 had no reply. A list of studies excluded after full text review is listed in Appendix II. The 12 remaining papers represented 11 unique studies; one study was reported in two of the identified papers.[40, 41] The 11 included studies were critically appraised and one was excluded due to low rigor.[42] A total of 10 studies were included in the systematic review.

2.5.2 Methodological quality

Overall, the methodological quality and rigor of the included studies was high (Table 1). The majority of the quality domains (*n*=7/10, 70%) were met by all 11 studies. Studies scored least well in two quality domains: Question 6 - Is there a statement locating the researcher culturally or theoretically? (*n*=6/11 studies, 54.5%), Question 7 - Is the influence of the researcher on the research, and vice- versa, addressed? (*n*=5/11 studies, 45.5%). This may have had a potential influence on study findings, regarding the dependability score (Q2-Q4, Q6, Q7) for determining the ConQual score. The remaining criteria relating to congruity of research methodology, study question, data collection and analysis techniques, and statement of ethics, were strong. One study was excluded,[42] since three of the 10 quality domains (30%) were unmet, which failed to satisfy one of the main criteria (Q5) affecting the overall methodological quality. Therefore, a total of 10 studies were included in the systematic review with meta-aggregative synthesis.

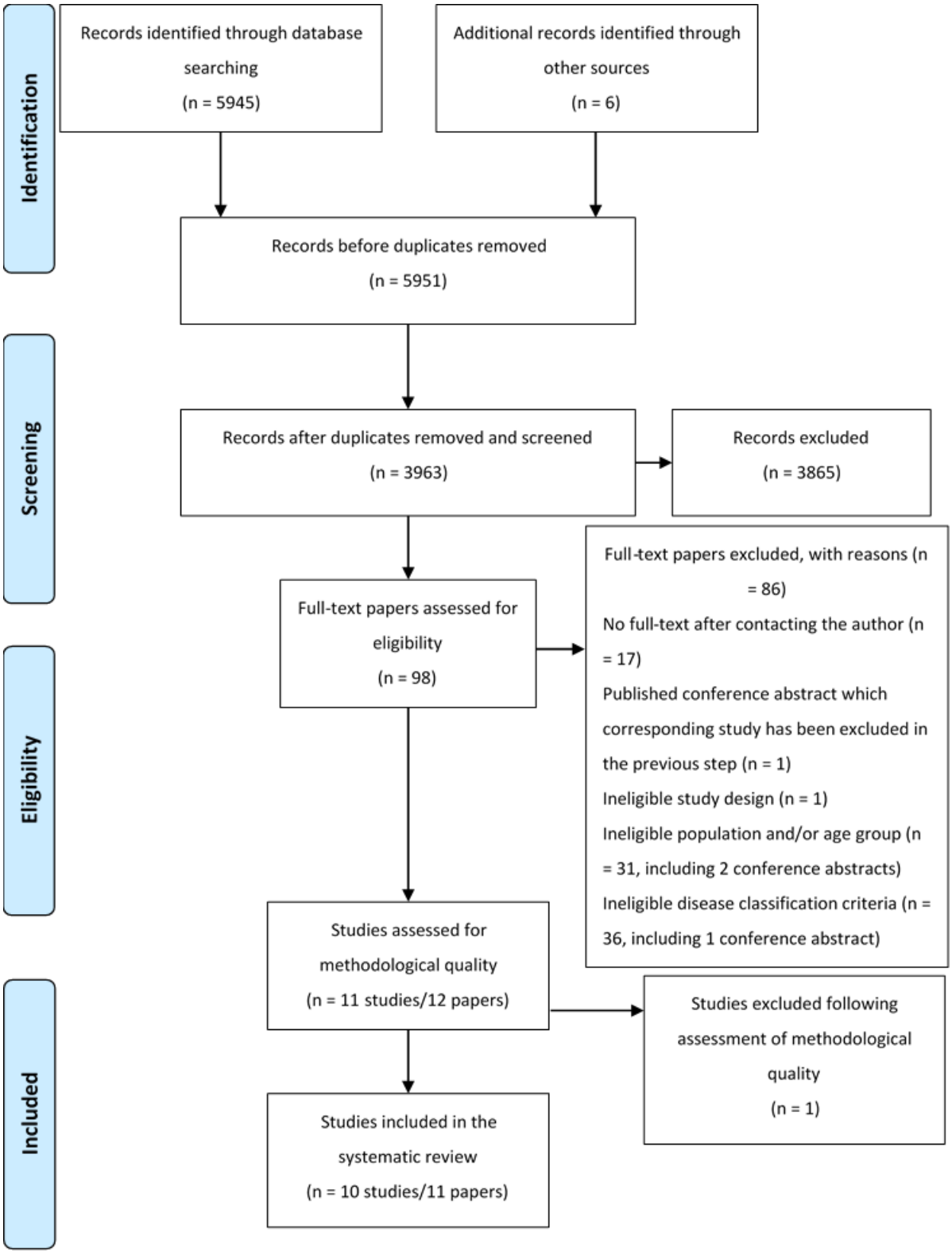

Figure 1: Search results and study selection and inclusion process[43]

Table 1: Critical appraisal results of eligible studies

Reference	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	% yes responses
Jones et al.[41] (Sherratt et al.[40])	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Torres-Made et al.[42*]	Y	Y	Y	Y	N	N	N	Y	Y	Y	70
Stinson et al.[44]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	80
Livermore et al.[45]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Leksell et al.[46]	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	90
Leksell et al.[47]	Y	Y	Y	Y	Y	N	U	Y	Y	Y	80
Khan et al.[48]	Y	Y	Y	Y	Y	N	U	Y	Y	Y	80
Shaw et al.[49]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
O'Sullivan et al.[50]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	80
Van Gulik et al.[51]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Beneitez et al.[52]	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100
Total %	**100**	**100**	**100**	**100**	**90.9**	**54.5**	**45.5**	**100**	**100**	**100**	

[*] study excluded due to low rigor.

N = No, U = Unclear, Y = Yes; JBI Critical Appraisal Checklist for Qualitative Research.

Q1 = Is there congruity between the stated philosophical perspective and the research methodology?;

Q2 = Is there congruity between the research methodology and the research question or objectives?;

Q3 = Is there congruity between the research methodology and the methods used to collect data?;

Q4 = Is there congruity between the research methodology and the representation and analysis of data?;

Q5 = Is there congruity between the research methodology and the interpretation of results?;

Q6 = Is there a statement locating the researcher culturally or theoretically?;

Q7 = Is the influence of the researcher on the research, and vice- versa, addressed?;

Q8 = Are participants, and their voices, adequately represented?;

Q9 = Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?;
Q10 = Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?

2.5.3 Characteristics of included studies

Dates of publication ranged from 2006 to 2020.[40, 41, 44-52] Four studies originated in the UK,[40, 41, 45, 49, 50] two in Canada,[44, 48] two in Sweden,[46, 47] one in Spain, [52] and one in Netherlands.[51] A total of 143 patients and 47 parents participated across all studies. No other family members other than parents were among participants in all of the included studies. Among the 143 patients, there were 96 female (67.1%) and the age range was six to 20 years. Of note, two Swedish studies shared the same study families with one study focusing on patients and the other on the parents.[46, 47] One of the UK studies included a journal article and also a book, which shared the same study group but published in different formats.[40, 41] The relevant chapter in the book was adapted from the journal article. The settings for the data collection included: hospital clinics or meeting rooms,[40, 41, 44, 46, 48, 49, 51] patients' homes,[40, 41, 46, 47] parents' workplaces,[40, 41] video-conference,[52] and by telephone.[40, 41, 46, 50] A range of qualitative methodologies were represented in the studies and are listed below: four studies were identified as qualitative,[40, 41, 50-52] two as grounded theory,[46, 47] two as phenomenological,[45, 49] and two as qualitative descriptive.[44, 48] Details of characteristics of these included studies, including their specific phenomena of interest, are shown in Appendix III.

2.5.4 Review findings

A total of 61 findings were extracted from the included studies (50 unequivocal and 11 credible; see Appendix IV) and assembled into 12 categories based on similarity in meaning. Five synthesized findings were created from the 12 categories and these formed the basis of recommendations for policy and practice aimed at improving care for families and children with JIA.

Synthesized finding 1: Self-management of JIA requires pain management, medication

management, and the acquisition of knowledge and professional support

This synthesized finding is informed by three categories and represents experiences and the struggle that patients and parents living with JIA have as well challenges with the process of acquiring knowledge and information, from a total of 22 findings (see Appendix V).

Self-management skills are the key to getting ahead when living with JIA. Acquiring adequate knowledge and information can help patients and parents become supported, confident, and independent in every disease course. As children grow older, the role of responsibility should gradually shift from parents to children, including sharing knowledge, attending hospital visits, balancing sports and pain, managing medication, and dealing with negative emotions.

Category 1.1: Experiences and needs of patients and parents for the development of self-management

Six findings are grouped into this category, which describes the challenging experiences of patients and parents, and the obstacles they encounter in the development of their self-management of JIA. These experiences and obstacles include lack of information, difficulties in medication management, attending hospital visits, and surveillance of symptoms. Knowledge of pain management and drug effect and access to appropriate vocational assistance can facilitate self-management.

Some parents feel that they lack information and education regarding disease flare, day-to-day management, and medications provided by their health professionals. Health professionals and parents disagree on the availability of information sources. However, they seem to agree that provision of a comprehensive consensus document for self-management is required. Parents' sources of information include: medical pamphlets, relevant websites, (e.g. arthritis support organizations on the internet or social media platforms), and from communication with parents who are more experienced with parenting a child with established JIA. Despite this, parent participants reported that they feel unsupported because of insufficient information sources.

"When you're online in American or Canadian stuff, they're [medications] different names! They don't know what we take, and they'll be taking different things. You have to Google what it is..." (Parent) Pg5[50]

Parents are the primary source of information regarding JIA for their children. Other parents of children with JIA can share information regarding pain management, tips for good sleep and ways to manage medication side effects. However, this may be limited because these parents are also struggling to obtain trusted information. Some older children have also gained knowledge by reading books and searching the Internet.

"I was quite young when I got it, so the doctors told my parents and my parents told me" (Adolescent) Pg 5[50]

Children and adolescents with JIA acknowledge that it is important to develop their knowledge and understanding of JIA in order to be more independent and develop the ability to communicate with others about their disease more confidently. Increased knowledge and understanding of the disease can also help children to manage pain and reduce negative emotions, such as fear and anxiety.

One adolescent explained: "When I was little I was really shy and when I started telling people [about arthritis], well I guess I was shy about having it, but then my friends asked me if there was anything wrong, I finally got it out, then I got more, um, confident" (Adolescent, Female, 12 years) Pg 69[44]

Patients of different ages cope and live with JIA in different ways. Children with JIA always endure their disease-related problems in silence and they want to differentiate themselves from the disease. There are three ways: objectifying, distancing, and normalizing their symptoms. For example,

"Daddy knows when you are in pain." (Child, Female, 6 years) Pg 226[47]

Most adolescents want to learn how to manage and live with JIA themselves before transferring to adult services but overprotection from parents can affect this process adversely. To become self-sufficient, some adolescents attend hospital visits

independently. It is an effective strategy to help young people to become more responsible for themselves and parents can provide appropriate assistance when needed.

"Mam takes care of hospital appointments and bloods. I take care of my injections… She tries not to remind me anymore, I have to learn one day" (Adolescent) Pg 3[50]

From parents' perspectives, increasing responsibility over a gradual period is encouraged for those at younger ages.

"She's twelve, but I get her into some OT [occupational therapy] appointments on her own, and I meet up with them after" (Parent) Pg 4[50]

Obstacles are encountered by both children and their parents while living with JIA. Medication self-management can become a major barrier to gaining independence for some children, as parents have been used to the role of supervising or administering medications for them.

"I take two injections every week and I always forget. I'll be in bed and Mum will shout up to me 'Have you taken your medications?' And I'm like 'Oh!'" (Adolescent) Pg 4[50]

Monitoring children's disease and symptoms can be a major challenge for parents, because signs and symptoms of JIA can be difficult to detect. However, parents will notice children's changes of behavior and/or moods, including avoidance to move and reluctance to take steps, even if very young children. Therefore, monitoring such changes can become the main method used by parents to assess disease activity and pain.

"I didn't know that he had headaches every day and I didn't reflect over why he only wanted yoghurt and not real food before we came to specialized dental care." (Parent) Pg 357[46]

For some parents, managing their children's medications and attending regular hospital visits are also challenging. For example, children with JIA may refuse to take medicine or injections, which requires parents' efforts to make their children cooperate.

Therefore, in addition to the difficulties described above, adolescents with JIA report some unmet needs. Health literacy is a key factor for the development of effective self-

management, and understanding how drugs work can help manage disease-related pain and discomfort.

"I just wanna know about what type of therapies to ease the pain because sometimes the pain can be really bad" (Adolescent, Female, 15 years) Pg 68[44]

In addition to knowledge and information, specialist career advice and skills training are also necessary, according to young people. Several participants found it difficult to deal with their disease in the context of interviews (e.g. college, university, and employment). Meeting other people with JIA who had successfully gone through an interview was also considered helpful, and confidence was also gained through conversations. Sharing relevant information on websites can also be valuable given the fact that careers advisers are not usually present at their usual hospital appointments.

"I think it would be wise to have a careers adviser at the adolescent clinic." (Adolescent, Male) Pg 101[49]

Category 1.2: Children usually reduce or change sports to manage pain

This category comprises two findings related to the impact of pain on patient's participation in sports. Children and adolescents with JIA report their limited participation in sports, especially in Physical Education (PE) lessons. For most, managing pain and discomfort can be achieved by reducing or changing their physical activities, although sometimes their peers do not understand why this has occurred. Children and adolescents express their desire to keep up with peers, rather than avoiding activities and being "different".

"I get out of PE as I can't do it at times, and people think I just use it as an excuse, I now go to the library and stamp books instead" (Child) Pg 4[45]

Category 1.3: It is a curious paradox that both patients and parents have positive and negative psychological experiences regarding JIA and medications

Fourteen findings are grouped into this category. It highlights that parents are likely to suffer more than their children with JIA, since the children identify more positive

psychological experiences.

Children and young people feel that others, apart from their immediate family, don't understand what it is like to have JIA.

"my five year old sister understands what I've got wrong with me" (Child) Pg 3[45]

However, children and young people feel proud of themselves when they deal with the disease successfully and are able to face the disease with optimism and courage.

"It seems like she (another JIA patient) isn't taking care of her disease. I'm proud that I'm able to take care of myself." (Child, Female, 16 years) Pg 227[47]

Some children are more afraid of surgery or injections than the possibility of developing joint damage or deformity. In addition, due to negative feelings associated with medications they prefer to bear the pain of JIA rather than take medications. However, positive experiences of overcoming fear and sadness and ways of dealing with negative emotions are also described by others.

"If you get an injection . . . I think it's rather painful. At first, I thought it would be painful, but when I got one here, I just said OW!" "But I didn't start crying, or did I?" (looks at her mother) "But when I was going to get it, I started crying because I thought it would be painful, but then when I got it, it didn't hurt." (Child, Female, 6 years) Pg 227[47]

"Because sometimes when you re at school you like wanna go home but you don t wanna miss the work and you don t wanna have to catch up and stuff so you just put it in the back of your mind and then eventually you just forget about it over time" (Adolescent, Female, 15 years) Pg 69[44]

Adolescents are able to discuss their disease more rationally, while parents tend to use more emotive language, emphasizing the stress they are living with.

"My daughter takes an injection every day. And the battle we have is every evening. It's a huge battle" (Parent) Pg 5[50]

In addition, the following part discuss the impact of three medications on daily

experiences, including MTX, corticosteroid and the biologic agent, Etanercept. Children have reported more negative experiences than parents.

Children with JIA describe various physical, emotional, and behavioral symptoms related to taking MTX, including vomiting, fatigue, fear, anxiety, crying and shaking. Children's dislike of MTX was seen by observing facial expressions and body language during interviews. In addition, relevant sensory cues, such as visual, olfactory, somatosensory and taste, can trigger the development of MTX intolerance and also provoke anticipatory symptoms.

One child explained that when she went down to the basement and was about to receive her MTX, "I'm shaking and full of fear" (Child, Female, 10 years) Pg 52[48]

Therefore, some children have to work hard to live with MTX, not just on the day of administration, but for the rest of the week. Some children show avoidant behaviors in the face of MTX-associated experiences, for example, the need for avoiding use of alcohol, use of swabs prior to injection or drinking apple juice afterwards to disguise the taste.

"Well, for every minute of the day [after receiving MTX] I feel like I'm about to throw up." She went on to explain that the day after MTX administration, "it takes a little bit longer for me to do my homework… I lose my, uhh, like, focus" (Child, Female, 11 years) Pg 52[48]

Adherence issues associated with MTX are discussed in detail by adolescents and their parents. Adolescents believe the side effects of MTX to be the main reason for non-adherence, while parents participants perceive that long-term anxiety/concern is also a significant factor.

"I'm tired every day. I'm not a morning person as it is, but the methotrexate makes it ten times worse" (Adolescent) Pg 7[50]

"She had a flare a while back; they had to increase the methotrexate and she was devastated. She said to me, "How am I ever going to get pregnant?"" (Parent) Pg 7[50]

According to children with JIA, they develop various strategies to manage MTX-related issues on their own or with the help of family members and clinicians by means of "trial and error". Distraction techniques can be used to cope with negative emotions and MTX intolerance by engaging in another activity, such as watching TV during the injection. Other strategies, such as comfort measures, self-talking and performing the injection whilst asleep, are widely used for some children to manage their intolerance. Additionally, taking an antiemetic prior to the dose and/or changing the route of administration are also suggested by clinicians.

Going to sleep after receiving a MTX injection (Child, Female, 10 years), (Child, Male, 9 years), (Child, Female, 11 years), (Child, Male, 9 years), (Child, Female, 10 years) or having an injection done while they were asleep (Child, Female, 11 years), (Child, Female, 6 years) was an effective way of managing intolerance for some children. Pg 52[48]

However, most children and young people demonstrated positive attitudes towards the biologic agent, Etanercept, although it may cause some injection issues, such as reluctant feelings of self-injection.

"I have to inject it into myself, it doesn't bother me, I used to inject my Methotrexate and Anakinra, so it's all the same" (Child) Pg 3[45]

A few negative experiences regarding Etanercept are reported by children.

"the Etanercept's useless 'cuz it doesn't work for me, I'm just a guinea pig, you get told all these things will work, they don't, nothing works" (Child) Pg 3[45]

Experiences and perceptions regarding four corticosteroid induction regimens in children and young people with JIA are described by patients and parents. Four corticosteroid delivery routes include intra-articular corticosteroid injection, oral prednisolone (tablets), intravenous injection and intramuscular injection. Use and effect, as well as benefits and drawbacks are thoroughly discussed by participants for each induction regimens in this category.[45]

Intra-articular corticosteroid injection is considered by participants as a more invasive treatment and suitable for children who had fewer affected joints or more severe disease activities, while the other three delivery routes are suitable for those with multiple affected joints.[45]

". . . it's powerful for a few joints but not when you've got more than a few affected." (Mother, 14-16 years) Pg 26[41]

Of note, the effect of oral prednisolone is reported to be short term, and symptoms can return after the dose is reduced or the treatment completed. However, it is described by parents that the tablet can act fast to control symptoms, similar to one of the advantages of intravenous injection.

"They gave us her steroid tablets and it went down then. The steroid tablets, it went down overnight, didn't it?" (Mother, two children with JIA, 1-4, 5-7 years) Pg 27[41]

Advantages of corticosteroid therapy have been reported by parents. For example, taking oral prednisolone is a good option for children on holiday/vacation, since it does not require hospitalization and some dissolvable tablets are easy to administer. Whereas, children only state their opinions regarding the drawbacks of each induction regimens.

"I think [clinician] would have done the joint injections sooner um but we were due to go on holiday, so that's why we tried the oral steroids first, 'cause he could continue taking those while we were on holiday." (Mother, 5-7 years) Pg 28[41]

"It hurts a lot afterwards, like it does get worse before it gets better, but only for like a few days like it gets worse . . . they did swell up and like it felt like your hand was broken . . . I couldn't have gone into school and like done all the writing and things." (Child, 14-16 years) Pg 27[41]

However, some parents disagree with their children about the drawbacks of intravenous injection as it will cause them to miss school.

". . . it took a long time, so I had to miss quite a lot of school, and I had to catch up on everything, so it means I'd have to write a lot." (Child, 11-13 years) Pg 30[41]

Synthesized finding 2: A promising relationship with healthcare professionals but unbalanced access to services

The second synthesized finding reflects patients' and parents' relationships with their healthcare professionals and their met and unmet needs regarding the care they received. This synthesized finding is informed by three categories: trust in healthcare professionals, lack of infrastructure and unequal access to services in some regions, varying ability to communicate with doctors, encompassing six findings (see Appendix V).

Category 2.1: Trust in healthcare professionals

Two findings form this category. For most patients, doctors are believed to provide help and represent hope, hence patients can feel very strong appreciation and trust in their doctors, and some also know when to ask for help.

"Well, that … not to care what anyone says because you'll get better if you do what your doctor tells you. If you have problems with your medications … well, um, if—if you don't like how it is, like, you don't wanna gain weight or whatever, just ask your doctor" (Adolescent, Male, 15 years) Pg 68[44]

However, healthcare professionals also remind children of the disease and the process of treatment which sometimes cause sadness and anxiety. Some patients cannot understand that their health professionals, such as dentists who help manage orofacial pain, may be unaware of the pain caused by their interventions. In addition, there is a small proportion of patients who express feelings of being hurt or humiliated by their doctors.

A good interaction between the patient and health care professional can improve experiences for both the child and the family.

"We are really thankful for the information we got from the dentist. It has been really helpful for us. L is very worried, as she is reading catastrophic information on the internet about her disease. When we are alone at home, she cries and tells me that she is so afraid, but when she meets others, also her caregivers, she is more moderate. I have to call dental caregivers and make appointments for advice." (Parent) Pg 358[46]

Category 2.2: Lack of infrastructure and unequal access to services in some regions

Two findings are grouped into this category, which represents barriers and difficulties encountered by families in accessing medical services in some regions. Even in developed countries such as Ireland, barriers to JIA management include lack of workforce and unequal access to services (e.g. lack of psychological support provided by healthcare professionals in Ireland). The main challenge for families with JIA patients is to receive timely diagnosis. For example, participants in an Irish study report experiences of delayed initial clinic visits and long waits for a definitive diagnosis, since pediatric rheumatologists are scarce and unevenly distributed in their country.

"We opted to go privately. The wait time for Rheumatology was two years or more going the public route…" (Parent) Pg 6[50]

Parents have found day-to-day management of JIA stressful. They appreciate that psychological assessment could help their child, but accessibility issues are prevalent.

"The service is disjointed. [Area] have a physio unit and OT, but mental health services are in a different area. It's difficult for people to get to" (Parent) Pg 5[50]

Access to health and care services is difficult in some areas. Families in these regions have to miss work and school to attend appointments. Some families even arrange several appointments in one day to reduce frequent trips but with the cost of a long and exhausting day.

"Yeah, early start. We'd get up at five in the morning, to be there for 8:30. And we wouldn't get home until 7pm" (Adolescent) Pg 6[50]

"I'm still struggling to get OT. I'd say if you were in Dublin it would be easier, but in [area] it's very hard" (Parent) Pg 6[50]

Category 2.3: Vary in ability to communicate with doctors

Two findings are grouped in this category. Most adolescents with JIA state that they do not want to exchange information about their current health status themselves. However, they recognize the need to learn these skills so that they can communicate with doctors

and transit successfully to adult centers. Young people vary in the rate of development of these skills, with two typical examples.

One adolescent welcomed her mother's presence during her appointments because she was afraid she would forget important information: "Right now my mom still does come in because I forget things" (Adolescent, Female, 12 years) Another adolescent who was more independent stated, "Uh when I was younger my mom did most of the talking but now that I'm getting older I do most of the talking. And if I get it wrong she just corrects me" (Adolescent, Female, 15 years) Pg 68[44]

Other adolescents consider being independent as planning their own activities, making their own decisions, and arranging the required support from professionals.

"I asked the paediatric rheumatologist for a medical certificate and brought it with me to school and then I asked if it would be possible to shorten my school days because of my JIA." (Child, Female, 17 years) Pg 7[51]

Synthesized finding 3: Parental financial burden and their adjustment to maintain family happiness

The third synthesized finding encompasses the great impact of JIA on family life and finances and the coping strategies adopted by parents. Two categories generated from four findings contribute to this synthesized finding (see Appendix V).

Parents are responsible for dealing with psychological and financial issues. Although the treatment used for JIA varies depending on the subtype and severity of the disease, patients require regular visits to the outpatient clinic. Children with high disease activity and those who need joint injections sometimes need to be hospitalized. A multidisciplinary team is also required for the daily management of JIA. In some countries such as Ireland, these above factors, including frequent hospital visits, multidisciplinary management, hospitalization fees, and travel costs, increase the burden of JIA on the family. Health care professionals also claim that high costs of treatment and loss of income due to carer's leave can cause lack of adherence.

Category 3.1: Maintaining family cohesion and happiness

Two findings are grouped into the category. Realignment of priorities in life is important for parents who live with JIA, to avoid the disease taking over their family lives. Some parents believe that the day-to-day struggle with JIA is an important factor contributing to divorce. However, most parents believe that maintaining family cohesion and daily happiness is important and they take responsibility for their child's disease as much as possible. Even though parents often feel depressed or stressed and it is hard work to achieve a balance between their own and their child's needs, they also feel proud of their child for being happy and positive despite the disease.

"We have become very close in our family as we have learned to be thankful and happy for every day we are healthy. Our friends are used to us being unpredictable. We cannot book any activity for sure because something is always happening with one of our children's health, which makes it impossible to come." (Parent) Pg 357[46]

Category 3.2: Great burden on parents' jobs and finances

Two findings are grouped into this category, which describes the heavy financial burden placed on families with a JIA patient. For most families, this financial burden only affects parents because the patients are too young to afford the expense and, thus, they did not discuss the costs of treatment for JIA in the interview. Conversely, parents are put under great pressure in deciding jobs, career, housing, and holidays/vacations, because they have to take their child's disease into consideration.

