Full question verification analysis of summary questions JIA PSP

KLACHTEN IN REMISSIE

Q1

Question	Ref		Article name	Article link
Pijn en vermoeidheid komen veel voor terwijl de ziekte rustig is. Hoe kan dit, wat kun je eraan doen, en kun je voorspellen welke patiënt hier last van krijgt?	[1]	Systematic review	Hyperexcitability of the Central Nervous System in Children with Chronic Pain: A Systematic Review.	https://www.ncbi.nlm.nih.gov/pubmed/29304243
	[2]	Longitudinal study	Patterns of pain over time among children with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29175824
	[3]	Longitudinal study	Predicting Which Children with Juvenile Idiopathic Arthritis Will Have a Severe Disease Course: Results from the ReACCh-Out Cohort.	https://www.ncbi.nlm.nih.gov/pubmed/27980015

Summary of findings	Hyperexcitability of the CNS may be an underlying cause of chronic pain in children. Secondary hyperalgesia has also been found in children with JIA. Studies "suggested that the presence of secondary hyperalgesia might be the result of long-lasting nociceptive bombardment from inflamed joints, leading to peripheral and central hyperexcitability of nociceptive afferents." [1] Factors associated with consistently high levels of pain included higher age at onset of disease and longer disease duration. [2] A severe course of disease could be predicted by higher joint count, RF positivity, presence of morning stiffness, and presence of enthesitis. [3]
Evaluation	CNS hyperexcitability is the only underlying factor found in literature. Several factors predictive of a severe disease course are specified. No suggestions of improvement of symptoms while in remission are made. No literature on fatigue in remission has been found.
Is the question answered?	Insufficiently answered

VERMOEIDHEID

Q2

Question	Ref		Article name	Article link
Waarom zijn kinderen met jeugdreuma sneller vermoeid, wat kan hieraan worden gedaan, en hoe kun je het beste met vermoeidheid omgaan in het dagelijks leven?	[4]	Systematic review	Fatigue in patients with juvenile idiopathic arthritis: A systematic review of the literature.	https://www.ncbi.nlm.nih.gov/pubmed/26656031
	[5]	Lab study	Juvenile Arthritis Patients Suffering from Chronic Inflammation Have Increased Activity of Both IDO and GTP-CH1 Pathways But Decreased BH4 Efficacy: Implications for Well-Being, Including Fatigue, Cognitive Impairment, Anxiety, and Depression.	https://www.ncbi.nlm.nih.gov/pubmed/30625990
	[6]	Qualitative design approach	Developing and Evaluating JIApp: Acceptability and Usability of a Smartphone App System to Improve Self-Management in Young People With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28811270
	[7]	RCT	The iPeer2Peer Program: a pilot randomized controlled trial in adolescents with Juvenile Idiopathic Arthritis	https://www.ncbi.nlm.nih.gov/pubmed/27590668
	[A]	Systematic review	Fatigue in patients with juvenile idiopathic arthritis: A systematic review of the literature	https://reader.elsevier.com/reader/sd/pii/S0049017215002693?token=7B6D9A913969B03011F8AE0A573CE091F328B3E8779A0B5C608FFA78C27BC684F910054FACDE7EFEFDBDA60189C2B400

Summary of findings	A review suggest that use of DMARDs , stress, anxiety, and psychiatric distress were associated with fatigue. [4] Another study suggest that due to the increased enzymatic activity of IDO and GTP-Ch1 and decreased efficacy of co-factor BH4, there is a decrease in dopamine levels, which has been associated with anhedonia and severe fatigue. [5] Fatigue is correlated with disease activity, HRQoL, sleep disturbances, mood, medication, stress, and most strongly - pain. There seems to be a complex interplay between these factors. Furthermore, a study found that muscle fibers are inflamed in JIA. So muscle weakness could also contribute to fatigue. [A] A self-management app [6] and an online peer mentoring program [7] are recommended for self-management of the disease.

Evaluation	There are several suggestions of reasons for fatigue and ways of managing it.
Is the question answered?	Partially answered

PIJN

Q3

Question	Ref		Article name	Article link
Hoe kan pijn het beste worden herkend en behandeld (met medicatie), en wat kun je als patiënt zelf doen?	[8]	Systematic review	Ottawa Panel Evidence-Based Clinical Practice Guidelines for Structured Physical Activity in the Management of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27932265
	[11]	RCT	Effect of Electromyographic Biofeedback Training on Pain, Quadriceps Muscle Strength, and Functional Ability in Juvenile Rheumatoid Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27149595
	[9]	Systematic review	Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents.	https://www.ncbi.nlm.nih.gov/pubmed/28770976
	[10]	Lit review, interviews, focus groups	Development and validation of the self-reported PROMIS pediatric pain behavior item bank and short form scale.	https://www.ncbi.nlm.nih.gov/pubmed/28394851
	[12]	RCT	Effects of Combined Resistive Underwater Exercises and Interferential Current Therapy in Patients with Juvenile Idiopathic Arthritis: A Randomized Controlled Trial.	https://www.ncbi.nlm.nih.gov/pubmed/26135372
	[13]	Systematic review	Effects of Structured Exercise Training in Children and Adolescents With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30557274
	[14]	randomized, double-blind, placebo-controlled trial	Long-Term Effect of Pulsed Nd:YAG Laser in the Treatment of Children with Juvenile Rheumatoid Arthritis: A Randomized Controlled Trial.	https://www.ncbi.nlm.nih.gov/pubmed/30016193
	[18]	randomised clinical trial	Multisite Randomized Clinical Trial Evaluating an Online Self-Management Program for Adolescents With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30204919

	[7]	RCT	The iPeer2Peer Program: a pilot randomized controlled trial in adolescents with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27590668
	[6]	Qualitative design approach	Developing and Evaluating JIApp: Acceptability and Usability of a Smartphone App System to Improve Self-Management in Young People With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28811270
	[15]	Systematic review	Ottawa Panel Evidence-Based Clinical Practice Guidelines for Foot Care in the Management of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/26707409
	[16]	Systematic review	Cannabinoids for the treatment of rheumatic diseases - where do we stand?	https://www.ncbi.nlm.nih.gov/pubmed/29884803
	[17]	Systematic review	Non-pharmacological options for managing chronic musculoskeletal pain in children with paediatric rheumatic disease: a systematic review.	https://www.ncbi.nlm.nih.gov/pubmed/30155667
	[B]	Systematic review	Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents	https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011118.pub2/full
	[C]	Systematic review	The clinical effectiveness of intra-articular corticosteroids for arthritis of the lower limb in juvenile idiopathic arthritis: a systematic review - 2014	https://ped-rheum.biomedcentral.com/articles/10.1186/1546-0096-12-23
	[D]	Systematic review	Orthodontic and dentofacial orthopedic management of juvenile idiopathic arthritis: a systematic review of the literature	https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-6343.2011.01514.x

Summary of findings	Physical exercise [13], including in the form of pilates [8] and combined resistive underwater exercises with interferential current therapy [12] is recommended for pain management. Pulsed Nd:YAG laser combined with exercise may also be effective in managing pain. [14] For foot pain management, foot orthotics may be useful. [15] Non-pharmacological options, namely exercise and psychological interventions have been shown to have a modest beneficial effect on pain in paediatric rheumatic disease. [17] EMG biofeedback training may improve pain symptoms. [11] It is unclear whether chronic pain in children can be effectively treated with NSAIDs. [9] Likewise, there is insufficient evidence for the recommendation of cannabinoids in rheumatic disease. [16] A

	pediatric pain measurement form has been developed. [10] A self-management app [6], an online peer mentoring program [7], and a self-directed online training program [18] are recommended for self-management of the disease. Psychological therapies delivered remotely, primarily via the Internet, confer benefit in reducing the intensity or severity of pain after treatment. [B] Intra-articular corticosteroid injections (IACIs) are often used as the main form of management in milder oligoarticular JIA, and also as an adjunct to systemic therapy in other JIA subtypes to induce rapid relief of symptoms through resolution of localised synovitis. Evidence is however weak and inconclusive[C] There is limited evidence that dentofacial orthopedic treatment using functional appliances can improve mandibular retrognathia and reduce pain in adolescent patients with JIA. [D]
Evaluation	Several non-medication options for pain management are recommended. Self-management options are suggested for personal pain management. IACIs may be an option for mild oligoarticular JIA.
Is the question answered?	Partially answered

GEVOLGEN

Q4

Question	Ref		Article name	Article link
Waarom hebben kinderen met jeugdreuma slaapproblemen en wat is er tegen te doen?	[19]	Polysomnography, surveys, MSLT, neurobehavioral performance tests	Sleep Disturbances and Neurobehavioral Performance in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28089981
	[20]	Polysomnography, questionnaires	Congruence between polysomnography obstructive sleep apnea and the pediatric sleep questionnaire: fatigue and health-related quality of life in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27987106
	[21]	Sleep diary, pain assesment	Prospective Mediation Models of Sleep, Pain, and Daily Function in Children With Arthritis Using Ecological Momentary Assessment.	https://www.ncbi.nlm.nih.gov/pubmed/26340651

	[254]	Sys review	A Systematic Review of Sleep in Pediatric Pain Populations	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3562475/
	[E]	Sys review	Sleep problems and associated factors in children with juvenile idiopathic arthritis: a systematic review -2014	https://ped-rheum.biomedcentral.com/articles/10.1186/1546-0096-12-19

Summary of findings	Two studies suggested undetected hypopnea or obstructive sleep apnoea may be a cause of sleep disturbance is some children with JIA. [19] [20] Another study suggests that pain is partially responsible for poor sleep quality. [21] There is evidence of a bidirectional relationship between sleep and pain. [254] There seems to be a complex inter-relationship between JIA and sleep, whereby physiological, disease-related, psychological and socio-cultural factors may contribute to the development and maintenance of sleep problems among JIA patients. [E]
Evaluation	Some suggestions are made as to possible causes of sleep disturbance. No recommendations for sleep improvement in JIA patients are made.
Is the question answered?	Insufficiently answered

Q5

Question	Ref		Article name	Article link
Hoe kunnen we jongeren met JIA het beste begeleiden mbt onderwijs/opleiding zodat de uitval/schoolverzuim zo min mogelijk is?	[22]	longitudinal data	Participation in school sports among children and adolescents with juvenile idiopathic arthritis in the German National Paediatric Rheumatologic Database, 2000-2015: results from a prospective observational cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/30744659
	[23]	cross-sectional study	Fatigue in patients with Juvenile Idiopathic Arthritis: relationship to perceived health, physical health, self-efficacy, and participation.	https://www.ncbi.nlm.nih.gov/pubmed/27919265
	[24]	cross-sectional	Pain in School: Patterns of Pain-Related School Impairment among Adolescents with Primary	https://www.ncbi.nlm.nih.gov/pubmed/27916882

			Pain Conditions, Juvenile Idiopathic Arthritis Pain, and Pain-Free Peers.	

Summary of findings	Non-participation in school sports was associated with higher levels of pain, fatigue and disability. [22] Pain also affected school attendance. [23] Another study failed to find a correlation between pain and school attendance. [24] No suggestion for providing support are made.
Evaluation	The question is not answered.
Is the question answered?	No relevant literature

PSYCHOSOCIALE ASPECTEN

Q6

Question	Ref		Article name	Article link
Hoe verminder je onbegrip in de directe omgeving van het kind met jeugdreuma?	[24]	Proof of concept study	Can Seeding in the Clinic Reach a Wide Audience? A Proof of Concept Study on Spreading a Health Message About Juvenile Idiopathic Arthritis Using a Shareable Online Video.	https://www.ncbi.nlm.nih.gov/pubmed/26903485

Summary of findings	*A shareable online video is suggested as a potential way of raising awareness about JIA. [24]
Evaluation	
Is the question answered?	Insufficiently answered

Q7

Question	Ref		Article name	Article link
Wat is de relatie tussen jeugdreuma en je mentale gesteldheid?	[241]	prospective longitudinal	Predictors of health-related quality of life in chronically ill children and adolescents over time.	https://www.ncbi.nlm.nih.gov/pubmed/29580563
	[242]	longitudinal	Physical Functioning, Pain, and Health-Related Quality of Life in Adults With Juvenile Idiopathic Arthritis: A Longitudinal 30-Year Followup Study.	https://www.ncbi.nlm.nih.gov/pubmed/28732134

	[243]	retrospective	Chronicity of mental comorbidity in children with new-onset physical illness.	https://www.ncbi.nlm.nih.gov/pubmed/30982997
	[255]	Cross sectional	Physical and social functioning in adolescents with rheumatological conditions: a study of predictors	https://onlinelibrary.wiley.com/doi/pdf/10.1111/apa.12094?casa_token=bnXOHLTIMPIAAAAA:OaTNMlQEg1RY9JelYvatWVzqw3dgCl4vpSJO7P9HyoEYR2sLqDlNJgiZfPZi9x1sBGp6FbXHlfgmivM

Summary of findings	Psychosocial variables were also strongly associated with physical functioning; regression analyses confirmed that depression and pain-specific anxiety were positively associated with poorer physical functioning, independent of any influence of pain intensity.[255] Mental health problems are related to four out of five generic HRQoL dimensions (to Psychological WB, Parent Relations, Social Support & Peers, and School WB, but not to Physical WB). [241] Adult patients with JIA reported poorer HRQoL at the 30-year followup compared with matched controls from the general population, with lower scores on all of the SF-36 subscales except mental health. During the longitudinal followup, patients' experience of well-being and physical HRQoL deteriorated, but pain and mental HRQOL did not change. [242] One study showed that a substantial proportion of children with a chronic physical illness experiences mental comorbidity —multimorbidity—which is most often persistent over time. Evidence suggests that the peri-diagnostic period is critical for the development of mental illness with risk for mental illness highest soon after children are diagnosed with a physical illness. [243]
Evaluation	Conflicting evidence.
Is the question answered?	Insufficiently answered

