LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Clínica Universitária de Reumatologia

Disease Activity Measures in Adult Patients with JIA: a Systematic Review

Marta Croca Morais

Orientado por:

Drª. Filipa Oliveira Ramos

Coorientado por:

Profº. Doutor Ricardo Cunha Fernandes

Maio'2023

Resumo

A Artrite Idiopática Juvenil (AIJ) é um termo que engloba várias doenças reumáticas crónicas de causa desconhecida e que, no seu conjunto, são as doenças reumáticas crónicas mais comuns na criança que, com frequência, se mantêm ativas na idade adulta. Contudo, não existem critérios específicos validados para medir a atividade da doença em adultos com AIJ, nem recomendações para o tratamento em idade adulta, o que pode ter um impacto negativo importante na transição de cuidados destes doentes para os serviços de adultos. Estudos prévios e revisões sistemáticas, de intervenções terapêuticas focaram-se na idade pediátrica, incluindo na seleção e medição de outcomes.

O nosso objetivo é perceber quais são as escalas mais usadas para medir a atividade da doença, em doentes adultos com AIJ, ao longo do tempo.

Realizámos uma revisão sistemática da literatura reportada de acordo com os critérios PRISMA. A pesquisa foi realizada via MEDLINE e Web of Science para estudos originais em inglês, na população com AIJ e mais de 18 anos, publicados depois dos anos 2000.

69 artigos cumpriram os critérios de inclusão. 53,6% mediram a atividade da doença com um único método, enquanto 46,4% utilizaram mais que um. 56,5% utilizaram Physician's Global Assessement nesta medição. As escalas mais usadas foram: 43,9% American College of Rheumatology Pediatric criteria (ACR), 27,3% Juvenile Arthritis Disease Activity (JADAS), 15,2% Disease Activity Score (DAS28), 10,6% Wallace Criteria, 1,5% 11- point Numeric Pain Rating Scale (NRS-0-10) e 1,5% Six-point Composite Disease Activity Index (mJPsADA). Entre 2022-2009 a proporção foi semelhante, enquanto antes de 2009 a única escala usada foi o ACR. 65,5% utilizaram o ACR em associação com outra escala, sendo as mais comuns o PGA e o JADAS. 83,3% utilizaram o JADAS em associação com outro método, sendo neste caso, os mais comuns o PGA e ACR. A versão do JADAS mais utilizada foi JADAS71 e JADAS27 (27,8% cada). A avaliação da atividade da doença na AIJ Oligoarticular, Poliarticular e Sistémica teve uma utilização de escalas semelhante. Relativamente às restantes categorias de AIJ, o número de

estudos foi limitativo para uma generalização. Um dos artigos concluiu que o JADAS27 é mais fidedigno que o DAS28 na avaliação da atividade da doença e outro artigo defendeu que o JADAS10 é um melhor parâmetro a refletir doença ativa que o DAS28 em doentes adultos com AIJ.

Assim, a evidência suporta que, apesar de o ACR ser, globalmente, o método mais utilizado, o JADAS teve um crescimento exponencial depois de 2009. A generalização da utilização do JADAS, juntamente com alguma evidência que lhe atribui melhor desempenho que outras ferramentas, torna-o o melhor candidato para ser validada na AIJ em idade adulta.

Palavras-Chave: Artrite Idiopática Juvenil, Atividade da Doença, Adulto

Abstract

Juvenile Idiopathic Arthritis (JIA) is the most common chronic rheumatic disease in children with an unknown cause, which, frequently, continues active into adulthood. However, there is no specific criteria to measure disease activity and there is an absence of specific treatment recommendations in patients over 18 years old which can have a negative impact in the transition of these patients to adult care.

Previous studies and systematic reviews focused on paediatric population, therefore, our aim is to understand which are the scales used to measure disease activity in adult patients with JIA throughout times.

We conducted a systematic review in accordance with PRISMA. The electronic database search was MEDLINE and Web of Science focused on original studies in English, with JIA patients over 18 years old, published after the year of 2000.

69 articles met the inclusion criteria for review. 53,6% assessed disease activity based on a single method, while 46,4% used more than one. 56,5% utilized Physician's Global Assessment to evaluate disease activity. The most used scales were 43,9% American College of Rheumatology Pediatric criteria (ACR), 27,3% Juvenile Arthritis Disease Activity (JADAS), 15,2% Disease Activity Score (DAS28), 10,6% Wallace Criteria, 1,5% 11-point Numeric Pain Rating Scale (NRS-0-10) and 1,5% Six-point Composite Disease Activity Index (mJPsADA). Between 2022-2009 the proportion was similar, whereas prior to 2009 the only scale utilized was ACR. 65,5% used ACR in association with another scale, being the most used PGA and JADAS. 83,3% used JADAS in association with another method, most frequently PGA and ACR. The most used version of JADAS was JADAS71 and JADAS27 (27,8% each). Oligoarticular, Polyarticular and Systemic JIA followed a similar utilization of scales to measure disease activity, the others categories of JIA did not have a significant number of studies attributed for a generalization. One of the articles concluded that JADAS27 was more accurate than DAS28 in measuring disease activity in adult population and another one that JADAS10 was a better reflector of active disease than DAS28.

Therefore, evidence supports that even though ACR is globally the most used method to measure disease activity, JADAS had an exponential increase after 2009. The generalization of JADAS, and the scientific evidence that demonstrates its better performance, makes it the better candidate to validate in adult population with JIA.

Keywords: Juvenile Idiopathic Arthritis, Disease activity, Adulthood

Index

Introduction

Juvenile Idiopathic Arthritis (JIA) is an umbrella term covering chronic arthritis in children with an unknown cause, which in most cases continues throughout adulthood (Barut *et al*., 2017).

JIA is defined as a group of chronic arthritis of unknown etiology, with onset prior to 16 years old, that persists for at least 6 weeks when other conditions are excluded. The definitive diagnosis may take time to be established due to the insidious course of the disease (Okamoto *et al*., 2019).

There are different categories of JIA, mainly subdivided by demographic characteristics, clinical features, treatment, and disease prognosis (Barut *et al*., 2017). According to the Paediatric Standing Committee of the International League of Associations for Rheumatology (ILAR), there are 7 categories of JIA: Oligoarticular, Polyarticular rheumatoid factor (RF) positive, Polyarticular RF negative, Systemic onset, Enthesitis-related arthritis (ERA), Psoriatic Arthritis and Undifferentiated JIA (Okamoto *et al*., 2019).

JIA is associated with considerable morbidity, as a result of articular and extra-articular manifestations, damage and chronic disability (Conti *et al*., 2018; Moorthy *et al*., 2010; Ravelli & Martini, 2007). This can lead to serious impairment of physical function and health-related quality of life (Oliveira Ramos *et al*., 2021; Trincianti & Consolaro, 2020).

Implementation of treatment with a multidisciplinary team is an important and significant process to start, as soon as possible, in JIA patients. The main objectives are to control disease activity, normalize joint function, preserve normal growth, and prevent long-term joint damage (Barut *et al*., 2017).

Currently, JIA treatment is based on a treat-to-target strategy, for which it is essential to measure disease activity with tools that allow the definition of the target (Ravelli *et al*., 2018). There are multiple assessment tools used in a paediatric population such as Physician's Global Assessment (PGA) based on a Visual Analogue Scale or Likert

Scale, number of active joints, laboratory parameters such as erythrocytes, leucocytes and platelets count, erythrocyte sedimentation rate (ERS) and C-reactive protein (CRP). Many instruments to measure disease activity have been implemented in a paediatric population such as American College of Rheumatology Pediatric criteria (ACR) and, more recently, Juvenile Arthritis Disease Activity Score (JADAS) (Barut *et al*., 2017).

The ACR Pedi item set includes 6 measures, namely physician global assessment of disease activity, parent/patient assessment of well-being, active joint count, restricted joint count, functional assessment, and laboratory measure of inflammation (Consolaro *et al*., 2009).

JADAS was the first disease activity score developed specifically for JIA in 2009, based on parameters used in ACR Pedi (Trincianti & Consolaro, 2020). It includes 4 measures from the scale mentioned previously: physician global assessment of disease activity measured on a 10cm visual analogue scale (VAS), parent/patient assessment of well-being, active joint count and erythrocyte sedimentation rate (Consolaro *et al*., 2009).

More than 4500 patients with median age at study visit of 10.6 years old were included in the Consolaro *et al.*, 2009 JADAS validation study. The performance of JADAS was compared with Disease Activity Score (DAS28) and Clinical Disease Activity Index (CDAI) and showed effectiveness for standard clinical applications, observational studies, and clinical trials (Consolaro *et al*., 2009).

In the course of validation, three versions of the original JADAS were developed: JADAS10, JADAS27 and JADAS71, where the difference relays on the number of active joints included (Trincianti & Consolaro, 2020).

In 2012, McErlane *et al*. validated a three-item version of JADAS. In this new version, they excluded ESR and CRP since they are not routinely used and created a clinical JADAS. They used a paediatric population with a median study visit age of 6.6 years old with a total of 956 patients, creating JADAS3-10, JADAS3-27 and JADAS3-71, currently named cJADAS, cJADAS-10, cJADAS-27 and cJADAS-71 (Consolaro *et al*., 2016; McErlane *et al*., 2013).

In 2015, E. B. Nordal *et al*. substituted ESR with CRP in JADAS and validated JADAS-CRP, in a study with 389 patients with median age at study visit of 9.7 years old, creating JADAS10-CRP, JADAS27-CRP and JADAS71-CRP (Consolaro et al., 2016; E. B. Nordal et al., 2012).

Nowadays, JADAS has three different main validated versions: classic JADAS, cJADAS and JADAS-CRP and for each of them the 71, 27 or 10 versions according to the number of evaluated joints (Consolaro *et al*., 2016).

The course of JIA continues into adulthood with active disease in more than 50% of the patients (Oliveira-Ramos *et al*., 2016). The transition to an adult health care facility is a critic moment with impact in future outcomes of these patients (Hazel *et al*., 2010; Stringer *et al*., 2015). However, many of the patients have a challenging transition which places them at risk for negative consequences (Hazel *et al*., 2010; Stringer *et al*., 2015). Some of the reasons for this poor capacity on following up adult patients with JIA are the differences among the terminology of chronic arthritis between children and adults, the absence of a specific criteria to measure disease activity and the absence of specific recommendations for treatment and follow up of this population (Conti *et al*., 2018).

Despite the similarities between Rheumatoid Arthritis (RA) and some forms of JIA, JIA is very heterogenous, and management of RA should not be used as guidance to all JIA categories, despite the recurrent use of RA assessment tools, by some doctors, for disease activity for adults with JIA (Conti *et al*., 2018) .

Therefore, with this systematic review we aimed to assess the scales used to measure disease activity in adult patients with JIA longitudinally.

Methods

This systematic review is reported in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 (Page *et al*., 2021).

Sources of Information

We conducted multiple electronic databases searches in MEDLINE (via Pubmed) and Web of Science, over 5 months, in order to identify literature that measured, as primary or secondary outcome, disease activity in adults with JIA.

1.1. Inclusion and Exclusion Criteria

We included studies in English with patients 18 years old or older, diagnosed with Juvenile Idiopathic Arthritis, regardless of the JIA category.

We only included originals articles, described according to Pubmed, as Clinical Trials, Clinical Studies, Controlled Clinical Trials, Multicenter Studies, Observational Studies and Randomized Controlled Trials. We excluded all the articles that were not in humans, and that were prior to the year 2000 due to scientific advances.

1.2. Search, Selection, Data Collection and Analysis

Search Strategy

The search was performed using the following keywords: “Juvenile Idiopathic Arthritis”, “Adult”, “Adulthood”, “Disease Activity” and “Outcome”.

The controlled specific vocabulary of each database was also used (e.g; MESH in MEDLINE).

Selection of Studies

Studies were initially selected based on their title and abstract by one author. All papers that could potentially match the inclusion criteria were critically read and their data was extracted using purpose-made data-extraction tables to support final selection. The articles were not blinded for author, affiliation or source.

After one initial screening on databases, the studies were uploaded to Mendeley, where they were screened to determinate if they met the inclusion criteria.

For that we answered these questions:

1. Is this an original study?
2. Is this a population with JIA patients?
3. Does this study cover an adult population, over 18 years old?
4. Does this study measure disease activity?

If the inclusion criteria were not met, the study was excluded. If by the abstract, we could not understand if patients were over 18 years old or if it measured disease activity, the study passed to the next phase of screening. If the study met some or all the inclusion criteria it, also passed to the next phase of screening.

In order to not dismiss any important study, a second abstract screening in the excluded studies was made based on these questions.

All the studies that fulfilled the previous criteria were fully analysed and read manually by one reviewer. The reviewer confirmed the eligibility and pointed out the important information data extraction. When articles were selected for inclusion, their bibliographies were also screened for further relevant articles.

Data Extraction

One reviewer extracted the relevant data that was considered eligible and included the information in a tailored table. Data extraction consisted of:

- First author and Year;
- Country;
- Sample size;
- Type of study;
- Years/Age of the population;
- JIA categories included;
- Disease activity assessment tool;
- Other outcomes assessment tools;
- Objective of the Study;
- Disease activity as a primary or secondary outcome;
- Study outcome.

Quality Assessment Risk of Bias

We did not perform risk of bias assessments as this review was focused on identifying measurement tools, and not on assessing the efficacy or safety of any interventions.

Data Synthesis

We used IBM SPSS Statistics (version 26) for statistical analysis.

A descriptive analysis of the initial variables was performed, and more variables were generated through cross-tables. We obtained the average for the quantitative variables, as well as the frequency and percentages for the qualitative variables.

Firstly, we analysed which articles used only one method to evaluate disease activity and which used more than one tool. Afterwards, we examined the use of PGA over time, and we established two-time frames: prior to 2009 and between 2009 and 2022, based on the creation and validation of JADAS.

Then, we analysed the most used scale over time and the differences over the two-time frames.

After examining the most used scales, we conducted a detailed search for each scale, that included: how studies used that scale, in association or as a single scale; which scales were used in association; the specific categories of JIA that used that scale and if the scale was used in a study with a primary or secondary outcome. For JADAS and DAS28, we also analysed the different versions used. Due to the subjectivity of PGA, we did not consider this method to measure disease activity in this part of the analysis.

Afterwards, we scanned the articles in search for those which compared the different scales, and we analysed and summarized these results.