"Neither I nor my husband has been able to have the careers that we expected because of all the appointments at the doctor, the physiotherapist, the dentist, the occupational therapist, meetings at school, and so on." (Parent) Pg 358[46]

In some countries, such as Ireland, government-sponsored medical care is not well guaranteed, and parents struggle to cope with spiraling prescription and appointment fees. This also support the views in previous synthesized finding.

"I have to apply for the long-term illness payment. [Son's] medication bills were 200 a

month. It's supposed to be about 140, that's a lot of money every month..." (Parent) Pg 6[50]

Some parents experienced a lack of understanding from employers, and some parents had jobs that made it difficult to call in sick. Some gave up working to care for their child as they felt they had no other choice.

"I gave up working. She was diagnosed at three and I never went back..." (Parent) Pg 6[50]

Synthesized finding 4: Patients and parents support the web-based approach to communicate and develop self-management skills and acknowledge the importance of clinical trials

This synthesized finding includes two categories: patients and parents' views on a web-based approach to gain self-management knowledge and skills, and communicate with others, and their views on participation in JIA clinical trials. This finding encompasses nine findings (see Appendix V).

Relevant website and online resources for JIA are effective and efficient mediums for improving self-management and knowledge-sharing for both children and their parents. In this synthesized finding, the majority of participants responded positively to the web-based approach, including a self-management website and two social networking platforms. Additionally, although participants recognize the importance of JIA clinical trials, the children and parents involved may have different views towards participation. Compared to children, parents need to consider whether the treatments are beneficial to their children. This makes parents more cautious about participating in trials.

Category 4.1: Appreciate/ Positive attitude towards the web-based approach

This category comprises six findings. Some adolescents spoke highly of the self-management website (i.e. Teens Taking Charge: Managing Arthritis Online), which contains lessons and videos for patients with JIA, as well as validated information about the disease, treatment, managing pain, and developing self-management skills.

Adolescents felt that this website fosters self-management and helps them obtain social support. In addition, the website also contains more sensitive topics, which patients may not wish to discuss with their parents, such as getting tattoos, alcohol intake, sexual activity, and contraception.

All adolescents thought that having a Web-based approach to learning about their arthritis would be a good way to overcome some of the current barriers to accessing self-management information and skills (e.g., lack of time and resources, group format not appealing, and associated direct and indirect costs of these therapies) Pg 69[44]

Information and communication technologies are important ways for JIA patients to access online resources, including searching for information, watching films, speaking with friends and using social networks. Most adolescents used a smartphone to access these resources and expressed favorable opinions. Additionally, preferred characteristics of an online resource for JIA, such as general information, interactions with peers with JIA, interactions with someone experienced, health professional's involvement, were also discussed in this finding. Of note, inclusion of "surveys" in the online resources or websites for children with JIA is suggested.

"The surveys could be very different from each other, for example, asking what joints are most affected, and so being able to contact people who are in the same situation as you are, or about what you would recommend, in other words, completely different responses from each other to guide you, that are always welcome, even though each case is different." (Adolescent, Female, 18 years) Pg 7[52]

Compared to Facebook, Moodle and WordPress, platforms such as Instagram and WhatsApp had the highest frequency of everyday use in adolescents with JIA. Therefore, Instagram and WhatsApp were thought to be the best choice to implement the online resource.

"I think the best option would be B, the one with Instagram and WhatsApp, because it is the combination of the two applications that kids our age use the most. So I think it is the most accessible option for everyone." (Adolescent, Female, 15 years) Pg 7[52]

Several parents find the website particularly useful for the families with a newly diagnosed patient.

"For newly-diagnosed parents, who are finding their way in the first year, who don't know what an appointment with an OT or a physio is…" (Parent) Pg 7[50]

Category 4.2: Facilitators and barriers to participation in clinical trials

Three findings are grouped into this category, which represents how patients and parents perceive JIA clinical trials. Families of children and young people with JIA recognized the importance of clinical trials. Most children and young people held an open view towards the participation in a JIA trial, because they believed that the trial is beneficial to others and themselves. In addition, their trust in their clinician also increased the enthusiasm for participation. However, parents can be more cautious regarding participation because of their concern over whether their child will still receive optimal care whilst participating in the clinical trial.

"I think I might have been a little bit more concerned 'cause I think I would want, at the beginning when we didn't know a lot about it, I think I would have been thinking, oh no, I need to have the consultant say what's best for him." (Mother, 14-16 years) Pg 33, Pg 5[40, 41]

"I don't know, I think I took it a bit better than my mum, 'cause mums are mums, so they get a bit worried." (Child, 11-13 years) Pg 36, Pg 6[40, 41]

Children, adolescents, and their parents identified several barriers to participation, including trial inconvenience, inappropriate treatment, and previous failure experience.

"If it's not worked this time, what makes them think it's going to work the second time?" (Mother, 5-7 years) Pg 41, Pg 5[40, 41]

In contrast, treatment targeted to the child's age and JIA subtype can facilitate participation.

"If you have a flare and it doesn't just affect one joint, then [IV], it'd kind of help you more." (Child, 11-13 years) Pg 36, Pg 6[40, 41]

Family perceptions of treatment suitability were largely influenced by treatment preferences of clinicians.

"Probably the joint injections [would be best] 'cause [the doctor] said they work better cause it's straight into the joint." (Child, 11-13 years) Pg 37, Pg 6[40, 41]

Families may be more willing to participate in trials at the time of diagnosis because negative treatment experiences could discourage subsequent participation. Nevertheless, some parents could also refuse to participate because of difficulties encountered in understanding and accepting the diagnosis of JIA.

"[At diagnosis] I haven't experienced any of them [treatments] so far so it wouldn't hurt to try any of them…" (Child, 14-16 years) Pg 33, Pg 4[40, 41]

"[We would participate] at the beginning when he had it, probably it will be different but now, no way we had such a big, big problems with his injection..." (Mother, 8-10 years) Pg 36, Pg 6[40, 41]

Synthesized finding 5: Desire to live a normal life without prejudice from school, social settings, and the workplace

The last synthesized finding reflects the challenges and difficulties associated with schooling, peer relationships, and social and employment issues. The patients' coping skills and the parents' perspectives are also included. Two categories generated 23 findings for this synthesized finding (see Appendix V).

Category 5.1: Children do not want to be different from peers

Seven findings are grouped into this category. Children with JIA believed that good relationships with parents, teachers, and peers are required. For younger children, it was most important to gain understanding and comfort from their parents, whilst older children were more concerned about what their peers think of them. Some older children do not want their peers to know that they have this disease, so that their special needs due to the disease are not obvious, and they will not be prejudiced by their peers.

"Now they want me to have a splint, but I don't know. I think that many people maybe

wouldn't want one because maybe they have a boyfriend or something. But me and my boyfriend would probably just laugh at it, because we are so . . . crazy. Yes, I don't know, I could actually have one, but I . . . it's just that I don't feel like." (Child, Female, 14 years) Pg 228[47]

Some decided to self-disclose their disease based on a high level of friendship and a good time of disclosure. Good friends can provide physical help to patients to perform some activities.

"I think I don't have anything to keep to myself, that is, I can say everything, and with my friends, I don't care whether I tell them or not. ... Well, if a new kid comes, I won't go and tell him –Hey, I have arthritis-, but if the topic comes up, I will tell him ... I'm not embarrassed either or anything like that ... Most of them are friends from a long time ago, and they already know about it, and so they don't even ask ... If they are interested, I explain it to them, if it's like – Why don't you do gym? - I tell them for no reason and that's that." (Adolescent, Female, 13 years) Pg 5[52]

Young people faced the challenges and difficulties associated with friendships. They had strong feelings about not wanting to be treated differently by others, including family and friends. In addition, they often felt not normal, which made them feel isolated.

"People treat you differently, the idea of being different is upsetting, well not that different, being different is quite a big thing, I don't want extra help as I don't want to be more different, people automatically think you can't do things and you can't be bothered to say you can, so you end up sitting watching and feeling sad" (Child) Pg 4[45]

However, some patients felt satisfied with their friendships as they could be themselves with their healthy peers.

"If I tell them what's going on, they usually help me, and yes, the truth is that I think we can talk about almost anything ..." (Adolescent, Male, 14 years) Pg 5[52]

Category 5.2: The needs of appropriate school facilities, academic assistance, social support and addressing discrimination in workplace

Sixteen findings form this category that relates to issues with schooling, social support, and employment. Challenges regarding education and schooling for JIA patients mainly included the availability of school facilities and whether or not they received academic-related assistance. Appropriate school facilities are essential because some facilities can trigger negative emotions, as reported by some patients. Lots of young people claimed they had been moved down to a lower academic group, and worried that their actual ability level was not understood. They believed that as long as they get the right assistance, such as obtaining laptops, scribes, and extra time to complete examinations, their qualifications and employment opportunities should not be affected.

"I didn't go to school for about 6 months, I didn't do any work, I get low school reports because I'm not there" (Child) Pg 3[45]

"They set up a room for me with a couch, when I was tired I could go and lie down for an hour. I didn't partake in gym class, I only had to go to classes of which the subject came up in my exams. I had permission to work on a laptop, therefore all my books were on the laptop. They offered school transport, but then I had to get up 45 min earlier, so I rejected." (Child, Male, 17 years) Pg 5[51]

Other patients reported that perseverance was a way to overcome academic difficulties and to maintain a balanced social life.

"I'm always attending school, even in my wheelchair, even on crutches." (Child, Female, 17 years) Pg 7[51]

Adolescents spoke highly about JIA support organizations and events because understanding and the feeling of being less isolated could be gained through meeting with other patients. Understanding, compassion, and assistance from caregivers, peers, parents, and teachers can help reduce the feeling of isolation. However, teachers need to be more equipped to understand the disease and its management because some children felt that they were identified as different from their healthy classmates if they received extra support from teachers. Furthermore, some adolescents emphasized the importance of social support from peers because they were much more likely to be influenced by

peer pressures regarding drugs, alcohol, and unsafe sex.

"It always felt like I was the only person on earth that had arthritis but I met a whole bunch of other kids who had it and I'm not the only one. It makes you feel a lot better" (Adolescent, Female, 12 years) Pg 69[44]

However, parents also reported that their child only discussed their condition with peers who have JIA, because they did not think healthy peers were able to understand their disease.

"I don't think [19A] was talking about her condition with her friends. I'm not sure that she shares with them how she's feeling every day" (Parent) Pg 8[50]

Most young people in this review had achieved some early work experiences, even though these experiences were negative. As reported, it is more important to solve workplace discrimination than issues from employment access or working environment. For example, patients report that the greatest pressure on their scope of employment was the attitude of others, rather than their limited physical capabilities caused by JIA.

"If they find out you've got a disability you never hear from them again." (Adolescent) Pg 100[49]

On the other hand, when colleagues were family or friends, work experiences were more likely to be positive.

"They arranged a switch with a colleague so I could help with the lessons and feeding in the evening instead of mucking out stables in the morning. My colleagues are my friends so they knew I have JIA and they didn't mind. (Working in an equestrian facility)" (Child, Female, 16 years) Pg 5[51]

Young people with JIA felt various jobs were not open to them because people generally underestimated their educational capability and vocational potential due to their disease and disability.

"My arthritis doesn't affect me all that much. I could do it. I'd pass the physical. But I wouldn't pass the medical. It's just unfair 'cos I could do it." (Adolescent, Female) Pg

100[49]

However, most JIA patients identified the importance of being determined, passionate, and confident, and they believed that their career choice or future life would not be affected by JIA. They also understood that despite possible parental overprotection, seeking advice from parents and health care professionals can be beneficial in vocational decisions.

"I feel really passionate about this. And if you really want something, your body can try to stop you, but if you know for sure, you'll just keep going." (Child, Female, 17 years) Pg 7[51]

Regarding the impact of JIA on the future, most of the adolescents' concerns related to careers; however, parents expressed concerns about social and financial issues.

"When he gets older, he has to pay for both TMJ and periodontal treatments, problems that are caused by the disease. I do not think this is right." (Parent) Pg 358[46]

However, planning or worrying for the future seemed less important for both adolescents and parents than managing day-to-day life.

2.6 Discussion

This review provides a comprehensive overview of experiences and perceptions of children, young people, and their parents living with JIA. All five synthesized findings support the viewpoint that patients with JIA suffer from various issues, including psychological health, physical well-being, and QOL. For the majority of the JIA patients who participated in these studies, relationships with parents, health care providers, teachers, and employers are suboptimal. Lack of knowledge and skills makes it difficult for patients and families to live with the disease. To facilitate a better self-management of day-to-day life and JIA patients' futures, appropriate web-based approaches and programs, career counseling, school facilities, and clinic trials are required. Our synthesis enables a consideration that can inform new policies and better care for JIA patients.

Synthesized finding 1

The first synthesized finding emphasized the importance of self-management knowledge and skills in living with JIA. General day-to-day experiences and the experiences regarding physical restrictions and psychological distress were discussed in detail, for patients and their parents. This synthesized finding described how some parents still feel unsupported, even though various sources of JIA information are available.[50] This view is substantiated in a qualitative study of adult patients with JIA in Belgium, which found there was inadequate information available regarding medication regimes.[53] Furthermore, a Canadian study on information needs in JIA (excluded for not using ILAR criteria) indicated that face-to-face contact with healthcare professionals is the most successful method for parents to obtain information about JIA.[54] This method was not reported in this review, which partly explains why some parent participants felt unsupported. To solve the debate between health care professionals and parents about whether there are sufficient sources of JIA-related information, a comprehensive self-management source is required.[50] Use of validated PREMs questionnaires in the clinical setting will also assist health care professionals to understand the experiences of JIA patients and families and to solve this disagreement. Our findings also showed that the most frequent source of information for children are their parents, although some children acquire knowledge via books or the internet. This is consistent with the evidence reported in the Canadian study.[54] Therefore information on the internet should be monitored and regulated, for example, by governments, to make sure it is reputable. The study also reported that an effective way to make children take more responsibility for their illness is to have a direct conversation with them during each appointment to prevent bias about children's experiences and needs from health care professionals and parents.[46] This is supported by synthesized finding 3.

In addition, this synthesized finding has demonstrated that many JIA patients cannot participate in their favorite sports and highlighted their desire to participate. Published literature informs us that most children with JIA experience a reduced participation in physical activities.[55] However, it is also well-recognized that JIA patients benefit from sports to improve muscle strength and to avoid physical deconditioning.[55, 56] Therefore,

JIA patients should be encouraged to participate in more sports and activities appropriate for their degree of disease activity. Assistance from clinicians and physiotherapists and support from teachers are important in helping children and adolescents with JIA achieve maximal physical, and thus psychological, potential.

Positive and negative psychological experiences regarding JIA and medications were illustrated in this synthesized finding. Children with JIA described a variety of psychological experiences, such as their feelings of loneliness and not being understood, their pride in themselves when they successfully manage the disease, their sadness and fear of treatment, and the ways to overcome it. Of note, the negative emotions described above, require great attention and people need to take corresponding actions to handle them. For example, some children believe no one except their close family members can understand what having JIA is like. However, findings from other papers found that peers started to understand the disease after watching informative videos at school.[45] In addition, lack of public awareness of the disease is evident in this finding and is supported by an Australian study on hospital/care experiences in JIA patients (excluded based on not using ILAR criteria and unclear age range with two included patients aged over 19 years), which found that deficiency of information about JIA also existed among some healthcare providers.[57] This review outlined the difficulties parents had in controlling their emotions as well as their children and health care professionals did because of the struggle coming to terms with the diagnosis of JIA.[50] Regarding medication-associated experiences, most findings focused on MTX, corticosteroid and Etanercept therapy. Children participating in this review described a variety of negative physical, emotional, behavioral and long-term experiences associated with taking MTX.[45, 48, 50] In addition, positive and negative experiences and perceptions of corticosteroid therapy were comprehensively studied as parents reported the advantages and children reported the drawbacks,[41] while relatively few negative issues regarding Etanercept were described.[45] Issues with other medications were not included. Interestingly, a paradox was proposed wherein none of the children likes MTX, but they learned to manage MTX intolerance and anticipatory symptoms in different ways.[48] Although doctors have applied many

clinical methods to avoid the side effects of MTX, successful management also requires personalized approaches from children and parents which are often achieved by "trial and error". Parents and children have expressed their opinions regarding MTX-related compliance issues, which showed that in addition to the known side effects of MTX, aforesaid long-term concerns have also contributed to poor adherence to MTX.[50] As an effective and low-cost medication, MTX remains the first-choice of second-line treatments after NSAIDs. However, intolerance or lack of response can limit its use. Questionnaires such as the MTX Intolerance Severity Score (MISS) have been used to measure the intolerance in the clinical setting,[58] and can assist with the recognition of intolerance as well as promote use of effective management strategies to minimize side effects.

Synthesized finding 2

The second synthesized finding reflected patients' and parents' relationships with their healthcare professionals and their attitudes toward services. Overall, patients trust doctors and seek help from them, although conflicts in the doctor-patient relationship have been reported.[44, 47] It is a common theme in the literature that children with chronic diseases can feel frustrated with their healthcare providers.[59, 60] For example, Kyngäs et al. reported that healthcare providers may be more concerned about the clinical rather than the emotional aspects of disease, such as depression and sadness.[59] Even when health care providers pay attention to the lived experiences of patients, patients indicate they want more understanding and positive attitudes from health care providers. It has been shown that improving patient-doctor relationships can improve health outcomes.[61, 62]

According to this finding, obstacles to services include lack of infrastructure and unequal access to services,[50] these may lead to unsatisfactory experiences and poor treatment outcomes for JIA patients and their families, such as traveling long distances or waiting a long time to access treatment. These are the direct adverse consequences of the obstacles mentioned previously to patients, families and their health outcomes. This

finding was supported by a qualitative study in Australia (excluded based on not using ILAR criteria and unclear age range with two patients aged greater than 19 years), in which delays in diagnosis were attributed to the lack of workforce.[57] The psychological consequences of waiting can amplify physical problems, such as joint pain, and whist the pain of JIA remains untreated, QOL is also affected.[63-65] Additionally, long waiting times to access treatment may result in a missed "window of opportunity" to treat the disease effectively, resulting in worse long-term outcomes.[66]

In clinical settings, the introduction of PROMs and PREMs may assist in alleviating the obstacles to obtaining services, because a questionnaire is able to measure disease activity for a period of time and can increase the continuity of outcome assessment between two clinic visits. If the treating rheumatologist is able to access questionnaire responses prior to an appointment, this can improve disease surveillance and patient-doctor communication. This could also help to reduce consulting time resulting in more efficient clinic flows. In addition, it has been reported that patient satisfaction and experiences during appointments are directly associated with the effects of treatment.[61] The application of PREMs can help hospitals and institutions evaluate service and patient satisfaction, thus help to improve care and management. The ideal model of care includes a multi-disciplinary clinic for JIA patients integrating care from a rheumatologist, physiotherapist, psychologist, occupational therapist, social worker, and, when necessary, an orthopedic surgeon.[67] This multi-disciplinary clinic provides holistic care and reduces the need for multiple appointments.

This synthesized finding emphasizes the importance of independent communication between adolescents and health care providers. However, in most cases, parents speak on behalf of their children when the children are either too young to speak for themselves or unwilling to communicate with doctors about their disease-related health conditions.[44] Nonetheless, it should be noted that parents cannot always play this role because when patients grow up, they have to communicate independently and manage their own illness and daily lives, which is the ultimate goal of both parents and health care providers. Other

published studies also support these findings.[68-71] For instance, research on daily life of children with JIA illustrated the disadvantages of overprotection, such as limited participation in sports and activities and unfair access to information sharing. Overprotection will not solve the underlying problem, and may actually decrease the chances of employment.[71] It was strongly advocated that parents should provide their children with autonomy and responsibility to manage their disease.[68] Also, research on transitional care suggests that strengthening adolescents' independence without affecting parental involvement is also important.[69, 70]

Health care providers can also play active roles in building a trusting relationship with children and stimulating successful self-management. Asking children more frequently about the disease as they get older makes it easier for children to take reponsibility.[72] Adolescents prefer to communicate by computer or telephone rather than face to face,[59] and understanding this can facilitate more efficient communication. Provision of medical certificates for exemption from school or PE when necessary may also provide adolescents with more autonomy, according to a study in Germany.[68] Ongoing research is needed to improve independent patient-doctor communication and to evaluate any changes implemented.

Synthesized finding 3

The third synthesized finding of this review identified that JIA had a great impact on family life and parents' finances, thus parents had to make efforts to maintain family cohesion and happiness. These two categories interact with each other, although the coping strategies were proposed only in the first. Parents identified six factors that make family life chaotic (protecting the integrity of parents, everyday routines, medication administration, monitoring treatment, psychological issues, and finances) and major strategies used by families in maintaining family functioning were discussed.[46] However, these findings were limited to the parents of JIA patients with orofacial pain, and patients did not give an opinion on family life in this review. As for parents' jobs and finances, the second category stated that families living with JIA were under greater financial

burden. [46, 50] This was also found in another Canadian study (using a self-reported questionnaire sent by mail and thus not considered to be a qualitative study) of a Nova Scotia JIA cohort, which similarly reported that this kind of financial burden can be divided into two parts: 1) the high cost related to the disease; 2) the poor availability of financial resources.[73] It was also proposed that financial assistance needs to be provided to those families with the most urgent needs, but few studies have studied this aspect. From the perspectives of this review, policies are urgently needed to help families living with JIA to overcome financial and career difficulties. For example, when a parent needs to take sick leave to take the child to appointment, the employer may be reimbursed by the policy.

Synthesized finding 4

Aspects of patients' and parents' views on a self-management website and online resources for JIA and their views on participation in JIA clinical trials were described in the synthesized finding 4.

In the papers discussing the views and experiences of the web-based program/approach, almost every teenager had a positive attitude towards the web-based approach because it allowed for the acquisition of relevant information and skills.[44, 50] This finding is also supported by other published literature.[25, 74] In one of the studies, an online program to assist JIA management was recommended, which made social support, information sharing, and management strategies available simultaneously.[25] However, parents' perspectives of such websites were not well described, although some parents reported finding the site useful in the context of a new diagnosis of JIA in their child.[50]

In the study identifying patients' and parents' perspectives on clinical trials, all families of JIA patients recognized the need for JIA trials.[40, 41] In the main, most children held an open attitude, while parents were more cautious. The contributing factors to participation included that the clinical trial should be beneficial to others and themselves, and the degree of trust they have in their child's clinician. However, the potential inconvenience of trial participation and previous experiences of failure and treatment unsuitability were

considered to be obstacles. Recently, it was stated by Muller et al. that knowledge gained from the environment also affected people's willingness to participate.[75] For instance, side effects such as gaining weight, would prevent patients from participating in trials that included taking prednisone. Similarly, using therapies that are inappropriate for the child's age and subtype could also be an obstacle factor.[40, 41] In addition to the factors listed in this review, the following tend to be considered as well: access to medication, the potential for drug addiction and the use for randomization (which might cause use of placebo rather than active drug).[76]

Synthesized finding 5

The final synthesized finding demonstrated that challenges and difficulties are widespread, including in interactions with peers, and schooling, social, and employment situations. The first category focused on the challenges of dealing with peers and the need to maintain good relationships, while the other category investigated more specific issues regarding school, social situations, and employment.

In the peer-related category, older children and teenagers were more concerned with what their peers thought of them than younger children. The fluctuating symptoms of JIA and invisibility of the disease created the main obstacles to maintaining good peer relationships. Therefore, some patients preferred not to let peers know about their disease to reduce any potential prejudice or harm arising from this knowledge.[47] Similarly, as reported by Gómez-Ramírez et al. (excluded for not using ILAR criteria), the inability of peers and teachers to understand the fluctuating symptoms made parents indignant and upset.[77] This also could influence the decision children make not to tell their peers about their disease. This review describes the emotional experiences and coping strategies reported by children and young people; none was reported by their parents.[45, 47]

In the second category, education and schooling aspects related to the disease, children and young people with JIA complain about inadequate/improper school facilities and illustrate the adverse impact this can have on academic ability.[45] They believe that receiving appropriate help is as important as being treated normally. Considerable

concerns about academic underachievement were still reported by the patients who received low levels of school supports.[49] Even though the literature suggested that JIA does not have a significant effect on academic achievement for patients with JIA,[18] attention should be paid to ensure long-term school supports and evaluate patients' academic achievements.

Compared to the previously mentioned support from peers or schools, peer-based support from other JIA patients was considered more valuable as it provided the opportunity for patients to share knowledge and experiences, in addition to understanding and empathy. A UK study suggested that peer-based social support based on electronic media can provide a novel method to benefit children and young people with JIA.[78] The finding also advocated for JIA support organizations and events, in which patients can feel as normal as others.

With regards to employment, the last aspect of synthesized finding 5, difficulties and countermeasures were presented by patients with JIA. A high unemployment rate was proven to be associated with active disease and longer disease duration.[79] However, in this review, young people perceived that it was more related to employer discrimination against JIA patients, with their vocational potential underestimated due to perceptions of disease and disability. Although most young patients have realized the importance of being confident and knowing how to seek help,[49] this finding still underlined that educational and vocational needs are the key issues to address in care and disease management. Hanson et al. also recommended that professionals equip young adults with the relevant knowledge and skills to assist in this process.[80] In addition, this finding demonstrated that patients and parents prioritized the management of day-to-day life over worries about the future. This view has been verified by literature reporting that uncertain disease activity has encouraged young people to maintain a "here and now" attitude without further consideration about their future.[81]

Strengths and limitations

A major strength of this systematic review was that the experiences of patients and

parents were included and integrated together. Understanding families' experiences and needs is an important step towards transitioning to person-centered care. Once we understand what matters most to patients and their parents, health care practitioners will be able to provide better care and services. Regional differences in medical resources and treatment possibilities should be considered, and some of the experiences and perspectives in these findings were based on certain countries/regions. This calls for particular care when using these findings to form policies.