Q8

Question	Ref		Article name	Article link
Hoe kun je als patiënt het beste mentaal omgaan met jeugdreuma, en hoe kan een ouder en/of behandelaar hierbij helpen?	[25]	cross-sectional	Parent and Child Report of Pain and Fatigue in JIA: Does Disagreement between Parent and Child Predict Functional Outcomes?	https://www.ncbi.nlm.nih.gov/pubmed/28146097
	[26]	questionnaires	Resilience Factors in Children with Juvenile Idiopathic Arthritis and Their	https://www.ncbi.nlm.nih.gov/pubmed/30256982

			Parents: The Role of Child and Parent Psychological Flexibility.	
	[27]	questionnaires	Patient's experiences with the care for juvenile idiopathic arthritis across Europe.	https://www.ncbi.nlm.nih.gov/pubmed/29422094
	[6]	RCT	Developing and Evaluating JIApp: Acceptability and Usability of a Smartphone App System to Improve Self-Management in Young People With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28811270
	[7]	Qualitative design approach	Multisite Randomized Clinical Trial Evaluating an Online Self-Management Program for Adolescents With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30204919

Summary of findings	Children whose parents underestimate their level of pain experienced more negative mood. [25] Psychological flexibility of children and their parents and pain acceptance buffer the negative impact of pain. [26] Healthcare professionals involved with children with JIA are recommended to refer more children for regular ophthalmologic screening, physiotherapy and support groups. Patients need to be better informed about available support, immunisations and what to do in case of worsening of symptoms. Transition to adult care needs to start earlier as well. [27] A self-management app [6] and an online peer mentoring program [7] are recommended for self-management of the disease.
Evaluation	Multiple suggestions are offered. Although not all of them are fully implemented, the information is out there.
Is the question answered?	Partially answered

VOEDING

Q9

Question	Ref		Article name	Article link

Wat is de invloed van voeding op jeugdreuma en kan een dieet helpen?	[28]	systematic review & meta analysis	Vitamin D and juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29769136
	[29]	longitudinal cohort study	Early feeding and risk of Juvenile idiopathic arthritis: a case control study in a prospective birth cohort.	https://www.ncbi.nlm.nih.gov/pubmed/28549465
	[30]	systematic review	Timing of Allergenic Food Introduction to the Infant Diet and Risk of Allergic or Autoimmune Disease: A Systematic Review and Meta-analysis.	https://www.ncbi.nlm.nih.gov/pubmed/27654604
	[31]	literature review	Breastfeeding and autoimmunity: Programing health from the beginning.	https://www.ncbi.nlm.nih.gov/pubmed/29083070
	[32]	exploratory study	Anti-inflammatory effect of exclusive enteral nutrition in patients with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27383427
	[33]	questionnaires	Parental Perception of Dietary Intervention in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/31112041

Summary of findings	There is evidence that a large proportion of children with JIA do not have adequate 25(OH)D levels. The optimal level of 25(OH)D for JIA patients is however not known. [28] One study found that a shorter duration of breastfeeding and exclusive breastfeeding was associated with a higher risk of JIA. Mothers are encouraged to exclusively breastfeed children for at least 4 months, and continue while introducing additional foods into the infant's diet. [29] A literature review however, states that the link between breastfeeding and JIA is ambivalent, but suggests that the two may be linked via the gut microbiome. [31] Exclusive enteral nutrition may be beneficial for children with JIA. [32] Introduction of allergenic foods into the infant's diet is not associated with a risk of autoimmune disease. [30] The introduction of a special diet was frequently perceived as having a beneficial effect. The underlying mechanisms of this remain to be discovered, as well as the potential placebo effect involved. [33]
Evaluation	There are some studies into the effect of dietary interventions, but there is no indication of concrete steps to be take in order to improve symptoms of JIA.
Is the question answered?	Insufficiently answered

Q10

Question	Ref		Article name	Article link
Wat is het effect van vitamines en supplementen op jeugdreuma?	[34]	RCT	Gut microbiome in children with enthesitis-related arthritis in a developing country and the effect of probiotic administration.	https://www.ncbi.nlm.nih.gov/pubmed/27861762
	[35]	RCT	Effect of probiotics on clinical and immune parameters in enthesitis-related arthritis category of juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27238895
	[36]	review	Protecting Bone Health in Pediatric Rheumatic Diseases: Pharmacological Considerations.	https://www.ncbi.nlm.nih.gov/pubmed/28290112

Summary of findings	Probiotic administration does not show promising results in normalising gut flora in children with JIA. [34] [35] A significant proportion of children with JIA are vitamin D deficient, however the evidence regarding vitamin D supplementation is not clear-cut. [36]
Evaluation	The question is partially answered. More research into the role of vitamin D supplementation is needed.
Is the question answered?	Partially answered

SPORTEN EN BEWEGEN

Q11

Question	Ref		Article name	Article link
Wat is de invloed van sporten en bewegen op jeugdreuma en omgekeerd?	[37]	lit review	Physical Exercise and Physical Activity for Children and Adolescents With Juvenile Idiopathic Arthritis: A Literature Review.	https://www.ncbi.nlm.nih.gov/pubmed/28654499
	[38]	review	Physical activity for paediatric rheumatic diseases: standing up against old paradigms.	https://www.ncbi.nlm.nih.gov/pubmed/28533552
	[39]	lit review	Ottawa Panel Evidence-Based Clinical Practice Guidelines for Structured Physical Activity in the Management of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27932265
	[40]	sys.review & meta-analysis	Exercise Therapy in Juvenile Idiopathic Arthritis: A Systematic Review and Meta-Analysis.	https://www.ncbi.nlm.nih.gov/pubmed/28729171
	[41]	lit review	Effects of Structured Exercise Training in Children and Adolescents With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30557274

	[42]	experiment	Inflammatory Response 24 h Post-Exercise in Youth with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30119133
	[43]	experiment	Single Bout Exercise in Children with Juvenile Idiopathic Arthritis: Impact on Inflammatory Markers.	https://www.ncbi.nlm.nih.gov/pubmed/30008613
	[44]	experiment	Impaired Muscular Fat Metabolism in Juvenile Idiopathic Arthritis in Inactive Disease.	https://www.ncbi.nlm.nih.gov/pubmed/31118902
	[247]	sys review, meta analysis	Physical activity and sedentary levels in children with juvenile idiopathic arthritis and inflammatory bowel disease. A systematic review and meta-analysis.	https://www.ncbi.nlm.nih.gov/pubmed/31029060
	[248]	Cross-sectional, qualitative	'It might hurt, but you have to push through the pain': Perspectives on physical activity from children with juvenile idiopathic arthritis and their parents	https://journals.sagepub.com/doi/full/10.1177/1367493516632616
	[F]	Systematic review	Leisure in Children and Adolescents with Juvenile Idiopathic Arthritis: A Systematic Review	https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0104642

Summary of findings	Physical activity and exercise therapy programs, combined with pharmacotherapy, have shown positive results. Improving muscular strength decreases stress on the joints. Hydrotherapy is a safe option. An individualized, specific, and intensive 12-week program of exercises with an average frequency of 3 times a week is proposed. [37] Exercise (and reducing sedentary behaviour) might restore normal mechanical, physical and biochemical processes within the body. [38] Pilates was found to be the most effective exercise intervention for reducing disease-related pain, and improving function and quality of life for JIA patients. There is no evidence that exercise exacerbates JIA symptoms. [39] There is consistent evidence that a structured physical therapy–led exercise program may have a beneficial effect on activity performance, body structure and function (pain and muscle strength), and QOL in patients with JIA. [40] There is moderate-quality evidence that exercise training can decrease pain, improve range of motion, knee strength, functional capability, and quality of life. No adverse effects are reported. [41] Physical activity in children with JIA resulted in a slight transient systemic inflammation (as indicated by calprotectin, cortisol, and IL-6 levels) which disappeared the next day. [42] Another study found that plasma calprotectin increased, but IL-6 did not. [43]

	Children with JIA have been found to have a metabolic disturbance (lower lipid oxidation rate) during exercise. [44] The greater the participation in organized sports, the better the mineral density of the patient's bones. Despite patients/caretakers' fears of disease exacerbation upon engaging in physical activity, there is no evidence that engaging in physical activity worsens symptoms. In fact, current evidence is in support of physical activity as a means of reducing pain and the number of inflamed joints, and improving overall aerobic endurance and bone health. [F] Level of Physical Activity is lower and sedentary behaviors are higher in children with JIA compared to healthy children. However, the difference between means of pathological and control groups is not constant across studies, particularly according to the assessment method (i.e., subjective or objective). Results showed that a lower PA level was observed in children with JIA only when assessed with an objective method. [247]Despite a preponderance of research that clearly espouses benefits of regular PA for the health and development of children, children with JIA are less active, have poorer cardiovascular fitness, reduced muscular endurance, and decreased bone density compared to children without JIA. They are also more likely to experience a number of psychological and social impairments as a result of their disease and/or lack of PA such as stress, anxiety, low self-esteem, depression, frustration, and difficulty making friends. Long-term follow-up of children diagnosed with JIA showed that many negative outcomes persisted well into adulthood. Together these factors highlight the need for early and effective PA interventions. Barriers to PA participation: pain, self-imposed barriers, parent-imposed barriers; facilitators of PA: enjoyment, pain management strategies, support.[248]
Evaluation	Patients with JIA engage in less PA than healthy persons. Exercise is strongly recommended for patients with JIA as it has multiple beneficial effects. No adverse effects are reported.
Is the question answered?	Sufficiently answered

Q12

Question	Ref		Article name	Article link

Hoe moet je omgaan met pijn bij sporten bij jeugdreuma?	[249]	Cross-sectional, qualitative	'It might hurt, but you have to push through the pain': Perspectives on physical activity from children with juvenile idiopathic arthritis and their parents	https://journals.sagepub.com/doi/full/10.1177/1367493516632616

Summary of findings	Children and parents highlighted three pain management strategies that children used often: (i) pushing through discomfort, (ii) taking short breaks, and (iii) switching activities. Pushing through discomfort. Children and parents perceived pushing through pain and discomfort rather than stopping as important. Reasons for pushing through varied from hiding arthritis from peers, enjoyment of the game/activity, or acknowledging the long-term benefits.Taking short breaks during lengthy periods of PA was another common strategy that helped many children participate, despite discomfort. This pacing strategy was used often during physical education class.Switching activities allowed for continued participation in PA, rather than quitting. A few previously diagnosed children and their parents described situations where children were unable to partake in activities because of discomfort. In such cases, children often switched to new activities, which caused less discomfort. [249]
Evaluation	Some suggestions provided
Is the question answered?	Partially answered

Q13

Question	Ref		Article name	Article link
Hoe kun je veilig je favoriete sport beoefenen met jeugdreuma?	[45]	review	Increasing Wellness Through Physical Activity in Children With Chronic Disease and Disability.	https://www.ncbi.nlm.nih.gov/pubmed/30531459
	[46]	review	Exercise for Athletes With Inflammatory Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30204634
	[39]	lit review	Ottawa Panel Evidence-Based Clinical Practice Guidelines for Structured Physical Activity in the Management of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27932265
	[41]	lit review	Effects of Structured Exercise Training in Children and Adolescents With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30557274

Summary of findings	There is no evidence that exercise exacerbates JIA symptoms. [39] No adverse effects are reported. [41] "All children with JIA should follow national guidelines for active healthy living. JIA patients can safely participate in sports as long as their disease is well controlled, and they have adequate physical capacity (1). Moderate fitness and strengthening exercises are recommended, but, when lower extremity joints are inflamed, low- to moderate-intensity weight-bearing exercise is preferred (30). Balance and flexibility activities should be promoted. Those with neck arthritis should undergo radiographic screening for C1-C2 instability. Arthritis affecting the jaw should encourage health care providers to prescribe a fitted mouth guard." [45] High-impact exercise on inflamed joints should be avoided. If the knee is involved, special focus on hip and knee strengthening should be considered. [46]
Evaluation	
Is the question answered?	Sufficiently answered

Q14

Question	Ref		Article name	Article link
Welke kennis en vaardigheden hebben kinderen met jeugdreuma en hun ouders nodig voor een gezonde en actieve leefstijl?	[47]	lit review	Physical activity for paediatric rheumatic diseases: standing up against old paradigms.	https://www.ncbi.nlm.nih.gov/pubmed/28533552

Summary of findings	Health professionals are advised to assess and track physical activity levels and sedentary behaviour on a routine basis. Several recommendations for health practitioners are given. [47] See questions 11, 13, and 14 for information that can be provided to patients and their parents in order to lead a healthy lifestyle. No literature discussing necessary skills has been found.
Evaluation	
Is the question answered?	Partially answered

Q15

Question	Ref		Article name	Article link
Kan je met jeugdreuma dezelfde fitheid bereiken als je				

leeftijdsgenootjes, en hoe lang duurt dat?				