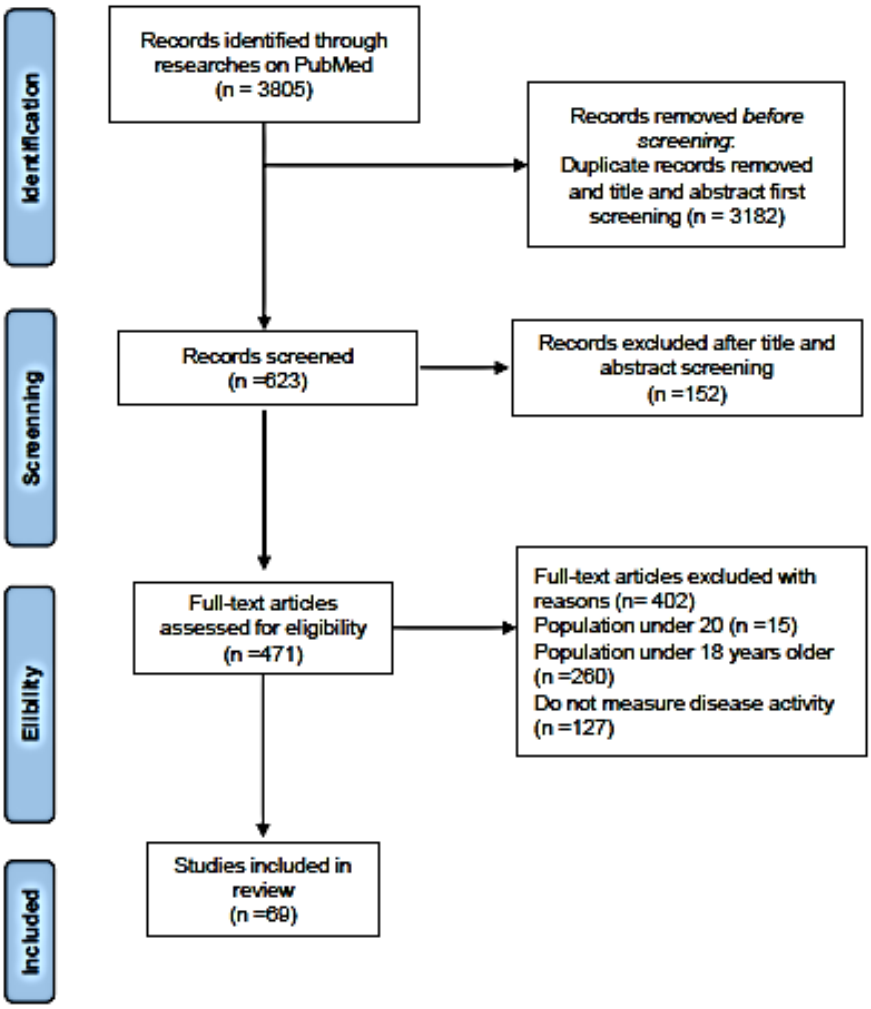

Figure 1 PRISMA 2020 flow-chart diagram

Table 1 Main characteristics of the 69 studies included

First Author (year)	Country	Type of Study	N	Age in years (range)	JIA categories included	Disease Activity Assessment Tool	Other outcomes assessment tools	Objective	Disease Activity as primary/secondary outcome	Study Outcome
(Vroegindeweij *et al*., 2022)	Netherlands	Randomized Controlled Trial	60 (20 JIA)	12-29*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	JADAS	VAS pain scale	Identification of the disrupted biological factors for chronic fatigue in patients with Q-fever fatigue syndrome, Chronic fatigue and JIA.	Secondary	This study is still on going and aims to contribute to biological research and personalized treatment in QFS and similar manifestations of chronic fatigue.
(Nesbitt *et al*., 2022)	Germany	Cohort Study	67 (32 JIA/35 control)	10-20 (mean age: 14.6) *	Oligoarticular and Polyarticular	PGA cJADAS	CHAQ VAS pain scale Triple-single-leg-hop test Incremental cycle ergometry test Indirect calorimetry	Evaluation of the secondary consequences of JIA in long-term health, such as physical activity, cardiorespiratory fitness, adiposity and functional performance.	Secondary	Patients with JIA showed lower capacity to daily moderate to vigorous physical activity than the control group, and that capacity decreased with age. Females tended to have lower peak oxygen consumption and greater adiposity than males.
(Sieczkowska *et al*., 2022)	Brazil	Randomized	51 (30 JIA)	10-19 (mean	Systemic, Oligoarticular,	ACR	PedsQL 4.0 SDQ	Investigation of the perception and	Secondary	The home-based exercise training program was suitable and well-accepted by

		Controlled Trial		age: 14.5) *	Polyarticular, Psoriatic, ERA and Undifferentiated		PSQI	acceptability of home-based exercise intervention in systemic lupus erythematosus and JIA adolescent patients during COVID-19 pandemic.		adolescents during the COVID-19 pandemic. The adherence of JIA patients was lower than JSE patients, suggesting that facilitators and barriers should be explored.
(García-Fernández *et al*., 2022)	Spain	Cohort Study	191	11-31*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA Wallace Criteria		Determination of the flare rate on a population of patients with JIA who tapered or abruptly discontinued biologic disease-modifying anti-rheumatic drugs (bDMARD), as well as, identifying predictors of flare.	Primary	There were identified some factors associated to flares such as: sex, higher number of previous bDMARDs and no longer time on that treatment. Tapering was a successful strategy to maintain remission with lower bDMARD doses.
(Nishimura *et al*., 2021)	Japan	Experimental Study	19	2-20 (mean age: 9) *	Systemic	PGA ACR	CHAQ-DI	Studying the efficacy and safety of Canakinumab in Systemic JIA.	Primary	All patients achieved ACR30 at week 8, and at week 48 ACR 50/70/90/100 were 100.0%/100.0%/87.5%/68.8% of the patients. The most common adverse events were infections.

										Therefore, Canakinumab demonstrated efficacy in Japanese patients with sJIA and was associated with substantial corticosteroid dose reduction.
(García-Fernández *et al*., 2021)	Italy	Observational Study	22	18.3-37.3 (mean age: 28) *	Systemic, Oligoarticular, Polyarticular and ERA	DAS28-CRP3		Studying the disease activity during pregnancy and obstetric outcomes in patients with JIA.	Primary	95% of the pregnancies started in a period of stable disease. There were 7 flares in 6/20 pregnancies and 8 flares occurred in the postpartum period, all of them in oligo and polyarticular JIA. 7 patients were taking biological treatments at conception and 6 stopped at positive test. 5 patients resumed bDMARDs during pregnancy. Therefore, continuing bDMARDs during pregnancy should be considered to minimize the risk of adverse pregnancy outcome, such as preterm delivery.
(Arnstad *et al*., 2021)	Norway	Cohort Study	377	20.2-27.1 (mean age: 23.3) *[2]	Oligoarticular	ACR JADAS71	VAS pain scale HAQ SF-36 FSS PSQI	Studying the fatigue in young adults with JIA 18 years after disease onset.	Secondary	26% reported severe fatigue compared to 12% among controls. Higher levels of fatigue were found among participants with sleep problems, pain, poor health, reduced participation in school, physical disability, active disease and use of DMARDs.
(Rypdal *et al*., 2021)	Denmark, Finlan	Cohort Study	434 (96 with	19.1-27-4 (mean	Systemic, Oligoarticular,	JADAS27 Wallace Criteria	VAS pain scale	Assessing the long-term outcome of	Secondary	Uveitis developed in 96 of 434 patients with JIA, corresponding to a total of 22,1%.

	d, Norway, Sweden		uveitis)	age: 23.5) *[2]	Polyarticular, Psoriatic, ERA and Undifferentiated		SUN criteria BCVA	uveitis in patients with JIA.		2,8% were diagnosed between 8 to 18 years of follow-up. Decreased visual acuity was found on 8,9% of the patients. In conclusion, if JIA is suspected or confirmed uveitis screening should start immediately.
(Aires *et al*., 2021)	Portugal	Observational Study	70	15.3±5,2*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	Wallace Criteria		Determination of the flare rates and remission after therapy discontinuation in patients with JIA.	Primary	After withdrawal, the mean time of inactive disease was 15,6 months. 25 patients had flares. There were no differences regarding sex, age, JIA subtype, disease duration or other factor.
(Mena-Vázquez *et al*., 2021)	Spain	Observational Study	104 (52 JIA/52 control)	22.8±5.1*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	JADAS27 DAS28		Evaluation of the cognitive function in adult patients with JIA.	Secondary	Cognitive function in patients with JIA is poorer than in healthier adults. The visual function in JIA patients was inversely associated with disease duration, inflammatory activity and lower education level.
(Oliveira Ramos *et al*., 2021)	Portugal	Cohort Study	585	18-over 60*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA DAS28	HAQ SF-36 JADI HADS	Comparison of physical disability, mental health, fatigue and health-related quality of life between the different categories of JIA.	Secondary	The categories with best health-related quality of life were persistent-oligoarticular JIA and ERA. JIA patients had lower functional ability.

(Brunner *et al*., 2020)	United States of America	Experimental Study	123 (70 fever/52 no fever)	2-20*	Systemic	PGA ACR JADAS 71-CRP	CHAQ-DI	Evaluation of the long-term efficacy and safety of Canakinumab, as well as, exploration the potential response with and without fever in patients with sJIA.	Primary	At day 15, efficacy was observed in both groups. Of the 71/123 patients who received glucocorticoids at the study, 27 discontinued the drug and 21 reached minimal dose with no difference between fever/no fever group. Therefore, Canakinumab provided a rapid and sustained improvement of active sJIA regardless of the presence of fever.
(Glerup *et al*., 2020)	Denmark	Cohort Study	510	20-28.7 (mean age: 23.9) *[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA JADAS71	HAQ JADI	Determination of the remission in JIA 18 years after disease onset on the biological era.	Primary	46% still had active disease and 15% were treated with DMARDs. Inactive disease indicated by JADAS71 was seen in 48% of participants.
(Glerup *et al*., 2019)	Nordic Countries	Cohort Study	293	23.7±4.4*[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	ACR JADAS71		Determination of the serum levels of the lectin pathway proteins at the early disease course of JIA and comparison after 17 years. Assessing the predictive value of lectin	Primary	Concentrations of lectin protein levels of the serum were higher at baseline compared to the levels after 17 years of disease onset. M-ficolin was higher at baseline (higher at systemic JIA) compared to 17 years later, and had correlation to higher levels of ESR, therefore to higher disease activity.

								pathway proteins with remission status.		Higher levels of MASP-1 and MASP-3 correlate to lower ERS. CL-K1 showed negative correlation to JADAS71 at baseline. MASP-1, MASP-3 and CL-K1 are inflammatory markers.
(Feger *et al*., 2019)	United States of America	Cross Sectional Study	139 (45 pJIA / 94 RA)	Older than 18 (median age: pJIA-27.4; RA-56.1) *	Polyarticular	ACR		Comparison of adults with polyarticular JIA and adults with Rheumatoid Arthritis.	Secondary	pJIA patients were less likely to be rheumatoid factor cyclic citrullinated peptide antibody positive. Time from diagnose and Methotrexate initiation was associated with longer disease duration in both groups.
(Relas and Kosola, 2019)	Finland	Cohort Study	291	16-20 (mean age: 18) *	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	DAS28-CRP	VAS pain scale HAQ-DI BASDAI	Comparison of the health-related quality of life and disease activity of JIA patients after being transferred to an adult clinic.	Primary	Adults had lower health-related quality of life and higher disease activity than JIA patients. Smoking was associated with more active disease and lower health-related quality of life.
(Tollisen *et al*., 2019)	Norway	Cohort Study	96	20.9-29.3 (mean age: 25.1) *	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	PGA	VAS pain scale HAQ-DI SF-12 BPI	Studying the longitudinal health status from childhood to adulthood in patients with JIA over 19 years.	Secondary	During the first 3 years, physical disability improved and the proportion of patients reporting best possible well-being increased. At 3-19 years follow-ups patients had similar levels but fatigue increased.

										After 19 years, patients had worse pain and physical quality of life.
(Connelly *et al*., 2019)	United States of America	Observational Study	7753	5-21*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	CHAQ	Determination of the relationship between high levels of pain, functional limitations and paediatric rheumatic diseases.	Secondary	Pain levels were higher among patients with juvenile primary fibromyalgia syndrome and lower for juvenile dermatomyositis. Pain was strongly correlated to functional limitation in juvenile dermatomyositis, JIA and mixed connective tissue disease.
(Shih *et al*., 2019)	Taiwan	Review Chart	1083	17.6±5.4*[2]	ERA	Wallace Criteria		Comparison of the clinical characteristics, treatments and outcomes of ERA patients in Taiwan, as well as, determination of risk factors.	Secondary	ERA is male predominant (86%), has a late onset and a majority of patients is HLA-B27 positive (97%). These patients were significantly less likely to achieve non active status in comparison to patients with persistent oligoarthritis. 26 patients remained active with TNF alfa inhibitor. Sacroiliitis is a risk factor to poorer treatment response.
(Arnstad *et al*., 2019)	Norway, Sweden, Finland and Denmark	Cohort Study	243	11.1-18.5 (mean age: 14.9) *[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	Wallace criteria	VAS pain scale JADI CHAQ CHQ-PF50 HAQ	Studying the self-reported pain early in the disease course of JIA as a predictor of disease outcome.	Primary	Early self-reported pain seems to be a good predictor of unfavourable long-term outcomes.

(Ursin *et al*., 2018)	Norway	Cohort Study	135	18-38 (median age: 29) *	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	DAS28-CRP	mHAQ SF-36	Studying the disease activity in women with JIA during and after pregnancy, as well as physical function, pain and mental health.	Primary	80% of the women were in remission or had low disease activity during and after pregnancy (until 1 year after). The highest value of DAS28-CRP was 6 weeks postpartum, correlating to the highest disease activity. mHAQ values were highest in the third trimester corresponding to lowest functionality, besides physical functioning score of SF-36 was lower in the same trimester.
(Opoka-Winiarska *et al*., 2018)	Poland	Observational Study	44	4-19 (mean age:12.0) *	Polyarticular	PGA ACR	CHAQ-DI	Determination of the efficacy and safety of Tocilizumab in the treatment of polyarticular JIA in the course of the CHERISH trial.	Primary	All patients in the study achieved ACR70 at baseline, and the number of patients who achieved inactive disease increased between baseline at visit 7 from 63.4% to 75.6%. The safety and efficacy of Tocilizumab for the treatment of pJIA were demonstrated in the study.
(Gabay *et al*., 2018)	Switzerland	Experimental Study	23	30-58.8 (mean age: 41) *	Adult Onset Still's Disease (AOSD)	PGA	Swollen Joint Count Tender Joint Count	Determination of the safety and efficacy of Tadekinig alfa in adult-onset Still's disease.	Primary	Most adverse effects were mild and resolved after drug discontinuation. The study demonstrated that Tadekinig alfa appeared to have a favourable safety profile and was associated with early signs of efficacy in patients with AOSD.