This review focused on ILAR classification criteria because ILAR is the international standard for JIA classification. The use of ILAR criteria allows higher comparability between studies and a better translation to current clinical practice. Additionally, only studies published in English were included in this review. This avoided potential distortion or loss of the meaning intended by researchers in the translation process. The use of ILAR and the English language did limit the size of data pooled in our review. Those studies and potential evidence excluded due to not using ILAR criteria may have been beneficial to our results by adding additional experiences regarding traditional medications. However, quality of the included findings was well guaranteed, and the main synthesized findings were consistent across the included studies. Therefore, we believe that our conclusions are generalizable.

2.7 Conclusions

This qualitative review has provided a complementary experience from the perspective of JIA patients and their parents. It is emphasized that the experiences are influenced by knowledge and understanding of the disease, which may help promote independence. Despite this, not receiving pertinent information while living with the disease is commonly experienced by patients and parents. Equally important is the need for appropriate web-based programs, career counseling, infrastructure, and school facilities. It has also been identified that both patients and their parents are affected by the disease and they have to learn to manage it together.

Recommendations for practice

The synthesized findings in this review inform several recommendations for practice. These recommendations are graded according to the JBI Grades for Recommendations. This review demonstrates that patients and families with JIA share specific subjective needs and they desire to lead a normal and happy life. The following qualitative findings can inform health care providers, policy makers and schools:

1. Health care professionals should provide adequate information and advice for parents to cope with daily lives and day-to-day medication management. The way to provide information should be face-to-face, in addition to providing medical pamphlets and internet resources. (Grade A)
2. Health care professionals need to increase direct communication with children during each appointment and let parents act in a supplementary role. (Grade A)
3. Policy makers need to improve medical and health care infrastructures, guarantee government-sponsored medical care, establish and maintain relevant websites and online platforms/programs, and provide special employment channels to ensure the normal employment of patients. (Grade B)
4. Schools need to be patient-friendly to children and adolescents with JIA. This may require providing appropriate facilities for patients and training teachers and healthy peers. Extra academic-related assistance should also be provided. (Grade A)

Recommendations for research

Few studies have been conducted on JIA-specific PREMs. In order to understand the perspectives of JIA patients and parents on their doctors, clinic appointments, and services, further research needs to focus on PREMs in JIA cohorts. Moreover, further research on the longitudinal benefits of relevant JIA programs is necessary to evaluate the effectiveness. A future systematic review of the quantitative research on JIA patients' experiences with relevant JIA programs is needed. Further, due to the diversity of medication intolerance in different JIA patients, there is an opportunity to research

management strategies of medication intolerance. These research studies will help fully describe the progression of learning and management of JIA.

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62. van Dijkhuizen EHP, Egert T, Egert Y, Costello W, Schoemaker C, Fernhout M, et al. Patient's experiences with the care for juvenile idiopathic arthritis across Europe. Pediatr Rheumatol Online J. 2018;16(1):10.

63. Ross CK, Lavigne JV, Hayford JR, Berry SL, Sinacore JM, Pachman LM. Psychological factors affecting reported pain in juvenile rheumatoid arthritis. J Pediatr

Psychol. 1993;18(5):561-73.

64. Vergne-Salle P, Pouplin S, Trouvin AP, Bera-Louville A, Soubrier M, Richez C, et al. The burden of pain in rheumatoid arthritis: Impact of disease activity and psychological factors. Eur J Pain. 2020.

65. Tupper SM, Rosenberg AM, Pahwa P, Stinson JN. Pain intensity variability and its relationship with quality of life in youths with juvenile idiopathic arthritis. Arthritis Care Res (Hoboken). 2013;65(4):563-70.

66. Foster H, Rapley T, May C. Juvenile idiopathic arthritis: improved outcome requires improved access to care. Rheumatology (Oxford). 2010;49(3):401-3.

67. Davies K, Cleary G, Foster H, Hutchinson E, Baildam E, British Society of P, et al. BSPAR Standards of Care for children and young people with juvenile idiopathic arthritis. Rheumatology (Oxford). 2010;49(7):1406-8.

68. Guell C. Painful childhood: children living with juvenile arthritis. Qual Health Res. 2007;17(7):884-92.

69. van Staa AL, Jedeloo S, van Meeteren J, Latour JM. Crossing the transition chasm: experiences and recommendations for improving transitional care of young adults, parents and providers. Child Care Health and Development. 2011;37(6):821-32.

70. Hilderson D, Westhovens R, Wouters C, Van der Elst K, Goossens E, Moons P. Rationale, design and baseline data of a mixed methods study examining the clinical impact of a brief transition programme for young people with juvenile idiopathic arthritis: the DON'T RETARD project. BMJ Open. 2013;3(12):e003591.

71. Jetha A, Badley E, Beaton D, Fortin PR, Shiff NJ, Rosenberg AM, et al. Transitioning to employment with a rheumatic disease: the role of independence, overprotection, and social support. J Rheumatol. 2014;41(12):2386-94.

72. Vanoni F, Suris JC, von Scheven-Gete A, Fonjallaz B, Hofer M. The difference of disease perception by juvenile idiopathic arthritis patients and their parents: analysis of the JAMAR questionnaire. Pediatr Rheumatol Online J. 2016;14(1):2.

73. Ens A, Lang B, Ramsey S, Stringer E, Huber AM. The financial burden of juvenile idiopathic arthritis: a Nova Scotia experience. Pediatr Rheumatol Online J. 2013;11(1):24.

74. Birks Y. Adolescents learned self-management of arthritis by acquiring knowledge and skills and experiencing understanding from social support. Evid Based Nurs. 2008;11(3):92.

75. Hissink Muller PCE, Yildiz B, Allaart CF, Brinkman DMC, van Rossum M, van Suijlekom-Smit LWA, et al. Participation in a single-blinded pediatric therapeutic strategy study for juvenile idiopathic arthritis: are parents and patient-participants in equipoise? BMC Med Ethics. 2018;19(1):96.

76. Woolfall K, Shilling V, Hickey H, Smyth RL, Sowden E, Williamson PR, et al. Parents' agendas in paediatric clinical trial recruitment are different from researchers' and often remain unvoiced: a qualitative study. PLoS One. 2013;8(7):e67352.

77. Gómez-Ramírez O, Gibbon M, Berard R, Jurencak R, Green J, Tucker L, et al. A recurring rollercoaster ride: A qualitative study of the emotional experiences of parents of children with juvenile idiopathic arthritis. Pediatric Rheumatology. 2016;14(1).

78. Waite-Jones JM, Swallow V. Peer-based Social Support for Young-People with Juvenile Arthritis: Views of Young People, Parents/Carers and Healthcare Professionals within the UK. J Pediatr Nurs. 2018;43:e85-e91.

79. Schlichtiger J, Haas JP, Barth S, Bisdorff B, Hager L, Michels H, et al. Education and employment in patients with juvenile idiopathic arthritis - a standardized comparison to the German general population. Pediatr Rheumatol Online J. 2017;15(1):45.

80. Hanson H, Hart RI, Thompson B, McDonagh JE, Tattersall R, Jordan A, et al. Experiences of employment among young people with juvenile idiopathic arthritis: a qualitative study. Disabil Rehabil. 2018;40(16):1921-8.

81. Farre A, Ryan S, McNiven A, McDonagh JE. The impact of arthritis on the educational and early work experiences of young people: a qualitative secondary analysis.

Appendix I: Search strategy

Search conducted on 9th December 2020.

PubMed: 1311 records retrieved

Search	Query
#1	experience*[tiab] OR impression*[tiab] OR attitude*[tiab] OR outlook*[tiab] OR viewpoint*[tiab] OR perception*[tiab] OR insight*[tiab] OR perspective*[tiab] OR perceived[tiab] OR understanding*[tiab] OR Attitude[mh] OR Perception[mh] OR qualitative research[tiab] OR qualitative study[tiab] OR qualitative studies[tiab] OR qualitative method*[tiab] OR interviews[tiab] OR interview[tiab] OR ethnograph*[tiab] OR phenomenol*[tiab] OR focus group*[tiab] OR grounded theory[tiab] OR Qualitative Research[mh] OR Focus Groups[mh] OR Interviews as Topic[mh]
#2	Infant, Newborn[mh] OR Infant[mh] OR Child, Preschool[mh] OR Child[mh] OR Adolescent[mh] OR Young Adult[mh] OR Parents[mh] OR Caregivers[mh] OR Family[mh] OR baby[tiab] OR babies[tiab] OR kid[tiab] OR kids[tiab] OR infant*[tiab] OR child*[tiab] OR youth*[tiab] OR teenage*[tiab] OR adolescent*[tiab] OR parent*[tiab] OR carer*[tiab] OR caregiver*[tiab] OR father*[tiab] OR mother*[tiab] OR young people[tiab] OR CYP[tiab] OR family[tiab] OR families[tiab] OR boy*[tiab] OR young adult*[tiab] OR girl*[tiab] OR AYA[tiab]
#3	Arthritis, Juvenile[mh] OR JIA[tiab] OR juvenile idiopathic arthritis[tiab] OR oligoarthritis[tiab] OR polyarthritis[tiab] OR psoriatic arthritis[tiab] OR enthesitis-related arthritis[tiab] OR systemic arthritis[tiab] OR systemic onset arthritis[tiab]
#4	#1 AND #2 AND #3
Limited to English language & Publication date from 2001 to present	

CINAHL: 447 records retrieved

Search	Query
#1	TI (experience* OR impression* OR attitude* OR outlook* OR viewpoint* OR perception* OR insight* OR perspective* OR perceived OR understanding* OR qualitative research OR qualitative study OR qualitative studies OR qualitative method* OR interviews OR interview OR ethnograph* OR phenomenol* OR focus group* OR grounded theory) OR AB (experience* OR impression* OR

	attitude* OR outlook* OR viewpoint* OR perception* OR insight* OR perspective* OR perceived OR understanding* OR qualitative research OR qualitative study OR qualitative studies OR qualitative method* OR interviews OR interview OR ethnograph* OR phenomenol* OR focus group* OR grounded theory) OR MH (Life Experiences OR Attitude OR Qualitative Studies OR Interviews OR Ethnographic Research OR Focus Groups OR Grounded Theory)
#2	TI (baby OR babies OR kid OR kids OR infant* OR child* OR youth* OR teenage* OR adolescent* OR parent* OR carer* OR caregiver* OR father* OR mother* OR young people OR CYP OR family OR families OR boy* OR young adult* OR girl* OR AYA) OR AB (baby OR babies OR kid OR kids OR infant* OR child* OR youth* OR teenage* OR adolescent* OR parent* OR carer* OR caregiver* OR father* OR mother* OR young people OR CYP OR family OR families OR boy* OR young adult* OR girl* OR AYA) OR MH (Infant, Newborn OR Child OR Adolescent OR Parents OR Caregivers OR Family OR Young Adult)
#3	TI (JIA OR juvenile idiopathic arthritis OR oligoarthritis OR polyarthritis OR psoriatic arthritis OR enthesitis-related arthritis OR systemic arthritis OR systemic onset arthritis) OR AB (JIA OR juvenile idiopathic arthritis OR oligoarthritis OR polyarthritis OR psoriatic arthritis OR enthesitis-related arthritis OR systemic arthritis OR systemic onset arthritis) OR MH Arthritis, Juvenile
#4	#1 AND #2 AND #3
Limited to English language & Publication date from 2001 to present	

PsycINFO: 85 records retrieved

Search	**Query**
#1	(experience* or impression* or attitude* or outlook* or viewpoint* or perception* or insight* or perspective* or perceived or understanding* or qualitative research or qualitative study or qualitative studies or qualitative method* or interviews or interview or ethnograph* or phenomenol* or focus group* or grounded theory) .ti,ab.
#2	(baby or babies or kid or kids or infant* or child* or youth* or teenage* or adolescent* or parent* or carer* or caregiver* or father* or mother* or young people or CYP* or family or families or boy* or young adult* or girl* or AYA) .ti,ab.
#3	(JIA or juvenile idiopathic arthritis or oligoarthritis or polyarthritis or psoriatic arthritis or enthesitis-related arthritis or systemic arthritis or systemic onset arthritis) .ti,ab.
#4	#1 AND #2 AND #3
Limited to English language & Publication date from 2001 to present	

Web of Science: 1122 records retrieved

Search	Query
#1	TOPIC: (experience* or impression* or attitude* or outlook* or viewpoint* or perception* or insight* or perspective* or perceived or understanding* or "qualitative research" or "qualitative study" or "qualitative studies" or "qualitative method*" or interviews or interview or ethnograph* or phenomenol* or "focus group*" or "grounded theory")
#2	TOPIC: (baby or babies or kid or kids or infant* or child* or youth* or teenage* or adolescent* or parent* or carer* or caregiver* or father* or mother* or "young people" or CYP* or family or families or boy* or "young adult*" or girl* or AYA)
#3	TOPIC: (JIA or "juvenile idiopathic arthritis" or oligoarthritis or polyarthritis or "psoriatic arthritis" or "enthesitis-related arthritis" or "systemic arthritis" or "systemic onset arthritis")
#4	#1 AND #2 AND #3
Limited to English language & Publication date from 2001 to present	

Embase: 2980 records retrieved

Search	Query
#1	'experience*':ab,ti OR 'impression*':ab,ti OR 'attitude*':ab,ti OR 'outlook*':ab,ti OR 'viewpoint*':ab,ti OR 'perception*':ab,ti OR 'insight*':ab,ti OR 'perspective*':ab,ti OR 'perceived':ab,ti OR 'understanding*':ab,ti OR 'qualitative research':ab,ti OR 'qualitative study':ab,ti OR 'qualitative studies':ab,ti OR 'qualitative method*':ab,ti OR 'interviews':ab,ti OR 'interview':ab,ti OR 'ethnograph*':ab,ti OR 'phenomenol*':ab,ti OR 'focus group*':ab,ti OR 'grounded theory':ab,ti
#2	'patient experience'/exp OR 'patient attitude'/exp OR 'patient perspective'/exp OR 'qualitative research'/exp OR 'semi structured interview'/de OR 'telephone interview'/de OR 'unstructured interview'/de OR 'ethnography'/de OR 'phenomenology'/de OR 'focus group'/de OR 'grounded theory'/de
#3	'baby':ab,ti OR 'babies':ab,ti OR 'kid':ab,ti OR 'kids':ab,ti OR 'infant*':ab,ti OR 'child*':ab,ti OR 'youth*':ab,ti OR 'teenage*':ab,ti OR 'adolescent*':ab,ti OR 'parent*':ab,ti OR 'carer*':ab,ti OR 'caregiver*':ab,ti OR 'father*':ab,ti OR 'mother*':ab,ti OR 'young people':ab,ti OR 'cyp':ab,ti OR 'family':ab,ti OR 'families':ab,ti OR 'boy*':ab,ti OR 'young adult*':ab,ti OR 'girl*':ab,ti OR 'aya':ab,ti
#4	'child'/exp OR 'adolescent'/exp OR 'parent'/exp OR 'caregiver'/de OR 'family'/exp OR 'young adult'/de OR 'young people'/de

#5	'jia':ab,ti OR 'juvenile idiopathic arthritis':ab,ti OR 'oligoarthritis':ab,ti OR 'polyarthritis':ab,ti OR 'psoriatic arthritis':ab,ti OR 'enthesitis-related arthritis':ab,ti OR 'systemic arthritis':ab,ti OR 'systemic onset arthritis':ab,ti
#6	'juvenile rheumatoid arthritis'/exp
#7	(#1 OR #2) AND (#3 OR #4) AND (#5 OR #6)
Limited to English language & Publication date from 2001 to present	

Appendix II: Studies ineligible following full text review

1. Britton C, Moore A. Views from the Inside, Part 2: What the Children with Arthritis said, and the Experiences of Siblings, Mothers, Fathers and Grandparents. The British Journal of Occupational Therapy. 2002;65(9):413-9.

Reason for exclusion: Not ILAR.

2. Britton C, Moore A. Views from the inside, Part 3: How and why families undertake prescribed exercise and splinting programmes and a new model of the families' experience of living with juvenile arthritis. The British Journal of Occupational Therapy. 2002;65(10):453-60.

Reason for exclusion: Not ILAR.

3. Britton CA, Moore A. Views from the inside, part 1: Routes to diagnosis - Families' experience of living with a child with arthritis. British Journal of Occupational Therapy. 2002;65(8):374-80.

Reason for exclusion: Not ILAR.

4. Sällfors C, Fasth A, Hallberg LRM. Oscillating between hope and despair - A qualitative study. Child: Care, Health and Development. 2002;28(6):495-505.

Reason for exclusion: Not ILAR.

5. Schroder N, Crabtree MJ, Lyall-Watson S. The Effectiveness of Splinting as Perceived by the Parents of Children with Juvenile Idiopathic Arthritis. British Journal

of Occupational Therapy. 2002;65(2):75-80.

Reason for exclusion: Not ILAR.

6. Shaw KL, Southwood TR, McDonagh JE, British Paediat Rheumatology G. IDENTIFYING THE NEEDS OF ADOLESCENTS WITH JUVENILE IDIOPATHIC ARTHRITIS: RESULTS OF NATIONWIDE FOCUS GROUPS. Rheumatology. 2002;41:77-.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

7. Beresford BA, Sloper P. Chronically ill adolescents' experiences of communicating with doctors: A qualitative study. Journal of Adolescent Health. 2003;33(3):172-9.

Reason for exclusion: Not ILAR.

8. Hackett J. Perceptions of Play and Leisure in Junior School Aged Children with Juvenile Idiopathic Arthritis: What are the Implications for Occupational Therapy? British Journal of Occupational Therapy. 2003;66(7):303-10.

Reason for exclusion: ILAR1998.

9. Kyngäs H. Patient education: Perspective of adolescents with a chronic disease. Journal of Clinical Nursing. 2003;12(5):744-51.

Reason for exclusion: Not ILAR.

10. Sallfors C, Hallberg LRM. A parental perspective on living with a chronically III child: A qualitative study. Families, Systems and Health. 2003;21(2):193-204.

Reason for exclusion: Not ILAR.

11. Kyngäs H. Support network of adolescents with chronic disease: Adolescents' perspective. Nursing and Health Sciences. 2004;6(4):287-93.

Reason for exclusion: Not ILAR.

12. McNeill T. Fathers' experience of parenting a child with juvenile rheumatoid arthritis. Qual Health Res. 2004;14(4):526-45.

Reason for exclusion: Not ILAR.

13. Shaw KL, Southwood TR, McDonagh JE, British Paediatric Rheumatology G. User perspectives of transitional care for adolescents with juvenile idiopathic arthritis. Rheumatology. 2004;43(6):770-8.

Reason for exclusion: Ineligible age range, including young adults with JIA aged 19-30 years.

14. Batthish M, Schneider R, Ramanan AV, Achonu C, Young NL, Feldman BM. What does "active disease" mean? patient and parent perceptions of disease activity in the systemic arthritis form of juvenile idiopathic arthritis (SO-JIA). Rheumatology (Oxford). 2005;44(6):796-9.

Reason for exclusion: Not ILAR.

15. LeBovidge JS, Lavigne JV, Miller ML. Adjustment to chronic arthritis of childhood: The roles of illness-related stress and attitude toward illness. Journal of Pediatric Psychology. 2005;30(3):273-86.

Reason for exclusion: ILAR1998.

16. Ostlie IL, Johansson I, Moller A. Growing up with juvenile idiopathic arthritis from the perspective of young adult patients. Annals of the Rheumatic Diseases. 2006;65:666-.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

17. Pelaez-Ballestas I, Romero-Mendoza M, Ramos-Lira L, Caballero R, Hernández-Garduño A, Burgos-Vargas R. Illness trajectories in Mexican children with juvenile idiopathic arthritis and their parents. Rheumatology. 2006;45(11):1399-403.

Reason for exclusion: Ineligible age range. Adult mean age 38±6 years.

18. Guell C. Painful childhood: children living with juvenile arthritis. Qual Health Res. 2007;17(7):884-92.

Reason for exclusion: Not ILAR.

19. Östlie IL, Dale O, Möller A. From childhood to adult life with juvenile idiopathic

arthritis (JIA): a pilot study. Disability & Rehabilitation. 2007;29(6):445-52.

Reason for exclusion: Not ILAR.

20. Rossato LM, Angelo M, Silva CA. Care delivery for the child to grow up despite the pain: the family's experience. Rev Lat Am Enfermagem. 2007;15(4):556-62.

Reason for exclusion: Not ILAR.

21. Waite-Jones JM, Madill A. Concealed concern: fathers' experiences of having a child with juvenile idiopathic arthritis. Psychol Health. 2008;23(5):585-601.

Reason for exclusion: Not ILAR.

22. Waite-Jones JM, Madill A. Amplified ambivalence: having a sibling with juvenile idiopathic arthritis. Psychol Health. 2008;23(4):477-92.

Reason for exclusion: Not ILAR.

23. de Monte R, Rodger S, Jones F, Broderick S. Living with juvenile idiopathic arthritis: children's experiences of participating in home exercise programmes. British Journal of Occupational Therapy. 2009;72(8):357-65.

Reason for exclusion: Not ILAR.

24. Jones F, Rodger S, Broderick S, de Monte R. Living with juvenile idiopathic arthritis: parents' experiences of treatment regimens and home exercise programmes. British Journal of Occupational Therapy. 2009;72(6):249-58.

Reason for exclusion: Not ILAR.

25. Östlie IL, Johansson I, Möller A. Struggle and adjustment to an insecure everyday life and an unpredictable life course. Disability & Rehabilitation. 2009;31(8):666-74.

Reason for exclusion: Ineligible age range. 15 young adults (22-38 years).

26. Blamires J, Dickinson A. The experience of young people with Juvenile Idiopathic Arthritis who have been transferred from paediatric to adult services. Clinical and Experimental Rheumatology. 2011;29(2):383.

Reason for exclusion: Published using other title, “Moving on: the experience of young people with juvenile idiopathic arthritis transferring from paediatric to adult services”. Ineligible age range - ranging in age from 16 to 21 year.

27. Eyckmans L, Hilderson D, Westhovens R, Wouters C, Moons P. What does it mean to grow up with juvenile idiopathic arthritis? A qualitative study on the perspectives of patients. Clin Rheumatol. 2011;30(4):459-65.

Reason for exclusion: Ineligible age range 20-30 years.

28. Ghio D, Thomson W, Baildam EM, Hyrich K, Beresford MW, Lydon C, et al. Investigating children's beliefs about juvenile arthritis: A study using cognitive interviewing. Arthritis and Rheumatism. 2011;63(10).

Reason for exclusion: Published using other title, “The prioritization of symptom beliefs over illness beliefs: The development and validation of the Pain Perception Questionnaire for Young People”. This corresponding study has been excluded in the previous step.

29. Rossato LM, Morete M, Borghi C, Lindenberg M, Pereira CA, Bousso RS, et al. The experience of child in pain with juvenile idiopathic arthritis. European Journal of Pain Supplements. 2011;5(1):245.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

30. van Staa AL, Jedeloo S, van Meeteren J, Latour JM. Crossing the transition chasm: experiences and recommendations for improving transitional care of young adults, parents and providers. Child Care Health and Development. 2011;37(6):821-32.

Reason for exclusion: Ineligible population and age range. 24 young adults (aged 15–22 years; diagnosed with haemophilia, diabetes mellitus, spina bifida, congenital heart disorders, cystic fibrosis, juvenile rheumatoid arthritis or sickle cell disease).

31. Hendry GJ, Turner DE, Lorgelly PK, Woodburn J. Room for improvement: patient, parent, and practitioners' perceptions of foot problems and foot care in juvenile idiopathic arthritis. Arch Phys Med Rehabil. 2012;93(11):2062-7.

Reason for exclusion: Ineligible age range. Four adult patients (17-33 y).

32. Stinson JN, Feldman BM, Duffy CM, Huber AM, Tucker LB, McGrath PJ, et al. Jointly managing arthritis: Information needs of children with juvenile idiopathic arthritis (JIA) and their parents. Journal of Child Health Care. 2012;16(2):124-40.

Reason for exclusion: Not ILAR.

33. Dickinson AR, Blamires J. Moving on: the experience of young people with juvenile idiopathic arthritis transferring from paediatric to adult services. Neonatal, Paediatric & Child Health Nursing. 2013;16(2):2-7.

Reason for exclusion: Ineligible age range - ranging in age from 16 to 21 year.

34. Hilderson D, Eyckmans L, Van der Elst K, Westhovens R, Wouters C, Moons P. Transfer from paediatric rheumatology to the adult rheumatology setting: experiences and expectations of young adults with juvenile idiopathic arthritis. Clin Rheumatol. 2013;32(5):575-83.

Reason for exclusion: Ineligible age range (aged 18-30).

35. Jacobson CJ, Farrell JE, Kashikar-Zuck S, Seid M, Verkamp E, DeWitt EM. Disclosure and self-report of emotional, social, and physical health in children and adolescents with chronic pain-A qualitative study of PROMIS pediatric measures. Journal of Pediatric Psychology. 2013;38(1):82-93.

Reason for exclusion: Ineligible population. Children and young with JIA or non-inflammatory chronic pain.

36. Lipstein EA, Lovell DJ, Denson LA, Moser DW, Saeed SA, Dodds CM, et al. Parents' information needs in tumor necrosis factor-alpha inhibitor treatment decisions. J Pediatr Gastroenterol Nutr. 2013;56(3):244-50.

Reason for exclusion: Ineligible population. Children with Crohn disease or JIA.

37. Lipstein EA, Muething KA, Dodds CM, Britto MT. "I'm the one taking it": adolescent participation in chronic disease treatment decisions. J Adolesc Health.

2013;53(2):253-9.

Reason for exclusion: Ineligible population. Adolescents have Crohn's disease or JIA.

38. Notman R. Just getting on with it: family experience of juvenile idiopathic arthritis: University of Leeds (United Kingdom); 2013.

Reason for exclusion: Not ILAR.