Summary of findings	
Evaluation	
Is the question answered?	No relevant literature

SELF-MANAGEMENT

Q16

Question	Ref		Article name	Article link
Zijn er alternatieve geneeswijzen die klachten van jeugdreuma kunnen verminderen?	[70]	systematic review	Non-pharmacological options for managing chronic musculoskeletal pain in children with pediatric rheumatic disease: a systematic review.	https://www.ncbi.nlm.nih.gov/pubmed/30155667
	[71]	RCT	Effects of Video Games-Based Task-Oriented Activity Training (Xbox 360 Kinect) on Activity Performance and Participation in Patients With Juvenile Idiopathic Arthritis: A Randomized Clinical Trial.	https://www.ncbi.nlm.nih.gov/pubmed/30020092
	[72]	systematic review	A systematic review of psychosocial therapies for children with rheumatic diseases.	https://www.ncbi.nlm.nih.gov/pubmed/28095871
	[251]	Sys review & meta analysis	Assessment of the Therapeutic Effect of Total Glucosides of Peony for Juvenile Idiopathic Arthritis: A Systematic Review and Meta-Analysis.	https://www.ncbi.nlm.nih.gov/pubmed/27525026
	[J]	systematic review	Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents	https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011118.pub2/full

Summary of findings	Psychological and exercise based interventions have shown mixed results on pain outcomes. [70]Another systematic review of psychosocial therapies states that the available evidence is too heterogeneous to draw meaningful conclusions. [72] Video game based task oriented activity training may be beneficial for upper limb muscular strength. [71] Overall, the results of this meta-

	analysis suggested favorable effects of Total Glucosides of Peony (TGP) plus DMARDs or NSAIDs in patients with JIA in intermediate term (9–26 W), and the overall incidence of AEs was lower in intervention group. However, statistical significance was not attained in most of the results in short term and long term, especially in the TGP alone versus DMARD alone groups, which might be explained by the lack of sufficient studies included. In addition, the overall methodological quality was low. Therefore, caution should be exercised in interpreting these positive results. [251] A review studying 8 trials that delivered psychological therapies could not ascertain the quality of evidence. [J]
Evaluation	Research is insufficient to draw meaningful conclusions.
Is the question answered?	insufficiently answered

Q17

Question	Ref		Article name	Article link
Hoe kunnen ouders en kinderen zelf sneller een ontsteking herkennen?				

Summary of findings	
Evaluation	
Is the question answered?	No relevant literature

MTX INTOLERANTIE

Q18

Question	Ref		Article name	Article link
Welke negatieve gevolgen heeft methotrexaat (MTX) en weegt dit op tegen de positieve effecten?	[73]	data collection/cross sectional	Adding patient-reported outcomes to a multisite registry to quantify quality of life and experiences of disease and treatment for youth with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29645010
	[74]	sys review	Methotrexate in juvenile idiopathic arthritis: advice and recommendations from the MARAJIA expert consensus meeting	https://www.ncbi.nlm.nih.gov/pubmed/29996864
	[75]	cross-sectional	The risk of hospitalized infection following initiation of biologic agents versus methotrexate in the treatment of juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27655411

	[G]	Systematic review	Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis	https://www.analesdepediatria.org/en-recommendations-for-use-methotrexate-in-articulo-S234128791600003X
	[H]	Systematic review	Summary of AHRQ's Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis	https://www.jmcp.org/doi/10.18553/jmcp.2012.18.S1-B.1

Summary of findings	42.2.% of patients reported intolerance to MTX. MTX intolerance was associated with a lower PedsQL score. Being on methotrexate without experiencing intolerance was associated with higher total, psychosocial, and physical PedsQL scores. [73] The most significant adverse effects of MTX involve the suppression of the haematopoietic system and gastrointestinal disorders. [G] Rare adverse events related to MTX use (such as nodulosis, lung fibrosis) have been reported.MTX toxicity has been hypothesized to be a result of an induced state of folate depletion. [74] MTX use is not associated with hospitalisations due to infections. [75] Although the available evidence suggests that the risk of harm associated with methotrexate is similar to placebo, 1 study reported more adverse events compared with placebo for methotrexate used in combination with infliximab. [H]
Evaluation	MTX is a safe and effective treatment option, however, MTXmay have several side effects and intolerance to MTX is associated with a lower quality of life.
Is the question answered?	Sufficiently answered

Q19

Question	Ref		Article name	Article link
Hoe is de misselijkheid van methotrexaat (MTX) te voorspellen, te voorkomen en/of te bestrijden?	[76]	open prospective study	Successful treatment of methotrexate intolerance in juvenile idiopathic arthritis using eye movement desensitization and reprocessing - treatment protocol and preliminary results.	https://www.ncbi.nlm.nih.gov/pubmed/29433504
	[77]	prospective study	Countermeasures against methotrexate intolerance in juvenile idiopathic arthritis instituted by parents show no effect.	https://www.ncbi.nlm.nih.gov/pubmed/28122960
	[78]	prospective study	Methotrexate efficacy, but not its intolerance, is associated with the dose and route of administration.	https://www.ncbi.nlm.nih.gov/pubmed/27301536

	[79]	cross sectional, observational	Methotrexate intolerance in oral and subcutaneous administration in patients with juvenile idiopathic arthritis: a cross-sectional, observational study.	https://www.ncbi.nlm.nih.gov/pubmed/26843067
	[80]	sys review	Methotrexate-induced nausea in the treatment of juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28629458
	[81]	observational cohort	Methotrexate persistence and adverse drug reactions in patients with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30851113
	[82]	review	Contradictory and weak evidence on the effectiveness of anti-emetics for MTX-intolerance in JIA-patients.	https://www.ncbi.nlm.nih.gov/pubmed/29448947
	[83]	questionnaires	Methotrexate efficacy and tolerability after switching from oral to subcutaneous route of administration in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27407272
	[I]	Systematic review	Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis	https://www.analesdepediatria.org/en-recommendations-for-use-methotrexate-in-articulo-S234128791600003X

Summary of findings	EMDR therapy may have a beneficial effect in reducing MTX intolerance. [76] Measures devised by parents (such as antiemetic drugs, covert dosing, taste masking and alternative/complementary medicine) showed no effect in reducing MTX intolerance. [77] Route of MTX administration had no effect on MTX toxicity either. [78] Another study found that subcutaneous administration of MTX was more strongly associated with MTX intolerance, as compared to oral administration. [79] A different study found that switching from oral to subcutaneous administration reduced adverse effects. [83] Older age and longer use of MTX were associated with MTX induced nausea. Supplementation with folic acid has been shown to reduce nausea in RA patients using MTX. The evidence regarding the impact of subcutaneous versus oral administration is mixed. Ondansetron (antiemetic) has been shown to be effective in reducing nausea in Crohn's patients and RA patients receiving MTX. Behavioural therapy may be effective in reducing anticipatory nausea. [80] 37% of patients using MTX experienced adverse effects. Patients with more active disease, those with RF-positive polyarthritis, and younger patients were less likely to experience adverse effects. [81] Evidence regarding

	effective of enti-emetics in treatment of MTX induced nausea is weak. [82] Administering folic acid in the form of a tablet is recommended to overcome side effects of nausea and dyspepsia. [I]
Evaluation	The evidence is highly mixed. It is difficult to draw meaningful conclusions. Insufficient solutions to MTX adverse effects are presented.
Is the question answered?	insufficiently answered

BEHANDELING

Q20

Question	**Ref**		**Article name**	**Article link**
Wanneer en hoe kun je medicatie voor jeugdreuma het beste afbouwen?	[83]	prospective study	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.	https://www.ncbi.nlm.nih.gov/pubmed/29604189
	[84]	longitudinal, observational	Time spent in inactive disease before MTX withdrawal is relevant with regard to the flare risk in patients with JIA.	https://www.ncbi.nlm.nih.gov/pubmed/29453217
	[85]	retrospective	Relapse of Juvenile Idiopathic Arthritis-Associated Uveitis after Discontinuation of Immunomodulatory Therapy.	https://www.ncbi.nlm.nih.gov/pubmed/29451845
	[86]	retrospective	Flares After Withdrawal of Biologic Therapies in Juvenile Idiopathic Arthritis: Clinical and Laboratory Correlates of Remission Duration.	https://www.ncbi.nlm.nih.gov/pubmed/28973842
	[87]	survey (of clinicians)	Attitudes and Approaches for Withdrawing Drugs for Children with Clinically Inactive Nonsystemic JIA: A Survey of the Childhood Arthritis and Rheumatology Research Alliance.	https://www.ncbi.nlm.nih.gov/pubmed/28148696

Summary of findings	Clinically inactive disease was an unstable state, and 18.5% of the patients were unable to maintain clinically inactive disease for 6 continuous months of observation. For each month less of disease duration prior to initiating aggressive therapy, the likelihood of reaching clinically inactive disease was increased 1.7-fold. Thus achievement of CID is dependent more on the start of therapy than the phasing out of medication. [83] Patients with inactive disease for longer than 12 months prior to MTX discontinuation had a significantly lower flare rate.[84] 61% of patients who discontinued use of TNF-alpha inhibitors had a relapse of uveitis. Tapering the medication rather than abrupt stopping is recommended so that a potential flare-up can be detected early. [85] Withdrawal of biologic therapies should be done following at least two years of inactive disease, as this lowers the risk of flares. [86] A study examining practice among pediatric rheumatology clinicians found that preferences among them varied with regard to timing and manner (taper/stop). [87]
Evaluation	It remains to be studied which is the best way of discontinuing medication.
Is the question answered?	insufficiently answered

Q21

Question	Ref		Article name	Article link
Wat is voor ieder individu het beste medicamenteuze behandelplan? (Bijv. direct een biological, welke dan, en wat als de eerste niet werkt)	[156]	retrospective	Real-life 10-year retention rate of first-line anti-TNF drugs for inflammatory arthritides in adult- and juvenile-onset populations: similarities and differences.	https://www.ncbi.nlm.nih.gov/pubmed/28597133
	[157]	clinical guide	Management of Juvenile Idiopathic Arthritis: A Clinical Guide.	https://www.ncbi.nlm.nih.gov/pubmed/27484749
	[158]	review	In the Pursuit of Methotrexate Treatment Response Biomarker in Juvenile Idiopathic Arthritis-Are We Getting Closer to Personalised Medicine?	https://www.ncbi.nlm.nih.gov/pubmed/28361333
	[159]	review	Genome Engineering for Personalized Arthritis Therapeutics.	https://www.ncbi.nlm.nih.gov/pubmed/28887050
	[160]	sys review	Efficacy of biologic therapy across individual juvenile idiopathic arthritis subtypes: A systematic review.	https://www.ncbi.nlm.nih.gov/pubmed/27914689

			Current and future perspectives in the management of juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30169269
	[161]	cohort	Relationship Between Polymorphisms in Methotrexate Pathway Genes and Outcome of Methotrexate Treatment in a Cohort of 119 Patients with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28572465
	[162]	retrospective	Patient characteristics associated with response to NSAID monotherapy in children with systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29304824
	[163]		Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study.	https://www.ncbi.nlm.nih.gov/pubmed/30848528
			Predicting Which Children with Juvenile Idiopathic Arthritis Will Not Attain Early Remission with Conventional Treatment: Results from the ReACCh-Out Cohort.	https://www.ncbi.nlm.nih.gov/pubmed/30647178
	[164]	prospective, non-randomized	Bayesian comparative effectiveness study of four consensus treatment plans for initial management of systemic juvenile idiopathic arthritis: FiRst-Line Options for Systemic juvenile idiopathic arthritis Treatment (FROST).	https://www.ncbi.nlm.nih.gov/pubmed/29542334
			Treating juvenile idiopathic arthritis to target: recommendations of an international task force.	https://www.ncbi.nlm.nih.gov/pubmed/29643108
	[248]	Sys review + expert panel	2019 American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis.	https://www.ncbi.nlm.nih.gov/pubmed/31021537

	[K]	Systematic review	Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis	https://www.analesdepediatria.org/en-recommendations-for-use-methotrexate-in-articulo-S2341287916000003X
	[L]	Systematic review	The role and utility of measuring red blood cell methotrexate polyglutamate concentrations in inflammatory arthropathies—a systematic review	https://link.springer.com/article/10.1007/s00228-015-1819-x
	[M]	Systematic review	Early predictors of prognosis in juvenile idiopathic arthritis: a systematic literature review	https://ard.bmj.com/content/74/11/1996.long
	[N]	Systematic review	Expert Panel Recommendations for the Use of Anti–Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders	https://www.sciencedirect.com/science/article/pii/S0161642013008932?via%3Dihub
	[O]	Systematic review	Summary of AHRQ's Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis	https://www.jmcp.org/doi/10.18553/jmcp.2012.18.S1-B.1
	[P]	Systematic review	Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons	https://ard.bmj.com/content/72/11/1806.long
	[Q]	Systematic review	The use of biologic response modifiers in polyarticular-course juvenile idiopathic arthritis: A systematic review	https://www-sciencedirect-com.proxy.library.uu.nl/science/arti

				cle/pii/S0049017212002636
	[R]	Systematic review	The clinical effectiveness of intra-articular corticosteroids for arthritis of the lower limb in juvenile idiopathic arthritis: a systematic review	https://ped-rheum.biomedcentral.com/articles/10.1186/1546-0096-12-23
	[S]	Systematic review	Blocking the effects of interleukin-6 in rheumatoid arthritis and other inflammatory rheumatic diseases: systematic literature review and meta-analysis informing a consensus statement	https://ard.bmj.com/content/annrheumdis/72/4/583.full.pdf
	[T]	Systematic review	Prediction of methotrexate efficacy and adverse events in patients with juvenile idiopathic arthritis: a systematic literature review	https://ped-rheum.biomedcentral.com/articles/10.1186/1546-0096-12-51
	[U]	Systematic review	Disease-Modifying Antirheumatic Drugs in Children With Juvenile Idiopathic Arthritis	https://www.ncbi.nlm.nih.gov/books/NBK66092/