(Tollisen *et al*., 2018)	Norway	Cohort Study	336	33.3-42.3 (mean age: 37.8) *	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	cJADAS	VAS pain scale HAQ-DI SCL-5 SF-36	Studying the physical function, pain and health-related quality of life in adults with JIA, as well as investigation of predictors of poorer quality of life after 30 years.	Secondary	47% had HAQ-DI scores higher than 0 and median VAS pain of 0.6. Patients had lower SF-36 compared to the control group. JIA has a detrimental effect on physical health-related quality of life.
(Bielak *et al*., 2018)	Germany	Cohort Study	200	2-21*	Systemic	Wallace Criteria		Evaluation of sJIA patients treated with Tocilizumab, regarding its response rate, disease course and adverse effects.	Primary	The clinical response rate after 12 weeks was 35%. Inactive disease or remission under medication was 75% in one year. Adverse events were seen in 24% of the patients.
(Ruperto *et al*., 2018)	Italy	Experimental Study	177	2-19*	Systemic	ACR JADAS71	CHAQ	Assessing the long-term efficacy and safety of Canakinumab in patients with sJIA.	Primary	The treatment with Canakinumab was associated with a glucocorticoid dose reduction or discontinuation.
(Lovell *et al*., 2018)	United States of	Cohort Study	137	4-20 (mean age: 11.6) *	Polyarticular, Oligoarticular	PGA ACR	CHAQ	Determination of the frequency, time-to-flare and predictors of	Primary	77% of the patients remained in clinical inactive disease on anti-TNF for the initial 6 months.

	America							disease flare after withdrawal of anti- TNF in patients with poly-JIA.		The withdrawal of anti-TNF led to an increase of disease flare in 37% of the patients by 8 months. One third of the patients with poly-JIA with clinical inactive disease will flare by 8 months after discontinuing anti-TNF.
(Ammerlaan *et al*., 2017)	Netherlands	Randomized Controlled Trial	72	16-25 (mean age: 19.1) *	Oligoarticular, Polyarticular and Systemic	Patient NRS-0-10	Dutch-ASES Dutch heiQ HAQ-DI	Investigation of the effectiveness of web-based self-management intervention guided by peer-trainers to support young adults with JIA, assessing self-efficacy, management, disease activity, quality of life, absenteeism of school/work, health care medication use and adherence to intervention.	Primary	No significant differences were found in any parameter between the control and intervention group.
(Brachat *et al*., 2017)	Italy	Experimental Study		2-19 (mean age: 9) *	Systemic	ACR		Characterization of the molecular response to Canakinumab and evaluation	Secondary	Treatment with Canakinumab in sJIA patients led to downregulation of innate immune response genes and

								of the potential marker's response, using samples from two pivotal trial in sJIA.		reductions in IL-6 and clinical symptoms. Nevertheless, there is a need to investigate potential differences in disease mechanisms in patients with heterogeneous gene transcription profiles.
(Selvaag *et al*., 2017)	Norway	Cohort Study	60	30-45 (mean age: 38.2) *[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	PGA JADAS71	HAQ SF-36 JADI	Studying the radiographic outcome after long-term disease duration in JIA.	Secondary	There was seen a modest radiographic damage, more frequently in wrists than fingers. The radiographic scores correlated well with measures of disease damage.
(Mourão *et al*., 2016)	Portugal	Cohort Study	812	Mean age: 19.9*	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	PGA JADAS10	CHAQ	Assessing the effectiveness and safety of biologic therapy and predictors of response after one year of treatment. As well as, retention rate, and predictors of discontinuation in JIA patients.	Primary	After 6 months of treatment, the number of active joints, ESR and CHAQ decreased significantly, as well as an important reduction of JADAS10 after one year of treatment, where 83,3% responded to the biologic therapy.
(Shukla, Gaur and Aggarwal, 2016)	India	Randomized Clinical Trial	46	14-19 (mean age: 15) *	ERA	mJSpADA		Studying how probiotics can modulate the gut-flora and the immune and clinical	Primary	There was no differences in mJSpADA between the control group and the intervention group. Serum IL-6 decreased in the probiotic group.

								parameters of ERA patients.		TH2 and IL-10 increased in the probiotic group. Probiotic therapy is well tolerated but failed to show any significant immune or clinical effects.
(Anderson *et al*., 2016)	United States of America	Cohort Study	Cohort 1: 82 (41 JIA/41 control) Cohort 2: 261 (170 JIA/91 control)	Cohort 1: over 30* Cohort 2: over 29*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	ACR		Studying the frequency of cardiovascular diseases and risk factors in patients with JIA versus control.	Secondary	There was no increase in cardiovascular disease events in patients with JIA when compared with the general population.
(el Eraky *et al*., 2016)	Egypt	Cross Sectional Study	68 (34 JIA/34 controls)	13.75± 4.36*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	JADAS27		Evaluation of the left ventricular function, left atrial mechanical functions and atrial eletromechanical delay in JIA.	Secondary	There was a subclinical cardiac involvement in JIA patients demonstrated by atrial electromechanical coupling intervals and left atrial mechanical functions impaired.

(Selvaag *et al*., 2016)	Norway	Cohort Study	176	20.6-39.9 (mean age: 29.6) *[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA JADAS3	HAQ SF-36	Evaluation of the disease activity 30 years after disease onset in patients with JIA.	Primary	At 30 years follow-up, 59% of the patients were in clinical remission off medication, 7% were in remission on medications, and 34% had active disease. 70% of the patients were in the same category of disease activity at 15 and 30 years.
(Oliveira-Ramos *et al*., 2016)	Portugal	Cross Sectional Cohort	426	34.1±12.8*[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA DAS28	HAQ JADI-A JADI-E	Assessing how adult JIA patients fulfil the criteria for adult rheumatic diseases, and evaluation of the outcome and clinical predictors of inactive disease.	Secondary	Most of the adult JIA patients fulfilled the criteria of adult rheumatic diseases. Younger age of disease onset was related to higher disability and decreased number of inactive diseases.
(Wu *et al*., 2016)	United Kingdom	Experimental Study	49	Over 10	Polyarticular	JADAS10 DAS28		Comparison of the efficacy between JADAS and DAS28 in measuring disease activity.	Primary	There was seen a good correlation between disease activity scores (p<0,0001) in childhood population. In adulthood, there were some discrepancies.
(Sandstad *et al*., 2015)	Norway	Cross-Over Study	18 (7 RA/ 11 JIA)	20-50 (mean age: 32.4±8.3) *	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and	DAS28	mHAQ	Assessing whether 10 weeks of high intensity interval training improves important risk	Secondary	HIIT resulted in an increase of 12.2% in the maximal oxygen uptake and 2.9% in heart rate recovery. There was a decrease in BMI, body fat and waist

					Undifferentiated			factors of cardiovascular diseases in rheumatic patients.		circumference whereas muscle mass increased. No changes were detected in disease activity or pain. Therefore, HIIT activity had a positive effect on several CVD risk factors.
(Nirmala *et al*., 2015)	United States of America	Clinical Trial	36 (17 AOSD/ 19 control)	AOSD: median age- 37* Control: median age- 26	Systemic and Adult Still's Disease	ACR		Studying the similarity between AOSD and sJIA at a molecular level using 2 genes sets, and investigation of how they response to Canakinumab.	Secondary	All genes downregulated in sJIA patients following Canakinumab treatment were upregulated in most patients with active ASOD prior to Canakinumab treatment compared to healthy subjects. Additionally, this study showed a correlation between an elevated number and upregulation of Canakinumab responsive genes. Therefore, these results support that Still's Disease includes both a paediatric onset and an adult-onset form.
(Anink *et al*., 2015)	Netherlands	Observational Study	43	18-24 (mean age: 22) *[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	ACR JADAS10	VAS pain scale CHAQ SF-36	Studying the long-term quality of life and functional outcome of patients with JIA in the biologic era.	Secondary	Patients reported increasing levels of bodily pain compared to earlier measurements. Use of biologic agents was predominantly made by Etanercept.
(van pelt *et al*., 2015)	Netherlands	Cross Sectional Study	176	10-27*	Systemic, Oligoarticular, Polyarticular,	PGA JADAS27 DAS28	CHAQ	Assessing the relationship between sites and online peer	Secondary	71% had use the internet to search for general information on JIA and 25% had visited a forum with peers online.

					Psoriatic, ERA and Undifferentiated	Wallace Criteria		support groups and demographic, disease-related and psychosocial variables in patients with JIA.		Disease related factors cannot be used to identify people with JIA online.
(Yokota *et al*., 2014)	Japan	Experimental Study	67	2-19 (mean age: 8.0) *	Systemic	PGA ACR	CHAQ	Assessing the long-term safety and effectiveness of Tocilizumab in Systemic JIA.	Primary	Tocilizumab demonstrated durability and effectiveness at the treatment of sJIA and had shown good tolerability and low discontinuation rate associated with adverse events.
(Ilowite *et al*., 2014)	United States of America	Randomized Controlled Study	71	18 months -19 years*	Systemic	PGA ACR	CHAQ PedsQL	Studying the efficacy and safety of Rilonacept in patients with Systemic JIA.	Primary	Time to response was shorter in the Rilonacept arm than the placebo arm. Exacerbation of sJIA was the most common adverse effect. Another detected adverse effects was elevated liver enzymes, but they were similar in both arms. Rilonacept was generally well tolerated and demonstrated efficacy in active sJIA.
(Jetha *et al*., 2014)	Canada	Cross Sectional Study	1043 (45.5% JIA)	18-30 (mean age: 23.2) *	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and	PGA	CHAQ 8-SF	Examination of the independence, overprotection and support on rheumatic	Secondary	59% were employed. These study findings demonstrated the importance of psychosocial perceptions such as independence, overprotection, and support.

					Undifferentiated			patients, and their employment participation.		
(Aoki *et al*., 2014)	Japan	Clinical Trial	40	2-19*	Systemic	ACR	CARSH	Studying the clinical and radiological discrepancy to Tocilizumab treatment in patients with sJIA.	Secondary	The modified Larsen score of the large joints deteriorated in half of the patients, having MMP-3 in high levels.
(Lovell *et al*., 2013)	United States of America	Experimental Study	24	4-20 (mean age:14) *	Systemic	PGA ACR	CHAQ	Determination of the long-term safety and efficacy of Rilonacept in patients with active Systemic JIA.	Primary	There were improvements in clinical and laboratory (D-dimer, MRP-8, MRP-14, CPR) measures of the articular and systemic manifestations of systemic JIA in more than 50% of Rilonacept treated patients over 2 years.
(Aikawa *et al*., 2013)	Brazil	Clinical Trial	186 (95 JIA/91 controls)	9-21*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	CHAQ	Assessing the response of the vaccination (anti-H1N1) in JIA patients and verifying the immunogenicity and safety of the vaccine.	Secondary	After vaccination, the seroconversion rate was lower in JIA patients, particularly in polyJIA. Nevertheless, it produced protective antibody response independent of disease parameters.
(Vidqvist *et al*., 2013)	Finland	Cohort Study	154	16-24 (mean age: 19) *[2]	Systemic, Oligoarticular, Polyarticular,	PGA		Assessing the use of DMARDs and biologic treatments and	Primary	21% of the patients were still on biologic therapies.

					Psoriatic, ERA and Undifferentiated			disease activity in patients with JIA.		The median duration of treatment, with at least one biologic agent, was 4.2 years. 58% still showed evidence of mild disease activity.
(Raab *et al*., 2013)	Germany	Cohort Study	344	19.7±2.8*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	HAQ SF-36	Assessing the prevalence of comorbidities in JIA patients and their impact on perceived health.	Secondary	Comorbidities had a significant impact on the perceived health of patients with JIA. Systemic JIA patients were at higher risk of comorbidities.
(Mori *et al*., 2012)	Japan	Multicenter Study	32	4-19 (mean age: 13.7) *	Polyarticular	PGA ACR DAS28	CHAQ	Studying the safety and efficacy of long-term Etanercept in the treatment of Methrotrexate-refratory polyarticular course JIA.	Primary	ACR30 and ACR50 were achieved by more than 90% of patients. Therefore, Etanercept was an effective therapeutic option for Japanese patients with polyarticular course JIA.
(Ruperto *et al*., 2012)	United States of America	Experimental Study	177	2-19*	Systemic	PGA ACR	CHAQ-DI	Assessing the efficacy and safety of Canakinumab in patients with Systemic JIA.	Primary	At day 15 of trial 1, more patients in the Canakinumab group versus placebo had a better ACR30 response. The average glucocorticoid dose was reduced. This study showed the efficacy of Canakinumab in sJIA.

(Quartier *et al*., 2011)	France	Randomized Controlled Trial	24	2-20*	Systemic	PGA ACR	VAS pain scale CHAQ	Assessing the efficacy of Anakinra in systemic onset JIA.	Primary	Anakinra treatment was effective in sJIA at least in the short term, as demonstrated in the study. It was associated with normalization of blood gene expression profiles in clinical responders and inducing a de novo IFN signature.
(Hinks *et al*., 2011)	United Kingdom	Cohort Study	407	7.93-18.91*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA ACR	CHAQ	Identification of the genetic predictors of response to MTX for the treatment in JIA.	Secondary	One SNO within the inosine triphosphate pyrophosphatase gene and two SNPs within 5-aminoimidazole-4-carboxamide ribonucleotide transformylase gene were significantly associated with poor response to MTX.
(E. Nordal *et al*., 2011)	Nordic Countries	Cohort Study	440	10.1-21.5*	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	PGA JADAS27	VAS pain scale C-HAQ HAQ SF-36 JADI	Studying the disease characteristics, long-term course and outcome of patients with JIA.	Secondary	58% of the patients were treated with DMARDs. Ongoing disease activity was mostly mild. At the last follow up, remission off medication was observed in 42.2% of the patients, 8.9% were in remission on medication and 48.7% were not in remission.
(Pileggi, de Souza and Ferriani, 2010)	Brazil	Cohort Study	43 (25 JIA/ 18 control)	2-19*	Oligoarticular, Polyarticular and Systemic	PGA ACR		Evaluation of the safety and immunogenicity of varicella vaccine in susceptible patients under	Primary	Positive VZV-IgG titters were detected in 10 of the 20 seronegative patients. One year after vaccination 8 of the 10 maintained positive VZV-IgG titters.