39. Tong A, Jones J, Speerin R, Filocamo K, Chaitow J, Singh-Grewal D. Consumer perspectives on pediatric rheumatology care and service delivery: a qualitative study. J Clin Rheumatol. 2013;19(5):234-40.

Reason for exclusion: Ineligible age range - age from 14 to 66 years.

40. Bechard MA, Lemieux JR, Roth J, Duffy WK, Duffy CM, Aglipay MO, et al. Procedural pain and patient-reported side effects with weekly injections of subcutaneous Methotrexate in children with rheumatic disorders. Pediatric Rheumatology. 2014;12(1).

Reason for exclusion: Ineligible population. Patients with JIA or other rheumatologic diseases.

41. Gomez-Ramirez O, Gibbon M, Berard RA, Jurencak R, Green J, Benseler S, et al. A96: The Roller Coaster of Juvenile Idiopathic Arthritis: A Qualitative Examination of Parents' Emotional Responses to the Disease and Its Management. Arthritis & Rheumatology. 2014;66:S131-S.

Reason for exclusion: Published using other title, "A recurring rollercoaster ride: A qualitative study of the emotional experiences of parents of children with juvenile idiopathic arthritis". Not ILAR.

42. Guzman J, Benseler S, Berard R, Rollin B, Duffy C, Jurencak R, et al. What matters the most for parents, patients and clinicians in predicting the course of juvenile idiopathic arthritis (JIA)? Journal of Rheumatology. 2014;40(6):997.

Reason for exclusion: Ineligible age range. 16 to 23 years old.

43. Hanson H, Hart R, Jordan A, Tattersall R, Thompson B, Foster HE. The vocational

experiences of young people with juvenile idiopathic arthritis and the role of the multidisciplinary team supporting positive employment outcomes. Arthritis and Rheumatology. 2014;66:S637.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

44. Knudsen LR, Bjerrum M. From the world of children to the world of adults-a qualitative interview study. Annals of the Rheumatic Diseases. 2014;73.

Reason for exclusion: Published using other title, "Transition from child to adult care in an outpatient clinic for adolescents with juvenile idiopathic arthritis: An inductive qualitative study". Ineligible age range. One patient was 23 years old.

45. Mannion M, Williams MS, McGwin G, Saag K, Beukelman T. Development of a long-term outcome measure in JIA. Clinical and Translational Science. 2014;7(3):212.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

46. Peeters MAC, Hilberink SR, Van Staa A. The road to independence: Lived experiences of youth with chronic conditions and their parents compared. Journal of Pediatric Rehabilitation Medicine. 2014;7(1):33-42.

Reason for exclusion: Ineligible population and age range. 16 young persons (15–22 years) and seven diagnostic groups including JIA, diabetes mellitus.

47. Tekano J, Tucker LB, Chen A. Children and parent satisfaction in the pediatric rheumatology clinic: Patient orientated quality service measures. Arthritis and Rheumatology. 2014;66:S823.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

48. Cartwright T, Fraser E, Edmunds S, Wilkinson N, Jacobs K. Journeys of adjustment: the experiences of adolescents living with juvenile idiopathic arthritis. Child Care Health Dev. 2015;41(5):734-43.

Reason for exclusion: Not ILAR.

49. Hart RI, Foster HE, McDonagh JE, Thompson B, Kay L, Myers A, et al. Young

people's decisions about biologic therapies: who influences them and how? Rheumatology (Oxford). 2015;54(7):1294-301.

Reason for exclusion: Ineligible population and age range. Young people (16-25 years of age) with JIA and other inflammatory arthritis.

50. Lipstein EA, Britto MT. Evolution of Pediatric Chronic Disease Treatment Decisions: A Qualitative, Longitudinal View of Parents' Decision-Making Process. Med Decis Making. 2015;35(6):703-13.

Reason for exclusion: Ineligible population. Families with their child had JIA or IBD.

51. Gilljam B-M, Arvidsson S, Nygren JM, Svedberg P. Promoting participation in healthcare situations for children with JIA: a grounded theory study. International Journal of Qualitative Studies on Health & Well-Being. 2016;11:1-N.PAG.

Reason for exclusion: Not ILAR.

52. Gómez-Ramírez O, Gibbon M, Berard R, Jurencak R, Green J, Tucker L, et al. A recurring rollercoaster ride: A qualitative study of the emotional experiences of parents of children with juvenile idiopathic arthritis. Pediatric Rheumatology. 2016;14(1).

Reason for exclusion: Not ILAR.

53. Hart RI, McDonagh JE, Thompson B, Foster HE, Kay L, Myers A, et al. Being as Normal as Possible: How Young People Ages 16-25 Years Evaluate the Risks and Benefits of Treatment for Inflammatory Arthritis. Arthritis Care & Research. 2016;68(9):1288-94.

Reason for exclusion: Ineligible population and age range. 7 young people (ages 16–20 years; 5 with JIA, 2 with other diagnoses) were included.

54. Lipstein EA, Dodds CM, Lovell DJ, Denson LA, Britto MT. Making decisions about chronic disease treatment: a comparison of parents and their adolescent children. Health Expect. 2016;19(3):716-26.

Reason for exclusion: Ineligible population. Parent–adolescent dyads in which the

adolescent had either juvenile idiopathic arthritis or Crohn's disease.

55. McDonagh JE, Shaw KL, Prescott J, Smith FJ, Roberts R, Gray NJ. "Sometimes I feel like a pharmacist": identity and medication use among adolescents with juvenile arthritis. Pediatr Rheumatol Online J. 2016;14(1):57.

Reason for exclusion: Blog. Ineligible study design.

56. Race DL, Sims-Gould J, Tucker LB, Duffy CM, Feldman DE, Gibbon M, et al. 'It might hurt, but you have to push through the pain': Perspectives on physical activity from children with juvenile idiopathic arthritis and their parents. Journal of Child Health Care. 2016;20(4):428-36.

Reason for exclusion: Not ILAR.

57. Slater H, Jordan JE, Chua J, Schütze R, Wark JD, Briggs AM. Young people's experiences of persistent musculoskeletal pain, needs, gaps and perceptions about the role of digital technologies to support their co-care: A qualitative study. BMJ Open. 2016;6(12).

Reason for exclusion: Ineligible population and age range. Young people aged 16–24 years with juvenile idiopathic arthritis or other systemic arthritides or non-specific conditions.

58. Arman N, Tarakci E, Barut K, Adrovic A, Sahin S, Kasapcopur O. The perceptions of patients with juvenile idiopathic arthritis about "having a rheumatic disease" and "doing exercise" via metaphors. Pediatric Rheumatology. 2017;15.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

59. Condon C, O'Regan D, MacDermott E, Killeen O. Self-management needs of children with JIA in Ireland: a qualitative survey of families. European Journal of Physiotherapy. 2017;19(4):237-42.

Reason for exclusion: Not ILAR.

60. Horton DB, Salas J, Wec A, Beukelman T, Boneparth A, Haverkamp K, et al. How

young people with juvenile idiopathic arthritis and their caregivers weigh the risks of the disease and its treatment: A mixed-methods study. Arthritis and Rheumatology. 2017;69:79-82.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

61. Kohut SA, Stinson J, Forgeron P, Luca S, Harris L. Been There, Done That: The Experience of Acting as a Young Adult Mentor to Adolescents Living With Chronic Illness. Journal of Pediatric Psychology. 2017;42(9):962-9.

Reason for exclusion: Ineligible population and age range. Age range 17–22 years; diagnosed with chronic pain or juvenile idiopathic arthritis.

62. Sen ES, Morgan MJ, MacLeod R, Strike H, Hinchcliffe A, Dick AD, et al. Cross sectional, qualitative thematic analysis of patient perspectives of disease impact in juvenile idiopathic arthritis-associated uveitis. Pediatr Rheumatol Online J. 2017;15(1):58.

Reason for exclusion: Ineligible population. One child was diagnosed with Blau syndrome and uveitis.

63. Yuwen WC, Lewis FM, Walker AJ, Ward TM. Struggling in the Dark to Help My Child: Parents' Experience in Caring for a Young Child with Juvenile Idiopathic Arthritis. Journal of Pediatric Nursing-Nursing Care of Children & Families. 2017;37:E23-E9.

Reason for exclusion: Not ILAR.

64. Carandang K, Poole JL. Determining the need for fatigue management resources for young adults with rheumatic disease. Arthritis and Rheumatology. 2018;70:2665-6.

Reason for exclusion: Ineligible population. 10 Women had varying diagnoses (e.g. JIA, MCTD, SLE, PsA, Scleroderma).

65. Chaplin H, Barnett R, Ioannou Y, Sen D, Lempp H, Cai RA, et al. The impact of juvenile idiopathic arthritis on adolescents and young adults: A qualitative study. Rheumatology (United Kingdom). 2018;57:iii170.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

66. Chaplin H, Ioannou Y, Sen D, Lempp H, Norton S. Exploring pain and the impact of Jia on adolescents and young adults: A mixedmethods study. Annals of the Rheumatic Diseases. 2018;77:101.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

67. Hanson H, Hart RI, Thompson B, McDonagh JE, Tattersall R, Jordan A, et al. Experiences of employment among young people with juvenile idiopathic arthritis: a qualitative study. Disabil Rehabil. 2018;40(16):1921-8.

Reason for exclusion: Ineligible age range. Young people (16–25 y) and adults (26–31 y).

68. Kembe JT. Experiences of participation in activities among children with juvenile idiopathic arthritis. Pediatric Rheumatology. 2018;16.

Reason for exclusion: Conference Abstract. No full text after contacting the author. In the process of trying to publish this paper in a journal.

69. Kirkpatrick S, Locock L, Farre A, Ryan S, Salisbury H, McDonagh JE. Untimely illness: When diagnosis does not match age-related expectations. Health Expect. 2018;21(4):730-40.

Reason for exclusion: Ineligible age range and mixed disease. the experiences of people with adult- onset asthma and young people diagnosed with arthritis. some JIA patients older than 21.

70. Knudsen LR, de Thurah A, Bjerrum M. Transition from child to adult care in an outpatient clinic for adolescents with juvenile idiopathic arthritis: An inductive qualitative study. Nursing Open. 2018;5(4):546-54.

Reason for exclusion: Ineligible age range. One patient was 23 years old.

71. Montagu G, Mevel E, Rossi Semerano L, Solau Gervais E, Trope S, Cohen JD. Do children with juvenile idiopathic arthritis play an active role in their treatment adherence?

First results of the Rumaji study. Annals of the Rheumatic Diseases. 2018;77:1667.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

72. Muller P, Yildiz B, Allaart CF, Brinkman DMC, van Rossum M, van Suijlekom-Smit LWA, et al. Participation in a single-blinded pediatric therapeutic strategy study for juvenile idiopathic arthritis: are parents and patient-participants in equipoise? Bmc Medical Ethics. 2018;19:9.

Reason for exclusion: Not ILAR.

73. Mulligan K, Pearce C, Newman S. Experience of illness uncertainty in parents of children with juvenile idiopathic arthritis. Rheumatology (United Kingdom). 2018;57:iii166.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

74. Simon TA, Bradley M, Lovell DJ, Shakley B, Zhang C, Clark L, et al. Using ethnography to understand transition in young adults with JIA. Pediatric Rheumatology. 2018;16.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

75. Sims-Gould J, Race DL, Macdonald H, Houghton KM, Duffy CM, Tucker LB, et al. "I just want to get better": experiences of children and youth with juvenile idiopathic arthritis in a home-based exercise intervention. Pediatr Rheumatol Online J. 2018;16(1):59.

Reason for exclusion: Not ILAR.

76. Toupin-April K, Stinson JN, Huber A, Duffy CM, Gaboury I, Morgan E, et al. Exploring decision making needs about pain management among adolescents with juvenile idiopathic arthritis and their families: Preliminary results from interviews. Arthritis and Rheumatology. 2018;70:2590-1.

Reason for exclusion: Conference Abstract. Poster. No full text after contacting the author. The author was writing the paper to publish the results.

77. Waite-Jones JM, Swallow V. Peer-based Social Support for Young-People with Juvenile Arthritis: Views of Young People, Parents/Carers and Healthcare Professionals within the UK. J Pediatr Nurs. 2018;43:e85-e91.

Reason for exclusion: Not ILAR.

78. Chaplin H, Verhey I, Ng N, Galloway J, Scott I, Sen D, et al. Exploring refractory disease & persistent symptoms in RA/polyjia despite bDMARDs: Patient & professional experiences. Annals of the Rheumatic Diseases. 2019;78:1646.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

79. Farre A, Ryan S, McNiven A, McDonagh JE. The impact of arthritis on the educational and early work experiences of young people: A qualitative secondary analysis. International Journal of Adolescent Medicine and Health. 2019.

Reason for exclusion: Not ILAR.

80. Grande SW, Longacre MR, Palmblad K, Montan MV, Berquist RP, Hager A, et al. Empowering Young People Living With Juvenile Idiopathic Arthritis to Better Communicate With Families and Care Teams: Content Analysis of Semistructured Interviews. JMIR Mhealth Uhealth. 2019;7(2):e10401.

Reason for exclusion: ILAR1998.

81. Sørensen K, Skirbekk H, Kvarstein G, Wøien H. Children's fear of needle injections: a qualitative study of training sessions for children with rheumatic diseases before home administration. Pediatr Rheumatol Online J. 2020;18(1):13.

Reason for exclusion: Not ILAR.

82. Munroe A, Huber A, Lang B, Ramsey S, Stringer E. Medication related decision-making in parents of children with juvenile idiopathic arthritis. Arthritis and Rheumatology. 2020;72:63-4.

Reason for exclusion: Conference Abstract. No full text after contacting the author.

83. Wright J, Curran J, Rose-Davis B, Cellucci T, Duffy CM, Tucker LB, et al. Parental

Perspectives about Research and Knowledge Translation in Juvenile Idiopathic Arthritis. ACR Open Rheumatology. 2020;2(3):138-46.

Reason for exclusion: Not ILAR.

84. Alongi A, Calandra S, Thornhill S, Stinson J, Horonjeff J, Horton D, et al. Patients' and parents' perception of disease and its impact on life in juvenile idiopathic arthritis: results from multinational virtual Focus Groups by the OMERACT JIA Working Group. Arthritis and Rheumatology. 2019;71:4790-3.

Reason for exclusion: Ineligible age range. Young adults with JIA (aged 18-25 years) were included.

85. Carandang K, Wells C, Chiraseveenuprapund P. Perspectives of adolescents and young adults around implementing rheumatology healthcare transition: Preliminary qualitative findings. Arthritis and Rheumatology. 2020;72:311-2.

Reason for exclusion: Ineligible age range. Young adults with JIA (aged 16-28 years) were included.

86. Mosor E, Studenic P, Alunno A, Padjen I, Olsder W, Ramiro S, et al. “when you read this, you really feel old!” perspectives of young people with inflammatory arthritis on patient reported outcome measures from a european qualitative study. Arthritis and Rheumatology. 2019;71:1521-3.

Reason for exclusion: Ineligible population and age range. 21 patients with RA/JIA/Still’s, 15 with spondyloarthritis, 17 with PsA. The age range of young people was 18-35 years.

Appendix III: Characteristics of included studies

Study	Country	Phenomena of interest	Setting/context/culture	Participant characteristics and sample size	Methods for data collection and analysis	Description of main results
Jones et al.[41] (Sherratt et al.[40])	UK	Families' views on a proposed randomized controlled trial of corticosteroid induction regimen in JIA	Participants were interviewed in their homes (*n* = 9), in a private setting in the paediatric rheumatology clinic (*n* = 4), in the parent's workplace (*n* = 1) or by telephone (*n* = 1).	Twenty-eight participants from 15 families completed or attempted an interview (58% response rate), comprising nine patients and 19 parents. In one of the 28 interviews, one of the patients (C8_8–10y) was excluded. CYP age from 1 to 16 years and most were female (9/16, 56%). One family had two CYP with JIA.	Collection: qualitative approach involving semi-structured topic-guided interviews Analysis: framework method, an approach to the thematic analysis of qualitative of data, and NVivo 10	Potential barriers to recruitment for a corticosteroid induction regimen trial in JIA, divergent views between parents and CYP, and areas for further exploration such as clinician treatment preferences.
Stinson et al.[44]	Canada	the self-management needs of adolescents with juvenile idiopathic	4 large rheumatology clinics in university-affiliated pediatric tertiary care centers across Canada. All interviews were conducted in a quiet room in the hospital	1) 12–20 years of age, 2) diagnosed with JIA by a rheumatologist (19), and 3) able to speak and read English and/or French. Thirty-six adolescents participated in the individual interviews (*n* = 25)	Descriptive exploratory qualitative design Collection: semi structured interview Analysis: thematic analysis and NUD*IST	Adolescents articulated how they developed effective self-management strategies through the process of "letting go" from others who had managed their

		arthritis	clinic or meeting room.	and 3 focus-group interviews (n = 11)	6.0	illness (health care professionals, parents) and "gaining control" over managing their illness on their own. The 2 strategies that assisted in this process were gaining knowledge and skills to manage the disease and experiencing understanding through social support. Five further subthemes emerged around skills to manage the disease, including knowledge and awareness about the disease, listening to and challenging care providers, communicating with the doctor, managing pain, and managing emotions.

Livermore et al.[45]	UK	young people's daily experiences of living with JIA and their thoughts, beliefs and feelings related to the biological drug Etanercept	This study was a sub-study of the Childhood Arthritis Response to Medication (CHARMS) Study. A tertiary care Paediatric Rheumatology Department.	The 6 participants recruited were aged 10–13 years, 2 female, 4 male, all Caucasian, had English as first language, and disease duration of 5–11 years. All patients were receiving both Methotrexate and Etanercept,	Interpretive Phenomenological approach. Methods for data collection: audio-taped open-ended interviews. Methods for data analysis: Colaizzi's seven stage process.	five themes; 1) Who understands me, 2) Medicines and injections, 3) Challenges of schooling and friendships, 4) Being different, and 5) Exclusion from sports.
Leksell et al.[46]	Sweden	To deepen knowledge of how parents of children diagnosed with juvenile idiopathic arthritis (JIA) perceive the orofacial manifestations of the disease, its treatments, and their encounters with dental care	In the subjects' homes or at the clinic, and one subject was interviewed on the telephone.	15 parents with a female to male ratio of 11 to 4. Parents were aged 30 to 46 years. Eleven of the parents were either married or living together with the other parent. Their children had been diagnosed with JIA since 1 to 12 years of age.	Grounded theory Collection: tape recorded interviews Analysis: no software was used to analyze the quotes and data; using an open coding process and reading the interview line by line, then coded the data using the parent's own words (in vivo coding).	The main problem was identified as controlling an unpredictable life situation that includes a child with JIA. To solve this main problem, the parent was trying to comprehend, help, and speak for the child with disability, a solution that permeated their life situation.

		providers.				
Leksell et al.[47]	Sweden	to increase knowledge about how children diagnosed with JIA perceive their oral health and dental care.	The first author performed tape-recorded interviews in the children's homes	15 children with a female: male ratio of 11:4	Grounded Theory Tape-recorded interviews with open-ended questions. No software was used to analyze the quotes and data. To identify major patterns in the group after coding the interview data.	The children's main concern about their oral health was identified as creating a positive identity after being diagnosed with JIA and learning to live with oral health problems. While attempting to cope with this concern, the children often endured in silence, the core category in the analysis. A variety of aspects were found of this core coping strategy, which were categorized as differentiating from the disease, working on personal caretaking and positive attitude, fighting fears and sadness, control of professional aid, and building supportive

						relationships.
Khan et al.[48]	Canada	to explore the perceptions of school-age children with JIA experiencing MTX intolerance, how they managed MTX intolerance, and how it impacted their daily life.	the rheumatology clinic of one Canadian, quaternary care pediatric hospital.	9 girls and 3 boys (n = 12) diagnosed with JIA and experiencing MTX intolerance from the rheumatology clinic of one Canadian, quaternary care pediatric hospital. Children ranged in age from 6 to 12 years; spoke English or French; and had been receiving oral (PO; n = 4) or subcutaneous (SC; n = 8) MTX at home with the assistance of their parents, for periods of time ranging from 11 months to 7.5 years	interpretive descriptive design was used Methods for data collection: individual 30-minute semi-structured interview using a storyboard technique Methods for data analysis: inductive content analysis	Children described MTX intolerance as extremely challenging. Three themes emerged from the data: (1) “No kid likes taking MTX”; (2) The importance of strategies and routines; and (3) Working hard to live with MTX intolerance.
Shaw et al.[49]	UK	to explore the prevocational and early employment needs of adolescents with JIA from their own perspectives.	attending one United Kingdom hospital (Birmingham Children’s Hospital).	n = 8 were four females and four males with JIA (with subtypes including persistent oligoarthritis, polyarthritis, systemic and enthesitis-related arthritis). They had a median age of 15.67 (14.2-16.6) years,	Focus group discussion. Interpretive phenomenological analysis.	The key themes were as follows: 1 Impact of JIA on academic ability 2 Negative expectations of ability 3 Vocational readiness skills 4 Support and advice.

				a median disease duration of 5.0 (2.3-13.0) years and a median age of onset of 10.5 (4.0-14.0) years.		
O'Sullivan et al.[50]	Ireland, UK	to explore the self-management needs of Irish adolescents.	Focus groups were arranged in three Irish cities closest to participating families. Those unable to attend any focus group were offered an individual interview.	Irish adolescents with JIA (*N*= 16), their parents (*N*= 13). The participating adolescents were mostly in early (11–14 years, *N*= 8) or mid adolescence (15–16 years, *N*= 7), with one late-stage adolescent (17–18 years; *N*= 1) (*M* = 14.19 years; *SD* = 2.07). Most were female (*N*= 10; 62.5%) and of Irish nationality (*N*= 15; 93.7%). Mean time since diagnosis was 3.6 years (*SD* = 3.28 years; range = 0.58–13.83 years) and the most frequent subtype was psoriatic arthritis (*N*= 5; 31.3%)	Focus groups and interviews analyzed using a thematic analysis approach and NVivo.11	Five themes emerged: independent self-management; acquiring skills and knowledge to manage JIA; unique challenges of JIA in Ireland; views on web-based interventions; and understanding through social support.
Van Gulik et al.[51]	Netherlands	Experiences during school life;	Using individual face-to-face interviews of 1 hr the	Participants between 14 and 18 years of age (*n* = 22), 6 males	Grounded theory approach.	Great differences were seen in the support and

		perspectives and expectations regarding future work participation of adolescents with JIA	researchers interviewed patients with JIA at the Amsterdam UMC, location Academic Medical Centre (AMC) between April 2017 and January 2018. The interviews took place without parental attendance and were scheduled just before or after a planned visit to the hospital to minimize inconvenience.	and 16 females.	Individual semi-structured interviews and followed a predefined interview guide without parental attendance. All interviews were audio recorded and transcribed verbatim. Open coding was performed, followed by axial coding and selective coding. MAXQDA Plus 12 was used.	understanding that adolescents received in dealing with JIA at school, leisure activities and work. Varying approaches were mentioned on how to pursue a desired vocation. Perspectives regarding disclosure varied. Participants wished to be approached like any other healthy adolescent. Expectations regarding work participation were positively expressed.
Beneitez et al.[52]	Spain	Adolescents' social needs living with juvenile idiopathic arthritis and their views about	Video-conference was used for the semi-structured interviews (except in one case where the adolescent preferred a face-to-face interview). For the second phase of the study, an online focus group was designed.	14 adolescents (female = 11) were interviewed, range 11-18 years old; 7 other adolescents (female =6) were invited to participate in the focus group, range 11-18 years old	Collection: semi-structured interviews and online focus group Analysis: Content analysis using the software Atlas.ti 6.2, deductive and inductive	They reported some social challenges related to their illness: feeling different, criticized by peers, or not believed. Additionally, they specified some of the coping strategies they

		digital resources	The interview and focus group were conducted by a health psychologist and all data were collected from the workplace.		open-coding approach	used, such as disclosing to others that they have JIA, using communication skills, maintaining activities with friends, trying to minimize pain, and ignoring negative comments. Adolescents considered an online resource useful and mentioned that they would like to find general information and to have the possibility to interact with others. They considered Instagram and WhatsApp as good platforms to implement the online resource.

Abbreviations: CYP=children and young people, JIA=juvenile idiopathic arthritis, MTX=Methotrexate, SD=standard deviation.