Summary of findings	***see also q35* A clinical guide based on subtypes is available, [157] as well as a systematic review evaluating the effectiveness of biologicals for each subtype. [160] A study comparing the effectiveness of various treatment plans is underway. [164] This guideline includes 39 recommendations for the treatment of children with JIA and non-systemic polyarthritis, sacroiliitis, and enthesitis. The quality of most of the available evidence was low or very low in relation to the relevant clinical PICO questions, resulting in 31 of the recommendations being conditional. [248] Biologicals as first line therapy may be more efficient than standard treatments. One study found that the percentage of patients with inactive disease after 1 year of therapy was >2-fold higher than the percentages in other prospective trials using biologic agents as second- or third-line therapy in systemic JIA. [163]Anti-TNF drugs have significantly lower drug survival in systemic-onset JIA than

	other subtypes. Inefficacy and adverse effects were the main reasons for discontinuation. [156] No validated biomarkers or genes(SNPs) to indicate response to MTX exist as of yet. [158] A cohort study found that several polymorphisms may be predictive for MTX toxicity. [161] NSAID monotherapy is able to achieve CID in a small subset of children with sJIA. Predicitve factors for this are age ≤ 8 years at presentation, joint count ≤5, and CRP ≤ 13 mg/dL. [162] Genome engineering may be key in developing personalised medicine. [159] Studies ascertaining some level of efficacy of relevant drugs are available. However it is unclear what circumstances make a drug effective for a particular patient. [K, L, M, N, O, P, Q, R, S, T, U]
Evaluation	Treatment plans are defined per category of JIA. Whilst this is relatively effective, personalised treatment is not yet available.
Is the question answered?	insufficiently answered

Q22

Question	Ref		Article name	Article link
Wat is de veiligheid en effectiviteit van vaccinaties bij jeugdreuma?	[88]	cross sectional, with control group	The safety and effectiveness of HBV vaccination in patients with juvenile idiopathic arthritis controlled by treatment.	https://www.ncbi.nlm.nih.gov/pubmed/26471922
	[89]	prospective longitudinal, with control group	Immunogenicity and safety of influenza vaccination in patients with juvenile idiopathic arthritis on biological therapy using the microneutralization assay.	https://www.ncbi.nlm.nih.gov/pubmed/28784185
	[90]	case control study	Immunogenicity and safety of the inactivated hepatitis A vaccine in children with juvenile idiopathic arthritis on methotrexate treatment: a matched case-control study.	https://www.ncbi.nlm.nih.gov/pubmed/28721859
	[91]	longitudinal, with control group	Varicella vaccination elicits a humoral and cellular response in children with rheumatic diseases using immune suppressive treatment.	https://www.ncbi.nlm.nih.gov/pubmed/28412076

	[92]	prospective study	Varicella-zoster-virus vaccination in immunosuppressed children with rheumatic diseases using a pre-vaccination check list.	https://www.ncbi.nlm.nih.gov/pubmed/29499726
	[93]	retrospective	The safety of live-attenuated vaccines in patients using IL-1 or IL-6 blockade: an international survey.	https://www.ncbi.nlm.nih.gov/pubmed/29562920
	[V]	Systematic review	Immunogenicity and safety of the human papillomavirus vaccine in patients with autoimmune diseases: A systematic review	https://www-sciencedirect-com.proxy.library.uu.nl/science/article/pii/S0264410X15006933

Summary of findings	The Hepatitis B vaccine is safe for patients with JIA. Adverse events resolved quickly and no worsening of JIA has been observed. [88] The influenza vaccine was safe and immunogenic in children with JIA. No serious adverse events were observed. [89] The Hepatitis A vaccine required two doses to induce seroprotection in children with JIA. [90] The VZV vaccine is safe and effective (best after 2 vaccines) for children with JIA. Only mild adverse events observed. Immunosuppressive drugs did not affect the immunogenicity of the vaccine, with the exception of biologics. Patients using biologics did not respond adequately to VZV vaccination. [91] Another study found similar results following VZV vaccine administration - only mild adverse events were observed and the vaccine was safe and effective for immunosuppressed patients with rheumatic disease. [92] A study examining the administration of live attenuated vaccines in patients using IL-1 or IL-6 blockade found that 3 patients reported adverse events(varicella zoster infection, pneumonia, and diarrhea), 2 of which were severe (required hospitalisation). 7 patients reported a flare following vaccination. A definitive conclusion cannot be drawn. [93] Some cases of exacerbation following vaccination against HPV have been reported in JIA patients. There does not seem to be an increased risk of disease flare following vaccination in JIA patients. [V]
Evaluation	Not all vaccines are examined
Is the question answered?	partially answered

Q23

Question	Ref		Article name	Article link

Wat is de waarde van het meten van medicijnspiegels tijdens de behandeling van jeugdreuma?	[48]	(selective) review	Current Practices for Therapeutic Drug Monitoring of Biopharmaceuticals in Pediatrics.	https://www.ncbi.nlm.nih.gov/pubmed/28703718
	[49]	observational study	Drug monitoring in long-term treatment with adalimumab for juvenile idiopathic arthritis-associated uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/30026253
	[W]	Systematic review	Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis	https://www.analesdepediatria.org/en-recommendations-for-use-methotrexate-in-articulo-S234128791600003X

Summary of findings	Therapeutic drug monitoring may be useful for determining minimum effective dose and presence of anti-drug antibodies, as well as optimising clinical efficiency. Determining the minimum effective dose could reduce the number of injections required, improving the quality of life for children with fear of needles. [48] Drug monitoring is also useful in reacting early to loss of response to a certain drug. [49] The development and degree of severity of adverse reactions to MTX depend on the dose and frequency of administration. Since severe adverse reactions may occur even at the lowest doses, it is imperative that physicians monitor these patients at regular intervals (every 3–4 months). [W]
Evaluation	The evidence is not yet certain or complete
Is the question answered?	Insufficiently answered

Q24

Question	Ref		Article name	Article link
Hoe vaak zijn bloedcontroles nodig bij het gebruik van medicijnen bij jeugdreuma?	[X]	Systematic review	Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis	https://www.analesdepediatria.org/en-recommendations-for-use-methotrexate-in-articulo-S234128791600003X

Summary of findings	In patients treated with MTX, it's recommended to test baseline parametes one month after treatment initiation, or 1-2 months after any increases in dosage. In patients receiving stable doses and no previously abnormal tests, surveillance lab testing is recommended every 3-4 months [5].
Evaluation	Recommendations are not unanimously supported and only available for MTX
Is the question answered?	Insufficient evidence

Q25

Question	Ref		Article name	Article link
Hoe kan antistofvorming tegen biologicals worden behandeld of voorkomen?	[94]	systematic review	Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review.	https://www.ncbi.nlm.nih.gov/pubmed/28612180
	[95]	sys review & meta analysis	Immunogenicity of biologic agents in juvenile idiopathic arthritis: a systematic review and meta-analysis.	https://www.ncbi.nlm.nih.gov/pubmed/30809664
	[Y]	Sys review	Immunogenicity of monoclonal antibodies against tumor necrosis factor used in chronic immune-mediated Inflammatory conditions: systematic review and meta-analysis.	https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1726977
	[Z]	Sys review	Recommendations for the use of methotrexate in patients with juvenile idiopathic arthritis	https://www.analesdepediatria.org/en-recommendations-for-use-methotrexate-in-articulo-S234128791600003X

Summary of findings	Biologic agents which are not identical to endogenous immunoglobulins, are capable of inducing immune responses and formation of anti drug antibodies (e.g. chimeric TNF inhibitors have a higher rate of ADAbs compared to fully human TNF inhibitors). Background immunosuppressive/anti-proliferative

	therapy reduces immunogenicity. Concomitant use of methotrexate, azathioprine, leflunomide, or mycophenolate is associated with lower rates of ADAbs. High biologic doses and induction therapy were also associated with decreased incidence of ADAbs. [94] Interestingly, antibodies to etanercept, abatacept or canakinumab did not appear to be associated with treatment failure or adverse events. Low immunogenicity of some biologics might also be associated with inhibition of their target molecule. For example, tocilizumab and canakinumab inhibit IL-6 and IL-1β respectively, which are both essential for T cell-dependent antibody production. Lower drug concentrations were associated with the presence of ADAbs and thus maintenance of therapeutic drug concentrations appears to be of importance. concomitant therapy with MTX significantly reduced the risk of ADAbs. More studies are warranted that address whether dose escalation is a safe strategy and which dose increase is required to counteract the presence of ADAbs. [95] The use of combined therapy of anti-TNF monoclonal antibodies with disease- modifying antirheumatic drugs (DMARDs), especially MTX, reduces the formation of antibodies against biological agents and the risks associated with it [Y,Z]
Evaluation	A lot of information is available on the topic. Several reasons for ADAbs formation and ways to handle this are presented. The drugs with the lowest potential for immunogenicity are known. However, the evidence regarding specific strategies to handle ADAbs formation is not yet complete.
Is the question answered?	Partially answered

Q26

Question	**Ref**		**Article name**	**Article link**
Hoe kunnen we gestandaardiseerde uitkomstmaten ontwikkelen om de goed bij te houden hoe het met de	[96]	questionnaire development & validation	Facilitating patient-centered care: the development of illustrated multidimensional patient-reported outcome measures for children/adolescents with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30834997
	[98]	questionnaire development & validation	The International Consortium for Health Outcome Measurement (ICHOM)Set of Outcomes that Matter to People Living with Inflammatory Arthritis Consensus from an international Working Group.	https://www.ncbi.nlm.nih.gov/pubmed/30358135

patiënt met jeugdreuma gaat?	[97]	questionnaire development & validation	Cross-cultural adaptation and psychometric evaluation of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR) in 54 languages across 52 countries: review of the general methodology.	https://www.ncbi.nlm.nih.gov/pubmed/29637323
	[101]	lit review	Open issues in the assessment and management of pain in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28967364
	[100]	systematic review	A Systematic Review of Quality Measures for Inflammatory Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29142026
	[99]	systematic review	Evidence for Updating the Core Domain Set of Outcome Measures for Juvenile Idiopathic Arthritis: Report from a Special Interest Group at OMERACT 2016.	https://www.ncbi.nlm.nih.gov/pubmed/28811355
	[102]	questionnaire development & validation	Development and validation of the self-reported PROMIS pediatric pain behavior item bank and short form scale.	https://www.ncbi.nlm.nih.gov/pubmed/28394851
	[103]	questionnaire validation	Patient-Reported Outcomes Measurement Information System Tools for Collecting Patient-Reported Outcomes in Children With Juvenile Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27159889
	[104]	review?	Clinical outcome measures in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27089922
	[105]	questionnaire validation	Finding specific 10-joint Juvenile Arthritis Disease Activity Score (JADAS10) and clinical JADAS10 cut-off values for disease activity levels in non-systemic juvenile idiopathic arthritis: a Finnish multicentre study.	https://www.ncbi.nlm.nih.gov/pubmed/26447164
	[107]	prospective cohort study	Evaluation of anti-cyclic citrullinated peptide antibodies may be beneficial in RF-negative juvenile idiopathic arthritis patients.	https://www.ncbi.nlm.nih.gov/pubmed/25994613

	[106]	progress report	Current Status of Efforts on Standardizing Magnetic Resonance Imaging of Juvenile Idiopathic Arthritis: Report from the OMERACT MRI in JIA Working Group and Health-e-Child.	https://www.ncbi.nlm.nih.gov/pubmed/25979714
	[AA]	Sys review	Summary of AHRQ's Comparative Effectiveness Review of Disease-Modifying Antirheumatic Drugs for Children with Juvenile Idiopathic Arthritis	https://www.jmcp.org/doi/10.18553/jmcp.2012.18.S1-B.1
	[AB]	Sys review	Psychometric characteristics of outcome measures in juvenile idiopathic arthritis: a systematic review -2012	https://onlinelibrary.wiley.com/doi/full/10.1002/acr.20667

Summary of findings	Questionnaire-based methods are proposed: PROMs, [96] JAMAR, [97] ICHOM IA Standard Set [98] and JADAS [104][105]. A study of the 1997 JIA Core Set suggests that the outcome measures need to be updated to include patient-centered outcomes, clinical data, and imaging data. [99] A systematic review of quality measure has identified 13 high-quality sets of qualitative measures that can be used to assess disease status. [100] A literature review suggests that pain is not adequately assessed by pediatric clinicians and proposes methods to comprehensively measure pain. [101] A self-reporting pain questionnaire (PROMIS) is proposed as an option of measuring pain. [102] [103] An ongoing study is in the process of standardising MRI assessment in children with JIA. [106] Anti-CCP levels may be indicative of erosive disease. [107] Measures of responsiveness rely on calculations of effect size. No single instrument or outcome measure appears superior in describing the various aspects of JIA with high reliability, validity, and responsiveness. [AA][AB]
Evaluation	Multiple patient-reported outcome and survey type assessments are proposed. Standardised imaging, as well as biomarkers remain to be developed.
Is the question answered?	partially answered