								Methotrexate and Corticosteroids with JIA.		No severe adverse reactions were observed. No worsening of clinical parameters and no flares of JIA, as well as, no changes in doses of medication were needed. VV appeared to be safe in patients with JIA.
(Abrahamyan *et al*., 2010)	Canada	Secondary data analysis Design	521	Over 18*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	ACR		Verification of the response times to treatment in patients with rheumatic diseases.	Secondary	Study designs might be more efficient if the response distributions are taken into consideration along the planning.
(Lequerré *et al*., 2008)	France	Experimental Study	35 (20 SoJIA/ 15 AoSD)	SoJIA: 3-23 (median age-12.4) * AoDS: 22-62 (median age-38.1) *	Systemic	PGA ACR	CHAQ	Assessing the efficacy and safety of Anakira treatment in Systemic onset JIA or adult onset Still disease.	Primary	After 6 months, 5 patients with SoJIA achieved ACR 50% and a total of 11, of the 15 AoSD patients, achieved at least 50% improvement of all disease markers, meaning that Anakira was effective in most AoSD patients, but less than half SoJIA patient achieved a marked and sustained improvement. Nevertheless, the use of steroids in both cases was decreased by 45% to 95%.
(Yokota *et al*., 2008)	Japan	Randomized Controlled Trial	56 (20 Tocilizum	2-19*	Systemic	PGA ACR		Assessing the efficacy and safety of Tocilizumab in	Primary	By week 48, ACR 30, 50 and 70 responses were achieved by 47 (98%), 45 (94%) and 43 (90%) of 43 patients, respectively.

			ab/ 23 placebo)					patients with Systemic JIA refratory to convencional treatment.		The serious adverse effects detected were anaphylactoid reaction, gastrointestinal haemorrhage, bronchitis and gastroenteritis. In conclusion, Tocilizumab was effective in children with sJIA.
(Zonneveld-Huijssoon *et al*., 2007)	Netherland	Cohort Study	234	1-19*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	CHAQ	Determination whether vaccinations aggravate the course of autoimmune diseases as JIA and whether the immune response to vaccinations may alter due to immunosuppressive therapy.	Secondary	There was no change in values for any 6 components of the core set criteria for JIA disease activity after giving MenC vaccine. Moreover, there was no increase on frequency or relapses. Therefore, patients with JIA can be vaccinated safely with MenC conjugate.
(van Rossum *et al*., 2007)	Netherlands	Randomized Controlled Trial	61	2-25 (mean age:19) *[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA ACR	VAS pain scale CHAQ HAQ	Determination of the long-term outcome and evaluation of the benefits of Sulfasalazine treatment over time.	Primary	Almost all the patients continued or started DMARD's. DMARD's treatment appeared to be less intensive in the Sulfasalazine group. Almost all outcomes score were better for the Sulfasalazine group.
(Brown *et al*., 2005)	Canada	Multicenter Study	92	8-20 (mean age: 12) *	Systemic, Oligoarticular, Polyarticular,	PGA	CHAQ HAQ JAFAR JASI	Assessing the responsiveness and comparison of the different	Secondary	The CHAQ was more responsive to change at 6 weeks but less responsive at 6 months.

					Psoriatic, ERA and Undifferentiated			scales JAFAR, CHAQ and JASI in patients with JIA.		All 3 questionnaires showed acceptable parent-child agreement and had few differences. Therefore, they were all adequate for clinic setting, being the choice based on the time available for completion, the intended use and the depth of the content required.
(Schmeling & Horneff, 2005)	Germany	Clinical Study	310	6-21*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	ACR		Studying the efficacy of Etanercept for chronic uveitis in patients with JIA.	Primary	Before treatment with Etanercept, 31 patients have had history of uveitis of a total of 102 flares. During treatment, 32 courses of uveitis occurred in 19 patients occurring for the first time in 2 patients. In 87% of the uveitis patients, arthritis demonstrated a significant or complete response. During treatment with Etanercept there were both relapses and first courses of uveitis. However, the frequency and severity of uveitis was not influenced by Etanercept.
(Powell *et al*., 2005)	United States of	Randomized Study	48	5-19 (mean age: 12) *	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA	PGA	PedsQL VAS pain scale Timed walking	Comparison of the clinical efficacy of custom foot orthotics,	Secondary	Patients using orthotics showed significantly greater improvements in pain, speed, activity limitation, foot pain and level of disability.

	America				and Undifferentiated		FFI	prefabricated "off-the-shelf" shoe inserts and supportive athletic shoes in reducing pain and improving function in patients with JIA.		
(Epps *et al*., 2005)	United Kingdom	Randomized Controlled Trial	200	4-19*	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	VAS pain scale CHAQ CHQ-PF50	Comparison of the effects of land-based physiotherapy only or the combination with hydrotherapy in health-related quality of life in JIA patients.	Secondary	There was a beneficial effect in the combination of hydrotherapy and land-based physiotherapy treatment.
(Quartier *et al*., 2003)	France	Multicenter Study	61	4-22 (mean age:12) *	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	CHAQ	Assessing the efficacy and tolerance of Etanercept in patients with JIA.	Primary	The most common side effects were neurologic or psychiatric disorders, retrobulbar optic neuropathy, major weight gain, severe infection, cutaneous vasculitis, haemorrhagic diarrhea, uveitis flare and pancytopenia. However, all of them disappeared with the discontinuation of Etanercept.

										The response rate was significantly lower in patients with sJIA.
(Foster *et al*., 2003)	United Kingdom	Cohort Study	82	17-68 (mean age: 30) *	Systemic, Oligoarticular, Polyarticular, Psoriatic, ERA and Undifferentiated	PGA	HAQ VAS pain scale SF-36	Evaluation of the quality of life in adult JIA patients.	Secondary	Active disease had a significant effect on health status.
(Minden *et al*., 2002)	Germany	Cohort Study	215	14-36*[2]	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	ACR	HAQ NRS-11 Stein-Brocker Criteria	Description of the long-term outcome of JIA.	Secondary	At follow up, half of the patients had active disease or changes in body structure. Since JIA often persists into adulthood, long-term follow up and care are necessary.
(Oen *et al*., 2002)	Canada	Cohort Study	392	8.6-35.8 (mean age: 18.8) *[2]	Oligoarticular, Polyarticular and Systemic	ACR	VAS pain scale CHAQ	Determination of disease course and outcome in patients with JIA.	Secondary	JIA often extends into adulthood. Functional outcome had improved, but the rate of arthroplasty remained very high. Patients with JIA had difficulty entering the work world.
(Zak & Pedersen, 2000)	Denmark	Follow-up Study	93	32.2±5.7*	Systemic, Oligoarticular, Polyarticular, Psoriatic and ERA	PGA	VAS pain scale HAQ Steinbrocker Criteria	Evaluation of JIA adulthood during 26.4 years.	Secondary	Active disease was present in 37% of the study participants. The duration of the disease proved to be the parameter most strongly associated with an unfavourable disease outcome.

*age at the beginning of the study

*[2]age at the end of follow up/end of the study

Acronym Caption: cJADAS- Clinical Juvenile Arthritis Disease Activity Score; JADAS71- 71 joint Juvenile Arthritis Disease Activity Score; JADAS27- 27 joint Juvenile Arthritis Disease Activity Score; JADAS10- 10 joint Juvenile Arthritis Disease Activity Score; ACR- American College of Rheumatology Score; DAS28- Disease Activity Score 28; DAS28-CRP3- Disease Activity Score 28 with C-Reactive Protein; mJSpADA- Six-point Composite Disease Activity Index; BASDAI- Bath Ankylosing Spondylitis Disease Activity Index; PGA- Physician Global Assessment; VAS pain scale- Visual Analogue Scale; BPI- Brief Pain Inventory; ; NRS-11- 11 point, numeric Pain Rating Scale; CHAQ- Childhood Health Assessment Questionnaire; CHAQ-DI- Childhood Health Assessment Questionnaire- Disability Index; CHAQ-PF50- Childhood Health Assessment Questionnaire- Parent Form; HAQ- Health Assessment Questionnaire; mHAQ- Modified Health Assessment Questionnaire; RAND-36- Health Questionnaire; SF-36- Short Form 36; SF-12- Short Form 12; Dutch-ASES- Dutch Arthritis Self-efficacy Scale; Dutch heiQ- Dutch Health Education Impact Questionnaire; JADI- Juvenile Arthritis Damage Index; JADI-A- Juvenile Arthritis Damage Index- articular; JADI-E- Juvenile Arthritis Damage Index- extra-articular; CARSH- Childhood Arthritis Radiographic Score of the Hip; JAFAR- Juvenile Arthritis Functional Assessment Report; JASI- Juvenile Arthritis Functional Status Index; CALI-21- Child Activity Limitations Interview; BASFAI- Bath Ankylosing Spondylitis Functional Index; SDQ- Strengths and Difficulties Questionnaire CASE- Children's Arthritis Self-Efficacy; MEPS- Medical Issues, Exercise, Pain and Social Support Questionnaire; Checklist FSS- Fatigue Severity Scale; PSQI- Pittsburgh Sleep Quality Index; RCADS- Revised Childhood Anxiety and Depression Scale; PCQ- Pain Coping Questionnaire; PROMIS- Paediatric Anxiety and Depression Short forms; HADS- Hospital Anxiety and Depression Scale; SCL-5- Hopkins Symptom; BCVA- Best Corrected Visual Acuity; EYE-Q- Effects of Youngster's Eyesight on Quality of Life; MISS- Methotrexate Intolerance Severity Score; FFI- Foot Function Index.

Results

3805 articles were identified with the search strategy, but only 69 articles met the inclusion criteria for review.

These articles applied different assessment tools to measure disease activity, such as PGA, based on a Visual Analogue Scale or Likert Scale, JADAS, ACR, DAS28, Wallace Criteria, NRS-0-10, mJSpADA.

37 articles, corresponding to 53,6%, used only one method to measure disease activity, while 32 publications (46,4%) used more than one method for that measurement.

1.1. Physician's Global Assessment

39 of the 69 studies used PGA as a method to evaluate disease activity, corresponding to 56,5% of the total of publications. Analysing the difference between 2022-2009 and prior to 2009, PGA was used in 52,7% (29 articles) and 76,9% (10 articles) respectively (figure 2). Among the studies that used PGA to measure disease activity, 53,8% (21) used it as a primary outcome, while 46,2% (18) used it as a secondary outcome.

Of the 39 articles using PGA, 25 of them (64,1%) added another scale to assess disease activity, in comparison to 35,9% (14 studies) that only used PGA to that measurement (figure 3).

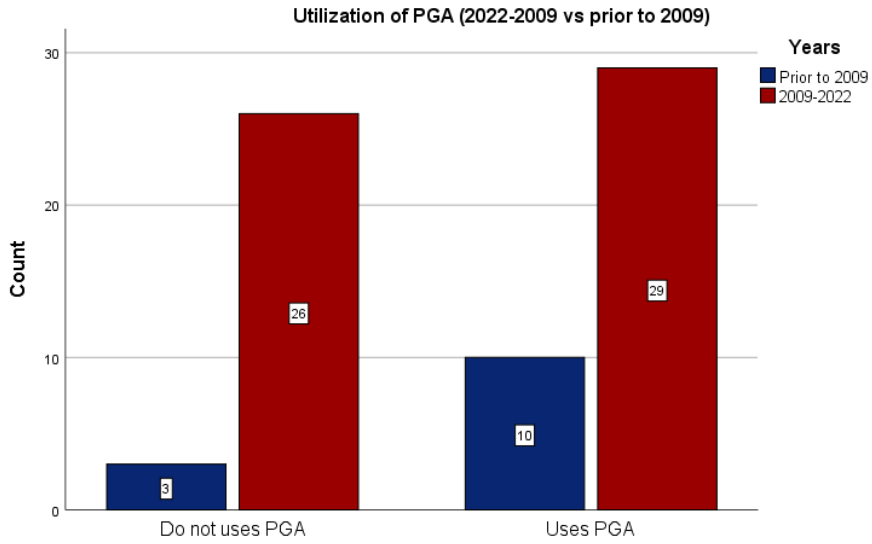

Figure 2 Comparison of articles using PGA between 2022-2009 vs prior to 2009

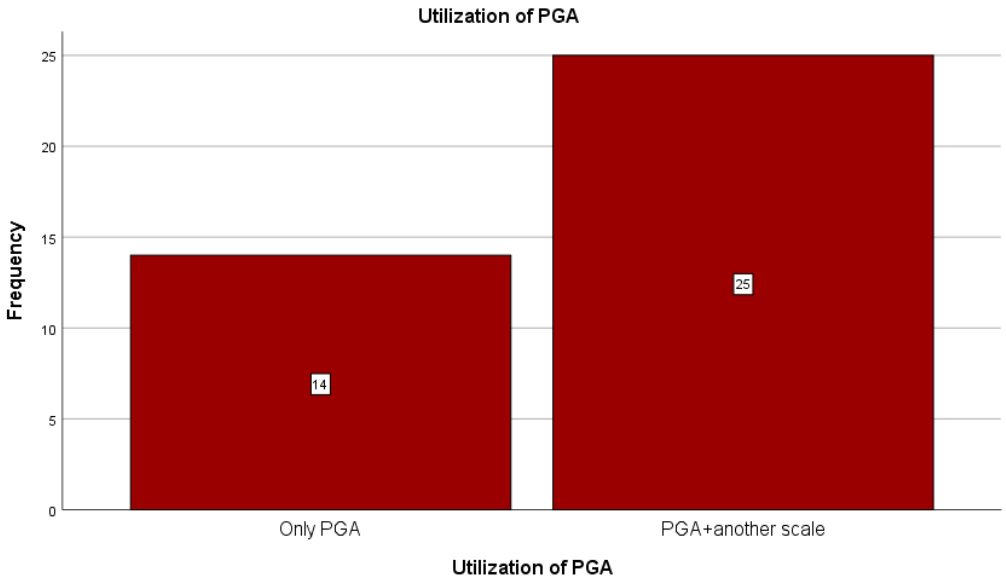

Figure 3 Utilization of PGA

In the analysed studies, PGA was used in several categories of JIA: 8 times (50%) in Systemic JIA, 3 times (18,8%) in Oligoarticular and 5 times (31,3%) in Polyarticular JIA. The age range of these studies was 2-38 years old.

1.2. Scales used to Measure Disease Activity

Of the 69 analysed studies, 18 used JADAS to measure disease activity corresponding to 27,3%, 29 (43,9%) used ACR, 10 (15,2%) applied DAS28, 7 (10,6%) utilized Wallace Criteria, 1 study (1,5%) used NRS-0-10 and 1 study (1,5%) used mJSpADA (figure 4).