Appendix IV: Study findings and illustrations

Jones AP, Clayton D, Nkhoma G et al. Different corticosteroid induction regimens in children and young people with juvenile idiopathic arthritis: the SIRJIA mixed-methods feasibility study, Health Technol Assess 2020;24:1-152.[41]

(Sherratt FC, Roper L, Stones SR, McErlane F, Peak M, Beresford MW, et al. Protective parents and permissive children: what qualitative interviews with parents and children can tell us about the feasibility of juvenile idiopathic arthritis trials. Pediatr Rheumatol Online J. 2018; 16(1):76.[40])

Finding	Families recognised the needs for clinical trials (U)
Illustration	"I think I might have been a little bit more concerned 'cause I think I would want, at the beginning when we didn't know a lot about it, I think I would have been thinking, oh no, I need to have the consultant say what's best for him." (Mother, 14-16 years) Pg 33, Pg 5
	"Interviewer: What was it like being told about having arthritis? C9: I don't know, I think I took it a bit better than my mum, 'cause mums are mums, so they get a bit worried." (Child, 11-13 years) Pg 36, Pg 6
Finding	Barriers and facilitators to participation (U)
Illustration	"Would that entail, mean more hospital visits though, to do this trial? Cause obviously with work we'd be struggling, it depends how often that would be." (Mother, 5-7 years) Pg 38, Pg 5
	"If it's not worked this time, what makes them think it's going to work the second time?" (Mother, 5-7 years) Pg 41, Pg 5
	"He's not going to want to stand there for hours. I would imagine if he got lots and lots of flare-ups, and he is older and he understands it, I can see the logic behind that." (Mother, 8-10 years) Pg 35, Pg 6
	"If you have a flare and it doesn't just affect one joint, then [IV], it'd

	kind of help you more." (Child, 11-13 years) Pg 36, Pg 6
	"Probably the joint injections [would be best] 'cause [the doctor] said they work better cause it's straight into the joint." (Child, 11-13 years) Pg 37, Pg 6
Finding	Being approached about research at diagnosis (U)
Illustration	"[We would participate] at the beginning when he had it, probably it will be different but now, no way we had such a big, big problems with his injection..." (Mother, 8-10 years) Pg 36, Pg 6
	"[At diagnosis] I haven't experienced any of them [treatments] so far so it wouldn't hurt to try any of them…" (Child, 14-16 years) Pg 33, Pg 4
Finding	Use and effect of corticosteroid induction regimens (U)
Illustration	"They gave us her steroid tablets and it went down then. The steroid tablets, it went down overnight, didn't it?" (Mother, 1-4, 5-7 years) Pg 27
	"They were okay the tablets but they were really short term . . . they would only work while she was taking them, after that the flare-up would come back." (Mother, 11-13 years) Pg 27
	"I don't think we saw any effect with the tablets so I think that's why we progressed to other things." (Mother, 14-16 years) Pg 27
	". . . it's powerful for a few joints but not when you've got more than a few affected." (Mother, 14-16 years) Pg 26
Finding	Benefits of corticosteroid induction regimens (U)
Illustration	"His behaviour changed in the summer . . . when he was on the oral steroids . . . his temper was quite . . . it was quicker than normal, um and his aggression would last longer and, you know, with his ADHD

	you can calm him down . . . whilst he was on these oral steroids it was quite a task." (Mother, 5-7 years) Pg 29
	"That looks alright . . . but do you get the same benefit out of it? . . . I mean it's saying that you get a lower dose than your joint injections." (Mother, 14–16 years) Pg 32
	"I think [clinician] would have done the joint injections sooner um but we were due to go on holiday, so that's why we tried the oral steroids first, 'cause he could continue taking those while we were on holiday." (Mother, 5-7 years) Pg 28
Finding	Drawbacks of corticosteroid induction regimens (U)
Illustration	"Horrendous . . . one of the worst days we've had to go through as a parent really . . . take our little girl and sort of put her under anaesthetic, and we weren't going to be there with her for that period of time . . . because she is little as well . . . I'm not saying it would be any easier if she was 7 or 8 or whatever, but at least . . . she would understand that we are going to be back, we'll see you in a bit." (Mother, 1–4 years) Pg 26
	"It hurts a lot afterwards, like it does get worse before it gets better, but only for like a few days like it gets worse . . . they did swell up and like it felt like your hand was broken . . . I couldn't have gone into school and like done all the writing and things." (Child, 14-16 years) Pg 27
	"I didn't like them at all, they made me feel sick even thinking about it, so I think it was just a mental thing." (Child, 11–13 years) Pg 28
	"Because he'd put a lot of weight on in the space of a couple of weeks he was really depressed at that time, very depressed." (Mother, 11–13 years) Pg 30

	". . . it took a long time, so I had to miss quite a lot of school, and I had to catch up on everything, so it means I'd have to write a lot." (Child, 11-13 years) Pg 30

Stinson JN, Toomey PC, Stevens BJ, Kagan S, Duffy CM, Huber A, et al. Asking the experts: exploring the self-management needs of adolescents with arthritis. Arthritis Rheum. 2008; 59(1):65-72.[44]

Finding	Acquiring knowledge and skills to manage the disease (U)
Illustration	"Well, that … not to care what anyone says because you'll get better if you do what your doctor tells you. If you have problems with your medications … well, um, if—if you don't like how it is, like, you don't wanna gain weight or whatever, just ask your doctor" (Adolescent, Male, 15 years) Pg 68
	One adolescent welcomed her mother's presence during her appointments because she was afraid she would forget important information: "Right now my mom still does come in because I forget things" (Adolescent, Female, 12 years) Another adolescent who was more independent stated, "Uh when I was younger my mom did most of the talking but now that I'm getting older I do most of the talking. And if I get it wrong she just corrects me" (Adolescent, Female, 15 years) Pg 68
	As one participant explained, "I just wanna know about what type of therapies to ease the pain because sometimes the pain can be really bad" (Adolescent, Female, 15 years) Pg 68
	"Because sometimes when you re at school you like wanna go home but you don t wanna miss the work and you don t wanna have to catch up and stuff so you just put it in the back of your mind and then

	eventually you just forget about it over time" (Adolescent, Female, 15 years) Pg 69
	One adolescent explained: "When I was little I was really shy and when I started telling people [about arthritis], well I guess I was shy about having it, but then my friends asked me if there was anything wrong, I finally got it out, then I got more, um, confident" (Adolescent, Female, 12 years) Pg 69
Finding	Experiencing understanding through social support (U)
Illustration	"It always felt like I was the only person on earth that had arthritis but I met a whole bunch of other kids who had it and I'm not the only one. It makes you feel a lot better" (Adolescent, Female, 12 years) Pg 69
Finding	Views on Web-based approach to learning about self-management (C)
Illustration	All adolescents thought that having a Web-based approach to learning about their arthritis would be a good way to overcome some of the current barriers to accessing self-management information and skills (e.g., lack of time and resources, group format not appealing, and associated direct and indirect costs of these therapies) Pg 69

Livermore P, Eleftheriou D, Wedderburn LR. The lived experience of juvenile idiopathic arthritis in young people receiving etanercept. Pediatr Rheumatol Online J. 2016; 14(1):21.[45]

Finding	Who understands me? (C)
Illustration	"I feel angry, angry all the time, angry that no-one understands me, it's very lonely to have arthritis" (Child) Pg 3
	"my five year old sister understands what I've got wrong with me" (Child) Pg 3

Finding	Experience of medicines and injections (U)
Illustration	"I have to inject it into myself, it doesn't bother me, I used to inject my Methotrexate and Anakinra, so it's all the same" (Child) Pg 3
	"the Etanercept's useless 'cuz it doesn't work for me, I'm just a guinea pig, you get told all these things will work, they don't, nothing works" (Child) Pg 3
Finding	Challenges to schooling and friendships (U)
Illustration	"I feel lonely, it affects your friendships, secondary school is so different, they even have a disability office, loads of wheelchairs and special glass lifts–makes you feel sad" (Child) Pg 3
	"I didn't go to school for about 6 months, I didn't do any work, I get low school reports because I'm not there" (Child) Pg 3
Finding	Being different (U)
Illustration	"People treat you differently, the idea of being different is upsetting, well not that different, being different is quite a big thing, I don't want extra help as I don't want to be more different, people automatically think you can't do things and you can't be bothered to say you can, so you end up sitting watching and feeling sad" (Child) Pg 4
Finding	Not being able to fully participate in sports, especially physical education (U)
Illustration	"I get out of PE as I can't do it at times, and people think I just use it as an excuse, I now go to the library and stamp books instead" (Child) Pg 4

Leksell E, Hallberg U, Horne A, Ernberg M, Hedenberg-Magnusson B. Parenting a Child with Juvenile Idiopathic Arthritis, Orofacial Pain, and Dysfunction: A Qualitative Study.

J Oral Facial Pain Headache. 2017; 31(4):353-61.[46]

Finding	Reflecting on and re-evaluating the life situation (C)
Illustration	"We have become very close in our family as we have learned to be thankful and happy for every day we are healthy. Our friends are used to us being unpredictable. We cannot book any activity for sure because something is always happening with one of our children's health, which makes it impossible to come." (Parent) Pg 357
Finding	Monitoring the child's symptoms and treatments (C)
Illustration	"I didn't know that he had headaches every day and I didn't reflect over why he only wanted yoghurt and not real food before we came to specialized dental care." (Parent) Pg 357
Finding	Adapting everyday routines (U)
Illustration	"When she cannot chew l have to come up with good alternatives. When she goes to a party with her friends I send food with her!" (Parent) Pg 358
Finding	Seeking doctors and information (U)
Illustration	"We are really thankful for the information we got from the dentist. It has been really helpful for us. L is very worried, as she is reading catastrophic information on the internet about her disease. When we are alone at home, she cries and tells me that she is so afraid, but when she meets others, also her caregivers, she is more moderate. I have to call dental caregivers and make appointments for advice." (Parent) Pg 358
Finding	Influencing school and society (U)
Illustration	"When he gets older, he has to pay for both TMJ and periodontal treatments, problems that are caused by the disease. I do not think this is right." (Parent) Pg 358

Finding	Managing job and family finances (U)
Illustration	"Neither I nor my husband has been able to have the careers that we expected because of all the appointments at the doctor, the physiotherapist, the dentist, the occupational therapist, meetings at school, and so on." (Parent) Pg 358

Leksell E, Hallberg U, Magnusson B, Ernberg M, Hedenberg-Magnusson B. Perceived Oral Health and Care of Children with Juvenile Idiopathic Arthritis: A Qualitative Study. J Oral Facial Pain Headache. 2015; 29(3):223-30.[47]

Finding	Children tried to differentiate themselves from the disease (U)
Illustration	"Daddy knows when you are in pain." (Child, Female, 6 years) Pg 226
Finding	Working on Personal Caretaking and Positive Attitude (U)
Illustration	"It seems like she (another JIA patient) isn't taking care of her disease. I'm proud that I'm able to take care of myself." (Child, Female, 16 years) Pg 227
Finding	Fighting Fears and Sadness (U)
Illustration	"If you get an injection . . . I think it's rather painful. At first, I thought it would be painful, but when I got one here, I just said OW!" "But I didn't start crying, or did I?" (looks at her mother) "But when I was going to get it, I started crying because I thought it would be painful, but then when I got it, it didn't hurt." (Child, Female, 6 years) Pg 227
Finding	Control of Professional Aid (C)
Illustration	"I know when I need cortisone injections in my jaw joints. It's happened several times now, when the disease has just been crazy painful. Then I call XX and get an appointment that's convenient." (Child, Female, 16

	years) Pg 227
Finding	Building Supporting Relationships (U)
Illustration	“Now they want me to have a splint, but I don’t know. I think that many people maybe wouldn't want one because maybe they have a boyfriend or something. But me and my boyfriend would probably just laugh at it, because we are so . . . crazy. Yes, I don't know, I could actually have one, but I . . . it's just that I don't feel like.” (Child, Female, 14 years) Pg 228

Khan S, Mancini J, Hopper C, Rennick JE. Perceptions of Methotrexate Intolerance and Its Impact on Daily Life in School-Age Children with Juvenile Idiopathic Arthritis. J Pediatr Nurs. 2019; 48:49-54.[48]

Finding	No child likes taking MTX (C)
Illustration	“I can see all the needles that I took, it just reminds me of, uh, how I felt those times” (Child, Female, 10 years) Pg 52
	“I don't like it” (Child, Female, 10 years), (Child, Female, 8 years), (Child, Male, 9 years), (Child, Female, 11 years), (Child, Female, 9 years) and “no kid likes taking MTX” (Child, Female, 10 years) Pg 52
	One child explained that when she went down to the basement and was about to receive her MTX, “I'm shaking and full of fear” (Child, Female, 10 years) Pg 52
Finding	Importance of strategies and routines (U)
Illustration	Children reported various distraction techniques to manage MTX intolerance, such as watching TV during their injection (Child, Female, 10 years), (Child, Female, 8 years), (Child, Male, 9 years). Some relied on comfort measures like having their parents present to support them

	through the MTX administration process (Child, Female, 7 years), (Child, Female, 10 years), (Child, Female, 8 years), (Child, Male, 9 years), (Child, Female, 11 years), (Child, Male, 9 years), (Child, Female, 9 years), (Child, Female, 10 years), (Child, Male, 12 years). Others used self-talk strategies to manage their anxiety (Child, Female, 11 years), (Child, Female, 9 years), (Child, Female, 10 years), such as one child who told herself on the day of her injection, it's not right now, it's later today (Child, Female, 9 years). Going to sleep after receiving a MTX injection (Child, Female, 10 years), (Child, Male, 9 years), (Child, Female, 11 years), (Child, Male, 9 years), (Child, Female, 10 years) or having an injection done while they were asleep (Child, Female, 11 years), (Child, Female, 6 years) was an effective way of managing intolerance for some children. Pg 52
Finding	Children struggled with MTX intolerance (U)
Illustration	"Well, for every minute of the day [after receiving MTX] I feel like I'm about to throw up." She went on to explain that the day after MTX administration, "it takes a little bit longer for me to do my homework… I lose my, uhh, like, focus" (Child, Female, 11 years) Pg 52

Shaw KL, Hackett J, Southwood TR, McDonagh JE. The Prevocational and Early Employment Needs of Adolescents with Juvenile Idiopathic Arthritis: The Adolescent Perspective. The British Journal of Occupational Therapy. 2006; 69(3):98-105.[49]

Finding	Impact of JIA on academic ability (U)
Illustration	Those in receipt of a statement of special educational need (SEN) felt that the provision of laptops, scribes and extra time to complete course work and examinations did provide valuable support that enabled them to produce work commensurate with their ability. Pg 100

Finding	Negative expectations of ability (U)
Illustration	One young woman had wanted to enter the police force but had been told that she would not be able to. As she said: “My arthritis doesn’t affect me all that much. I could do it. I’d pass the physical. But I wouldn’t pass the medical. It’s just unfair ’cos I could do it.” (Adolescent, Female) Pg 100
Finding	Vocational readiness skills (U)
Illustration	"I want to get a paper round to get some money but I’ve been to the shops and it’s like 100 papers and I can’t physically walk to the shops, deliver the papers and walk back.” (Adolescent) “I don t look 14 and when I go in to hairdressers, they are like ‘Oh no, I’m sorry, you’ve got to be over 13’ and I’m like ‘Yeah I am, I’m 14’ but they don t believe you.” (Adolescent) “If they find out you’ve got a disability you never hear from them again.” (Adolescent) Pg 100
Finding	Support and advice (U)
Illustration	"I think it would be wise to have a careers adviser at the adolescent clinic." (Adolescent, Male) Pg 101
	“I’d like to get to know somebody that’s been through the UCAS [Universities and Colleges Admissions Service] thing for a highly competitive course and see what the outcome was like.” (Adolescent) Pg 102

O'Sullivan G, O'Higgins S, Caes L, Saetes S, McGuire BE, Stinson J. Self-management needs of Irish adolescents with Juvenile Idiopathic Arthritis (JIA): how can a Canadian web-based programme meet these needs? Pediatr Rheumatol Online J. 2018; 16(1):68.[50]

Finding	Independent self-management (U)

Illustration	"Mam takes care of hospital appointments and bloods. I take care of my injections… She tries not to remind me anymore, I have to learn one day" (Adolescent) Pg 3
	"She's twelve, but I get her into some OT [occupational therapy] appointments on her own, and I meet up with them after" (Parent) Pg 4
	"I take two injections every week and I always forget. I'll be in bed and Mum will shout up to me 'Have you taken your medications?' And I'm like 'Oh!'" (Adolescent) Pg 4
Finding	Acquiring arthritis knowledge and awareness (U)
Illustration	"I was quite young when I got it, so the doctors told my parents and my parents told me" (Adolescent) Pg 5
	"When you're online in American or Canadian stuff, they're [medications] different names! They don't know what we take, and they'll be taking different things. You have to Google what it is..." (Parent) Pg5
Finding	Managing pain and discomfort (C)
Illustration	"I'm very sporty. I did Irish dancing, boxing and hurling. But I had to give up all of them, I was too sore" (Adolescent) Pg 5
	"It can affect your friendships. If they're going out and you come too, you can't keep up. Or if you try, you need physio for the next three days" (Adolescent) Pg 5
Finding	Managing emotions (C)
Illustration	"My daughter takes an injection every day. And the battle we have is every evening. It's a huge battle" (Parent) Pg 5
Finding	Long wait times for diagnosis (U)

Illustration	“They wanted us to see [a psychologist] when I got diagnosed, which is nearly three years ago, and we’re still waiting to see one” (Adolescent) Pg 6
	“We opted to go privately. The wait time for Rheumatology was two years or more going the public route…” (Parent) Pg 6
Finding	Unequal access to services (U)
Illustration	“I'm still struggling to get OT. I'd say if you were in Dublin it would be easier, but in [area] it's very hard” (Parent) Pg 6
	“The service is disjointed. [Area] have a physio unit and OT, but mental health services are in a different area. It’s difficult for people to get to” (Parent) Pg 5
	“Yeah, early start. We’d get up at five in the morning, to be there for 8:30. And we wouldn’t get home until 7pm” (Adolescent) Pg 6
Finding	High expenditure associated with the disease (U)
Illustration	“I have to apply for the long-term illness payment. [Son’s] medication bills were 200 a month. It’s supposed to be about 140, that’s a lot of money every month...” (Parent) Pg 6
	“I gave up working. She was diagnosed at three and I never went back...” (Parent) Pg 6
Finding	Issues with MTX (U)
Illustration	“I'm tired every day. I'm not a morning person as it is, but the methotrexate makes it ten times worse” (Adolescent) Pg 7
	“She had a flare a while back; they had to increase the methotrexate and she was devastated. She said to me, "How am I ever going to get pregnant?"” (Parent) Pg 7

Finding	Impact of JIA on the future (C)
Illustration	"I've always wanted to do teaching… But I'm worried I'm not going to be able to stand for six hours" (Adolescent) Pg 4
Finding	Views on web-based approach to self-management (U)
Illustration	"I've never seen anything like it before. I've never seen a website that has all the information that you could think of." (Adolescent) Pg 7
	"For newly-diagnosed parents, who are finding their way in the first year, who don't know what an appointment with an OT or a physio is…" (Parent) Pg 7
Finding	Gaining understanding through social support (C)
Illustration	"I went on [organization's] road trip and met loads of new friends I talk to [14A] all the time because she understands what I'm going through" (Adolescent) Pg 8
	"I don't think [19A] was talking about her condition with her friends. I'm not sure that she shares with them how she's feeling every day" (Parent) Pg 8

van Gulik EC, Verkuil F, Barendregt AM et al. Experiences, perspectives and expectations of adolescents with juvenile idiopathic arthritis regarding future work participation; a qualitative study, Pediatr Rheumatol Online J 2020;18:33.[51]

Finding	Understanding (U)
Illustration	"Sometimes I couldn't take a test because I was sick or had to go to the hospital and everyone was like 'she can always skip tests and this and that'. They knew I have JIA, but in time they seem to forget, because you can't see it. So they don't understand." (Child, Female, 16 years)

	Pg 5
	"My teacher was really... he has a sister who has a rheumatic disease, so he really understood what was going on." (Child, Female, 17 years) Pg 5
Finding	Support (U)
Illustration	"They set up a room for me with a couch, when I was tired I could go and lie down for an hour. I didn't partake in gym class, I only had to go to classes of which the subject came up in my exams. I had permission to work on a laptop, therefore all my books were on the laptop. They offered school transport, but then I had to get up 45 min earlier, so I rejected." (Child, Male, 17 years) Pg 5
Finding	Impact of JIA on participation in school, sports and part-time employment (U)
Illustration	"I've always had less energy, especially last year. Sometimes I'm even unable to do my homework, because I'm too tired after school and all I want to do is sleep. Or when I try to do my homework, I just fall asleep studying." (Child, Female, 16 years) Pg 5
	"They arranged a switch with a colleague so I could help with the lessons and feeding in the evening instead of mucking out stables in the morning. My colleagues are my friends so they knew I have JIA and they didn't mind. (Working in an equestrian facility)" (Child, Female, 16 years) Pg 5
Finding	Applying for a (part-time) job or further education (U)
Illustration	"They thought I wasn't up for the job, that I wouldn't be able to make long hours or stand for a longer period. If that was the case, they couldn't use me and I just didn't got the job." (Child, Female, 17 years)

	Pg 5
Finding	Normality (U)
Illustration	"The school doctor asked me if I needed any adjustments. I told I had a pillow and a laptop and such on high school but that I don't want any of it anymore. I just want to live a normal life." (Child, Male, 17 years) Pg 7
	"I want them to see me as I am, I don't want them to treat me as someone who isn't capable of anything." (Child, Female, 17 years) Pg 7
Finding	Disclosure (U)
Illustration	"I think I'm less likely to be employed than someone who doesn't have it. Because, they might think I won't be able to walk for a long period or something like that, though I can do that easily." (Child, Male, 16 years) Pg 7
	"It depends on how I'm feeling. If I have a lot of complaints, of course I'll tell, otherwise they can't take it into account. But like now, I don't think it's necessary." (Child, Male, 17 years) Pg 7
Finding	Independence (U)
Illustration	"I asked the paediatric rheumatologist for a medical certificate and brought it with me to school and then I asked if it would be possible to shorten my school days because of my JIA." (Child, Female, 17 years) Pg 7
	"I might think about it, but if I think I can manage, I will listen to myself. I know my body better than anyone else." (Child, Female, 16 years) Pg 7
	"I advise to just organize things yourself and not just wait for something

	to happen. I've learned to ask for the things I need and to say when I need help instead of just ploughing on." (Child, Female, 6 years) Pg 7
Finding	Perseverance (U)
Illustration	"I'm always attending school, even in my wheelchair, even on crutches." (Child, Female, 17 years) Pg 7
	"Most of the time I notice directly (red. I pushed the limit) and then I'll probably continue for some time. The day after, it'll be much worse. And then I think: this wasn't a smart move. But then again, I had fun and I'll stay happy. Because when you're always in pain, staying at home does not do you any good. You'll become completely secluded." (Child, Female, 16 years) Pg 7
Finding	Influence of JIA on career choice (U)
Illustration	"I'll look for something that I would like and want to do. Of course I'll pay some attention to what's possible, but if I'll take that seriously, I'm not able to do anything." (Child, Female, 16 years) Pg 7
	"I feel really passionate about this. And if you really want something, your body can try to stop you, but if you know for sure, you'll just keep going." (Child, Female, 17 years) Pg 7
Finding	Work participation (U)
Illustration	"I'll have graduated from this programme and have started the next, I might have graduated from that one as well. And by that time, I want to have two children and be married." (Child, Female, 17 years) Pg 8
	"I might not be able to stand for a long period or my knees and feet might hurt after a long day of work. But I'll see what happens, I'm not worrying about it too much." (Child, Male, 16 years) Pg 8

Beneitez I, Nieto R, Hernandez E et al. Adolescents' social needs living with juvenile idiopathic arthritis and their views about digital resources, Adv Rheumatol 2020;60:36.[52]

Finding	Friendship and pain interference (U)
Illustration	"If I tell them what's going on, they usually help me, and yes, the truth is that I think we can talk about almost anything …" (Adolescent, Male, 14 years) Pg 5
Finding	Feelings about friendship and JIA (U)
Illustration	"One of my classmates 1 day called me -fat ankles- and said that I was pretending..." (Adolescent, Female, 12 years) Pg 5
	"I have had to learn to be patient with people … because not everyone believes it …" (Adolescent, Female, 14 years) Pg 5
Finding	How they socially cope with JIA (U)
Illustration	"I think I don't have anything to keep to myself, that is, I can say everything, and with my friends, I don't care whether I tell them or not. … Well, if a new kid comes, I won't go and tell him –Hey, I have arthritis-, but if the topic comes up, I will tell him … I'm not embarrassed either or anything like that … Most of them are friends from a long time ago, and they already know about it, and so they don't even ask … If they are interested, I explain it to them, if it's like – Why don't you do gym? - I tell them for no reason and that's that." (Adolescent, Female, 13 years) Pg 5
Finding	Needs to better socially cope with JIA (U)
Illustration	"… because at the beginning, they only said –the pain is like that but we don't know why- if they had said that it would keep me from doing things, well I would have accepted gradually, and not all of a sudden, that I would have to stop dancing." (Adolescent, Female, 15 years) Pg

	5
	"When I'm in the middle of a flare-up, I mean, when I'm bloated or having a flareup, they have to help me to climb the stairs sometimes, even though it seems stupid …" (Adolescent, Female, 14 years) Pg 5
Finding	Information and communication technologies use and perceptions about an online resource for JIA (C)
Illustration	"It's pretty interesting because it has to help you a lot and, well, even though you don't have them (friendship problems) it will always help you in some way, I suppose, the truth is that it can be really good." (Adolescent, Male, 14 years) Pg 6
Finding	Characteristics of an online resource for JIA (C)
Illustration	"Doctors or a psychologist or someone like that who has experience or knows about that." (Adolescent, Female, 12 years) Pg 6
Finding	Including surveys (U)
Illustration	"The surveys could be very different from each other, for example, asking what joints are most affected, and so being able to contact people who are in the same situation as you are, or about what you would recommend, in other words, completely different responses from each other to guide you, that are always welcome, even though each case is different." (Adolescent, Female, 18 years) Pg 7
Finding	Instagram + WhatsApp (U)
Illustration	"I think the best option would be B, the one with Instagram and WhatsApp, because it is the combination of the two applications that kids our age use the most. So I think it is the most accessible option for everyone." (Adolescent, Female, 15 years) Pg 7

Appendix V: Results of meta-synthesis

<table>
<tr><td>Acquiring arthritis knowledge and awareness (U)</td><td rowspan="6">1.1 Experiences and needs of patients and parents for the development of self-management</td><td rowspan="13">1. Self-management of JIA requires pain management, medication management, and the acquisition of knowledge and professional support</td></tr>
<tr><td>Children tried to differentiate themselves from the disease (U)</td></tr>
<tr><td>Independent self-management (U)</td></tr>
<tr><td>Monitoring the child's symptoms and treatments (C)</td></tr>
<tr><td>Acquiring knowledge and skills to manage the disease (U)</td></tr>
<tr><td>Support and advice (U)</td></tr>
<tr><td>Managing pain and discomfort (C)</td><td rowspan="2">1.2 Children usually reduce or change sports to manage pain</td></tr>
<tr><td>Not being able to fully participate in sports, especially physical education (U)</td></tr>
<tr><td>Working on personal caretaking and positive attitude (U)</td><td rowspan="6">1.3 It is a curious paradox that both patients and parents have positive and negative psychological experiences regarding JIA and medications</td></tr>
<tr><td>Fighting fears and sadness (U)</td></tr>
<tr><td>Acquiring knowledge and skills to manage the disease (U)</td></tr>
<tr><td>Importance of strategies and routines (U)</td></tr>
<tr><td>Independent self-management (U)</td></tr>
<tr><td>Issues with MTX (U)</td></tr>
</table>

No child likes taking MTX (U)		
Children struggled with MTX intolerance (U)		
Who understands me? (U)		
Experience of medicines and injections (U)		
Managing emotions (C)		
Use and effect of corticosteroid induction regimens (U)		
Benefits of corticosteroid induction regimens (U)		
Drawbacks of corticosteroid induction regimens (U)		
Control of professional aid (C)	**2.1 Trust in healthcare professionals**	**2. A promising relationship with healthcare professionals but unbalanced access to services**
Seeking doctors and information (U)		
Long wait times for diagnosis (U)	**2.2: Lack of infrastructure and unequal access to services in some regions**	
Unequal access to services (U)		
Acquiring knowledge and skills to manage the disease (U)	**2.3: Vary in ability to communicate with doctors**	
Independence (U)		
Reflecting on and re-evaluating the life	**3.1 Maintaining**	**3. Parental**

situation (C)	**family cohesion and happiness**	**financial burden and their adjustment to maintain family happiness**
Adapting everyday routines (U)		
High expenditure associated with the disease (U)	**3.2 Great burden on parents' jobs and finances**	
Managing job and family finances (U)		
Views on web-based approach to self-management (U)	**4.1 Appreciate/ Positive attitude towards the web-based approach**	**4. Patients and parents support the web-based approach to communicate and develop self-management skills and acknowledge the importance of clinical trials**
Views on web-based approach to learning about self-management (C)		
Information and communication technologies use and perceptions about an online resource for JIA (C)		
Characteristics of an online resource for JIA (C)		
Including surveys (U)		
Instagram + WhatsApp (U)		
Families recognised the needs for clinical trials (U)	**4.2 Facilitators and barriers to participation in clinical trials**	
Barriers and facilitators to participation (U)		
Being approached about research at diagnosis (U)		
Building supporting relationships (C)	**5.1 Children do not want to be different**	**5. Desire to live a normal life**
Being different (U)		

Normality (U)	**from peers**	**without prejudice from school, social settings, and the workplace**
Feelings about friendship and JIA (U)		
Friendship and pain interference (U)		
How they socially cope with JIA (U)		
Needs to better socially cope with JIA (U)		
Gaining understanding through social support (C)	**5.2 The needs of appropriate school facilities, academic assistance, social support and addressing discrimination in workplace**	
Impact of JIA on the future (C)		
Understanding (U)		
Support (U)		
Impact of JIA on participation in school, sports and part-time employment (U)		
Applying for a (part-time) job or further education (U)		
Disclosure (U)		
Perseverance (U)		
Influence of JIA on career choice (U)		
Work participation (U)		
Influencing school and society (U)		
Challenges to schooling and friendships (U)		
Impact of JIA on academic ability (U)		

Vocational readiness skills (U)		
Experiencing understanding through social support (U)		
Negative expectations of ability (U)		

Chapter 3. Juvenile Idiopathic Arthritis in South Australia

The following chapter presents the manuscript 'Juvenile Idiopathic Arthritis in South Australia', which was submit to *the Journal of Rheumatology*. As per the journal requirements, American English spelling was used in this publication, and in this chapter.