Q27

Question	Ref		Article name	Article link

Hebben kinderen met jeugdreuma meer kans op een gecomplicee rd beloop van waterpokke n?	[108]	retrospectiv e	Clinical course and therapeutic approach to varicella zoster virus infection in children with rheumatic autoimmune diseases under immunosuppression.	https://www.ncbi.nlm.nih.gov/pubmed/27256096
	[109]	sys review & meta-analysis	Risk of Serious Infections Associated with Biologic Agents in Juvenile Idiopathic Arthritis: A Systematic Review and Meta-Analyses.	https://www.ncbi.nlm.nih.gov/pubmed/30318371
	[110]	cohort observation	Primary varicella infection in children with systemic juvenile idiopathic arthritis under tocilizumab therapy.	https://www.ncbi.nlm.nih.gov/pubmed/27846755

Summary of findings	A systematic review reports that children treated biologic agents were not at a higher risk of serious infections. [109] Infection with VZV in immunosuppressed children may result in complications (cellulitis, sepsis). [108] Another study reported MAS as a complication of VZV infection. [110]
Evaluation	The available studies have a limited sample size. Additional research required to be able to answer the question.
Is the question answered?	insufficiently answered

Q28

Question	Ref		Article name	Article link
Hoe werkt methotrexaat (MTX) bij JIA?	[244]	review	Management of Juvenile Idiopathic Arthritis: A Clinical Guide.	https://www.ncbi.nlm.nih.gov/pubmed/27484749
	[245]	review	Management of Children with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/26639461
	[246]	cross-sectional	Nicotinamide Phosphoribosyltransferase Deficiency Potentiates the Antiproliferative Activity of Methotrexate through Enhanced Depletion of Intracellular ATP.	https://www.ncbi.nlm.nih.gov/pubmed/29420256

Summary of findings	MTX is widely known as a folic acid analog and an inhibitor of several different enzymes in the folate pathway. Its immunomodulatory and anti-inflammatory actions are believed to

	be mediated through release of endogenous adenosine, especially locally at the site of inflammation. [244] It is a folic acid analogue and in low doses an inhibitor of dihydrofolate reductase, interfering with DNA synthesis by reducing the purine and pyrimidine supply in rapidly dividing cells reducing production of cytokines. [245] MTX is a potent inhibitor of dihydrofolate reductase (DHFR) and is metabolized intracellularly to form a series of pharmacologically active polyglutamated metabolites that function as direct inhibitors of several folate-dependent enzymes. Through inhibition of the folate-dependent biochemical pathways, MTX causes the inhibition of various downstream one-carbon transfer reactions, including nucleotide and methionine biosynthesis, which are believed to be responsible for its pharmacological activity in the treatment of autoimmune arthritis. reductions in the enzymatic activity of NAMPT increase the sensitivity of cells to the inhibition of nucleotide biosynthesis by MTX and potentiate the MTX-mediated depletion of cellular ATP. Together, these findings illustrate a novel mechanism through which disruption of cellular NAD metabolism, through reduction in the enzymatic activity of NAMPT, enhances the pharmacological activity of the antifolate therapeutic MTX. [246]
Evaluation	Mechanism of action not fully understood
Is the question answered?	insufficiently answered

Q29

Question	**Ref**		**Article name**	**Article link**
Heeft het dragen van een spalk bij jeugdreuma effect?	[50]	systematic review	Physical and Mechanical Therapies for Lower-Limb Problems in Juvenile Idiopathic Arthritis: A Systematic Review with Meta-Analysis.	https://www.ncbi.nlm.nih.gov/pubmed/28738165
	[51]	retrospective longitudinal	3D evaluation of mandibular skeletal changes in juvenile arthritis patients treated with a distraction splint: A retrospective follow-up.	https://www.ncbi.nlm.nih.gov/pubmed/27003225

Summary of findings	The effectiveness of foot orthoses for foot and ankle pain in children with JIA is unclear. [50] The use of a distraction splint for unilateral TMJ involvement may be effective. [51]
Evaluation	Limited evidence for a limited number of joints is available.
Is the question answered?	Insufficiently answered

PRIKKEN EN TOEDININGSVORMEN

Q30

Question			Article name	Article link
Hoe kunnen pillen zo worden gemaakt dat ze makkelijk in te nemen zijn (denk aan vorm, kleur en smaak)?				

Summary of findings	
Evaluation	
Is the question answered?	no relevant literature

Q31

Question	Ref		Article name	Article link
Hoe kunnen injecties minder pijnlijk zijn bij de toediening (betere verdeling, vloeistof, type naald)?	[52]	experimental	Efficacy and cost savings with the use of a minimal sedation / anxiolysis protocol for intra-articular corticosteroid injections in children with juvenile idiopathic arthritis: a retrospective review of prospectively collected data.	https://www.ncbi.nlm.nih.gov/pubmed/30894194
	[53]	literature review	The effect of repeated methotrexate injections on the quality of life of children with rheumatic diseases.	https://www.ncbi.nlm.nih.gov/pubmed/30448866
	[54]	literature review	Intra-articular joint injections in juvenile idiopathic arthritis: state of the art.	https://www.ncbi.nlm.nih.gov/pubmed/30243614

Summary of findings	Conscious sedation or local anaesthesia are recommended for pain minimisation. [54] Minimum sedation is an effective and cost-effective way of minimising pain during intra-articular injections. [52] No research regarding mitigation of needle fear in children has been done up to date. [53]
Evaluation	Only anaesthetic solutions presented
Is the question answered?	Partially answered

Q32

Question	Ref		Article name	Article link
Is er een alternatief medicijn in de vorm van een pil als				

vervanging voor de prikken/infusen?				

Summary of findings	
Evaluation	
Is the question answered?	no relevant literature

Q33

Question	Ref		Article name	Article link
Waarom is het beter om twee dagen niet te lopen als je een prik in de knie hebt gehad?				

Summary of findings	
Evaluation	
Is the question answered?	no relevant literature

GENEZING & RELAPSE

Q34

Question	Ref		Article name	Article link
Hoeveel van de patiënten met jeugdreuma groeit er definitief over heen?	[166]	longitudinal	Real-World Effectiveness of Common Treatment Strategies for Juvenile Idiopathic Arthritis: Results from a Canadian Cohort.	https://www.ncbi.nlm.nih.gov/pubmed/31074591
	[167]	retrospective	Juvenile idiopathic arthritis managed in the new millennium: one year outcomes of an inception cohort of Australian children.	https://www.ncbi.nlm.nih.gov/pubmed/30413164

	[168]	randomised, single-blinded	Treat to target (drug-free) inactive disease in DMARD-naive juvenile idiopathic arthritis: 24-month clinical outcomes of a three-armed randomised trial.	https://www.ncbi.nlm.nih.gov/pubmed/30309970
	[169]	retrospective	Impact of biologics on disease course in systemic onset juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30238379
	[170]	retrospective	Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood.	https://www.ncbi.nlm.nih.gov/pubmed/30044538
	[171]	sys review	How common is remission in juvenile idiopathic arthritis: A systematic review.	https://www.ncbi.nlm.nih.gov/pubmed/28625712
	[172]	cohort study	How common is clinically inactive disease in a prospective cohort of patients with juvenile idiopathic arthritis? The importance of definition.	https://www.ncbi.nlm.nih.gov/pubmed/28389553

Summary of findings	NSAID monotherapy - 54.4% success; NSAID plus joint injections had 64.7% success; methotrexate + NSAID and/or joint injections, had 60.5% success. Success defined as attainment of inactive disease or maintenance of this state when stepping down treatment. [166] 65% of patients had inactive joint disease at 12 months. [167] 71% of recent-onset patients with JIA had inactive disease after 24 months of treatment (39% were drug free). [168] 82% of sJIA patients had inactive disease at last visit after a median follow-up of approximately 6 years. [169] Especially important is the finding that after 10 years of disease, 19% of patients with early bDMARD use were in a state of medication-free remission as defined by PhGA, compared to 10% and 5% of those with bDMARD treatment after 2–5 years and after 5 years of JIA, respectively. [170] The achievement of remission increased with increasing disease duration, although after over a decade of disease, fewer than half of patients have achieved this state. The frequency of current remission increased with increasing disease duration from 7% at 18 months to around 40% after at least 10 years. In cohorts using Wallace's preliminary criteria, remission rates ranged from 33% at 6 months to 67% at 8 years. Patients with persistent oligoarticular disease seem to have the most favourable disease course and patients with enthesitis-related JIA and patients with RF+ polyarthritis appear to have relatively poor prognosis. Those

	with systemic JIA were reported to have the largest variation in achievement of clinically inactive disease and remission, ranging from 0% to 100% irrespective of time followed. [171] Broad achievement of CID was around 30% and Minimal Disease Activity around 50% at 1 year following initial presentation. [172]
Evaluation	Multiple estimates available. Systematic review available as well. Due to heterogeneity of JIA, and multiple treatment strategies it is not possible to provide one simple average, however numbers for each are available. There isn't really a way to answer this question.
Is the question answered?	TBD

Q35

Question	Ref		Article name	Article link
Hoe kan jeugdreuma genezen worden?	[176]	retrospective	Time of Disease-Modifying Antirheumatic Drug Start in Juvenile Idiopathic Arthritis and the Likelihood of a Drug-Free Remission in Young Adulthood.	https://www.ncbi.nlm.nih.gov/pubmed/30044538
			Treating juvenile idiopathic arthritis to target: recommendations of an international task force.	https://www.ncbi.nlm.nih.gov/pubmed/29643108
	[177]	report	Bayesian comparative effectiveness study of four consensus treatment plans for initial management of systemic juvenile idiopathic arthritis: FiRst-Line Options for Systemic juvenile idiopathic arthritis Treatment (FROST).	https://www.ncbi.nlm.nih.gov/pubmed/29542334
	[178]	review	How I treat juvenile idiopathic arthritis: A state of the art review.	https://www.ncbi.nlm.nih.gov/pubmed/28778702
	[179]	RCT	A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study.	https://www.ncbi.nlm.nih.gov/pubmed/28166785
	[180]	sys review	Efficacy of biologic therapy across individual juvenile idiopathic arthritis subtypes: A systematic review.	https://www.ncbi.nlm.nih.gov/pubmed/27914689

Summary of findings	***see also q21*

	Patients who started bDMARDs within the first 2 years of JIA diagnosis had a significantly higher likelihood of having a drug free remission and full functional capability in early adulthood and a significantly lower likelihood of requiring joint or eye surgery. This supports the concept of a window of opportunity for JIA. [176] A study comparing the effectiveness of 4 different treatment plans is underway. [177] General treatment recommendations are available. [178] Patients with recent-onset non-systemic JIA achieved significantly more clinical improvement on initial combination therapy with MTX/etanercept than on initial MTX or SSZ monotherapy. [179] A systematic review found that there was some evidence that response to a particular biologic differed depending on JIA subtype. Also, there was a trend to better response to certain biological classes within the individual JIA subtypes. However, real comparison between trials is difficult. Specific recommendations given. [180]
Evaluation	While treatment has vastly improved in the past decade, there is still no definitive evidence on how to treat JIA
Is the question answered?	insufficiently answered

Q36

Question	Ref		Article name	Article link
Hoe kunnen we het beloop (opvlammingen, uitbreidingen, genezing) van jeugdreuma beter verklaren en voorspellen?	[197]	review	Predicting Remission Remains a Challenge in Patients with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/31154444
	[198]	sys review	Predicting disease severity and remission in juvenile idiopathic arthritis: are we getting closer?	https://www.ncbi.nlm.nih.gov/pubmed/31085941
	[199]	prospective longitudinal	Predicting Which Children with Juvenile Idiopathic Arthritis Will Not Attain Early Remission with Conventional Treatment: Results from the ReACCh-Out Cohort.	https://www.ncbi.nlm.nih.gov/pubmed/30647178
	[200]	prospective longitudinal	Calprotectin strongly and independently predicts relapse in rheumatoid arthritis and polyarticular psoriatic arthritis patients treated with tumor necrosis factor inhibitors: a 1-year prospective cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/30545393
	[201]	cross-sectional	A Granulocyte-Specific Protein S100A12 as a Potential Prognostic Factor Affecting	https://www.ncbi.nlm.nih.gov/pubmed/30426025

			Aggressiveness of Therapy in Patients with Juvenile Idiopathic Arthritis.	
	[202]	prospective, observational	Prediction of inactive disease in juvenile idiopathic arthritis: a multicentre observational cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/29931340
	[203]	retrospective cohort	Early reduction of serum interleukin-6 levels as a predictor of clinical remission in systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29888930
	[204]	retrospective + prospective	Juvenile idiopathic arthritis in the biologic era: predictors of the disease progression and need for early introduction of biologic treatment.	https://www.ncbi.nlm.nih.gov/pubmed/29845429
	[205]	cross-sectional	Soluble CD163, a unique biomarker to evaluate the disease activity, exhibits macrophage activation in systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29801971
	[206]	longitudinal	Predicting unfavorable long-term outcome in juvenile idiopathic arthritis: results from the Nordic cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/29724248
	[207]	longitudinal	Predictors of Flare Following Etanercept Withdrawal in Patients with Rheumatoid Factor-negative Juvenile Idiopathic Arthritis Who Reached Remission while Taking Medication.	https://www.ncbi.nlm.nih.gov/pubmed/29717035
	[208]	prospective observational	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.	https://www.ncbi.nlm.nih.gov/pubmed/29604189
	[209]	prospective observational	Time spent in inactive disease before MTX withdrawal is relevant with regard to the flare risk in patients with JIA.	https://www.ncbi.nlm.nih.gov/pubmed/29453217
	[210]	longitudinal	Baseline ultrasound examination as possible predictor of relapse in patients affected by juvenile idiopathic arthritis (JIA).	https://www.ncbi.nlm.nih.gov/pubmed/29437586