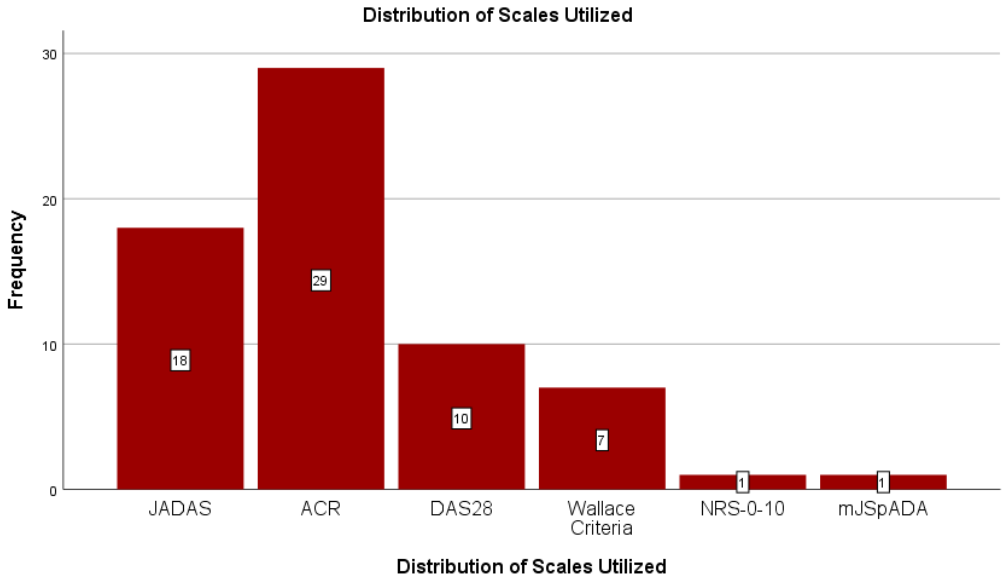

Figure 4 Scales used to measure disease activity

We also analysed if there were any differences between 2022-2009 and years prior to 2009.

Prior to 2009, the only scale utilized in the existing 6 studies was ACR (100%), while between 2022-2009 all the other methods where utilized: JADAS (30,0%), ACR (38,3%), DAS28 (16,7%), Wallace Criteria (11,7%), NRS-0-10 (1,7%) and mJSpADA (1,7%) (figure 5).

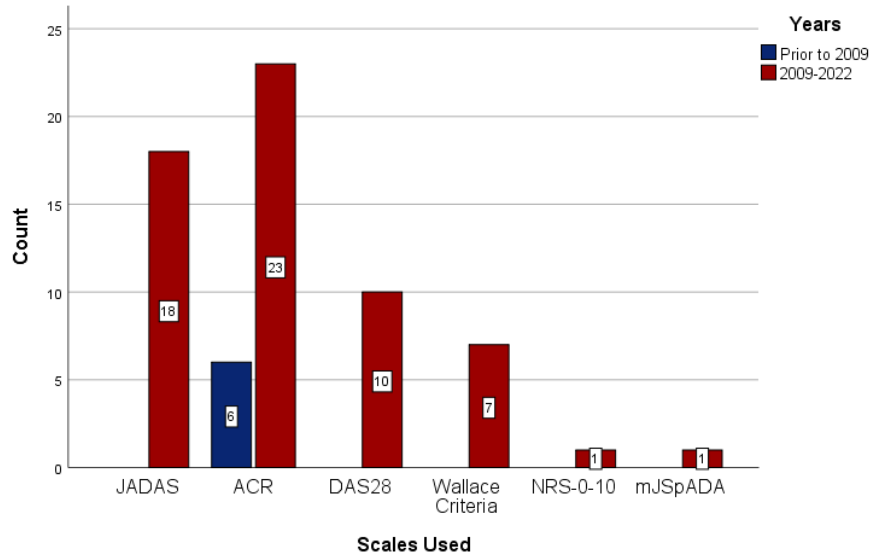

Figure 5 Distribution of scales between 2022-2009 vs prior to 2009

1.2.1. ACR Scale

Twenty-nine studies (43,9%) used ACR as a tool to assess disease activity. Of these studies, 10, corresponding to 34,5%, used only ACR to this objective, while 19 publications (65,5%) associated ACR with another method of measurement of disease activity. Of the latest, 17 (89,5%) used only a scale in association with ACR and 2 (10,5%) used more than one method (table 2). Among the studies that used ACR to measure disease activity, 58,6% (17) used it as a primary outcome, while 41,4% (12) used it as secondary outcome.

In association with ACR, 5 studies (23,8%) used JADAS, 1 article (4,8%) used DAS28 and 15 (71,4%) used PGA (table 3).

Table 2 Number of scales used in association with ACR

Number of scales	*Frequency*	*Percentage (%)*
One scale	17	89,5
More than one scale	2	10,5

Table 3 Scales used in association with ACR

Scales	*Frequency*	*Percentage (%)*
JADAS	5	23,8
DAS28	1	4,8
PGA	15	71,4

Of all the studies previously analysed, only 22 specified the category of JIA analysed. Of these 22, ACR was used 14 times to measure disease activity in patients with Systemic JIA, corresponding to 63,6%, 3 times to Oligoarticular JIA (13,6%) and 5 times to measure Polyarticular JIA (22,7%). The age range of these studies was 2-38.5 years old.

1.2.2. JADAS Scale

18 of the analysed studies (27,3%) used JADAS scale to measure disease activity. Of these studies 3 of them, corresponding to 16,7% used only JADAS to measure disease activity, while 15 (83,3%) associated JADAS with another tool to assess disease activity. Of the latest, 13 (86,7%) associated only one method, while 2 (13,3%) associated more than one method (table 4). Among the studies that used JADAS, 38,6% (7) used it as a primary outcome, while 61,1% (11) used it as a secondary outcome.

In association with JADAS, 5 studies (27,8%) used ACR, 3 (16,7%) used DAS28, 2 (11,1%) used Wallace Criteria and 8 (44,4%) used PGA (table 5).

Table 4 Number of scales associated with JADAS

Number of scales	*Frequency*	*Percentage (%)*
One scale	13	86,7
More than one scale	2	13,3

Table 5 Scales used in association with JADAS

Scales	*Frequency*	*Percentage (%)*
ACR	5	27,8
DAS28	3	16,7
Wallace Criteria	2	11,1
PGA	8	44,4

Of the 18 studies using JADAS, 3 of them (16,7%) used cJADAS, another 3 (16,7%) JADAS10, 5 (27,8%) used JADAS27, 5 (27,8%) used JADAS71, 1 (5,6%) used JADAS-CRP and another study (5,6%) did not specify the type of JADAS used (figure 6).

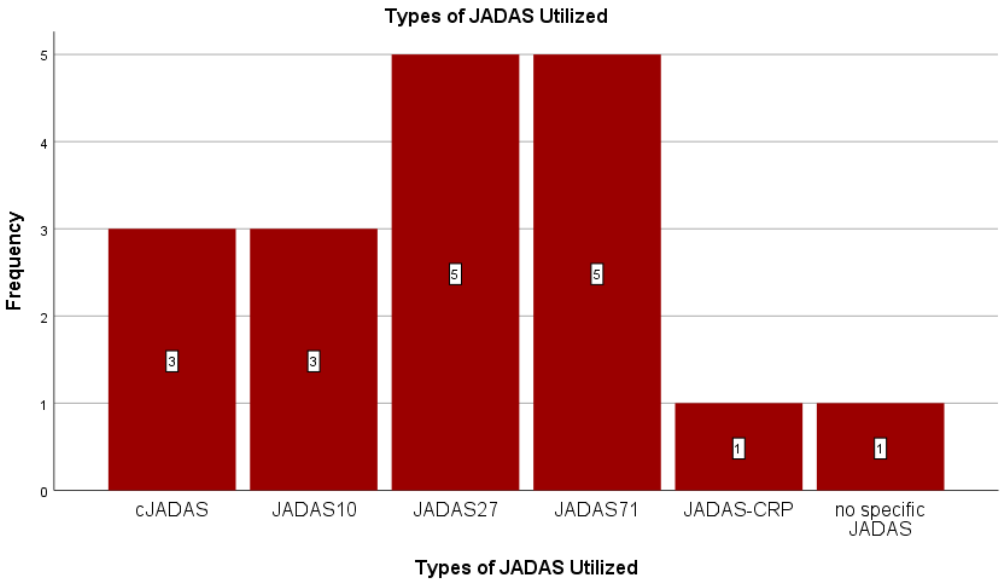

Figure 6 Types of JADAS used

Of all the studies analysed, only 6 specified the category of JIA analysed. In these 6 studies, JADAS was used to measure disease activity 2 times in patients with Systemic JIA, corresponding to 33,3%, 2 times to measure Oligoarticular JIA (33,3%) and another

2 times to measure Polyarticular JIA (33,3%). The age range of these studies was 2-27.1 years old.

1.2.3. DAS28

10 studies (15,2%) used DAS28 as a method to measure disease activity. Of these, 4 studies (40,0%) used only DAS28, while 6 publications (60,0%) associated DAS28 with another scale to measure disease activity. Of the last, 4, corresponding to 66,7%, used only one scale in association, whereas 2 (33,3%) used more than one scale (table 6). Among the studies that used DAS28 to measure disease activity, 50% used it as a primary outcome and the other 50% as a secondary outcome.

In association with DAS28, 3 studies (33,3%) used JADAS, 1 study (11,15%) used ACR, another one (11,15%) used Wallace Criteria and 4 (44,4%) used PGA (table 7).

Table 6 Number of Scales associated with DAS28

Number of scales	*Frequency*	*Percentage (%)*
One scale	4	66,7
More than one scale	2	33,3

Table 7 Scales used in association with DAS28

Scales	*Frequency*	*Percentage (%)*
JADAS	3	33,3
ACR	1	11,15
Wallace Criteria	1	11,15
PGA	4	44,4

Of the 10 studies using DAS28, 7 (70,0 %) used DAS28 while 3 of them (30,0%) used DAS28-CRP.

The studies did not specify the category of JIA analysed.

1.2.4. Wallace Criteria

7 studies (10,6%) used Wallace Criteria to measure disease activity. Of these, 4 (57,1%) used Wallace Criteria as the only method to assess disease activity, while 3 (42,9%) associated it with another scale. Of the last, 66,7% (2) used only one scale associated with Wallace Criteria and the other study (33,3%) used more than one scale (table 8). Among the studies that used this tool to assess disease activity, 57,1% (4) used it as a primary outcome, while 42,9% (3) used it as a secondary outcome.

In association with Wallace Criteria, JADAS was used 2 times (40,0%), DAS28 one time (20,0%), and PGA was used 2 times (40,0%) (table 9).

Table 8 Number of Scales associated with Wallace Criteria

Number of scales	*Frequency*	*Percentage (%)*
One scale	2	66,7
More than one scale	1	33,3

Table 9 Scales used in association with Wallace Criteria

Scales	*Frequency*	*Percentage (%)*
JADAS	2	40,0
DAS28	1	20,0
PGA	2	40,0

Of all the previous analysed studies, only two used Wallace Criteria to measure disease activity in specific categories of JIA. One (50%) was used at Systemic JIA and the other one (50%) at ERA. The age range of these studies was 2-23 years old.

1.2.5. NRS-0-10

Only one study (1,6%) (Ammerlaan *et al.*, 2017) used NRS-0-10 to measure disease activity as a primary outcome. This scale was used with no association with another

method in a randomized controlled trial with a population of 72 patients. The age range of this study was 16-25 years old, with a mean age of 19.1.

The primary objective was to investigate the effectiveness of web-based self-management intervention guided by peer-trainers to support young adults with JIA, assessing self-efficacy, management, disease activity, quality of life, absenteeism, health care medication use, and adherence to intervention in patients with Oligoarticular, Polyarticular and Systemic JIA.

1.2.6. mJSpADA

Only one study (1,6%) (Shukla *et al*., 2016) used mJSpADA to measure disease activity as a primary outcome. This scale was used with no association with another method in a randomized clinical trial with 46 patients with ages between 14-19 years old and ERA.

The primary objective of the study was to assess how probiotics can modulate the gut-flora and the immune and clinical parameters of ERA patients.

1.3. Comparison of Scales to Measure Disease Activity

Of the 69 analysed studies, 32 used more than one method to measure disease activity, and 3, also tried to demonstrate which method was the most reliable.

In Mena-Vázquez *et al*., 2021 , JADAS27 and DAS28 were used to assess disease activity and the remission level of the patients included in the study, with the aim of evaluating the cognitive function and associated factors in adult patients with JIA. Those authors used increased levels of anti-TNF alpha, IL-2, IL-6, inflammatory cytokines and the previous scales mentioned, to verify if there was a correlation between impairment of cognitive function and disease activity and severity. They established that visual functional performance was inversely associated with greater disease duration and inflammatory activity, measured with JADAS27, not being able to establish a correlation with DAS28. For that reason, they concluded that the measurement of inflammatory activity in JIA, in their population, was more accurate with JADAS27 than DAS28.

Wu *et al*., 2016 compared the efficacy of JADAS10 and DAS28 in adult patients with Polyarticular JIA. In their study, they saw a good correlation between activity scores (Spearman's r=0,69; p<0,0001) in children. However, they analysed a discrepancy in the adult population, where active disease defined by JADAS was not included in DAS28 in several patients, due to differences in the number and distribution of joints surveyed. In that way, they concluded that JADAS10 was a better reflector of active diseased in adult population.

Ruperto *et al*., 2018 study evaluated the long-term efficacy and safety of Canakinumab in patients, with age between 2-19 years old, with Systemic JIA, measuring the disease activity with ACR and JADAS71. In their study, there was an improvement of JADAS in 96,4% during treatment, having 44,6% achieved JADAS remission disease in less than 6 months. With ACR, they had similar response rates, with ACR 50/70/90 of 73,4%, 65,5% and 52,0%, respectively. Therefore, in this study they saw similarities in both methods to measure disease activity, not having concluded which was the better one.

Discussion

This systematic review summarized the evidence regarding the methods of measurement of disease activity in patients with JIA over 18 years old.

Of the 69 analysed studies, 53,6% used only one method to evaluate disease activity, while 46,4% used more than one method. Some of the reported methods are largely used in the children population with JIA, such as PGA and JADAS (Barut *et al*., 2017), while others, such as Wallace Criteria, DAS28, NRS-0-10 and mJSpADA are used in other rheumatic diseases such as Rheumatoid Arthritis (Ringold *et al*., 2010).

Regarding the use of PGA, 56,5% studies used PGA to analyse disease activity, with a slight difference between 2022-2009 (52,7%) and prior to 2009 (76,9%). Therefore, the usage of PGA was higher prior to 2009, most likely due to the absence of pre-existing scales and validation on the children population. We also analysed the use of PGA as an exclusive or associated method, concluding that PGA was more used in association with another scale (64,1%). However, none of the authors justified the use of an associated scale. However, Trincianti & Consolaro, 2020 considered PGA more as a scale to measure quality of life, instead of disease activity. Nevertheless, PGA was more used in Systemic JIA (50%), Polyarticular (31,3%) and Oligoarticular JIA (18,8%).

Our main objective was to analyse the most used scale to measure disease activity with 43,9% to ACR, 27,3% to JADAS, 15,2 % to DAS28, 10,6% to Wallace Criteria, 1,5% to NRS-0-10 and 1,5% to mJSpADA. Regarding the gaps mentioned above, prior to 2009 the only method used was ACR, while between 2022-2009 the proportion was similar to the global percentages with the most used scale being ACR (38,3%) followed by JADAS (30,0%). We can conclude that JADAS started to be used after 2009, which corresponds to its implementation as a method of measuring disease activity in children (Consolaro *et al*., 2009), aside from the fact that ACR is, tendentially, the most used scale.