3.1 Abstract

Objectives: 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).

Method: Patients' data were prospectively collected at the Women's and Children's Hospital in Adelaide, between August 2019 and March 2020. 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, socio-economic indexes for areas (SEIFA) scores, complications/comorbidities, medications, disease activity and patient-reported data using Childhood Health Assessment Questionnaire (CHAQ) were documented. Non-identified data from baseline visits were extracted from this registry and utilized in descriptive analysis and comparative studies.

Results: The n = 112 JIA patients enrolled into the newly established registry included n = 11 incident cases (9.8%), with a predominance of female (n = 75, 67.0%). At recruitment, 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%). Approximately half of the patients (n = 52/112, 46.4%) had clinically inactive disease and most (n = 85/112, 75.9%) reported no to low functional disability.

Conclusions: The JIA cohort in SA is female-dominated with persistent oligoarthritis as the most common subtype, consistent with other studies. Most patients with established disease 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.

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

Key-points:

- The JIA cohort in SA was found to be female-dominated with persistent oligoarthritis as the most common subtype.
- Approximately half of the patients were assessed as clinically inactive disease and most of the patients reported no or mild disability.
- Patient-reported functional disability and pain were positively correlated with clinical assessment of disease activity.

3.2 Statement of Authorship

Statement of Authorship

Title of Paper	Juvenile Idiopathic Arthritis in South Australia
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☒ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Plan to submit to Medical Journal of Australia.

Principal Author

Name of Principal Author (Candidate)	Ming Min		
Contribution to the Paper	First author and main contributor. Study design, investigation, project administration, data collection and analysis, formulation of draft and reviewing and incorporating co-author comments and suggestions.		
Overall percentage (%)	60%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	14/05/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Suzanne Edwards		
Contribution to the Paper	Methodology support, data analysis and interpretation, and manuscript review.		
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Contribution to the Paper	Concept and methodological design, interpretation of the data, and manuscript review.		
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Please cut and paste additional co-author panels here as required.

Name of Co-Author	Tania Crotti		
Contribution to the Paper	Concept and methodological design, methodology, planning and supervision of the project, review of the manuscript.		
Signature		Date	14/05/21

Name of Co-Author	Christina Boros		
Contribution to the Paper	Project concept and design, investigation, methodology, data collection and further analysis, manuscript review. Due to illness Dr Boros is on long term leave. A/Prof Crotti has signed on her behalf		
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3.3 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% to 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 occurrence 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 normalized 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. The prevalence and incidence of JIA have been found to differ in different ethnic groups and regions [7,5,8], 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]. Studies presented a relatively higher prevalence rate in developed countries, varying from 16 to 150 per 100,000 [11]. However, it should be noted that the current low reported prevalence in developing countries may be related to limited data sources [12].

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

[13]. The 2004-05 Australian Institute of Health and Welfare (AIHW) reports a prevalence of 100 to 400 per 100,000 Australian children [12]. This estimate was far higher than found in other published studies [9,10,14,11,15].

The only current JIA registry in Australia - The Childhood Arthritis Risk Factor Identification Study (CLARITY) has the primary aim of analyzing DNA and environmental data to identify risk factors for JIA [16]. An inception cohort study with comprehensive epidemiological data for newly diagnosed JIA patients in Victoria was performed between 2010 and 2014, to help initial understanding of the demographics, treatment and outcomes of Australian children [17]. Their results have shown a high similarity in patient demographics, disease course and treatment with cohorts in North America and Europe [17]. More recently, CLARITY has been extended to include children in the rest of Australia as well as New Zealand. However, no published data are available.

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.

3.4 Methods

3.4.1 Study design

The JIA registry in SA is a single-center, 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.

3.4.2 Patient cohort and recruitment

This cross-sectional study captured and analyzed 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 an outpatient visit to the Pediatric Rheumatology Clinic at the Women's and Children's Hospital (WCH), in Adelaide, SA. This center receives referrals from the whole of SA as well as the Northern Territory and western parts of New South Wales, and Victoria. The minority of patients in SA are referred to private clinics but these patients were not included in the registry, given the differences in patient experience.

The identification of JIA cases was made by three pediatric rheumatologists and the rheumatology nurse in the clinic setting based on the International League of Associations for Rheumatology (ILAR) criteria [18]. Incident cases were defined as those enrolled within six months of initial diagnosis. Prevalent cases older than 18 years were excluded, as patients in WCH then transit to adult services.

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

3.4.3 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, socio-economic indexes for areas (SEIFA) scores, JIA subtype, disease onset, disease duration, complications/comorbidities, medications used as well as investigation results and the 10-joint clinical Juvenile Arthritis Disease Activity Score (cJADAS) [19] were documented. Patients/carers were asked to complete the paper-based Childhood Health Assessment Questionnaire (CHAQ) [20] at each clinic visit.

3.4.4 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 minimize the potential misclassification of patients, a 6-month period has been provided to ensure an accurate clinical diagnosis, prior to the finalization 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.

3.4.5 Definitions of disease activity states

The cJADAS, which consist of active joint count, physician global assessment (PGA), and patient global evaluation (PGE), is a validated tool in clinical practice to describe disease activity in JIA [21]. In accordance with Consolaro et al. in 2014 [19], cutoff values for the classification of disease activity states were defined. Children were classified into functional oligoarthritis or polyarthritis categories based on their subtypes and the number of affected joints. Clinically inactive disease (CID) was defined as $\leqslant 1$ for both functional oligoarthritis and polyarthritis. The selected cutoffs for low, moderate and high disease activity for functional oligoarthritis and polyarthritis were: 1.1-1.5, 1.1-2.5; 1.51-4, 2.51-8.5; >4, >8.5 [19].

3.4.6 Complications and comorbidities

Complications and comorbidities were recorded and categorized based on case-note reports. Complications categories included: ocular, musculoskeletal, medication intolerance and side effects, growth failure/retardation and macrophage activation syndrome [22-25]. Ocular complications included uveitis and uveitis-related complications such as glaucoma, cataract and macular oedema [23]. Musculoskeletal complications included joint deformity, joint damage/erosive disease and muscle wasting [26-28]. Medication intolerance and side effects included MTX-associated nausea,

anxiety, needle phobia and liver function test derangement [24].

3.4.7 Statistical analysis

Analyses were calculated from the extracted data at the first registry visit and were conducted using SPSS software package, version 25 (SPSS Inc., Chicago, IL, USA). Categorical variables are presented as frequencies and percentages, and continuous variables are presented as mean ± 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. 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.

3.5 Results

3.5.1 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 years (IQR 2.0-9.7) and the mean ± SD age at recruitment was 11.7 ± 4.4 years. The most common subtype of JIA was persistent oligoarticular onset disease (PO) (*n* = 35, 31.3%), with median onset at age of 2.8 years (IQR 1.7-7.0) and predominantly occurring in females (*n* = 26/35, 74.3%). The least common subtype was psoriatic arthritis (PsA) (*n* = 2, 1.8%). No patients had undifferentiated disease. Comparisons to other cohorts are presented in Table 2. Among those patients who underwent relevant blood tests, *n* = 63/101 (62.4%) of the children in the registry were antinuclear antibody (ANA) positive, and among the ANA positive, *n* = 26/63 (41.3%) had PO. Human leukocyte antigen B27 (HLA-B27) was determined in *n* = 65/112 (58%) JIA patients, and HLA-B27 was present in *n* = 19/65 (29.2%).

The cohort included *n* = 11/112 (9.8%) newly diagnosed JIA cases, seven (63.6%) of which were female. The most common diagnosis was PO (*n* = 5/11, 45.5%), followed by *n* = 3/11 (27.3%) with rheumatoid factor negative (RF-) polyarthritis, *n* = 2/11 (18.2%) with enthesitis-related arthritis (ERA) and *n* = 1/11 (9.1%) with rheumatoid factor positive (RF+) polyarthritis. The median age at symptom onset and the median age at recruitment was 13.3 years (IQR 2.7-16.3) and 15.8 years (IQR 7.3-17.4) for incident cases, and 4.9 years (IQR 1.8-9.3) and 11.9 years (IQR 8.4-14.9) for prevalent cases.

Table 1 Characteristics of 112 children with juvenile idiopathic arthritis in South Australia.

Female sex, n (%)	75 (67%)	
Prevalent cases, n (%)	101 (90.2%)	
JIA subtype, ILAR criteria	***N* (%)**	**Female sex, *n* (%)**
Persistent oligoarthritis	35 (31.3%)	26 (74.3%)
Extended oligoarthritis	23 (20.5%)	16 (69.6%)
RF- Polyarthritis	32 (28.6%)	22 (68.8%)
RF+ Polyarthritis	3 (2.7%)	2 (66.7%)
Enthesitis-related arthritis	12 (10.7%)	2 (16.7%)
Psoriatic arthritis	2 (1.8%)	2 (100%)
Systemic onset arthritis	5 (4.5%)	5 (100%)
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 ± SD, years	11.7 ± 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 Comparison of juvenile idiopathic arthritis subtype distribution among different geographical regions.

JIA subtype, ILAR criteria, *n* (%)	**South Australia *n* = 112**	**CLARITY, Victoria [17] *n* = 134**	**Nordic countries [31] *n* = 440**	**United Kingdom [38] *n* = 1415**	**North America [33] *n* = 1192**	**Taiwan, China [40] *n* = 195**	**India [41] *n* = 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.

3.5.2 Medications

The exposure of the cohort to medications is detailed in Table 3. At enrollment, 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 extended oligoarticular onset disease (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 enrollment, *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.

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

JIA subtype, ILAR criteria, *n*	**NSAIDs**	**DMARDs**	**Biologics**	**Steroids IV**	**Steroids oral**	**Steroids IA**
Persistent oligoarthritis (*n* = 35)	30 (86%)	13 (37%)	1 (3%)	0 (0%)	2 (6%)	25 (71%)
Extended oligoarthritis (*n* = 23)	22 (96%)	20 (87%)	6 (26%)	0 (0%)	9 (39%)	18 (78%)
RF- Polyarthritis (*n* = 32)	30 (94%)	31 (97%)	10 (31%)	7 (22%)	19 (59%)	8 (25%)
RF+ Polyarthritis (*n* = 3)	2 (67%)	3 (100%)	1 (33%)	1 (33%)	2 (67%)	1 (33%)
Enthesitis-related arthritis (*n* = 12)	10 (83%)	9 (75%)	5 (42%)	2 (17%)	5 (42%)	0 (0%)
Psoriatic arthritis (*n* = 2)	2 (100%)	2 (100%)	1 (50%)	0 (0%)	1 (50%)	1 (50%)
Systemic onset arthritis (*n* = 5)	4 (80%)	5 (100%)	2 (40%)	4 (80%)	5 (100%)	0 (0%)
Overall (*n* = 112)	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.

3.5.3 Disease course

At the time of recruitment, the median active joint count was zero (IQR 0-0.8), the median PGA was zero (IQR 0-1.1) and the median PGE was 0.5 (IQR 0-2.4) for all JIA patients (Table 4).

Among *n* = 101 patients with established disease, the median number of active joints was zero (IQR 0-0) and the median PGA was zero (IQR 0-1.0). In contrast, *n* = 11 incident patients had a median of one active joint count (IQR 0-2.0), and a higher median PGA of 1.2 (IQR 0-1.9).

Based on the aforementioned cJADAS cut-offs [19], *n* = 18/112 (16.1%) children had high disease activity, including PO (*n* = 10), RF- polyarthritis (*n* = 6), EO (*n* = 1) and RF+ polyarthritis (*n* = 1). Patients with EO had significantly longer disease duration [median 7.5 years (IQR 3.4-9.9)] than those with PO [median 3.9 years (IQR 1.2-6.4)] (*p* = 0.016). In the prevalent cohort, high disease activity was present in less (*n* = 13/101, 12.9%) children, including PO (*n* = 7), RF- polyarthritis (*n* = 4), EO (*n* = 1) and RF+ polyarthritis (*n* = 1).

The median CHAQ score (disability index) was 0.1 (IQR 0-0.6); most (*n* = 85/112, 75.9%) had no or only mild disability. The distribution of the CHAQ score was highly skewed (mean 0.37) [29]. When we explored the differences in CHAQ scores between 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 years (IQR 1.8-8.9) and 6.2 years (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 years (IQR 0.2-0.9) and there was no significant between-group difference (*p* = 0.571).

Table 4 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

3.5.4 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 recruitment. Most of those with uveitis (*n* = 17/21, 81%) were 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, including micrognathia (*n* = 4), fixed flexion deformity (*n* = 3), and erosive disease/joint damage (*n* = 3). The majority (*n* = 8/10, 80%) are in functional polyarthritis category.

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. Among patients experiencing anticipatory nausea and vomiting *n* = 2/3 (66.7%) patients were treated with MTX where subcutaneous injection was the mode of delivery. 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/anemia (*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%).

3.5.5 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 $R = -0.206$, $p = 0.029$).

3.6 Discussion

We have developed a JIA registry of the SA cohort, and here we describe our cohort in detail. Our findings regarding sex distribution, disease activity and patient-reported data are comparable to the data of similar populations in geographical regions such as North America and Europe [30-35]. However, there are differences in JIA subtype distribution and complications such as uveitis and MTX intolerance between our cohort and those in other published studies [36,33,37,17,24].

Of note, although the majority of the population of SA is Caucasian, 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 [37,38,30-32]. In the present study, PO was the most widely distributed subtype (n = 35/112, 31.3%), which is consistent with the UK (n = 638/1415, 45.1%) and four Nordic countries (i.e. Denmark, Finland, Sweden, and Norway) (n = 132/440, 30%) [31,30,38]. However, North American, Latin American and South African children are more likely to develop polyarticular onset JIA [33,37,39]. 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 [40,41], where in this study, Nordic countries and the UK around ten percent of patients had ERA (10.7, 11.1% and 5.4% respectively). The frequency of systemic onset JIA was the highest in Latin America (> 20%) [37], Asia (10-20%) [40] and North America (10-20%) [33], and had similar frequencies in Australia and Europe (<10% for both) [31,38]. Compared to North America, the rate of functional polyarthritis (as per Consolaro et al. [19]) 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) [33]. 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 ($p < 0.001$) [17]. It can be partly explained by the fact that 13% of patients from the CLARITY cohort had undifferentiated arthritis at enrollment 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 in part due to the overrepresentation of patients with ERA and the underrepresentation of patients with both PO and EO [8], our data have a similar profile to that of European and North American regions which is predominantly female [31,30,33]. In Australia, the sex ratio in this study is also comparable with CLARITY

data, in which 67% versus 62% of patients were female ($p = 0.416$) [17].

In a cross-sectional PRINTO study describing JIA cohorts from various geographic areas, prevalent cohorts in Western Europe, Southern Europe, and North American had a similar median disease duration of around 4.1 years. Incident cases were not available in the study thus this comparison could not be conducted. 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 $p = 0.1275$) [32]. However, a significantly higher median cJADAS was observed in the Western European cohort ($p = 0.0086$) [32]. 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 ($p = 0.0418$) [32].

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) [34]. 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 [33]. 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), similar to the Canadian inception cohort study with a median cJADAS of 6.5 (IQR 4-10) (p = 0.2707) [35]. To our knowledge, this was the only recent paper that used cJADAS to measure disease activity and reported relevant data for newly diagnosed JIA patients.

Worldwide, the prevalence of JIA-associated uveitis is reported to be up to 30% [1,32]. In this registry, n = 21/94 (22.3%) of patients had uveitis. This 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 [36,31,33]. 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 [42]. The lowest rates of n = 19/379 (5%) and n = 44/726 (6%) were recorded in India and Japan [43,32]. 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 [36]. In our study, both active and previous episodes of uveitis were recorded at enrollment.

Musculoskeletal complications occurred in n = 10/112 (8.9%) patients in this study, which included joint deformity, 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% to 14.7% in European and North American countries, measured by Juvenile Arthritis Damage Index (JADI)-Articular > 0 [32].

In a recent systemic JIA cohort study in Turkey [22], 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 [44]. However, it is difficult to make a comparison with our data because of the comparatively smaller number of our systemic JIA patients, which included n = 1/5 (20%) growth retardation and n = 1/5 (20%) MAS. It is interesting to

point out that the patient was diagnosed with MAS later in the course of JIA and biologics were never used. 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.

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 [24]. 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) [45]. 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 [30-33,45,34], 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 center. We will continue to collect prospective data in our registry with ongoing patient recruitment of incident and prevalent 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 SA. Moreover, it was difficult to compare different ethnic groups in SA in terms of distribution of JIA subtypes and disease manifestations since ethnicity data were not recorded. Another limitation is that the complications and comorbidities were extracted retrospectively from medical records, at times without a clear record date of onset. However, collection of these data is important in the assessment of disease activity and outcomes.

3.7 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, environmental features, disease course and activity, major complications and comorbidities, medication exposure and patient-reported data were recorded. 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 optimization of the clinical care of our JIA cohort and provides an important resource for collaborative research in Australia and internationally.

3.8 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.

3.9 Declarations

3.9.1 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). Written informed consent was obtained from all participants included in the study.

3.9.2 Consent for publication

Not applicable.

3.9.3 Availability of data and materials

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

3.9.4 Competing interests

The authors declare that they have no competing interests.

3.9.5 Funding

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

3.9.6 Conflicts of interest

We have no conflict of interest.

3.9.7 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.

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Chapter 4. Analysis of clinical outcomes and patient-reported data in Juvenile Idiopathic Arthritis: a prospective outcome study

The following chapter presents the manuscript 'Analysis of clinical outcomes and patient-reported data in Juvenile Idiopathic Arthritis: a prospective outcome study', which was submit to *Arthritis Care & Research*. As per the journal requirements, American English spelling was used in this publication, and in this chapter.

4.1 Abstract

Objective: This prospective study aimed to describe the Juvenile Idiopathic Arthritis (JIA) population in South Australia and to better understand patient-reported outcome measures (PROMs) and experience measures (PREMs) in routine clinic visits.

Methods: JIA patients were recruited between August 2019 and March 2020. Data regarding demographics, disease onset, investigation results, and clinical JIA Disease Activity Score-10 (cJADAS) was documented. Patients/carers completed questionnaires at a clinic visit, including the Childhood Health Assessment Questionnaire (CHAQ), the Quality of My Life and the British Society for Paediatric and Adolescent Rheumatology (BSPAR) PROMs and PREMs questionnaire.

Results: Data was obtained from 120 patients and 204 clinic visits. Patients were predominantly female (n = 80, 66.7%), with a median age of 12.5 years (IQR 7.9-15.2). Those with higher cJADAS reported lower quality of life (QOL; $p < 0.001$), lower health-related QOL (HRQOL; $p < 0.001$), and higher CHAQ-score ($p < 0.001$). Patients with high disease activity had a higher odds ratio (3.4 [95% CI 1.3-8.8], $p = 0.012$) than those with inactive disease to report fatigue. Findings were similar regarding pain, medication side effects, poor sleep, poor social and emotional wellbeing. The majority of participants were satisfied with the clinic environment during hospital visits (98.5%)

and felt well-supported in between visits (92.6%). Disease activity was verified to have a negative impact on both.

Conclusion: A direct relationship between clinical disease activity and PROMs, such as QOL, HRQOL, CHAQ-score and all PROM items was shown for our JIA cohort. The relationship with PREMs was partially proven. Larger studies are required to examine the associations.

Significance and Innovations:

- Patient-reported data was recorded from more than 204 clinic appointments for 120 patients with JIA attending the Paediatric Rheumatology clinic at the Women's and Children's Hospital, South Australia (SA). For each appointment, the clinical JIA Disease Activity Score-10 (cJADAS) was calculated and disease activity state was measured for clinical assessment.
- Patient-reported experience measures (PREMs) have rarely been recorded in pediatric rheumatology clinics. This study utilized the novel JIA-specific patient-reported outcome measures (PROMs) and PREMs questionnaire (designed by the British Society for Paediatric and Adolescent Rheumatology [BSPAR]), to better understand the patient experience and their relationship with clinical outcomes.
- According to the results of ordinal logistic regression analysis of the BSPAR PREMs outcomes versus various predictors, children with high disease activity had odds of feeling less supported between visits three times that of children with inactive disease. A similar result was obtained for patients feeling less satisfied with the clinic environment.
- Incorporating PROMs and PREMs in addition to clinical disease activity measures may improve understanding around patient outcomes and in turn, quality of care.

4.2 Statement of Authorship

Statement of Authorship

Title of Paper	Analysis of clinical outcomes and patient-reported data in Juvenile Idiopathic Arthritis: a prospective outcome study
Publication Status	☐ Published ☐ Accepted for Publication ☐ Submitted for Publication ☒ Unpublished and Unsubmitted w ork w ritten in manuscript style
Publication Details	

Principal Author

Name of Principal Author (Candidate)	Ming Min
Contribution to the Paper	First author and main contributor. Study conception and design, investigation, data collection and interpretation, formulation of draft, reviewing and incorporating co-author comments and suggestions.
Overall percentage (%)	60%
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.
Signature	Date: 14/05/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Suzanne Edwards
Contribution to the Paper	Methodology, data analysis advice and guidance and manuscript review.
Signature	Date: 14/5/21

Name of Co-Author	Catherine Gibson
Contribution to the Paper	Conceptualisation and manuscript review.
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Please cut and paste additional co-author panels here as required.

Name of Co-Author	Tania Crotti		
Contribution to the Paper	Concept and methodological design, supervision of the findings of the work, review of the manuscript.		
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Name of Co-Author	Christina Boros		
Contribution to the Paper	Theory development, study design and project direction, conceptualisation, methodology, supervision and review Due to illness Dr Boros is on long term leave. A/Prof Crotti has signed on her behalf		
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Contribution to the Paper			
Signature		Date	

4.3 Introduction

Juvenile Idiopathic Arthritis (JIA) is an inflammatory disease with onset in children under the age of 16. The International League of Associations for Rheumatology (ILAR) classification criteria uses seven subtypes to classify the disease [1]. However, patients with the same subtype can exhibit heterogeneity in disease course, disease activity and outcomes. In addition, response to treatment can be variable for each individual. Thus, attention to the personalized needs and patient-centered care and treatment is needed. Studies have shown that more than 50% of all JIA patients maintain active disease into adulthood with long-standing physical and psychosocial impacts [2, 3]. As such, traditional clinical outcome measures may fail to assess the impact of treatment and management from a patient perspective [4, 5]. Studies indicate that the physician global assessment (PGA) score tended to be higher than those of patients or parents [6]. Parents were more likely to rate the global assessment of disease activity higher if their child was experiencing pain or functional impairment [6, 7]. Of note, patients themselves can consider persistent pain as active disease which may overestimate disease activity from the patient's perspective [8]. These findings demonstrate that simultaneously monitoring clinical outcomes and patient-reported outcomes are key to describing the full spectrum of disease in order to develop appropriate therapeutic paradigms in JIA patients.