	[211]	cross-sectional	S100A12 Is Associated with Response to Therapy in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29335345
	[212]	retrospective	Patient characteristics associated with response to NSAID monotherapy in children with systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29304824
	[213]	retrospective	Reasons for inactive disease and flare in systemic onset juvenile idiopathic arthritis patients during tocilizumab treatment.	https://www.ncbi.nlm.nih.gov/pubmed/29303703
	[214]	longitudinal	Low synovial double negative T and γδ T cells predict longer free-disease survival in oligoarticular JIA.	https://www.ncbi.nlm.nih.gov/pubmed/29059705
	[215]	retrospective	Flares After Withdrawal of Biologic Therapies in Juvenile Idiopathic Arthritis: Clinical and Laboratory Correlates of Remission Duration.	https://www.ncbi.nlm.nih.gov/pubmed/28973842
	[216]	prospective	Predictors of the response to etanercept in patients with juvenile idiopathic arthritis without systemic manifestations within 12 months: results of an open-label, prospective study conducted at the National Scientific and Practical Center of Children's Health, Russia.	https://www.ncbi.nlm.nih.gov/pubmed/28615036
	[217]	retrospective	Treatment response to etanercept in methotrexate refractory juvenile idiopathic arthritis: an analysis of predictors and long-term outcomes.	https://www.ncbi.nlm.nih.gov/pubmed/28540607
	[218]	retrospective	A Retrospective Study on Possible Predictive Factors for Long-term Temporomandibular Joint Degeneration and Impaired Mobility in Juvenile Arthritis Patients.	https://www.ncbi.nlm.nih.gov/pubmed/28437514
	[219]	prospective	High-sensitive CRP as a predictive marker of long-term outcome in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28283733
	[220]	longitudinal	Dynamic contrast-enhanced magnetic resonance imaging can play a role in	https://www.ncbi.nlm.nih.gov/pubmed/28189212

			predicting flare in juvenile idiopathic arthritis.	
	[221]	longitudinal	Non-HLA gene polymorphisms in juvenile idiopathic arthritis: associations with disease outcome.	https://www.ncbi.nlm.nih.gov/pubmed/28145159
	[222]	sys review	Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks?	https://www.ncbi.nlm.nih.gov/pubmed/27411444
	[223]	longitudinal	High mobility group box protein 1-A prognostic marker for structural joint damage in 10-year follow-up of patients with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27756498
	[224]		Predicting Which Children with Juvenile Idiopathic Arthritis Will Have a Severe Disease Course: Results from the ReACCh-Out Cohort.	https://www.ncbi.nlm.nih.gov/pubmed/27980015
	[225]	retrospective	Intra-articular injection in patients with juvenile idiopathic arthritis: factors associated with a good response.	https://www.ncbi.nlm.nih.gov/pubmed/27914595
	[226]	retrospective	Inactive Disease in Enthesitis-related Arthritis: Association of Increased Body Mass Index.	https://www.ncbi.nlm.nih.gov/pubmed/26980582
			Prediction of long-term remission of oligo/polyarticular juvenile idiopathic arthritis with S100A12 and vascular endothelial growth factor.	https://www.ncbi.nlm.nih.gov/pubmed/26474088
	[227]	retrospective	The risk and nature of flares in juvenile idiopathic arthritis: results from the ReACCh-Out cohort.	https://www.ncbi.nlm.nih.gov/pubmed/25985972
	[AC]	Sys review	EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice	https://ard.bmj.com/content/74/11/1946.long
	[AD]	Sys review	Treatment non-adherence in pediatric long-term medical conditions: systematic review and synthesis of qualitative studies of caregivers' views	https://bmcpediatr.biomedcentral.com/articles/10.1186/1471-2431-14-63

Summary of findings	**Clinical features:** The strongest predictor of remission in JIA is International League of Associations for Rheumatology (ILAR) category, with the oligoarticular ILAR category consistently associated with greater achievement and rheumatoid factor–positive polyarticular JIA with the lowest achievement of remission. [197] The most consistent predictors of a lower chance of remission were measures of high disease activity at baseline (number of active joints, the physician global assessment of disease activity, duration of morning stiffness and higher levels of ESR or CRP). A shorter time between disease onset and the start of treatment was predictive of early remission and of response to methotrexate and biologic agents. Age less than 7 years and ANA positivity are the strongest predictors of uveitis development. Predictors for uveitis complications were older age at JIA onset, more severe inflammation, use of topical corticosteroids and short interval between JIA diagnosis and uveitis development. Two studies identified older age at onset, longer disease duration, female sex and higher number of active joints as likely predictors of persisting pain. Another two studies reported that greater disease activity, polyarthritis and worse patient reported outcomes at baseline, were likely predictors of a poor quality of life. Signs of synovitis on ultrasound may predict flare. Studies regarding the predictive potential of biomarkers are not definitive at this point. Further validation and trials of the existing predictive models are necessary. [198] baseline calprotectin serum levels independently predicted disease relapse in RA and PsA patients under TNFi therapy. [200] The following factors emerged as early indices of poor prognosis regarding the disease course and need for early implementation of biologic treatment: young age at the disease onset (≤ 6 years), high level of disease activity at first presentation (initial JADAS71 score > 9), presence of uveitis, polyarticular course, failure to accomplish an inactive disease state within the first year of specialized medical care and cumulative time with active disease > 35% within the first year of disease course. [204] A significant proportion of patients with JIA who maintain CID for at least 6 months experience a relapse after ETN withdrawal. Male sex, presence of ANA, and elevated CRP at baseline were associated with higher risk of flare. [207] Over one-third of patients with polyarticular JIA with sustained clinically inactive disease will experience a flare by 8 months after discontinuation of anti-TNF therapy. In this study there was an increased risk of disease flare with longer duration of clinically inactive disease. These data certainly do not support the existence of a protective effect of longer duration of clinically inactive disease before considering stopping anti-TNF therapy. In fact, the data suggest that clinically inactive disease, even in those who did demonstrate it consistently for the first 6 months of the study, continued to be an unstable clinical state and prolonged clinically inactive disease resulted in a significantly greater risk of flare.There is a “window of opportunity” early in the treatment of JIA that supports early

	introduction of aggressive therapy and that rapid achievement of clinically inactive disease will result in better long-term control of JIA and improved outcomes. [208] Patients who spent at least 12 months in inactive disease before MTX discontinuation had a significantly lower flare rate. [209] US abnormalities are a strong predictor of relapse at individual patient level. The combination of grey scale and Power Doppler abnormalities displayed a much higher predictive value of relapse[210] Joint damage found by medical imaging can be used as predictors of further joint deterioration. [AC] Age at presentation (≤8 years old), initial joint count (≤5), and C-reactive protein (CRP) (≤13 mg/dL) at diagnosis were associated with achievement of CID on NSAIDs alone. [212] sJIA children with milder disease course have more posssibilty of achieving disease remission during TCZ treatment. Male sex, signs of high disease activity, previous CS treatment, the long time needed to achieve inactive disease and treatment protocol deviations increased the risk of sJIA flare. [213] Patients in remission for >2 years taking biologics were likely to sustain remission longer than those with <2 years of remission. [215] predictors of treatment efficacy included persistent oligoarticular JIA, a shorter disease duration before the initiation of etanercept therapy, a smaller number of DMARDs used before the initiation of etanercept therapy, and a smaller number of joints with LOM. Lower C-reactive protein levels at baseline were a laboratory predictor. Polyarticular and enthesitis-related arthritis with a longer disease duration before the initiation of etanercept were predictors of poor response to etanercept treatment. [216] Patients using etanercept who achieved remission more rapidly were less likely to have disease flares. [217] JIA patients with early physical limitations and prolonged disease are at risk of long-term TMJ degeneration and impaired mobility. [218] The assessment of 'maximum enhancement' upon DCE-MRI may be able to predict a clinical flare within 2 years in inactive JIA patients. [220] One study showed that a younger age at the diagnosis of JIA, occurrence of uveitis in the course of the disease, as well as knee, wrist and elbow injection and lower VAS values both from the physician and patient were factors associated with a better response to IIC. [225] Being overweight or obese was associated with failure to achieve inactive disease in patients with ERA. [226] Children with a severe disease course or positive ANA had an increased risk of flare. [227] Non-adherence to prescribed treatments is the primary cause of treatment failure in pediatric long-term conditions. [AD] **Biomarkers:** Serum S100A12 concentrations were noticeably increased in patients with high disease activity however decrease of its serum concentration was related to the decline in the JADAS27 value only in 66.7% of patients. [201] An early reduction in serum IL-6 levels is significantly associated with clinical remission at 2 years in SJIA patients. [203] Serum sCD163 levels

	were significantly elevated in patients with s-JIA associated macrophage activation syndrome (MAS) and EBV-HLH. Serum sCD163 levels profoundly increased with the progress of MAS and correlated positively with the disease activity of s-JIA, even in patients receiving tocilizumab. Furthermore, serum sCD163 levels significantly decreased in the inactive phase compared to those in the active phase and normalized in remission. [205] Baseline serum S100A12 was associated with response to both MTX and anti-TNF therapy. [211] In oJIA relapse Synovial Fluid present an activated B phenotype. Patients at disease onset with DNTs <1.8% and/or γδ T cells <16% of CD3+ in synovial fluid have longer free-disease survival. [214] Baseline CRP concentrations above 10 mg/l are predictive of a poor outcome at 8-year follow-up. [219] One study found some evidence of an association between two SNPs in STAT4 and increased risk of having joints with persistently active arthritis; a SNP in the ADAD1-IL2-IL21 region, was associated with reduced risk of joints with LOM; an association between a reduced risk of a persistently active disease and the TT genotype in the PTPN2 gene. [221] A systematic review identified 68 candidates for potentially useful biomarker in diagnosing sJIA, however, few were validated, and further validation studies are needed to ascertain the role of these biomarkers. [222] HMGB1 is a marker of inflammatory activity in children with JIA. Higher serum HMGB1 levels are related to more destructive JIA. [223] **Predictive models:** Predictive models are available. [199][202][206][224]
Evaluation	A lot of studies are available, however there is a lack of systematising. For the question to be fully answered, a very good predictive model, including novel biomarkers, must be developed.
Is the question answered?	partially answered

PROGNOSE

Q37

Question	Ref		Article name	Article link
Wat zijn de gevolgen/ bijwerkingen van de medicijnen bij jeugdreuma op korte	[181]	trial	Etanercept treatment for extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis, or psoriatic arthritis: 6-year efficacy and safety data from an open-label trial.	https://www.ncbi.nlm.nih.gov/pubmed/31122296
	[182]	*	Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more	https://www.ncbi.nlm.nih.gov/pubmed/30587248

en lange termijn?			than 15,000 patients from Pharmachild and national registries.	
	[183]	retrospective	Surveillance of adverse drug events associated with etanercept prescribed for juvenile idiopathic arthritis in a single center up to 9-years: A retrospective observational study.	https://www.ncbi.nlm.nih.gov/pubmed/30412634
	[184]	trial	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.	https://www.ncbi.nlm.nih.gov/pubmed/30269054
	[185]	trial	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.	https://www.ncbi.nlm.nih.gov/pubmed/29654485
	[AE]	Sys review	Expert Panel Recommendations for the Use of Anti–Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders	https://www.sciencedirect.com/science/article/pii/S0161642013008932?via%3Dihub

Summary of findings	The most frequently reported TEAEs after 6 years of etanercept treatment, not including infections and injection site reactions, were headache, arthralgia, pyrexia, diarrhea, and leukopenia. MOst common infections were those of the upper respiratory tract, pharyngitis, gastroenteritis, and bronchitis. Overall long term safety of etanercept was deemed acceptable. [181] Another study found that the most common ADEs of long term use of etanercept were infections of the upper respiratory tract, neuropsychiatric symptoms, and Injection Site Reactions. Infection rates did not increase with MTX or TNF-inhibitor use, but was significantly increased with at least a moderate dose of glucocorticoids. [183] Long-term corticosteroid use leads to chushington changes, iatrogenic diabetes, osteoporosis, and hypercholesterolemia [AE] In long term treatment with canakinumab infections were the most common AEs. Despite disease control, new MAS events occurred while on canakinumab therapy. Overall safety was deemed acceptable. [184]

	Continuing treatment over 104 to 131 weeks or longer with intravenous TCZ (8 mg/kg administered every 4 weeks) is safe for the management of pJIA. [185] *A proposal for data merging exists in order to monitor the long-term effects of drug use in JIA. [182]
Evaluation	No generalised, validated data is available on overall long term safety of drug use in JIA
Is the question answered?	insufficiently answered