Consolaro *et al*., 2016 consider ACR a method to measure therapeutic response in patients with JIA. In our analyses, 65,5% of the studies used ACR in association with another scale, more commonly with only one method, being the most common PGA (71,4%), JADAS (23,8%) and DAS28 (4,8%).

Regarding JADAS, Consolaro *et al*., 2016 consider it a validated method to measure disease activity in children with JIA. Of the analysed studies, 83,3% associated this scale with another tool, most frequently with only one method. The most associated was PGA (44,4%), ACR (27,8%), DAS28 (16,7%) and Wallace Criteria (11,1%). JADAS was used to measure disease activity in specific categories of JIA, such as Systemic, Oligoarticular and Polyarticular JIA. However, in Trincianti & Consolaro, 2020 study, they defend that JADAS scale should be used carefully in specific categories of JIA such as ERA, Psoriatic JIA and Systemic JIA. The most used version of JADAS, in our analysis, was JADAS71 and JADAS27. According to Ringold *et al*., 2010, there was a slightly better correlation between JADAS10 and ACR values in comparison to JADAS27 and JADAS71. However, in this study they did not consider it a relevant difference. They also demonstrated a correlation between DAS28 and the three versions of JADAS, and concluded that RA measures and JADAS tended to perform similarly in the detection of flares and disease activity in children with JIA. And in our analysis, 60% used DAS28 associated with another scale to measure disease activity in patients with JIA, being one scale the most common, as PGA, JADAS and ACR.

Wallace Criteria was used more as an only scale (57,1%), especially with only one scale, than in association with another scale (42,9%). The most associated scale was PGA and JADAS, followed by DAS28. Wallace Criteria was less used in specific categories, being used only one time in Systemic JIA and another in ERA. In the children population, Wallace Criteria is most used as a remission criteria instead of a disease activity criteria (Shoop-Worrall *et al*., 2017).

Regarding the use of NRA-0-10 and mJSpADA throughout this systemic review, each one was used only once, with no association with another scale to measure disease activity. The first was used simultaneously to measure disease activity at Oligoarticular, Polyarticular and Systemic JIA and mJSpADA was used to measure ERA.

Aside from all the different scales used to assess disease activity, very few studies compared different scales. Mena-Vázquez *et al*., 2021 concluded that JADAS27 was more accurate than DAS28 in their population, due to the relationship established between visual function performance and disease duration and inflammatory activity measured with JADAS27. Wu *et al*., 2016 established that JADAS10 was a better reflector

of active disease than DAS28, based on active disease present on JADAS10 and not on DAS28. Ruperto *et al*., 2018 saw a good correlation between JADAS71 and ACR, not having concluded which was the better one. All these three studies reinforce the accuracy of JADAS scale to measure disease activity in comparison with other scales, specially DAS28, used in RA. In our systematic review, JADAS scale was also one of the most used scales, especially after its validation in children population in 2009. The most accurate version of JADAS is not yet clear. However, its general accuracy in comparison with the most used scale until now, ACR, has been described.

During our research, we could not find any article regarding Systemic JADAS (sJADA) in adult population, only its validation in children (Tibaldi *et al*., 2020). Regarding Juvenile Spondyloarthrits Disease Activity (JSpADA) Index, we could not find many articles in the adult population, most likely due to the fact that this scale hasn't been validated, yet, in longitudinal cohorts, only retrospective (Tibaldi *et al*., 2020).

Even though in Systemic JIA and ERA, JADAS scale might not be the most suitable scale, it has demonstrated good performances in validation studies with these patients.

Strengths and Limitations

To the best of our knowledge, this is the first systematic review that studied the most common method to measure disease activity in patients with Juvenile Idiopathic Arthritis over 18 years old. This has a special interest as there is no validated method to assess disease activity in this age group. This could have a negative impact in the follow up of these patients (Conti *et al*., 2018) in comparison with a paediatric population, having a need to establish a specific method to assess disease activity in these diseases in adulthood that could be used worldwide for all physicians.

However, there are not many studies regarding the adult population with this disease, which made it difficult to find enough information to allow a conclusion. Additionally, the number of studies regarding a specific JIA category was even minor, therefore, resulted in less obvious conclusions.

Conclusion

Our systematic review showed that the most used method to measure disease activity in adults with JIA is ACR followed by JADAS. However, an exponential increase was noted in the use of JADAS after 2009, when this scale was validated into the childhood population with JIA. Along side with the generalization of its utilization, the scientific evidence suggests its better performance in comparison with other scales in adult population.

Physician's Global Assessment is also very used, most of the times in association with another method instead of being used as an only scale.

DAS28, Wallace Criteria, NRS-0-10 and mSJpADA were also utilized, but in a very less percentage of publications.

In our systematic review, we also analysed some articles that compared scales with one another. One of the studies showed that JADAS27 is more accurate than DAS28 in measuring disease activity and remission level of inflammatory activity in JIA population. Another concluded that JADAS10 is a better reflector of active disease in adult population with polyarticular JIA than DAS28, and the last one showed similarities between ACR and JADAS71 in their capacity to measure disease activity in patients with systemic JIA, reinforcing the accuracy of JADAS scale in adult patients.

Having a global and validated scale to assess disease activity represents a major need, not only to have more homogeneity among studies, but also to allow the development of evidence-based recommendations for the management of adults with JIA.

References

1. Abrahamyan, L., Beyene, J., Feng, J., Chon, Y., Willan, A. R., Schmeling, H., Horneff, G., Keystone, E. C., & Feldman, B. M. (2010). Response times follow lognormal or gamma distribution in arthritis patients. *Journal of Clinical Epidemiology*, *63*(12), 1363–1369. https://doi.org/10.1016/j.jclinepi.2009.11.019
2. Aikawa, N. E., Campos, L. M. A., Goldenstein-Schainberg, C., Saad, C. G. S., Ribeiro, A. C., Bueno, C., Precioso, A. R., Timenetsky, M. C., Silva, C. A. A., & Bonfá, E. (2013). Effective seroconversion and safety following the pandemic influenza vaccination (anti-H1N1) in patients with juvenile idiopathic arthritis. *Scandinavian Journal of Rheumatology*, *42*(1), 34–40. https://doi.org/10.3109/03009742.2012.709272
3. Aires, P., Terreri, M., Silva, V., Vieira MM, & Len, C. (2021). *Duration of inactive disease while off disease-modifying anti-rheumatic drugs seems to influence flare rates in juvenile idiopathic arthritis: an observational retrospective study*.
4. Ammerlaan, J., van Os-Medendorp, H., de Boer-Nijhof, N., Scholtus, L., Kruize, A. A., van Pelt, P., Prakken, B., & Bijlsma, H. (2017a). Short term effectiveness and experiences of a peer guided web-based self-management intervention for young adults with juvenile idiopathic arthritis. *Pediatric Rheumatology*, *15*(1). https://doi.org/10.1186/s12969-017-0201-1
5. Ammerlaan, J., van Os-Medendorp, H., de Boer-Nijhof, N., Scholtus, L., Kruize, A. A., van Pelt, P., Prakken, B., & Bijlsma, H. (2017b). Short term effectiveness and experiences of a peer guided web-based self-management intervention for young adults with juvenile idiopathic arthritis. *Pediatric Rheumatology*, *15*(1). https://doi.org/10.1186/s12969-017-0201-1
6. Anderson, J. H., Anderson, K. R., Aulie, H. A., Crowson, C. S., Mason, T. G., Ardoin, S. P., Reed, A. M., & Flatø, B. (2016). Juvenile idiopathic arthritis and future risk for cardiovascular disease: a multicenter study. *Scandinavian Journal of Rheumatology*, *45*(4), 299–303. https://doi.org/10.3109/03009742.2015.1126345

7. Anink, J., Prince, F. H. M., Dijkstra, M., Otten, M. H., Twilt, M., ten Cate, R., Gorter, S. L., Koopman-Keemink, Y., van Rossum, M. A. J., Hoppenreijs, E. P. A., & van Suijlekom-Smit, L. W. A. (2015). Long-term quality of life and functional outcome of patients with juvenile idiopathic arthritis in the biologic era: A longitudinal follow-up study in the Dutch Arthritis and Biologicals in Children Register. *Rheumatology (United Kingdom)*, *54*(11), 1964–1969. https://doi.org/10.1093/rheumatology/kev195
8. Aoki, C., Inaba, Y., Choe, H., Kaneko, U., Hara, R., Miyamae, T., Imagawa, T., Mori, M., Oba, M. S., Yokota, S., & Saito, T. (2014). Discrepancy between clinical and radiological responses to tocilizumab treatment in patients with systemic-onset juvenile idiopathic arthritis. *Journal of Rheumatology*, *41*(6), 1171–1177. https://doi.org/10.3899/jrheum.130924
9. Arnstad, E. D., Glerup, M., Rypdal, V., Peltoniemi, S., Fasth, A., Nielsen, S., Zak, M., Aalto, K., Berntson, L., Nordal, E., Herlin, T., Romundstad, P. R., Rygg, M., Marhaug, G., Anderson-Gäre, B., Pedersen, F. K., Lahdenne, P., & Pelkonen, P. (2021). Fatigue in young adults with juvenile idiopathic arthritis 18 years after disease onset: data from the prospective Nordic JIA cohort. *Pediatric Rheumatology*, *19*(1). https://doi.org/10.1186/s12969-021-00499-0
10. Arnstad, E. D., Rypdal, V., Peltoniemi, S., Herlin, T., Berntson, L., Fasth, A., Nielsen, S., Glerup, M., Ekelund, M., Zak, M., Aalto, K., Nordal, E., Romundstad, P. R., & Rygg, M. (2019). Early Self-Reported Pain in Juvenile Idiopathic Arthritis as Related to Long-Term Outcomes: Results From the Nordic Juvenile Idiopathic Arthritis Cohort Study. *Arthritis Care and Research*, *71*(7), 961–969. https://doi.org/10.1002/acr.23715
11. Barut, K., Adrovic, A., Şahin, S., & Kasapçopur, Ö. (2017). Juvenile idiopathic arthritis. In *Balkan Medical Journal* (Vol. 34, Issue 2, pp. 90–101). Galenos Yayinevi Tic. Ltd. Sti. https://doi.org/10.4274/balkanmedj.2017.0111
12. Bielak, M., Husmann, E., Weyandt, N., Haas, J. P., Hügle, B., Horneff, G., Neudorf, U., Lutz, T., Lilienthal, E., Kallinich, T., Tenbrock, K., Berendes, R., Niehues, T., Wittkowski, H., Weißbarth-Riedel, E., Heubner, G., Oommen, P., Klotsche, J., Foell, D., & Lainka, E. (2018). IL-6 blockade in systemic juvenile idiopathic arthritis - achievement of inactive disease and remission (data from the German

AID-registry). *Pediatric Rheumatology*, *16*(1). https://doi.org/10.1186/s12969-018-0236-y

13. Brachat, A. H., Grom, A. A., Wulffraat, N., Brunner, H. I., Quartier, P., Brik, R., McCann, L., Ozdogan, H., Rutkowska-Sak, L., Schneider, R., Gerloni, V., Harel, L., Terreri, M., Houghton, K., Joos, R., Kingsbury, D., Lopez-Benitez, J. M., Bek, S., Schumacher, M., … Morris, P. (2017). Early changes in gene expression and inflammatory proteins in systemic juvenile idiopathic arthritis patients on canakinumab therapy. *Arthritis Research and Therapy*, *19*(1). https://doi.org/10.1186/s13075-016-1212-x
14. Brown, G. T., Wright, F. V., Lang, B. A., Birdi, N., Oen, K., Stephens, D., McComas, J., & Feldman, B. M. (2005). Clinical responsiveness of self-report functional assessment measures for children with juvenile idiopathic arthritis undergoing intraarticular corticosteroid injections. *Arthritis Care and Research*, *53*(6), 897–904. https://doi.org/10.1002/art.21599
15. Brunner, H. I., Quartier, P., Alexeeva, E., Constantin, T., Koné-Paut, I., Marzan, K., Schneider, R., Wulffraat, N. M., Chasnyk, V., Tirosh, I., Kallinich, T., Kuemmerle-Deschner, J., Wouters, C., Lauwerys, B., Nikishina, I., Trachana, M., Vougiouka, O., Martini, A., Lovell, D. J., … Ruperto, N. (2020). Efficacy and Safety of Canakinumab in Patients With Systemic Juvenile Idiopathic Arthritis With and Without Fever at Baseline: Results From an Open-Label, Active-Treatment Extension Study. *Arthritis and Rheumatology*, *72*(12), 2147–2158. https://doi.org/10.1002/art.41436
16. Connelly, M., Weiss, J. E., Abramson, L., Anderson, E., Andrew, M., Battle, N., Becker, M., Benham, H., Beukelman, T., Birmingham, J., Blier, P., Brown, A., Brunner, H., Cabrera, A., Canter, D., Carlton, D., Caruso, B., Ceracchio, L., Chalom, E., … Zhu, A. (2019). Pain, functional disability, and their Association in Juvenile Fibromyalgia Compared to other pediatric rheumatic diseases. *Pediatric Rheumatology*, *17*(1). https://doi.org/10.1186/s12969-019-0375-9
17. Consolaro, A., Giancane, G., Schiappapietra, B., Davì, S., Calandra, S., Lanni, S., & Ravelli, A. (2016). Clinical outcome measures in juvenile idiopathic arthritis. In *Pediatric Rheumatology* (Vol. 14, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/S12969-016-0085-5