Extensive research has facilitated the development of disease activity measures [9-11]. Compared to the American College of Rheumatology core outcome set [9], the Juvenile Arthritis Disease Activity Score (JADAS) not only comprises of fewer and more accessible variables but can evaluate the absolute level of disease activity for JIA patients [10]. Recognizing the impact of frequent unnecessary blood tests for some JIA patients the clinical JADAS-10 (cJADAS) was developed. The cJADAS excludes the erythrocyte sedimentation rate (ESR) variable from JADAS and was demonstrated to have a great concordance with JADAS [12]. Optimized cut-offs for cJADAS for non-systemic subtypes have since been suggested by Consolaro et al. [13]. However, research shows that these objective clinical outcomes fluctuate in accuracy and robustness. Despite

clinical remission as assessed by disease activity scores, many patients with clinically inactive JIA report suboptimal health-related quality of life (HRQOL) or ongoing symptoms [5, 14]. Additionally, patients' experiences of consultations have been shown to be positively associated with efficacy of treatment, which is mainly influenced by patient beliefs and treatment adherence [15]. This prompted the development of patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs) to more comprehensively and accurately assess disease outcomes.

PROMs evaluate outcomes including HRQOL, activities of daily living, pain and overall disease activity from the patient or care givers perspective, whilst PREMs focus on patients' and parents' self-reported experiences in accessing care and services. Although the measurement of PROMs has been recognized as a key component in the assessment of overall health outcomes in JIA [16-18], there is limited information in the published literature regarding the association between PROMs and clinical measures of disease outcomes in JIA [19-21]. Moreover, PREMs have rarely been captured and implemented in paediatric rheumatology clinics, neither in South Australia (SA) nor internationally, thus their relationships with clinical outcomes have remained unexplored. Most recently, a novel questionnaire integrated JIA-specific PROMs and PREMs was designed by the British Society for Paediatric and Adolescent Rheumatology (BSPAR) team [22]. The BSPAR questionnaire incorporates the evaluation of physical, social and emotional well-being in the PROMs questionnaire. The PREMs questionnaire includes six main themes, including communication, clinic environment, confidence, information/education, access/coordination of care and needs/involvement [22]. The BSPAR PROMs and PREMs questionnaire has since been validated as a part of CAPTURE-JIA (Consensus derived, Accessible [information], Patient-focused, Team-focused, Universally-collected (UK), Relevant to all and containing Essential data items) project [22, 23]. The occurrence and initial validation of this questionnaire in the clinic setting provided a valuable basic resource for further research on its relationship with clinical outcomes. Therefore, the purpose of this study is to understand the relationship between PROMs

and PREMs and clinical measures of disease activity and health outcomes, in the JIA cohort in SA, by using traditional and novel tools.

4.4 Patients and Methods

4.4.1 Ethics

This study was approved by the Human Research Ethics Committee of the Women's and Children's Health Network (HREC/19/WCHN/59) and conducted in accordance with the Declaration of Helsinki.

4.4.2 Participants

Patients with JIA fulfilling ILAR classification criteria [1] and attending the Paediatric Rheumatology outpatient clinic at Women's and Children's Hospital (WCH), SA, were invited to participate. Written informed consent was provided by patients or parents/carers according to ethics. In the case of children younger than 16 years of age or had difficulty understanding the study process or questionnaires, parents/carers were asked to give the consent and fill out the questionnaires.

Patients were recruited between August 2019 and March 2020. In general, routine appointments were performed every three months unless otherwise recommended by the treating rheumatologist considering the arthritis course and disease activity of the patient.

4.4.3 Data collection

Of the 125 eligible patients, 121 children and/or their parents/carers agreed to participate. Four families declined participation. One was excluded because the data was incomplete. Thus, 120 participants were included in this study.

After obtaining written informed consent, a retrospective review of the case notes was made by the treating Rheumatologist and the principal investigator (MM). Data regarding demographics, socio-economic indexes for areas (SEIFA) scores, JIA subtype, disease onset, disease duration, complications/comorbidities, and previous medications

used were documented. In the clinic setting, prospective and longitudinal data collection including serial data - investigation results, ongoing medications and cJADAS as well as patient-reported questionnaire data were performed at each routine clinic visit. Three standardized questionnaires were utilized in this study, the Childhood Health Assessment Questionnaire (CHAQ), Quality of My Life (QoML) and the BSPAR PROMs and PREMs questionnaire. The principal investigator (MM) or the Rheumatology Nurse distributed the questionnaires to patients and parents/carers upon their arrival in the clinic waiting room and these were collected directly after the appointment. Estimated time for completion of all study questionnaires was approximately 15 minutes for each participant. Participants were assigned a newly generated study ID number upon collection and this number was employed to link patient-reported questionnaires to the matched clinical data, whilst maintaining confidentiality.

When missing information was identified in questionnaires the principal investigator (MM) contacted participants by telephone or e-mail. After two failed attempts, the corresponding questionnaire was considered to be missing data and excluded from the analysis. From the 214 clinic visits, $n = 9$ were excluded because of missing key content in at least one patient-reported questionnaire. Of these, one patient had no analyzable data from any visit.

Therefore, the study group consisted of $n = 120$ patients ($n = 80$ girls, $n = 40$ boys) with data from $n = 204$ visits for analysis.

Medications were classified into four categories: 1) non-steroidal anti-inflammatory drugs (NSAIDs), 2) Disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX), leflunomide and sulfasalazine, 3) biological drugs, such as tumor necrosis factor (TNF), interleukin (IL)-1 and IL-6 blockers, and 4) intra-articular, oral and/or intravenous corticosteroid therapy [24].

Complications for JIA patients were classified into four categories: 1) eye problems such as uveitis, cataract and glaucoma; 2) growth and bone problems, e.g. joint deformity, joint damage, and growth retardation; 3) side effect of the intervention, for example,

MTX-associated nausea, anxiety, and liver function test derangement, and subcutaneous atrophy, which resulted from intra-articular steroid injection; and 4) macrophage activation syndrome as per Vastert et al. [25].

Comorbidities reported included coeliac disease, diabetes, inflammatory bowel disease and thyroid disorder. Recent evidence suggest that these comorbidities share many genetic overlaps with JIA [26, 27].

Disease activity was monitored by the treating rheumatologist. In accordance with clinic practice/management, cJADAS was used, which is a validated and commonly used measure in the context of JIA clinical settings. Clinically inactive disease (CID) and cut-offs of cJADAS were defined as per Consolaro et al. (2014) [28].

Laboratory testing included ESR, C-reactive protein (CRP), antinuclear antibody (ANA), rheumatoid factor (RF) and human leukocyte antigen B27 (HLA-B27).

Quality of life (QOL) and HRQOL were measured by the QoML questionnaire.

Functional disability and pain were measured by the CHAQ. The cut-offs for Disability Index were suggested by Dempster et.al in 2001 [29], so that the disability level for patients can be characterized by mild, moderate, and severe.

JIA-specific PROMs and PREMs were measured by the novel BSPAR questionnaire [22].

4.4.4 Data analysis

Categorical variables are presented as frequencies and percentages. Continuous variables are presented as the mean ± 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. *P* values less than 0.05 were considered as statistically significant. Spearman rank correlation coefficient was used for correlation analysis.

Associations between clinical disease activity and patient-reported outcomes were assessed using ordinal logistic regression. Results are reported as odds ratio (OR) and

associated 95% confidence intervals (CIs). All analyses were performed using SPSS software package, version 25 (SPSS Inc., Chicago, IL, USA).

4.5 Results

4.5.1 Patient characteristics

For the *n* = 120 patients with JIA included in this analysis, the demographic and clinical characteristics are presented in Table 1. The majority of participants were female (*n* = 80/120, 66.7%) and the median age was 12.5 years (IQR 7.9-15.2). The median age of symptom onset was 5.8 years (IQR 2.0-10.0; one patient had no clear onset information) and the median disease duration was 3.5 years (IQR 1.2-7.4). The ILAR subtype distribution included persistent oligoarthritis (*n* = 39, 32.5%) as the most common subtype, RF- polyarthritis (*n* = 32, 26.7%), extended oligoarthritis (*n* = 24, 20.0%), enthesitis-related arthritis (ERA; *n* = 14, 11.7%), systemic onset arthritis (*n* = 5, 4.2%), psoriatic arthritis (PsA; *n* = 3, 2.5%), and RF+ polyarthritis (*n* = 3, 2.5%). None of the registry participants were classified as the undifferentiated category.

Table 1. Characteristics of 120 children with juvenile idiopathic arthritis.

Patient characteristics	***n* (%)**
Total registered patients	*n* = 120
Female	80 (66.7)
Prevalent cases	107 (89.2)
JIA subtype, ILAR criteria	
Persistent oligoarthritis	39 (32.5)
Extended oligoarthritis	24 (20.0)
RF- Polyarthritis	32 (26.7)
RF+ Polyarthritis	3 (2.5)

Enthesitis-related arthritis	14 (11.7)
Psoriatic arthritis	3 (2.5)
Systemic onset arthritis	5 (4.2)
Biologics exposure	28 (23.3)
ANA+	66 (55.0)
Uveitis ever	23 (19.2)
	Median (IQR)
Age at onset, years	5.8 (2.0-10.0)
Age at diagnosis, years	6.5 (2.7-11.3)
Age at recruitment, years	12.5 (7.9-15.2)
Disease duration, years	3.5 (1.2-7.4)
cJADAS, 0-30	1.4 (0.1-5.0)
Active joint count, 0-10	0 (0-1)
PGA, 0-10 cm VAS	0.0 (0.0-1.1)
PGE, 0-10 cm VAS	0.6 (0.0-2.6)

Abbreviations: ANA: antinuclear antibody; cJADAS: clinical Juvenile Arthritis Disease Activity Score-10; ILAR: International League of Associations for Rheumatology; IQR: interquartile range; JIA: juvenile idiopathic arthritis; PGA: physician global assessment; PGE: patient or parent global evaluation; RF: rheumatoid factor; VAS: visual analogue scale.

At enrolment, *n* = 13/120 (10.8%) patients were identified as newly diagnosed JIA (or incident cases) as their diagnoses were within the six months period prior to the recruitment. Of these, *n* = 8/13 (61.5%) were female, the most common subtype was persistent oligoarthritis (*n* = 6/13, 46.2%), and the median age at onset was 13.3 years (IQR 4.8-16.6). The remaining 107 cases (89.2%) were defined as prevalent cases with

established disease for at least six months. The median age at onset for prevalent cases was 4.9 years (IQR 1.8-9.4), significantly lower than those for incident cases ($p = 0.002$).

4.5.2 Correlations between disease activity and four patient-reported outcomes (data from baseline and follow-up visits)

Between August 2019 and March 2020, a total of $n = 204$ analyzable clinic visits were recorded. The average number of clinic visits for each participant was 1.7 ($SD = 0.8$). Sixty-five (54.2%) participants experienced two or more visits within the data collection period. One (0.8%) participant had up to five visits.

For these $n = 204$ visits, correlation analysis results investigating the relationship between disease activity and four patient-reported outcomes, including QOL, HRQOL, CHAQ-score and Pain visual analogue scale (VAS) are presented in Table 2. There were significant negative correlations between disease activity and both QOL ($r1 = -0.30$, $p < 0.001$) and HRQOL ($r2 = -0.46$, $p < 0.001$). In children with persistent oligoarthritis, the correlations were stronger ($r3 = -0.58$, $p < 0.001$ and $r4 = -0.72$, $p < 0.001$) respectively. In $n = 204$ visits, there were significant positive correlations between disease activity and both CHAQ-score ($r1 = 0.48$, $p < 0.001$) and Pain VAS ($r2 = 0.67$, $p < 0.001$). In children with RF- polyarthritis, the correlation was stronger ($r3 = 0.59$, $p < 0.001$ and $r4 = 0.72$, $p < 0.001$).

Table 2. Pearson correlation matrix for disease activity and four patient-report outcomes ($n = 204$).

	Disease Activity	**QOL**	**HRQOL**	**CHAQ-score**	**Pain VAS**
Disease Activity	1.000				
QOL	-.304**	1.000			
HRQOL	-.463**	.648**	1.000		

CHAQ-score	.483**	-.265**	-.374**	1.000	
Pain VAS	.665**	-.271**	-.455**	.551**	1.000

** Correlation is significant at the 0.001 level (2-tailed).

Abbreviations: CHAQ: Childhood Health Assessment Questionnaire; HRQOL: health-related quality of life; QOL: quality of life; VAS: visual analogue scale.

Out of n = 204 patient visits, n = 113 were in active disease and n = 91 were in CID. During CID, no correlations between cJADAS and CHAQ-score were found (r = 0.18, p = 0.098); while during active disease, a correlation between cJADAS and CHAQ-score was present (r = 0.30, p = 0.001). Similarly, a stronger correlation between cJADAS and HRQOL was found during active than inactive disease (r = -0.30, p = 0.001 versus r = -0.21, p = 0.048).

The largest proportion of questionnaire respondents were adolescent patient participants (n = 121/204, 59.3%), with a median age of 14.1 years (IQR 12.5-16.3). During the visits where questionnaires were completed by patients themselves, the correlation between disease activity and CHAQ-score was r = 0.60 (p < 0.001). The correlation between disease activity and QOL was r = -0.27 (p = 0.003), between disease activity and HRQOL was r = -0.44, (p < 0.001). For those visits where the questionnaires were completed by parents/carers only (n = 57/204, 27.9%), mainly because of the relatively younger age of patients (median age 5.8 years [IQR 4.1-7.1]), the correlation between disease activity and CHAQ-score was r = 0.29 (p = 0.032). The correlation between disease activity and QOL was r = -0.42 (p = 0.001), between disease activity and HRQOL was r = -0.61 (p < 0.001). In this registry, n = 26/204 (12.7%) questionnaires were completed by children accompanied with their parents/carers. The median age at recruitment for these patients was 12.1 years (IQR 10.4-13.8). For these visits (n = 26), there was no significant correlation found between disease activity and QOL (r = -0.20, p = 0.35). The correlation between disease activity and CHAQ-score was r = 0.40 (p = 0.045), between disease activity and HRQOL was r = 0.48 (p = 0.013).

4.5.3 Univariate analysis investigating BSPAR PROMs items

The univariate ordinal logistic regression analysis of the BSPAR questionnaire outcomes versus various predictors is presented in Table 3. When patients with high disease activity were compared with those with CID, they were three times more likely to report fatigue (OR 3.4, 95% CI 1.3-8.8, $p = 0.012$), 31 times more likely to report pain (OR 31.1, 95% CI 10.2-94.8, $p < 0.001$), three times more likely to report medication side effects (OR 3.2, 95% CI 1.2-8.7, $p = 0.02$) and four times more likely to report poor sleep (OR 3.7, 95% CI 1.3-10.1, $p = 0.012$). Patients who had high disease activity were 38 times more likely to report an interference with social activities (OR 38.2, 95% CI 15.5-93.8, $p < 0.001$) and 8 times more likely to report emotional problems, such as sad, worried or frustrated (OR 8.0, 95% CI 2.6-24.4, $p < 0.001$), than those who had CID. In the univariate analysis, the decile of the SEIFA score was only associated with reporting poor sleep (OR 0.9, 95% CI 0.8-1.0, $p = 0.018$).

Table 3. Ordinal logistic results of the BSPAR PROMs and PREMs questionnaire outcomes versus various predictors.

Outcome	**Predictor**	**Comparison**	**OR (95% CI)**	**Global *P*-value**
[Fatigue]	**Disease activity**	**HDA vs CID**	3.39 (1.30-8.83)	0.012
[Pain]	**Disease activity**	**HDA vs CID**	31.12 (10.22-94.76)	<0.001
[Medication]	**Disease activity**	**HDA vs CID**	3.23 (1.20-8.65)	0.020
[Sleep]	**Disease activity**	**HDA vs CID**	3.68 (1.34-10.12)	0.012
[Sleep]	**Rank within Australia - decile (SEIFA)**		0.87 (0.77-0.98)	0.018
[Social]	**Disease activity**	**HDA vs CID**	38.19 (15.55-93.83)	<0.001

[Emotional]	**Disease activity**	**HDA vs CID**	7.98 (2.62-24.37)	<0.001
[Understand]	**Disease Duration**		1.11 (1.02-1.22)	0.015
[Support]	**Disease activity**	**HDA vs CID**	3.34 (1.29-8.61)	0.010
[Environment]	**Disease activity**	**HDA vs CID**	3.68 (1.24-10.91)	0.038

Abbreviations: BSPAR: British Society for Paediatric and Adolescent Rheumatology; CI: confidence interval; CID: clinically inactive disease; HDA: high disease activity; OR: odds ratio; PREMs: patient-reported experience measures; PROMs: patient-reported outcome measures; SEIFA: socio-economic indexes for areas.

4.5.4 Univariate analysis investigating BSPAR PREMs items

The BSPAR PREMs questionnaire covers five domains (areas include being listened to, understanding treatment plan, feeling supported between visits, environment satisfaction and waiting time in being seen) with a score ranging from 0-3 and with higher score representing lower satisfaction on the item [22, 23]. Responses to the PREMs questionnaire for $n = 204$ clinic visits are represented by Fig 1. The majority of registry participants were satisfied with the clinic environment during their hospital visits (Fully 88.7%, Mostly 9.9%), whereas relatively fewer participants felt well supported in between hospital visits (Fully 76.0%, Mostly 16.7%). Responses of 'No delay' were classified into 'Acceptable delay' and took up the majority of visits ($n = 194/204$, 95.1%). Unacceptable delay was then classified into five groups from score = 1 (< 15-min delay) to score = 5 (> 2-hour delay). No participants had experienced a > 2-hour delay during the study period.

According to the significant results of ordinal logistic regression analysis of the BSPAR PREMs outcomes versus various predictors (Table 3), those children with high disease activity were three times more likely to report feeling less supported between visits than that of children with CID (OR 3.3, 95% CI 1.3-8.6, $p = 0.01$). Similar result was obtained for feeling less satisfied with the clinic environment (OR 3.7, 95% CI 1.2-10.9, $p = 0.038$). Additionally, for a one unit increase in disease duration, the odds of less understanding

of treatment plan were 1.1 times greater (OR 1.1, 95% CI 1.0-1.2, $p = 0.015$).

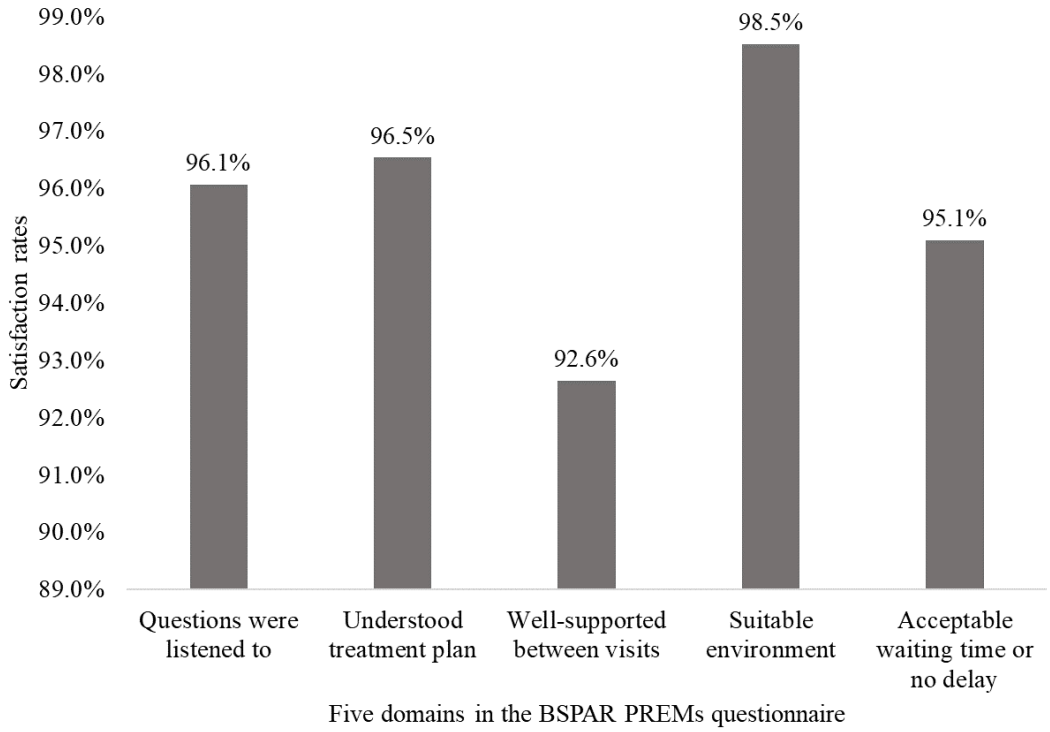

Fig 1. Satisfaction rates of BSPAR PREMs during $n = 204$ clinic visits.

4.6 Discussion

The present study is the first analysis to examine the relationships between disease activity and PROMs and PREMs in a JIA cohort in SA. All PROMs correlated with disease activity, whereas PREMs demonstrated a weaker correlation.

Overall, clinically measured disease activity was significantly correlated with traditional patient-reported outcomes, including QOL, HRQOL, functional disability and pain. However, the results also reflected the perception differences between patient and parent assessments of functional disability and QOL. In the current study, the correlation between disease activity and patient-reported CHAQ-score was stronger than those with parent-reported CHAQ-score. It may be due to the fact that patients themselves have a better perception of physical function than their parents. The discrepancy corresponds with the results of previous research that found parents and children often disagree about the extent of functional disability caused by arthritis [30]. Similarly, this result is also

supported and explained by April et, al. that some parents are not aware that their child's mobility is limited, especially for precision motor function [31]. On the other hand, it is possible that parents are likely to have a more accurate assessment of QOL and HRQOL than children, as evidenced by a stronger association with disease activity in parent- than patient-reported data. A study carried out in Poland by Mańczak et al. showed that parents' evaluation of QOL is lower than that of children and it may because various parameters are associated with QOL assessment, such as pain, emotional and social well-being, from parents' perspectives [32]. Moreover, other studies in part support this difference, finding that parent-child assessment agreement was lower in terms of pain, emotional functioning and well-being assessment. However, the findings of April et al. and Lundberg et al. suggested that parents evaluate QOL and/or HRQOL similarly to their children [31, 33]. Finally, considering there are no errors in either method [34], we advocate using both assessments in practice, but taking into account their respective biases.

Discordance between parent/patient- and physician- reported assessment of functional ability, pain, QOL, and CID in JIA have been well described in previous literature, with the physician tending to have a more optimistic view of these measures than the patient/parent [5, 7, 8, 35-37]. However, in this study, there was a good association between patient and physician assessment during active disease regarding functional ability, pain, QOL and HRQOL. By contrast, during CID, patients and/or parents still reported unmatched low QOL and functional ability. A study reporting similar results claimed that this discrepancy suggests an inaccuracy of measurement when the disease is inactive [20]. However, our findings suggest that such inconsistencies should raise concerns in professionals.

To our knowledge, this is the first report of the BSPAR questionnaire being used clinically outside the UK, the developer country. The implementation of patient-centered care in Australia and worldwide determines that subjective perceptions of patients are receiving unprecedented consideration. Patients and parents were involved in the design

process of the questionnaire [22]. Therefore, this questionnaire is qualified to collect the data that do matter to them in a short time. In this study, patient-reported outcomes measured by the novel BSPAR questionnaire [22] were associated with disease activity. The association is in line with expectations and it also verifies the applicability of this questionnaire to our population. Besides, it suggests that in addition to pain, the other five issues need extra concerns by healthcare providers to enhance better care. Previous literature found that fatigue, medication side effects, poor sleep, social and emotional problems are prevalent among patients with JIA and may have interactive effects [38-40]. Interestingly, fatigue, a unique key measure in this questionnaire, has been shown to be associated with pain, sleep, QOL and well-being in JIA patients and thus has been suggested to be considered in the holistic evaluation [41]. It, however, has not been included in previous routine questionnaires.

The relatively poor correlation between disease activity and PREMs indicates that current measures need to pay more attention to patients' subjective experiences and perceptions. By better recognition of patients' subjective experiences, the heterogeneity of JIA may be better addressed. This study found that patients with higher disease activity were more likely to feel less supported between visits. This may be attributed to the major psychological and social impacts on children and family by severe disease, as per previous literature [42, 43]. Further, it may be important to consider whether there was a potential reason that children felt unsupported because they have received insufficient assistance and this had led to high severity of their illness. To our best knowledge, no other studies have assessed PREMs in JIA populations. In addition, the BSPAR questionnaire has only been used in one clinical study [23]. The pioneering nature of this study has also led to the absence of comparable datasets.

In this study, the assessment of pain was included in two questionnaires, the CHAQ and the BSPAR questionnaire. Although the use of both questionnaires led to overlaps in the content of data collection, this repeated collection is meaningful due to the difference in time spans (a week versus a month) and types of measurement scales (VAS versus rating

scale).

The questionnaires used in the study were deemed suitable to be completed in the clinic environment, with the mean time to complete CHAQ ranging from 3.75-10 minutes, according to previous studies [44, 45]. The completion time for QoML of three items has been reported approximately less than five minutes [46]. In contrast, the BSPAR questionnaire encompassing more information has been reported as taking a median of no more than two minutes to complete [23].

Limitations identified in this study included follow-up visits for different patients not being particularly comparable, nor were the relationships between disease activity modifications and the number of follow-up visits explored. In the future, an inception cohort study regarding a long-term collection of disease data from patients with newly diagnosed JIA will compare the data in each visit to assess treatment and service. This study could examine the relationship between baseline disease activity score and improvement after interventions prescribed [47-50].

Although a small number of participants (n = 120) have been included in the registry due to regional characteristics and the limited time frame (in part due to COVID-19), all JIA patients attending the clinic were invited and all follow-up visits were recorded (n = 204). This enabled the continuity of information and assessment and avoided potential bias.

This outcome study partly demonstrated a direct relationship between clinical disease activity and PROMs and PREMs. Considering both PROMs and PREMs is essential to holistic assessment of patients by playing a supplementary role in clinical outcomes. Future work is needed to present a standardized patient-reported dataset in Australia and over the world.