Q38

Question	Ref		Article name	Article link
Wat zijn de lichamelijke gevolgen van jeugdreuma op lange termijn?	[173]	longitudinal	Long-term outcomes in juvenile idiopathic arthritis: 18 years of follow-up in the population-based Nordic Juvenile Idiopathic Arthritis (JIA) cohort.	https://www.ncbi.nlm.nih.gov/pubmed/30762291
	[174]	sys review	The impact of underlying disease on fracture risk and bone mineral density in children with rheumatic disorders: A review of current literature.	https://www.ncbi.nlm.nih.gov/pubmed/27020068
	[175]	longitudinal	Radiographic damage in hands and wrists of patients with juvenile idiopathic arthritis after 29 years of disease duration.	https://www.ncbi.nlm.nih.gov/pubmed/28399930
	[AF]	Sys review	Juvenile idiopathic arthritis-and now?: a systematic literature review of changes in craniofacial morphology.	https://link.springer.com/article/10.1007%2Fs00056-012-0091-2
	[AG]	Sys review	Orthodontic and dentofacial orthopedic management of juvenile idiopathic arthritis: a systematic review of the literature	https://onlinelibrary.wiley.com/doi/full/10.1111/j.1601-6343.2011.01514.x

Summary of findings	Articular damage was seen in 19.8% of patients at the follow -up visit, while 12.5% had developed extra-articular damage. Ocular damage was the most common extra-articular damage and was observed 7.9% of the participants. [173] Juvenile arthritis is associated with an increased risk of Vertebral Fractures and non-VF. The data is strongest for VF, but fracture risk is likely also increased for long bones. Juvenile arthritis is associated with

	reductions in Bone Mineral Density, independent of corticosteroid effect. The data are suggestive that some subtypes are associated with greater reductions (systemic and polyarticular) than others (pauci/oligoarticular). Juvenile arthritis may be associated with an increased risk of reduced BMD in adulthood. The quality of this data is limited. [174] The majority of patients with long-term active JIA had modest radiographic damage (25% had severe damage), but more frequently in wrists than in fingers. Patients with polyarticular RF-positive or anti-CCP-positive JIA had the worst damage. The majority of patients with radiographic damage had both erosions and Joint Space Narrowing. The radiographic scores correlated well with measures of disease damage. Restricted mobility in joints at 15 years was the most important predictor of radiographic damage at 29 years. [175] It appears as if JIA patients tend to develop a hyperdivergent vertical jaw base relationship and a skeletal Class II pattern. However, findings regarding craniofacial morphological changes in JIA is inconclusive. [AF] If unrecognized, or left untreated, a temporomandibular joint (TMJ) involvement can lead to pain-impaired functional disorders, such as reduced mandibular mobility and bite force as well as tenderness of the masseter and temporalis muscles and headaches. From the orthodontic aspect, the TMJ arthritis may cause significant limitations in sagittal and vertical mandibular growth, conditionally resulting in severe micrognathia and anterior open bites with strong esthetic and functional restrictions. [AG]
Evaluation	Data is available, but its quality is not always satisfactory. More long term studies required.
Is the question answered?	partially answered

UVEITIS

Q39

Question	Ref		Article name	Article link
Wat is de beste behandeling van uveïtis bij jeugdreuma en zijn er factoren die de	[138]	RCT	Adalimumab in combination with methotrexate for refractory uveitis associated with juvenile idiopathic arthritis: a RCT.	https://www.ncbi.nlm.nih.gov/pubmed/31033434
	[139]	sys review + expert panel	2019 American College of Rheumatology/Arthritis Foundation Guideline for the Screening, Monitoring,	https://www.ncbi.nlm.nih.gov/pubmed/31021540

effectiviteit voorspellen?			and Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis.	
			Therapeutic advances in juvenile idiopathic arthritis - associated uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/30844943
	[140]	retrospective	Changing biological disease modifying treatment for paediatric uveitis in the real world.	https://www.ncbi.nlm.nih.gov/pubmed/30834650
	[141]	sys review + expert panel	Update of the evidence based, interdisciplinary guideline for anti-inflammatory treatment of uveitis associated with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30595409
	[142]	longitudinal	Longterm Safety and Efficacy of Adalimumab and Infliximab for Uveitis Associated with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29657140
		RCT	ADJUVITE: a double-blind, randomised, placebo-controlled trial of adalimumab in early onset, chronic, juvenile idiopathic arthritis-associated anterior uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/29275333
	[143]	review	Update on the Treatment of Uveitis in Patients with Juvenile Idiopathic Arthritis: A Review.	https://www.ncbi.nlm.nih.gov/pubmed/29143927
	[144]	retrospective	Safety of weekly adalimumab in the treatment of juvenile idiopathic arthritis and pediatric chronic uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/29103180
	[145]	RCT	Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28445659
	[146]	retrospective	Comparable Efficacy of Abatacept Used as First-line or Second-line Biological Agent for Severe Juvenile Idiopathic Arthritis-related Uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/27633826
	[147]	review	Treatment of Juvenile Idiopathic Arthritis-Associated Uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/27800265

	[148]	retrospective	Anti-Interleukin-6 Receptor Tocilizumab for Severe Juvenile Idiopathic Arthritis-Associated Uveitis Refractory to Anti-Tumor Necrosis Factor Therapy: A Multicenter Study of Twenty-Five Patients.	https://www.ncbi.nlm.nih.gov/pubmed/27696756
	[149]	retrospective	Evidence for Tocilizumab as a Treatment Option in Refractory Uveitis Associated with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27633821
	[AH]	Sys review	Expert Panel Recommendations for the Use of Anti–Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders	https://www.sciencedirect.com/science/article/pii/S0161642013008932?via%3Dihub
	[AI]	Sys review	Systematic Review on the Effectiveness of Immunosuppressants and Biological Therapies in the Treatment of Autoimmune Posterior Uveitis	https://www.sciencedirect.com/science/article/pii/S0049017210000843?via%3Dihub

Summary of findings	**Pharmacological:** Adalimumab significantly controlled inflammation and reduced the rate of treatment failure in patients with active uveitis on a stable dose of MTX. [138] Topical glucocorticoids should be used as initial treatment to achieve control of inflammation. Methotrexate and the monoclonal antibody tumor necrosis factor inhibitors adalimumab and infliximab are recommended when systemic treatment is needed for the management of uveitis. The timely addition of nonbiologic and biologic drugs is recommended to maintain uveitis control in children who are at continued risk of vision loss. [139] Biological therapy over 1 year was effective with prednisolone dose reduced to <5 mg/day in five of six patients (83%), number of systemic steroid-sparing agents was reduced to ≤1 in two of four patients (50%) and cessation of topical steroid achieved in 12/41 of eyes (29%). Improvement of anterior chamber cells by two grades occurred in 20/25 eyes (80%), improvement of logMAR to ≤0.3 occurred in 12/18 eyes (67%) and macular oedema decreased in 4/5 eyes (80%). Treatment failure occurred in six eyes (13.01%) and five patients (18.5%) developed an adverse reaction. [140] Thus, methotrexate shall be introduced for uveitis not responding to low-dose (≤ 2 applications/day) topical corticosteroids, and a TNFalpha antibody (preferably adalimumab) used, if uveitis inactivity is not achieved. In very severe active uveitis with uveitis-related deterioration of vision, systemic corticosteroids should be

	considered for bridging until DMARDs take effect. If TNFalpha antibodies fail to take effect or lose effect, another biological should be selected (tocilizumab, abatacept or rituximab). De-escalation of DMARDs should be preceded by a period of ≥ 2 years of uveitis inactivity. [141] At the 2-year followup, ADA showed a better efficacy and safety profile than IFX for the treatment of refractory JIA-associated uveitis. [142] The treatment stepladder of JIA-associated uveitis involves topical steroids and NSAIDs as first-line treatment. In cases with suboptimal response, peribulbar, subconjunctival, intravitreal or systemic steroids may need to be administered. Methotrexate, azathioprine and cyclosporine A can be useful in recalcitrant cases.However, if these drugs prove ineffective in controlling ocular inflammation, biologics such as an anti-TNF agent (adalimumab, etanercept or infliximab) or the T cell inhibitor abatacept needs to be administered. [143] Serious adverse events, laboratory abnormalities, and injection site reactions from the off-label use of weekly adalimumab were rare. Infections were not uncommon; however, the majority of infections were common childhood infections including viral illnesses, sinusitis, pharyngitis, and otitis. Interestingly, two patients on weekly adalimumab developed new autoimmune disease. TNF-inhibitor-induced autoimmune disease and demyelinating disease are rare but recognized risks of TNF-inhibitors. [144] Treatment with adalimumab significantly delayed the time to treatment failure, as compared with methotrexate alone. Adalimumab was associated with a higher incidence of adverse and serious adverse events than was placebo plus methotrexate.The most common adverse events in the adalimumab group were minor infections, respiratory disorders, and gastrointestinal disorders. [145] When used as first-line treatment, ABA showed a good efficacy; 57% were in complete remission after 12 months of treatment. When ABA was used as second-line biologic treatment, more than half of the patients in our series responded to treatment. There was no significant difference between the ABA-1 and ABA-2 groups in terms of response rate. [146] The choice of therapeutic regimen needs to be tailored to each individual case. Local and systemic corticosteroids have long been the mainstay of therapy; however, long-term corticosteroid therapy should be avoided due to serious side effects. Steroid-sparing agents in the treatment of JIA-associated uveitis include antimetabolites and biologic agents in refractory cases. Among the various immunomodulatory agents, methotrexate is generally the first choice, as it has a well-established safety and efficacy profile in pediatric cases and does not appear to increase the risk of cancer. Other classic immunomodulators that may also be used in combination with methotrexate include azathioprine, mycophenolate mofetil, and cyclosporin A. Biologic agents, primarily tumor necrosis factor alpha inhibitors including infliximab or adalimumab, should be considered in cases of treatment failure with classic immunomodulatory agents. [147] TCZ may be an effective therapy

	for severe JIA-associated uveitis refractory to conventional immunosuppressive and biologic drugs including anti-TNF and other biologic agents such as RTX or ABA. In this regard, in our study, we observed an improvement in all of the ocular parameters analyzed. [148] Following treatment with TCZ, inactive uveitis was achieved in 7 out of 17 patients. Considering that all of these patients had a severe course of persisting uveitis being refractory to at least 1 synthetic and 1 or more biological DMARD, TCZ holds promise as a rescue drug. [149] [AH] [AI] ***surgical** treatment articles excluded
Evaluation	A conventional treatment strategy exists. Several options for treatment of unresponsive uveitis are proposed, but not yet validated. No literature on factors affecting effectiveness of treatment for uveitis found.
Is the question answered?	partially answered

Q40

Question	Ref		Article name	Article link
Hoe ontstaat uveïtis bij jeugdreuma en hoe vaak komt het voor?	[228]	retrospective	Clinical features and characteristics of uveitis associated with juvenile idiopathic arthritis in Japan: first report of the pediatric rheumatology association of Japan (PRAJ).	https://www.ncbi.nlm.nih.gov/pubmed/30975163
	[229]	case-control	Genetic aspects of idiopathic paediatric uveitis and juvenile idiopathic arthritis associated uveitis in Chinese Han.	https://www.ncbi.nlm.nih.gov/pubmed/30940621
	[230]	cross-sectional	Transcriptomic and proteomic analysis of iris tissue and aqueous humor in juvenile idiopathic arthritis-associated uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/30885419
	[231]	prospective, observational	Vitamin D deficiency is associated with higher disease activity and the risk for uveitis in juvenile idiopathic arthritis - data from a German inception cohort.	https://www.ncbi.nlm.nih.gov/pubmed/30545399
	[232]	cross-sectional	Multiplex Cytokine Analysis of Aqueous Humor in Juvenile Idiopathic Arthritis-Associated Anterior Uveitis With or Without Secondary Glaucoma.	https://www.ncbi.nlm.nih.gov/pubmed/29675026

	[233]	retrospective	Identification of an Amino Acid Motif in HLA-DRβ1 That Distinguishes Uveitis in Patients With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29513936
	[234]	cross-sectional	Peripheral blood monocytes reveal an activated phenotype in pediatric uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/28923439
	[237]	cohort	Incidence and prevalence of uveitis in South Korea: a nationwide cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/28596287
	[235]	cross-sectional	Association of TRAF1-C5 with risk of uveitis in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27369649
	[236]	cross-sectional	Ocular Fluid Analysis in Children Reveals Interleukin-29/Interferon-λ1 as a Biomarker for Juvenile Idiopathic Arthritis-Associated Uveitis.	https://www.ncbi.nlm.nih.gov/pubmed/26866822
	[AJ]	Sys review	Expert Panel Recommendations for the Use of Anti–Tumor Necrosis Factor Biologic Agents in Patients with Ocular Inflammatory Disorders	https://www.sciencedirect.com/science/article/pii/S0161642013008932?via%3Dihub