18. Consolaro, A., Ruperto, N., Bazso, A., Pistorio, A., Magni-Manzoni, S., Filocamo, G., Malattia, C., Viola, S., Martini, A., & Ravelli, A. (2009). Development and validation of a composite disease activity score for juvenile idiopathic arthritis. *Arthritis Care and Research*, *61*(5), 658–666. https://doi.org/10.1002/art.24516
19. Conti, F., Pontikaki, I., Andrea, M., Ravelli, A., & Benedetti, F. (2018). *Patients with juvenile idiopathic arthritis become adults: the role of transitional care*.
20. el Eraky, A. Z., Handoka, N. M., Ghaly, M. S., Nasef, S. I., Eldahshan, N. A., Ibrahim, A. M., & Shalaby, S. (2016). Assessment of left atrial mechanical functions and atrial electromechanical delay in Juvenile idiopathic arthritis by tissue Doppler echocardiography. *Pediatric Rheumatology*, *14*(1). https://doi.org/10.1186/s12969-016-0122-4
21. Epps, H., Ginnelly, L., Utley, M., Southwood, T., Gallivan, S., Sculpher, M., & Woo, P. (2005). 39 Is hydrotherapy cost-effective? *Health Technology Assessment*, *9*(39). http://www.ncchta.org
22. Feger, D. M., Longson, N., Dodanwala, H., Ostrov, B. E., Olsen, N. J., & June, R. R. (2019). Comparison of Adults With Polyarticular Juvenile Idiopathic Arthritis to Adults With Rheumatoid Arthritis: A Cross-sectional Analysis of Clinical Features and Medication Use. *Journal of Clinical Rheumatology*, *25*(4), 163–170. https://doi.org/10.1097/RHU.0000000000000819
23. Foster, H. E., Marshall, N., Myers, A., Dunkley, P., & Griffiths, I. D. (2003). Outcome in adults with juvenile idiopathic arthritis: A quality of life study. *Arthritis and Rheumatism*, *48*(3), 767–775. https://doi.org/10.1002/art.10863
24. Gabay, C., Fautrel, B., Rech, J., Spertini, F., Feist, E., Kötter, I., Hachulla, E., Morel, J., Schaeverbeke, T., Hamidou, M. A., Martin, T., Hellmich, B., Lamprecht, P., Schulze-Koops, H., Courvoisier, D. S., Sleight, A., & Schiffrin, E. J. (2018). Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. *Annals of the Rheumatic Diseases*, *77*(6), 840–847. https://doi.org/10.1136/annrheumdis-2017-212608
25. García-Fernández, A., Briones-Figueroa, A., Calvo-Sanz, L., Andreu-Suárez, Á., & Boteanu, A. (2022). Evaluation of flare rate and reduction strategies for bDMARDs in juvenile idiopathic arthritis: real world data from a single-centre

cohort. *Rheumatology International*, *42*(7), 1133–1142. https://doi.org/10.1007/s00296-022-05108-1

26. García-Fernández, A., Gerardi, M. C., Crisafulli, F., Filippini, M., Fredi, M., Gorla, R., Lazzaroni, M. G., Lojacono, A., Nalli, C., Ramazzotto, F., Taglietti, M., Zanardini, C., Zatti, S., Franceschini, F., Tincani, A., & Andreoli, L. (2021). Disease course and obstetric outcomes of pregnancies in juvenile idiopathic arthritis: are there any differences among disease subtypes? A single-centre retrospective study of prospectively followed pregnancies in a dedicated pregnancy clinic. *Clinical Rheumatology*, *40*(1), 239–244. https://doi.org/10.1007/s10067-020-05404-w
27. Glerup, M., Rypdal, V., Arnstad, E. D., Ekelund, M., Peltoniemi, S., Aalto, K., Rygg, M., Toftedal, P., Nielsen, S., Fasth, A., Berntson, L., Nordal, E., & Herlin, T. (2020). Long-Term Outcomes in Juvenile Idiopathic Arthritis: Eighteen Years of Follow-Up in the Population-Based Nordic Juvenile Idiopathic Arthritis Cohort. *Arthritis Care and Research*, *72*(4), 507–516. https://doi.org/10.1002/acr.23853
28. Glerup, M., Thiel, S., Rypdal, V., Arnstad, E. D., Ekelund, M., Peltoniemi, S., Aalto, K., Rygg, M., Nielsen, S., Fasth, A., Berntson, L., Nordal, E., & Herlin, T. (2019). Complement lectin pathway protein levels reflect disease activity in juvenile idiopathic arthritis: A longitudinal study of the Nordic JIA cohort. *Pediatric Rheumatology*, *17*(1). https://doi.org/10.1186/s12969-019-0367-9
29. Hazel, E., Zhang, X., Duffy, C. M., & Campillo, S. (2010). High rates of unsuccessful transfer to adult care among young adults with juvenile idiopathic arthritis. *Pediatric Rheumatology*, *8*. https://doi.org/10.1186/1546-0096-8-2
30. Hinks, A., Moncrieffe, H., Martin, P., Ursu, S., Lal, S., Kassoumeri, L., Weiler, T., Glass, D. N., Thompson, S. D., Wedderburn, L. R., & Thomson, W. (2011). Association of the 5-aminoimidazole-4-carboxamide ribonucleotide transformylase gene with response to methotrexate in juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases*, *70*(8), 1395–1400. https://doi.org/10.1136/ard.2010.146191
31. Ilowite, N. T., Prather, K., Lokhnygina, Y., Schanberg, L. E., Elder, M., Milojevic, D., Verbsky, J. W., Spalding, S. J., Kimura, Y., Imundo, L. F., Punaro, M. G., Sherry, D. D., Tarvin, S. E., Zemel, L. S., Birmingham, J. D., Gottlieb, B. S., Miller, M. L.,

O'Neil, K., Ruth, N. M., … Sandborg, C. I. (2014). Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. *Arthritis and Rheumatology*, *66*(9), 2570–2579. https://doi.org/10.1002/art.38699

32. Jetha, A., Badley, E., Beaton, D., Fortin, P. R., Shiff, N. J., Rosenberg, A. M., Tucker, L. B., Mosher, D. P., & Gignac, M. A. M. (2014). Transitioning to employment with a rheumatic disease: The role of independence, overprotection, and social support. *Journal of Rheumatology*, *41*(12), 2386–2394. https://doi.org/10.3899/jrheum.140419
33. Lequerré, T., Quartier, P., Rosellini, D., Alaoui, F., de Bandt, M., Mejjad, O., Kone-Paut, I., Michel, M., Demis, E., Khellaf, M., Limai, N., Job-Deslandre, C., Fautrel, B., le Loët, X., & Sibilia, J. (2008). Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: Preliminary experience in France. *Annals of the Rheumatic Diseases*, *67*(3), 302–308. https://doi.org/10.1136/ard.2007.076034
34. Lovell, D. J., Giannini, E. H., Reiff, A. O., Kimura, Y., Li, S., Hashkes, P. J., Wallace, C. A., Onel, K. B., Foell, D., Wu, R., Biedermann, S., Hamilton, J. D., & Radin, A. R. (2013). Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. *Arthritis and Rheumatism*, *65*(9), 2486–2496. https://doi.org/10.1002/art.38042
35. Lovell, D. J., Johnson, A. L., Huang, B., Gottlieb, B. S., Morris, P. W., Kimura, Y., Onel, K., Li, S. C., Grom, A. A., Taylor, J., Brunner, H. I., Huggins, J. L., Nocton, J. J., Haines, K. A., Edelheit, B. S., Shishov, M., Jung, L. K., Williams, C. B., Tesher, M. S., … Giannini, E. H. (2018). Risk, Timing, and Predictors of Disease Flare After Discontinuation of Anti–Tumor Necrosis Factor Therapy in Children With Polyarticular Forms of Juvenile Idiopathic Arthritis With Clinically Inactive Disease. *Arthritis and Rheumatology*, *70*(9), 1508–1518. https://doi.org/10.1002/art.40509
36. McErlane, F., Beresford, M. W., Baildam, E. M., Chieng, S. E. A., Davidson, J. E., Foster, H. E., Gardner-Medwin, J., Lunt, M., Wedderburn, L. R., Thomson, W., & Hyrich, K. L. (2013). Validity of a three-variable Juvenile Arthritis Disease Activity Score in children with new-onset juvenile idiopathic arthritis. *Annals of the*

Rheumatic Diseases, *72*(12), 1983–1988. https://doi.org/10.1136/annrheumdis-2012-202031

37. Mena-Vázquez, N., Cabezudo-García, P., Ortiz-Márquez, F., Díaz-Cordovés Rego, G., Muñoz-Becerra, L., Manrique-Arija, S., & Fernández-Nebro, A. (2021). Evaluation of cognitive function in adult patients with juvenile idiopathic arthritis. *International Journal of Rheumatic Diseases*, *24*(1), 81–89. https://doi.org/10.1111/1756-185X.14009
38. Minden, K., Niewerth, M., Listing, J., Biedermann, T., Bollow, M., Schöntube, M., & Zink, A. (2002). Long-term outcome in patients with juvenile idiopathic arthritis. *Arthritis and Rheumatism*, *46*(9), 2392–2401. https://doi.org/10.1002/art.10444
39. Moorthy, L. N., Peterson, M. G. E., Hassett, A. L., & Lehman, T. J. A. (2010). Burden of childhood-onset arthritis. In *Pediatric Rheumatology* (Vol. 8). https://doi.org/10.1186/1546-0096-8-20
40. Mori, M., Takei, S., Imagawa, T., Imanaka, H., Nerome, Y., Higuchi, R., Kawano, Y., Yokota, S., Sugiyama, N., Yuasa, H., Fletcher, T., & Wajdula, J. S. (2012). Safety and efficacy of long-term etanercept in the treatment of methotrexate-refractory polyarticular-course juvenile idiopathic arthritis in Japan. *Modern Rheumatology*, *22*(5), 720–726. https://doi.org/10.1007/s10165-011-0578-5
41. Mourão, A. F., Santos, M. J., Melo Gomes, J. A., Martins, F. M., Mendonça, S. C., Oliveira Ramos, F., Fernandes, S., Salgado, M., Guedes, M., Carvalho, S., Costa, J. A., Brito, I., Duarte, C., Furtado, C., Lopes, A., Rodrigues, A., Sequeira, G., Branco, J. C., Fonseca, J. E., & Canhão, H. (2016). Effectiveness and long-term retention of anti-tumour necrosis factor treatment in juvenile and adult patients with juvenile idiopathic arthritis: Data from Reuma.pt. *Rheumatology (United Kingdom)*, *55*(4), 697–703. https://doi.org/10.1093/rheumatology/kev398
42. Nesbitt, C., Kuntze, G., Toomey, C., Esau, S., Brooks, J., Mosher, D., Twilt, M., Nettel-Aguirre, A., Palacios-Derflingher, L. M., Ronsky, J., Benseler, S., & Emery, C. A. (2022). Secondary consequences of juvenile idiopathic arthritis in children and adolescents with knee involvement: physical activity, adiposity, fitness, and functional performance. *Rheumatology International*, *42*(2), 319–327. https://doi.org/10.1007/s00296-021-04920-5

43. Nirmala, N., Brachat, A., Feist, E., Blank, N., Specker, C., Witt, M., Zernicke, J., Martini, A., & Junge, G. (2015). Gene-expression analysis of adult-onset Still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatric Rheumatology*, *13*(1). https://doi.org/10.1186/s12969-015-0047-3

44. Nishimura, K., Hara, R., Umebayashi, H., Takei, S., Iwata, N., Imagawa, T., Shimizu, M., Tomiita, M., Seko, N., Kitawaki, T., & Yokota, S. (2021). Efficacy and safety of canakinumab in systemic juvenile idiopathic arthritis: 48-week results from an open-label phase III study in Japanese patients. *Modern Rheumatology*, *31*(1), 226–234. https://doi.org/10.1080/14397595.2020.1783163

45. Nordal, E. B., Zak, M., Aalto, K., Berntson, L., Fasth, A., Herlin, T., Lahdenne, P., Nielsen, S., Peltoniemi, S., Straume, B., & Rygg, M. (2012a). Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. *Annals of the Rheumatic Diseases*, *71*(7), 1122–1127. https://doi.org/10.1136/annrheumdis-2011-200237

46. Nordal, E. B., Zak, M., Aalto, K., Berntson, L., Fasth, A., Herlin, T., Lahdenne, P., Nielsen, S., Peltoniemi, S., Straume, B., & Rygg, M. (2012b). Validity and predictive ability of the juvenile arthritis disease activity score based on CRP versus ESR in a Nordic population-based setting. *Annals of the Rheumatic Diseases*, *71*(7), 1122–1127. https://doi.org/10.1136/annrheumdis-2011-200237

47. Nordal, E., Zak, M., Aalto, K., Berntson, L., Fasth, A., Herlin, T., Lahdenne, P., Nielsen, S., Straume, B., & Rygg, M. (2011). Ongoing disease activity and changing categories in a long-term nordic cohort study of juvenile idiopathic arthritis. *Arthritis and Rheumatism*, *63*(9), 2809–2818. https://doi.org/10.1002/art.30426

48. Oen, K., Malleson, P. N., Cabral, D. A., Rosenberg, A. M., Petty, R. E., & Cheang, M. (2002). *Disease Course and Outcome of Juvenile Rheumatoid Arthritis in a Multicenter Cohort*. www.jrheum.org

49. Okamoto, N., Yokota, S., Takei, S., Okura, Y., Kubota, T., Shimizu, M., Nozawa, T., Iwata, N., Umebayashi, H., Kinjo, N., Kunishima, T., Yasumura, J., & Mori, M.

(2019). Clinical practice guidance for juvenile idiopathic arthritis (JIA) 2018. *Modern Rheumatology*, *29*(1), 41–59. https://doi.org/10.1080/14397595.2018.1514724

50. Oliveira Ramos, F., Rodrigues, A., Magalhaes Martins, F., Melo, A. T., Aguiar, F., Brites, L., Azevedo, S., Duarte, A. C., Furtado, C., Mourão, A. F., Sequeira, G., Cunha, I., Figueira, R., Melo Gomes, J. A., Santos, M. J., & Fonseca, J. E. (2021). Health-related quality of life and disability in adults with juvenile idiopathic arthritis: Comparison with adult-onset rheumatic diseases. *RMD Open*, *7*(3). https://doi.org/10.1136/rmdopen-2021-001766
51. Oliveira-Ramos, F., Eusébio, M., Martins, F. M., Mouraõ, A. F., Furtado, C., Campanilho-Marques, R., Cordeiro, I., Ferreira, J., Cerqueira, M., Figueira, R., Brito, I., Canhaõ, H., Santos, M. J., Melo-Gomes, J. A., & Fonseca, J. E. (2016). Juvenile idiopathic arthritis in adulthood: Fulfilment of classification criteriafor adult rheumatic diseases, long-term outcomes and predictors of inactive disease, functional status and damage. *RMD Open*, *2*(2). https://doi.org/10.1136/rmdopen-2016-000304
52. Opoka-Winiarska, V., Żuber, Z., Alexeeva, E., Chasnyk, V., Nikishina, I., Dębowska, G., & Smolewska, E. (2018). Long-term, interventional, open-label extension study evaluating the safety of tocilizumab treatment in patients with polyarticular-course juvenile idiopathic arthritis from Poland and Russia who completed the global, international CHERISH trial. *Clinical Rheumatology*, *37*(7), 1807–1816. https://doi.org/10.1007/s10067-018-4071-9
53. Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., Mcdonald, S., … Mckenzie, J. E. (2021). PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. In *The BMJ* (Vol. 372). BMJ Publishing Group. https://doi.org/10.1136/bmj.n160
54. Pileggi, G. S., de Souza, C. B. S., & Ferriani, V. P. L. (2010). Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. *Arthritis Care and Research*, *62*(7), 1034–1039. https://doi.org/10.1002/acr.20183

55. Powell, M., Seid, M., & Szer, I. S. (2005). Efficacy of Custom Foot Orthotics in Improving Pain and Functional Status in Children with Juvenile Idiopathic Arthritis. In *The Journal of Rheumatology*. www.jrheum.org

56. Quartier, P., Allantaz, F., Cimaz, R., Pillet, P., Messiaen, C., Bardin, C., Bossuyt, X., Boutten, A., Bienvenu, J., Duquesne, A., Richer, O., Chaussabel, D., Mogenet, A., Banchereau, J., Treluyer, J. M., Landais, P., & Pascual, V. (2011). A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Annals of the Rheumatic Diseases*, *70*(5), 747–754. https://doi.org/10.1136/ard.2010.134254

57. Quartier, P., Taupin, P., Bourdeaut, F., Lemelle, I., Pillet, P., Bost, M., Sibilia, J., Koné-Paut, I., Gandon-Laloum, S., LeBideau, M., Bader-Meunier, B., Mouy, R., Debré, M., Landais, P., & Prieur, A. M. (2003). Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. *Arthritis and Rheumatism*, *48*(4), 1093–1101. https://doi.org/10.1002/art.10885

58. Raab, A., Sengler, C., Niewerth, M., Klotsche, J., Horneff, G., Zink, A., Girschick, H., Weber, K., Minden, K., Raab, A., Sengler, C., Niewerth, M., Klotsche, J., Horneff, G., Zink, A., Girschick, H., Weber, K., & Minden, K. (2013). Paediatric rheumatology Comorbidity profiles among adult patients with juvenile idiopathic arthritis: results of a biologic register PAEDIATRIC RHEUMATOLOGY Comorbidities in adult JIA / A. Raab et al. In *Clinical and Experimental Rheumatology* (Vol. 31).