4.7 Declarations

4.7.1 Declaration of Funding

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

4.7.2 Conflict of Interest Statement

The authors declare no conflicts of interest.

4.7.3 Acknowledgements

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Chapter 5. Thesis general discussion and future considerations

5.1 Summary

With the development of paediatric medicine and patient-centred health care, the course of arthritis has been well controlled, lives of children with JIA have been extended, but increasing new challenges are emerging. While addressing the initial stress in early diagnosis, modifications in the treatment plan, management strategy, and lifestyle can be more challenging for the wellbeing of patients and families. This thesis presents a systematic review evaluating qualitative evidence regarding the perspectives and experiences of children and families living with JIA. In addition, the first JIA registry in SA is established assessing disease activity and the status quo of treatment, as well as investigating the benefits/difficulties patients experience in living with JIA and receiving care. The following chapter will organise the discussion of results presented in the previous chapters and expand to allow further considerations in research and clinical care.

5.2 Significance and clinical impact

Based on the findings of the systematic review and registry study presented in this thesis, measures aimed at understanding patients' perspectives and experiences, either as qualitative methods or more rapid data acquisition using questionnaires, can help professionals to monitor disease activity and understand the discrepancies between patients- and clinical- measures. This highlights the need to conduct review studies analysing the qualitative findings, as well as registry studies collecting and examining patient-reported data in JIA.

In the systematic review (Chapter 2), we found that patients with JIA experience a variety of challenges in their daily lives and their experiences are determined mainly on the level of self-management of the disease. This agrees with other studies that found improved self-management improve outcomes [186, 187]. Similarly, self-management is

acknowledged as the key of living with immunodeficiency diseases [188]. In this dissertation, the obstacles that some parents and children encounter in developing self-management in JIA were presented, including lack of information and education. Our review findings are consistent with previous literature [189, 190].

Obtaining sufficient and pertinent knowledge and information on JIA, including symptoms, disease course, medications, and response to treatment is a prerequisite for optimising self-management in JIA [191]. However, this thesis (Chapter 2) found that healthcare professionals and patient families disagree on the availability of information sources. This may result in inadequate access to information, leading to difficulties in self-management and feelings of unsupported (Chapter 4). Research suggests that hospitals and healthcare professionals are the primary source for patients and parents to obtain information about JIA [192]. Therefore, the domains regarding "Information/education" and "Access/coordination of care" in the PREMs questionnaire (Chapter 4) can help professionals understand the perspectives of patients and reach an agreement, thus promoting effective communication and understanding [192, 193].

In this registry and single-centre study, a preliminary analysis of patient-reported outcomes and experiences was performed. To my knowledge, this is the first study to examine the relationships between routine clinical outcomes and patient-reported outcomes and experiences among JIA populations in the SA region. Findings from this thesis support that, for long-term management and optimal health outcomes, healthcare providers should not only treat symptoms, but also consider the subjective experience of patients when they deal with medical issues and provide medical services. The potential impact of patient-reported data on disease outcomes are considered further to achieve better wellbeing and future.

Reviewing published research on JIA, a limited number of studies focused on clinical characteristics and prognosis/outcomes of JIA patients, regardless of the research type, whether large observational studies or registry-associated studies. This shortage is even more obvious in SA. Moreover, comparable international studies on JIA are not adequate,

considering the differences in sample sizes and data collection modes (Chapter 3). The data collection in this dissertation (Chapter 3 & 4) utilised a collaborative mode from ANZ-CLARITY to provide valuable standardised data from a unique SA perspective.

In SA, this single-centre registry (Chapter 3 & 4) was initiated by the Paediatric Rheumatology Department at the WCH. Two major weaknesses of the current situation have been overcome with the establishment of this registry and ongoing data collection.

First, WCH serves as the major paediatric hospital and receives referrals from the whole of SA. The minority of JIA patients in SA are referred to private clinics but these patients are not included in the registry, given the differences in patient experiences. Previously, the health and medical records of JIA patients were kept on paper and physical file systems in the WCH. At present, the digital storage, access, and update of data through the construction of a patient registry bring about many benefits [169, 194]. For individuals, obtaining good care becomes easier and safer when records can be easily shared. In the event of an emergency, where questions need to be answered during the emergency decision-making process, clinicians have quick access to this registry. In addition, if hospitals across Australia share a JIA electronic registry system that allows records to be shared for patients in their health systems, a hospital can have an interstate access to the records made by a hospital in his or her hometown through the system.

Second, with the application of biological agents used for RA in paediatric rheumatology, the traditional treatment mode of JIA has changed and the outcomes of JIA children have been improved. More and more children are living longer with their symptoms and inflammations under control. Subsequently, the next issue is the subjective experiences and burden of children and families. In addition, the nature of JIA requires focusing not only on controlling the progress of the disease, but also on quality of life, medication side effects, psychosocial health, and the long-term outcomes [78, 127, 195, 196]. Among them, in the course of JIA, patients often present multiple functional somatic symptoms, such as fatigue, sleep difficulties and gastrointestinal discomfort [197, 198]. This is supported by the results of this thesis (Chapter 2 - 4), which indicated that a cluster

of patients report the aforesaid symptoms in their view. In the WCH, the establishment of the JIA registry enables systematic and longitudinal comparison and analysis of the information. This guarantees a better documentation and accelerates the corresponding procedures.

In this thesis, medication side effects were investigated throughout Chapter 2 - 4. The systematic review (Chapter 2) found that the majority of patient-reported medication side effects and negative experiences are involved in MTX. In the SA JIA cohort, we have identified that most of the physician-reported side effects are related to MTX, and among them, gastrointestinal and psychological reactions are the most common, which is consistent with a recent paper [199]. Moreover, this latest paper ascertains that parents reported more side effects than their physicians [199], which demonstrates an urgent need to include patient-reported side effects in the holistic assessment and management (Chapter 3 & 4). To my knowledge, there is no systematic review to date of patient-reported medication side effects and the associations with HRQOL in JIA.

Of note, the "medication side effects" domain in the PROMs questionnaire (Chapter 4) directly help physicians notice if a patient has recently experienced side effects of medications, and provide timely assistance in medication management and information sharing with other patients. The importance of information exchange with other experienced patients is highlighted in previous literature and our previous research (Chapter 2), that it may assist in anticipation of disease courses and management of pain and medications [200]. Although young patients and parents are aware of and appreciate JIA-related online platforms and programs, not all have access to or use them for information [200]. More websites and apps regulated by the government and authorities are needed.

Although the results of our study (Chapter 3) showed that most of the patients with JIA in SA have good disease control, the results from Chapter 4 provided evidence that social activities of the patients with high disease activity are greatly interfered with. Results from the systematic review (Chapter 2) suggested the importance of a healthy and

balanced social life for JIA patients, especially for older children and adolescents. Other studies are consistent with this, suggesting that patients with JIA benefit from healthy and positive friendships and social activities [78, 189]. However, pain and pain avoidance may affect a patient's willingness to participate in social activities [201, 202]. This is also supported by the great distinction in patient-reported pain between patients with high disease activity and those with inactive disease (Chapter 4).

5.3 Implications for future research

A major challenge for registry development is consistency between agreements on data collection items. The current study (Chapter 3 & 4) utilised the clinician questionnaire of ANZ-CLARITY (unpublished, https://www.mcri.edu.au/clarity) to collect data at our clinic. It is easier to form domestic and international collaborations with other studies and registries at least from across Australia and New Zealand. Furthermore, QOL, pain, functional ability, medication side effects, social and psychological health were assessed in this study (Chapter 3 & 4). This is consistent with the results of the thesis (Chapter 2) and other literature [78, 127, 195, 196]. Further inclusion of other items will be enabled by the development of data collection tools and continuous clinical practice.

In the future, comparisons in terms of life experience data will enable further analyses on the difference between different ethnic groups and regions. Individual experiences, as personalised data, will be combined with clinical, genetic, microbial data, etc. for holistic care and management in JIA. For example, novel federated learning approach can be applied to JIA research to protect sensitive data and patient privacy and build a registry network research worldwide [203]. This study developed a prognostic model in RA by the integration and analysis of electronic health record data from two health care systems [203], which also suggested a promising trend in JIA research.

During the time of data collection for this study (Chapter 3 & 4), Coronavirus 19 disease (COVID-19) became a global issue [204], which hindered the data collection for our clinical studies. Given the protective effects of immunosuppressive agents on COVID-19, we are concerned about the impact of COVID-19 on patients with JIA [205].

However, a recent research shows that patients treated with DMARDs are no more likely to experience a high risk of COVID-19 than others [206]. Research on other medications in addition to DMARDs is needed to determine how to manage immunosuppressive therapies on patients with JIA and other rheumatic diseases during the pandemic time.

5.4 Thesis conclusion

In summary, this is the first study in SA to explore the development of a registry for patients with JIA. Since JIA occurs in an earlier stage of life with no established cure, it can cause long-lasting damage impacting on the physical and mental health and social wellbeing of patients as well as their families. Therefore, in clinical practice, understanding the evaluation of patients and their families on the disease outcomes and treatment and their understanding of medication management are beneficial to a better doctor-patient communication and better disease prognosis. Outside the clinic, concerning patients' experiences, their physical and mental difficulties, their understanding of the disease and the future assist in optimising patient self-management and thus promoting a better life living with JIA. The results of the systemic review on experiences of living with JIA (Chapter 2) identified that considering patient-reported experiences and needs is an important part of overall management in JIA. The establishment of registry and initial analysis presented in the subsequent studies (Chapter 3 & 4) further highlight PROMs and PREMs in describing characteristics and assess treatment in a JIA cohort. The results suggest that incorporating PROMs and PREMs in addition to clinical disease activity measures can improve understanding around patient outcomes and quality of care. Additional investigations will need to address the longitudinal impacts of PROMs and PREMs on disease management and health outcomes, with ongoing data collection.

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Appendix I. Experiences of living with juvenile idiopathic arthritis: a qualitative systematic review protocol

Statement of Authorship

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Principal Author

Name of Principal Author (Candidate)	Ming Min		
Contribution to the Paper	First author and main contributor. Study conception and design, investigation, data collection, formulation of draft and reviewing and incorporating co-author comments and suggestions.		
Overall percentage (%)	70%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	14/05/2021

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	David G. Hancock		
Contribution to the Paper	Co-reviewer. Investigation, methodology, initial data collection and analysis, and review of the manuscript.		
Signature		Date	14/05/2021

Name of Co-Author	Edoardo Aromataris		
Contribution to the Paper	Concept and methodological design, methodology, planning and supervision of the work, review of the manuscript.		
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Please cut and paste additional co-author panels here as required.

Name of Co-Author	Tania Crotti		
Contribution to the Paper	Study concept and design, methodology, supervision of the work and review of the manuscript.		
Signature		Date	14/05/21

Name of Co-Author	Christina Boros		
Contribution to the Paper	Study concept and design,Investigation, methodology, initial data collection, planning and supervision of the work, review of the manuscript. Due to illness Dr Christina Boros is on long term leave. A/Prof Crotti has signed on her behalf		
Signature		Date	14/05/21

Name of Co-Author			
Contribution to the Paper			
Signature		Date	

Experiences of living with juvenile idiopathic arthritis: a qualitative systematic review protocol

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Abstract

Objective: The objective of this review is to identify, critically appraise and synthesize the available qualitative evidence to understand the experiences of children, young adults and their carers living with juvenile idiopathic arthritis (JIA) in any setting.

Introduction: Juvenile idiopathic arthritis is the most common rheumatic disease in childhood. Despite the availability of effective treatments, disease still have negative impacts on patients' and carers' lives. Patients' and carers' experiences of living with JIA have been recognized as important in the measurement of health status and treatment implementation. Addressing these needs will facilitate more effective management and treatment of the disease. This protocol describes a method for a systematic review regarding the perspectives from patients and carers in order to highlight the needs of families throughout their JIA journey.

Inclusion criteria: Studies on the experiences of patients aged <21 years who have been diagnosed with JIA according to the International League of Associations for Rheumatology criteria, as well as the experiences of their carers, will be considered. Papers included in this review will include but not be limited to designs such as phenomenology, grounded theory and ethnography.

Methods: A comprehensive search using PubMed, CINAHL, Embase, PsycINFO and Web of Science was undertaken in August 2019. Available studies published in English from 2001 to 2019 will be included. The recommended JBI method to study selection, critical appraisal, data extraction and data synthesis will be used.

Systematic review registration number: CRD42019133165

Keywords: Children and young adults; experience; juvenile idiopathic arthritis; parents and carers; views

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic rheumatic disease that occurs in childhood. It is characterized by arthritis of unknown cause with onset before 16 years of age, and has persistent symptoms for at least six weeks.[1] There are seven different subtypes according to the International League of Associations for Rheumatology (ILAR) classification criteria.[1] The prevalence and incidence of JIA varies in different regions. Studies report a prevalence of JIA in European Caucasians as 32.6 / 100,000,[2] although less than 1% of Australian children are affected.[3] This prevalence estimate, however, may be underestimated since many cases are undiagnosed.

Although major advances have been made in the treatment of JIA, patients experience reduced quality of life (QoL) even when arthritis is well controlled.[4] Thus, the experience of living with JIA needs to be considered in the holistic management of patients.

Physical damage and functional disability have been identified as the main contributors to poor outcomes in JIA patients, and can last for a lifetime, with half of these children still maintaining active disease as adults.[5, 6] Joint-related complications include permanent joint damage and deformity, growth retardation and osteopenia.[6] Extra-articular complications such as uveitis (eye inflammation), also impact upon lifestyle and wellbeing. Uveitis affects approximately 10% of JIA patients, and if untreated can lead to blindness and an associated reduction in QoL.[7]

Reduced QoL is attributed to not only chronic and recurrent pain experienced by patients with JIA, but also to restrictions on participation at school, daily physical activities and social events. Thus, critical to understanding the patient experience is the recognition that, in addition to pain and physical limitations, children with JIA may also experience depression, anxiety, fatigue, stress, family dysfunction as well as school and workplace discrimination.[8] In addition, although educational achievement of JIA patients is comparable to that of healthy children,[9] patients can also experience a higher unemployment rate.[10] These findings suggest that psychosocial support needs to be given sufficient priority in the treatment of JIA patients.

Pain, depression and social problems can still occur in JIA patients whose disease is well controlled.[4] Patient views regarding what constitutes well-controlled disease may differ from the information obtained by laboratory and imaging tests or from the opinions of healthcare providers.[11] In order to better recognize the importance of patients' perspectives, multidimensional measurements are required, so that the patients themselves may be better equipped to identify subtle changes in disease status.

Some studies have investigated and described the experiences of carers in caring for children and adolescents with JIA.[12] The domains generated by the authors included emotional turmoil,

financial burden, difficulties in continuing work and lack of social support.[12] Parents and other family members may also experience significant emotional distress at seeing their children suffer, supervising injections, monitoring disease and communicating with healthcare team members and teachers.[13] Additionally, the incorporation of the varying values, experiences and priorities of patients and carers can improve their treatment adherence and satisfaction, and optimize health outcomes.[14] Thus, experiences reported by patients and families play increasingly important roles in the measurement of overall health outcomes and the successful management of JIA.

With the revolution of personalized medicine, combined with participant-driven care, the importance of QoL and patient participation in decision making has been increasingly acknowledged and studied. In Australia, patient-and-family-centered care has been established as one of the guiding principles in improving JIA care.[15] According to the American College of Rheumatology (ACR) guidelines, the decision-making process should be based on the participation of patients, and account for patients' values, preferences and comorbidities.[16] Similarly, other international published guidelines for JIA management (the British Standards of Care, BSAPR; the Canadian Rheumatology Association, CRA) also stated the importance of informed choices and patient-centered care.[17,18] However, patient and carer self-reported data has not been consistently included in these recommendations.

Healthcare providers need to identify changing patient needs during disease course and adapt treatment accordingly. Patient-related tools, such as patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs), can be used to capture information from patients' and carers' perspectives in the context of disease and management.[19] Information such as self-reported pain, functional ability, and health-related QoL can help healthcare providers to determine when treatment plans require adjustment.[20] However, very few of these validated tools are readily utilized in the clinical environment. If widely used in the clinical settings, these tools can facilitate more effective management and treatment of disease.

A preliminary search of MEDLINE, PROSPERO, the Cochrane Database of Systematic Reviews and the *JBI Database of Systematic Reviews and Implementation Reports* was conducted. A systematic review was conducted by Tong et al.[21] in 2012 to address a similar issue, but it did not include eligible studies from recent years. Also, this review considered patients' experiences but did not include those of carers. Although multiple diagnostic criteria were considered in this review, it failed to focus on the experiences of patients who have been diagnosed with JIA according to the ILAR criteria. Cavallo et al.[22] systematically reviewed social and physical leisure activities of JIA patients, but only included quantitative studies. A systematic review by Stinson et al.[23] examined evidence about sleep disturbances in children

with JIA and associated prognostic factors. This review highlighted that JIA patients appear to have poor sleep when compared to healthy children. However, disease-related experiences other than sleep disturbances was not in the scope of this review. A systematic review protocol by Saetes et al.[24] examined family resilience of JIA patients with chronic or recurrent pain. In this protocol, although family members were considered, inconsistencies between the aims/outcomes and the electronic searches in this paper may have biased their findings. For example, the authors cared about resilience regarding academic and communication, but did not include relevant keywords in the searches. Finally, a 2019 meta-analysis by Bourdier et al.[25] analyzed physical activity level and sedentary behaviors in patients with JIA or inflammatory bowel disease (IBD), compared to healthy children. However, this meta-analysis failed to examine the qualitative aspects of the included studies. Overall, although the findings of existing reviews have provided a significant overview and knowledge base regarding the lived experiences of JIA patients and parents, a number of gaps exist as stated.

This review aims to provide a comprehensive understanding of JIA patients' and carers' experiences of living with JIA.

Review question(s)

The questions to be answered by this review are the following:

- What are the experiences of children and young adults living with JIA?
- What are the experiences of their carers?

Inclusion criteria

Participants

The review will consider studies that include the experiences of patients aged <21 years who have been diagnosed with JIA according to ILAR criteria. Studies including the experiences of carers in managing JIA in children and young adults, as well as their interpretation of the children's experiences, will be considered.

Phenomena of interest

The review will consider studies that describe the experiences of JIA patients and of their carers. These include physical and/or psychosocial experiences, psychological reactions, financial burden, and disease complications. In addition, studies that investigate patient/carers ability to manage disease, school and social activities, as well as met and unmet needs, will be included. Carers' interpretation of their child's experience will also be considered.

Context

Studies conducted in any country will be included in the review. All lived experiences of JIA will be considered, independent of the location of the primary study's participants, (e.g. home, clinics, hospitals and community settings).

Types of studies

The review will include empirical qualitative studies including, but not limited to, designs based on phenomenology, grounded theory and ethnography. Descriptive qualitative studies that focus on the experience will also be considered. Studies will be limited to those published in English (full papers), as we lack resources for translation, and the meaning of qualitative data can be lost or modified by translation.[26]

Editorials, non-research articles and observational epidemiologic studies are considered to be outside the scope of our study.

The search strategy will be limited to studies from 2001, to align with publication of the revised ILAR JIA classification criteria.[1]

Methods

This proposed systematic review will be conducted in accordance with the JBI methodology for systematic reviews of qualitative evidence.[27] The protocol was registered with PROSPERO with the registration number: CRD42019133165.

Search strategy

The search strategy will aim to find both published and unpublished studies. A three-step search strategy will be utilized.

An initial limited search of PubMed and Embase (Elsevier) was undertaken to identify articles on the topic, followed by an analysis of text words contained in the title and abstract, and of the index terms used to describe the articles. This informed the development of a search strategy which will be tailored for each information source.

A second search using all identified keywords and index terms will then be undertaken across each included database. Searches will be developed and combined using broad search terms, key words, medical subject headings (MeSH)/Emtree and filters. The search for qualitative research will be combined with these terms: experience, impression, perspective, attitude, outlook, viewpoint, perception, insight, perceived and understanding. Details about the full

search strategy for PubMed are presented in Appendix I. The search strategy will be adapted for each source database, including all identified keywords and corresponding index terms.

Finally, the reference list of all identified studies selected for critical appraisal will be screened for additional and potential studies. Citations of all included studies will also be searched for additional studies and considered for inclusion.

Information sources

The databases to be searched include: PubMed, Embase (Elsevier), Web of Science (Clarivate), CINAHL (EBSCO) and PsycINFO (Ovid). The search for gray literature will include Google Scholar and conference proceedings of ACR and the Australian Rheumatology Association (ARA) (2018–2019), with keywords of “JIA and qualitative or experience”.

Study selection

Following the search, all identified citations will be collated and uploaded into EndNote X8.2 (Clarivate Analytics, PA, USA), and duplicates removed.

The article selection will be conducted in three steps. The first step is citation screening, in which the titles and abstracts of articles identified from the indicated electronic database and Internet searches will be screened by one reviewer (MM). In the second step, the titles and abstracts of the results of citation screening will be manually reviewed by two reviewers (MM and DH). In the third step, the full-text of articles selected from the previous step will be obtained and screened for eligibility by two reviewers (MM and DH) independently.

After the search and preliminary screening phases, potentially relevant studies will be retrieved in full and their citation details imported into the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI SUMARI) (JBI, Adelaide, Australia).[27] The full text of selected citations will be assessed in detail against the inclusion criteria by two independent reviewers (MM and DH). Reasons for excluding any full-text studies will be recorded in detail.

At any phase of the article selection process, disagreements about the inclusion or exclusion of the studies between the reviewers will be resolved through consensus discussion, or with the third reviewer (CB). The study processes and results of study selection will be reported in the final review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[28]

Assessment of methodological quality

In order to appraise the methodological quality of studies, two reviewers (MM & DH) will critically appraise all eligible studies, using the standard JBI critical appraisal checklist for qualitative research.[29] A group meeting will be held with three reviewers (MM, DH and CB) in order to achieve consensus when discrepancies arise between reviewers. Authors of papers will be contacted to request missing or additional data for clarification. A narrative report will be generated to summarize the results of this part (i.e. critical appraisal). Studies rated as “no” or “unclear” in three or more of the 10 questions (30% or greater) on the critical appraisal tool will be excluded, to ensure that only rigorous research informs the synthesized findings of this review.

Data extraction

Data will be extracted independently by two reviewers (MM and DH), using the standardized JJBI data extraction tool integrated in JBI-SUMARI.[27] Another reviewer (CB) will join in the data extraction process to resolve disagreements that arise between the first two reviewers. The qualitative data extracted in this study will relate to: populations, context setting, geographical location, culture, study methods and the phenomena of interest (patients' and/or carers' experience of living with JIA) and other information that may be relevant to the review questions and specific objective. Findings, and their illustrations, will be extracted and assigned a level of credibility.[30] If relevant findings of primary studies that are eligible for the review are not available, attempts will be made to contact the corresponding authors, except those over 10 years since publication.

Data synthesis

To present the main findings of this systematic review, qualitative research findings will be pooled using JBI-SUMARI with the meta-aggregation approach. Meta-aggregation[29] will be performed involving the aggregation or synthesis of findings to generate a set of statements that represent that aggregation, through assembling the findings (level 1 findings), and categorizing these findings on the basis of similarity in meaning (level 2 findings). These categories will then be subjected to a meta-synthesis in order to produce a single comprehensive set of synthesized findings (level 3 findings) that can be used as a basis for evidence-based practice. Where textual pooling is not possible, the findings will be presented in narrative form.

Assessing confidence in the findings

To establish confidence in the synthesized findings of the qualitative review, the grade of each finding will be determined using the ConQual approach.[30] The Summary of Findings table will include the major elements of the review and details how the ConQual score is developed. Included in the table will be the title, population, phenomena of interest and context for the specific review. Each synthesized finding from the review will be presented, along with the type of research informing it, score for dependability and credibility and the overall ConQual score.

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Conflicts of interest

EA is Editor-in-Chief of *JBI Database of Systematic Reviews and Implementation Reports*; he has been blinded to the editorial process associated with this manuscript.

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Appendix I: Search strategy

PubMed: #1 + #2 + #3 = 1172 results

Searched conducted on 24 August 2019 through PubMed's own platform.

Search	Query
#1	experience*[tiab] OR impression*[tiab] OR attitude*[tiab] OR outlook*[tiab] OR viewpoint*[tiab] OR perception*[tiab] OR insight*[tiab] OR perspective*[tiab] OR perceived[tiab] OR understanding*[tiab] OR Attitude[mh] OR Perception[mh] OR qualitative research[tiab] OR qualitative study[tiab] OR qualitative studies[tiab] OR qualitative method*[tiab] OR interviews[tiab] OR interview[tiab] OR ethnograph*[tiab] OR phenomenol*[tiab] OR focus group*[tiab] OR grounded theory[tiab] OR Qualitative Research[mh] OR Focus Groups[mh] OR Interviews as Topic[mh]
#2	Infant, Newborn[mh] OR Infant[mh] OR Child, Preschool[mh] OR Child[mh] OR Adolescent[mh] OR Young Adult[mh] OR Parents[mh] OR Caregivers[mh] OR Family[mh] OR baby[tiab] OR babies[tiab] OR kid[tiab] OR kids[tiab] OR infant*[tiab] OR child*[tiab] OR youth*[tiab] OR teenage*[tiab] OR adolescent*[tiab] OR parent*[tiab] OR carer*[tiab] OR caregiver*[tiab] OR father*[tiab] OR mother*[tiab] OR young people[tiab] OR CYP[tiab] OR family[tiab] OR families[tiab] OR boy*[tiab] OR young adult*[tiab] OR girl*[tiab] OR AYA[tiab]
#3	Arthritis, Juvenile[mh] OR JIA[tiab] OR juvenile idiopathic arthritis[tiab] OR oligoarthritis[tiab] OR polyarthritis[tiab] OR psoriatic arthritis[tiab] OR enthesitis-related arthritis[tiab] OR systemic arthritis[tiab] OR systemic onset arthritis[tiab]
#4	#1 AND #2 AND #3
Limited to English language & Publication date from 2001 to present	