59. Ravelli, A., Consolaro, A., Horneff, G., Laxer, R. M., Lovell, D. J., Wulffraat, N. M., Akikusa, J. D., Al-Mayouf, S. M., Antón, J., Avcin, T., Berard, R. A., Beresford, M. W., Burgos-Vargas, R., Cimaz, R., De Benedetti, F., Demirkaya, E., Foell, D., Itoh, Y., Lahdenne, P., … Smolen, J. S. (2018). Treating juvenile idiopathic arthritis to target: Recommendations of an international task force. *Annals of the Rheumatic Diseases*, *77*(6), 819–828. https://doi.org/10.1136/annrheumdis-2018-213030

60. Ravelli, A., & Martini, A. (2007). Juvenile idiopathic arthritis. In *www.thelancet.com* (Vol. 369). www.thelancet.com

61. Relas, H., & Kosola, S. (2019). Acceptable quality of life and low disease activity achievable among transition phase patients with rheumatic disease. *Clinical Rheumatology*, *38*(3), 785–791. https://doi.org/10.1007/s10067-018-4351-4

62. Ringold, S., Bittner, R., Neogi, T., Wallace, C. A., & Singer, N. G. (2010). Performance of rheumatoid arthritis disease activity measures and juvenile arthritis disease activity scores in polyarticular-course juvenile idiopathic arthritis: Analysis of their ability to classify the american college of rheumatology pediatric measures of response and the preliminary criteria for flare and inactive disease. *Arthritis Care and Research*, *62*(8), 1095–1102. https://doi.org/10.1002/acr.20205

63. Ruperto, N., Brunner, H. I., Quartier, P., Constantin, T., Wulffraat, N., Horneff, G., Brik, R., McCann, L., Kasapcopur, O., Rutkowska-Sak, L., Schneider, R., Berkun, Y., Calvo, I., Erguven, M., Goffin, L., Hofer, M., Kallinich, T., Oliveira, S. K., Uziel, Y., … Lovell, D. J. (2012). Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. *New England Journal of Medicine*, *367*(25), 2396–2406. https://doi.org/10.1056/nejmoa1205099

64. Ruperto, N., Brunner, H. I., Quartier, P., Constantin, T., Wulffraat, N. M., Horneff, G., Kasapcopur, O., Schneider, R., Anton, J., Barash, J., Berner, R., Corona, F., Cuttica, R., Fouillet-Desjonqueres, M., Fischbach, M., Foster, H. E., Foell, D., Radominski, S. C., Ramanan, A. v., … Lovell, D. J. (2018a). Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: Results from the 5-year long-term extension of the phase III pivotal trials. *Annals of the Rheumatic Diseases*, *77*(12), 1710–1719. https://doi.org/10.1136/annrheumdis-2018-213150

65. Ruperto, N., Brunner, H. I., Quartier, P., Constantin, T., Wulffraat, N. M., Horneff, G., Kasapcopur, O., Schneider, R., Anton, J., Barash, J., Berner, R., Corona, F., Cuttica, R., Fouillet-Desjonqueres, M., Fischbach, M., Foster, H. E., Foell, D., Radominski, S. C., Ramanan, A. v., … Lovell, D. J. (2018b). Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: Results from the 5-year long-term extension of the phase III pivotal trials. *Annals of the Rheumatic Diseases*, *77*(12), 1710–1719. https://doi.org/10.1136/annrheumdis-2018-213150

66. Rypdal, V., Glerup, M., Songstad, N. T., Bertelsen, G., Christoffersen, T., Arnstad, E. D., Aalto, K., Berntson, L., Fasth, A., Herlin, T., Ekelund, M., Peltoniemi, S., Toftedal, P., Nielsen, S., Leinonen, S., Bangsgaard, R., Nielsen, R., Rygg, M., Nordal, E., & Zak, M. (2021). Uveitis in Juvenile Idiopathic Arthritis: 18-Year Outcome in the Population-based Nordic Cohort Study. *Ophthalmology*, *128*(4), 598–608. https://doi.org/10.1016/j.ophtha.2020.08.024

67. Sandstad, J., Stensvold, D., Hoff, M., Nes, B. M., Arbo, I., & Bye, A. (2015). The effects of high intensity interval training in women with rheumatic disease: a pilot study. *European Journal of Applied Physiology*, *115*(10), 2081–2089. https://doi.org/10.1007/s00421-015-3186-9

68. Schmeling, H., & Horneff, G. (2005). Etanercept and uveitis in patients with juvenile idiopathic arthritis. *Rheumatology*, *44*(8), 1008–1011. https://doi.org/10.1093/rheumatology/keh658

69. Selvaag, A. M., Aulie, H. A., Lilleby, V., & Flatø, B. (2016). Disease progression into adulthood and predictors of long-term active disease in juvenile idiopathic arthritis. *Annals of the Rheumatic Diseases*, *75*(1), 190–195. https://doi.org/10.1136/annrheumdis-2014-206034

70. Selvaag, A. M., Kirkhus, E., Törnqvist, L., Lilleby, V., Aulie, H. A., & Flatø, B. (2017). Radiographic damage in hands and wrists of patients with juvenile idiopathic arthritis after 29 years of disease duration. *Pediatric Rheumatology*, *15*(1). https://doi.org/10.1186/s12969-017-0151-7

71. Shih, Y. J., Yang, Y. H., Lin, C. Y., Chang, C. L., & Chiang, B. L. (2019). Enthesitis-related arthritis is the most common category of juvenile idiopathic arthritis in Taiwan and presents persistent active disease. *Pediatric Rheumatology*, *17*(1). https://doi.org/10.1186/s12969-019-0363-0

72. Shoop-Worrall, S. J. W., Kearsley-Fleet, L., Thomson, W., Verstappen, S. M. M., & Hyrich, K. L. (2017). How common is remission in juvenile idiopathic arthritis: A systematic review. In *Seminars in Arthritis and Rheumatism* (Vol. 47, Issue 3, pp. 331–337). W.B. Saunders. https://doi.org/10.1016/j.semarthrit.2017.05.007

73. Shukla, A., Gaur, P., & Aggarwal, A. (2016). Effect of probiotics on clinical and immune parameters in enthesitis-related arthritis category of juvenile idiopathic

arthritis. *Clinical and Experimental Immunology*, *185*(3), 301–308. https://doi.org/10.1111/cei.12818

74. Sieczkowska, S. M., Astley, C., Marques, I. G., Iraha, A. Y., Franco, T. C., Ihara, B. P., Martins Lavorato, S. S., Lindoso, L., Demitrol Setoue, D. N., Tanigava, N. Y., Campos, L. M. A., Pereira, R. M. R., Aikawa, N. E., Roschel, H., Queiroz, L. B., Polanczyk, G. v., Silva, C. A., & Gualano, B. (2022). A home-based exercise program during COVID-19 pandemic: Perceptions and acceptability of juvenile systemic lupus erythematosus and juvenile idiopathic arthritis adolescents. *Lupus*, *31*(4), 443–456. https://doi.org/10.1177/09612033221083273
75. Stringer, E., Scott, R., Mosher, D., MacNeill, I., Huber, A. M., Ramsey, S., & Lang, B. (2015). Evaluation of a rheumatology transition clinic. *Pediatric Rheumatology*, *13*(1). https://doi.org/10.1186/s12969-015-0016-x
76. Tibaldi, J., Pistorio, A., Aldera, E., Puzone, L., El Miedany, Y., Pal, P., Giri, P. P., De, H., Khubchandani, R., Chavan, P. P., Vilaiyuk, S., Lerkvaleekul, B., Yamsuwan, J., Sabui, T. K., Datta, P., Pardeo, M., Bracaglia, C., Sawhney, S., Mittal, S., … Ravelli, A. (2020). Development and initial validation of a composite disease activity score for systemic juvenile idiopathic arthritis. *Rheumatology (United Kingdom)*, *59*(11), 3505–3514. https://doi.org/10.1093/rheumatology/keaa240
77. Tollisen, A., Selvaag, A. M., Aasland, A., Lerdal, A., & Flatø, B. (2019). Longitudinal health status from early disease to adulthood and associated prognostic factors in juvenile idiopathic arthritis. *Journal of Rheumatology*, *46*(10), 1335–1344. https://doi.org/10.3899/jrheum.180948
78. Tollisen, A., Selvaag, A. M., Aulie, H. A., Lilleby, V., Aasland, A., Lerdal, A., & Flatø, B. (2018). Physical Functioning, Pain, and Health-Related Quality of Life in Adults With Juvenile Idiopathic Arthritis: A Longitudinal 30-Year Followup Study. *Arthritis Care and Research*, *70*(5), 741–749. https://doi.org/10.1002/acr.23327
79. Trincianti, C., & Consolaro, A. (2020). Outcome Measures for Juvenile Idiopathic Arthritis Disease Activity. *Arthritis Care and Research*, *72*(S10), 150–162. https://doi.org/10.1002/acr.24192
80. Ursin, K., Lydersen, S., Skomsvoll, J. F., & Wallenius, M. (2018). Disease activity of juvenile idiopathic arthritis during and after pregnancy: A prospective

multicenter study. In *Journal of Rheumatology* (Vol. 45, Issue 2, pp. 257–265). Journal of Rheumatology. https://doi.org/10.3899/jrheum.161410

81. van pelt, P. A., Drossaert, C. H. C., Kruize, A. A., Huisman, J., Dolhain, R. J. E. M., & Wulffraat, N. M. (2015). Use and perceived relevance of health-related internet sites and online contact with peers among young people with juvenile idiopathic arthritis. *Rheumatology (United Kingdom)*, *54*(10), 1833–1841. https://doi.org/10.1093/rheumatology/kev193
82. van Rossum, M. A. J., van Soesbergen, R. M., Boers, M., Zwinderman, A. H., Fiselier, T. J. W., Franssen, M. J. A. M., ten Cate, R., van Suijlekom-Smit, L. W. A., Wulffraat, N. M., van Luijk, W. H. J., Oostveen, J. C. M., Kuis, W., & Dijkmans, B. A. C. (2007). Long-term outcome of juvenile idiopathic arthritis following a placebo-controlled trial: Sustained benefits of early sulfasalazine treatment. *Annals of the Rheumatic Diseases*, *66*(11), 1518–1524. https://doi.org/10.1136/ard.2006.064717
83. Vidqvist, K. L., Malin, M., Varjolahti-Lehtinen, T., & Korpela, M. M. (2013). Disease activity of idiopathic juvenile arthritis continues through adolescence despite the use of biologic therapies. *Rheumatology (United Kingdom)*, *52*(11), 1999–2003. https://doi.org/10.1093/rheumatology/ket256
84. Vroegindeweij, A., Swart, J. F., Houtveen, J., Eijkelkamp, N., van de Putte, E. M., Wulffraat, N. M., & Nijhof, S. L. (2022). Identifying disrupted biological factors and patient-tailored interventions for chronic fatigue in adolescents and young adults with Q-Fever Fatigue Syndrome, Chronic Fatigue Syndrome and Juvenile Idiopathic Arthritis (QFS-study): study protocol for a randomized controlled trial with single-subject experimental case series design. *Trials*, *23*(1), 683. https://doi.org/10.1186/s13063-022-06620-2
85. Wu, Q., Chaplin, H., Ambrose, N., Sen, D., Leandro, M. J., Wing, C., Daly, N., Webb, K., Fisher, C., Suffield, L., Josephs, F., Pilkington, C., Eleftheriou, D., Al-Obaidi, M., Compeyrot-Lacassagne, S., Wedderburn, L. R., & Ioannou, Y. (2016). Juvenile arthritis disease activity score is a better reflector of active disease than the disease activity score 28 in adults with polyarticular juvenile idiopathic arthritis. In *Annals of the Rheumatic Diseases* (Vol. 75, Issue 3, pp. 635–636). BMJ Publishing Group. https://doi.org/10.1136/annrheumdis-2015-208462

86. Yokota, S., Imagawa, T., Mori, M., Miyamae, T., Aihara, Y., Takei, S., Iwata, N., Umebayashi, H., Murata, T., Miyoshi, M., Tomiita, M., Nishimoto, N., & Kishimoto, T. (2008). Articles Effi cacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. In *www.thelancet.com* (Vol. 371). www.thelancet.com

87. Yokota, S., Imagawa, T., Mori, M., Miyamae, T., Takei, S., Iwata, N., Umebayashi, H., Murata, T., Miyoshi, M., Tomiita, M., Nishimoto, N., & Kishimoto, T. (2014). Longterm safety and effectiveness of the anti-interleukin 6 receptor monoclonal antibody tocilizumab in patients with systemic juvenile idiopathic arthritis in Japan. *Journal of Rheumatology*, *41*(4), 759–767. https://doi.org/10.3899/jrheum.130690

88. Zak, M., & Pedersen, F. K. (2000). Juvenile chronic arthritis into adulthood: a long-term follow-up study. In *Rheumatology* (Vol. 39).

89. Zonneveld-Huijssoon, E., Ronaghy, A., van Rossum, M. A. J., Rijkers, G. T., van der Klis, F. R. M., Sanders, E. A. M., Vermeer-De Bondt, P. E., Hoes, A. W., van der Net, J. J., Engels, C., Kuis, W., Prakken, B. J., van Tol, M. J. D., & Wulffraat, N. M. (2007). Safety and efficacy of meningococcal C vaccination in juvenile idiopathic arthritis. *Arthritis and Rheumatism*, *56*(2), 639–646. https://doi.org/10.1002/art.22399