Summary of findings	**Associations:** Oligoarthritis, earlier arthritis onset, ANA-positivity, RF-negativity and anti-CCP antibody-negativity could be risk factors for uveitis development in JIA patients. [228] Six SNPs (PRM1/rs11074967, JAZF1/rs73300638, IRF5/rs2004640, MEFV/rs224217, PSMA3/rs2348071 and PTPN2/rs7234029) showed an association with JIA uveitis. [229] 25(OH)D deficiency was associated with risk of developing uveitis in JIA patients. [231] One study found a positive association between the AA TRAF1-C5 rs10818488 genotype and the risk of uveitis among ANA-positive patients in the oligoarticular and polyarticular forms of the disease. [235] **Pathogenesis:** One study showed an intense intraocular gene and protein expression of B cell and Plasma Cell-associated molecules in iris tissues from JIAU patients, indicating a crucial role of these cells in JIAU. The concurrently increased concentrations of the B cell survival factors BAFF, APRIL, and IL-6 in the AqH of patients might possibly be responsible for the longevity of PC in the affected tissues, even during phases of inactive disease. [230] Pro- and anti-

	inflammatory cytokine, chemokine, or metalloproteinase levels are increased in clinically inactive JIAU eyes, suggesting that in these eyes disease is seemingly not inactive from an immunological point of view and that the eyes show a cytokine profile typical of chronic inflammation. The pathogenetic process for the development of glaucoma in some of the JIAU patients may be related to the severity of ocular inflammation, the use of corticosteroids, and complications such as posterior synechiae, damage of anterior chamber angle or to the TM. The study concludes that the etiologic mechanisms involved are multifactorial. However, the significantly increased levels of SAA in JIAUwoG and of TGFβ-2 in JIAUwG suggest that the cytokines could play important roles in modulating intraocular pressure. [232] The amino acid serine at position 11 in the HLA–DRB1 gene is strongly associated with an increased risk of uveitis in female JIA patients. the serine 11 signal is sexually dimorphic and unique to female patients with JIA. The relatively high frequency of serine 11 in the JIA patients who did not develop uveitis indicates the likely involvement of additional (epi)genetic and environmental factors in uveitis. [233] One study found differential expression of molecules with both costimulatory and regulatory potential (CD86, CD39, CD73), as well as changes in CCR2-expression on monocytes from patients with juvenile idiopathic arthritis and/or uveitis as compared to pediatric controls. The difference in monocyte phenotype may represent changes due to autoimmune cell activation and regulating mechanisms in general, which may point to systemic immune deviation that could in part contribute to the overlapping articular and ocular manifestations of idiopathic inflammatory arthritis and/or uveitis. [234] In summary, we identified IL-29/IFNλ1 as an intraocular biomarker for JIA-associated uveitis. This finding suggests that aberrant IFNλ signaling might be important in uveitis associated with JIA. [236] The primary factors contributing to the pathogenesis of uveitis seems to be the cytokines IL-2 and tumor necrosis factor-***α*** (TNF-***α***), as well as Th1 mediators.[AJ] **Incidence**: The average incidence of anterior and non-anterior uveitis were 9.0 and 1.5 per 10 000 person-years. [237] ← *this study refers to all types of uveitis, not only JIA-associated uveitis*
Evaluation	Some information regarding the pathogenesis and associated factors is available. The exact mechanism behind uveitis in JIA is not known.
Is the question answered?	insufficiently answered

Q41

Question	Ref		Article name	Article link

Hoe kunnen patiënten en ouders/verzorgers zelf beter herkennen of er ontstekingen zijn in de gewrichten en/of ogen?				

Summary of findings	
Evaluation	
Is the question answered?	no relevant literature

SYSTEMISCHE JIA

Q42

Question	Ref		Article name	Article link
Wat is de optimale behandeling van systemische jeugdreuma en zijn er factoren die de effectiviteit van de verschillende behandelingen kunnen voorspellen?	[186]	longitudinal	Treatment to Target Using Recombinant Interleukin-1 Receptor Antagonist as First-Line Monotherapy in New-Onset Systemic Juvenile Idiopathic Arthritis: Results From a Five-Year Follow-Up Study.	https://www.ncbi.nlm.nih.gov/pubmed/30848528
			Predictors of Effectiveness of Anakinra in Systemic Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30647180
	[187]	retrospective	Tocilizumab in the treatment of systemic-onset juvenile idiopathic arthritis - single-centre experience.	https://www.ncbi.nlm.nih.gov/pubmed/30505008
	[188]	longitudinal	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.	https://www.ncbi.nlm.nih.gov/pubmed/30269054
	[189]	review	The role of IL-1 inhibition in systemic juvenile idiopathic arthritis: current status and future perspectives.	https://www.ncbi.nlm.nih.gov/pubmed/29922038

	[190]	retrospective	IL-6 blockade in systemic juvenile idiopathic arthritis - achievement of inactive disease and remission (data from the German AID-registry).	https://www.ncbi.nlm.nih.gov/pubmed/29622022
	[191]	cross-sectional	IL1RN Variation Influences Both Disease Susceptibility and Response to Recombinant Human Interleukin-1 Receptor Antagonist Therapy in Systemic Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29609200
	[192]	mixed methods	Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany.	https://www.ncbi.nlm.nih.gov/pubmed/29357887
	[193]	review	Update on the management of systemic juvenile idiopathic arthritis and role of IL-1 and IL-6 inhibition.	https://www.ncbi.nlm.nih.gov/pubmed/29184458
	[194]	retrospective	Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry.	https://www.ncbi.nlm.nih.gov/pubmed/29166924
	[195]	pilot study	Pilot study comparing the Childhood Arthritis & Rheumatology Research Alliance (CARRA) systemic Juvenile Idiopathic Arthritis Consensus Treatment Plans.	https://www.ncbi.nlm.nih.gov/pubmed/28399931
	[196]	longitudinal	Tocilizumab in systemic juvenile idiopathic arthritis in a real-world clinical setting: results from 1 year of postmarketing surveillance follow-up of 417 patients in Japan.	https://www.ncbi.nlm.nih.gov/pubmed/26644233
	[AJ]	Sys review	Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials -2015	https://academic.oup.com/rheumatology/article/55/4/669/2899445
	[AK]	Sys review	Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons	https://ard.bmj.com/content/72/11/1806.long

Summary of findings	The treat-to-target strategy using rIL-1Ra as first-line monotherapy for systemic JIA described herein resulted in rapid attainment of inactive disease, prevention of damage and functional limitations,

	and avoidance of glucocorticoids in the majority of patients. inactive disease while not receiving medication could be achieved in more than half of the patients within the first year of therapy.The percentage of patients with inactive disease after 1 year of therapy in our study was >2-fold higher than the percentages in other prospective trials using biologic agents as second- or third-line therapy in systemic JIA. findings suggest that, especially in the early phase of systemic JIA, which is characterized by pronounced innate immune activation and neutrophilia, patients may be highly responsive to IL-1 blockade, indicating the existence of a window of opportunity. [186] TCZ shows both high effectiveness and a satisfactory drug safety profile. It may be especially useful in patients resistant to other DMARDs and with high doses of corticosteroid dependency. [187] There was a marked, rapid improvement of sJIA activity with canakinumab treatment at 6 months, which was maintained for up to 5 years and allowed for the marked reduction or even discontinuation of glucocorticoids (in 44%).Canakinumab/MTX combination therapy is unlikely expected to improve sJIA control versus using canakinumab alone. [188] NSAIDs are the first choice of treatment for SJIA, as they are for other JIA subtypes. GCS are used for the treatment of persistent systemic signs. In cases with persistent arthritis as the leading clinical feature of the disease, methotrexate (MTX) is the drug of choice after systemic signs have subsided. In patients with a polycyclic course with relapses of systemic features during tapering of GCS, biologic therapy is recommended. The use of anakinra is currently recommended in SJIA patients with persistent systemic signs of the disease who are refractory to GCS treatment.It was suggested that a better response to anakinra can be expected in patients with arthritis in only a few joints compared to those with polyarthritis. A canakinumab dose of 4 mg/kg was associated with rapid and sustained clinical improvement. Canakinumab and also the anti-IL-6 agent tocilizumab were more effective than rilonacept. [189] ut of 200 sJIA children reported in the German AID-registry, 46 were treated with TCZ, showing a clinical response rate of 35% during the first 12 weeks, and inactive disease and/or remission under medication in 75% after one year. [190] Homozygosity for the high expression alleles of systemic JIA–associated IL1RN SNPs is strongly associated with nonresponsiveness to anakinra treatment in patients with systemic JIA. [191] Consensus based treatment strategies are presented. [192] With the number of treatment options now available for SJIA, there is a wide variability in treatment approaches among practitioners, and the ideal treatment approach is unknown and also likely dependent on the features and severity of each individual case of SJIA. [193] No marked difference was observed between patients receiving ANA or CAN. Effectiveness in early disease upon either treatment with TOC or IL-1-inhibitors was higher than in longer disease duration. This fits the observation that there has been a movement toward earlier treatment with

	biologics, probably because of a suggested "window of opportunity" that drives this trend, but still remains unproven. [194] A large study using Consensus Treatment Plan response to better determine the relative effectiveness of treatments for new-onset systemic JIA is now underway. [195] TCZ was effective, with a tolerable safety profile. [196] [AK] [AL]
Evaluation	Many individual studies are available but it is still unknown why (and which) patients do not respond to treatment. More research into the idea of "window of opportunity" is needed as well.
Is the question answered?	partially answered

Q43

Question	**Ref**		**Article name**	**Article link**
Welke interne en externe factoren bepalen hoe systemische jeugdreuma zich uit en verandert dit in het beloop van de ziekte?	[238]	cross-sectional	Serum Leucine-Rich α2-Glycoprotein as a Biomarker for Monitoring Disease Activity in Patients with Systemic Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30863782
	[239]	cross-sectional	The role of extracellular histones in systemic-onset juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30642364
	[240]	cross-sectional	Plasma interleukin-37 is increased and inhibits the production of inflammatory cytokines in peripheral blood mononuclear cells in systemic juvenile idiopathic arthritis patients.	https://www.ncbi.nlm.nih.gov/pubmed/30305171

Summary of findings	**Internal markers:** serum LRG levels were elevated in the active phase of s-JIA and normalized in the inactive phase. [238] Serum histone level in active SoJIA group was significantly higher than in remissive SoJIA group. The proportion of neutrophils producing NETs in the active group was the highest among three groups, that suggested that the serum histones in patients with active SoJIA are produced by activated neutrophils. [239] Plasma IL-37 levels were higher in sJIA patients compared with HCs. Moreover, we further investigated that plasma IL-37 levels were significantly elevated in patients with active disease than in patients with inactive disease and in HCs. [240]
Evaluation	Some biomarkers may be used as internal factors. However, it is unclear what drivers are behind the elevations of these biomarkers

	in sJIA patients. No info on external factors found. Very limited literature on the topic.
Is the question answered?	insufficiently answered

ERFELIJKHEID

Q44

Question	Ref		Article name	Article link
Is jeugdreuma erfelijk, en zo ja, op welke manier is het overdraagbaar?			Implications of juvenile idiopathic arthritis genetic risk variants for disease pathogenesis and classification.	https://www.ncbi.nlm.nih.gov/pubmed/31169548
			HLA associations in inflammatory arthritis: emerging mechanisms and clinical implications.	https://www.ncbi.nlm.nih.gov/pubmed/31092910
	[148]	lab	NFIL3 mutations alter immune homeostasis and sensitise for arthritis pathology.	https://www.ncbi.nlm.nih.gov/pubmed/30552177
	[149]	cross-sectional	Brief Report: The Genetic Profile of Rheumatoid Factor-Positive Polyarticular Juvenile Idiopathic Arthritis Resembles That of Adult Rheumatoid Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29426059
	[150]	review	Review: Genetics and the Classification of Arthritis in Adults and Children.	https://www.ncbi.nlm.nih.gov/pubmed/29024575
	[151]	cross-sectional	The genetics of juvenile idiopathic arthritis: Searching for new susceptibility loci.	https://www.ncbi.nlm.nih.gov/pubmed/28990043
	[152]	review	Genetics of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28711144
	[153]	retrospective	Juvenile idiopathic arthritis in multiplex families: longitudinal follow-up.	https://www.ncbi.nlm.nih.gov/pubmed/28513071
	[154]	GWAS	Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications.	https://www.ncbi.nlm.nih.gov/pubmed/27927641
	[155]	cross-sectional	Association of interleukin-6 single nucleotide polymorphisms with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27646136
	[156]	whole genome sequencing	Genetic insights into juvenile idiopathic arthritis derived from deep whole genome sequencing.	https://www.ncbi.nlm.nih.gov/pubmed/28572608

Summary of findings	Mutations in immunological factor NFIL3 results in IL-1β overproduction.[148] RF-positive polyarticular JIA is genetically more similar to adult RA than to the most common JIA categories. The HLA region was strongly associated with RF-positive polyarticular JIA. [149] A re-classification of arthritis based on genetic similarities among various RA and JIA subtypes is proposed (seronegative, seropositive, spondyloarthritis, systemic). [150] eNOS VNTR polymorphism is associated with susceptibility to JIA. [151] Several candidate genes/gene regions are listed. [152] A study discovered earlier onset of disease in familial JIA patients. Additionally, there was an increase in JIA frequency among the parents in families with multiple affected siblings. Linkage analysis localized systemic JIA to a region on chromosome 13. Whole-exome sequencing identified a homoallelic missense mutation in LACC1, which encodes the enzyme laccase. [153] Two novel susceptibility loci met genome-wide significance criteria for association with sJIA and 23 other loci demonstrated highly suggestive evidence of association. Systemic JIA has been found to be genetically distinct from other types of JIA. [154] The frequency of the IL-6 −174 G allele was significantly elevated in patients compared to controls. CG genotype at the same position was found to be negatively associated with JIA proneness. These findings both contradict some, and support other previous studies. [155] Another study identified multiple candidate JIA loci, most prominently on Chromosome 6, location of MHC genes. Further validation of these is needed. [156]
Evaluation	The evidence is fragmented and incomplete
Is the question answered?	insufficiently answered

OORZAAK

Q45

Question	Ref		Article name	Article link
Hoe ontstaat jeugdreuma en welke factoren hebben daar invloed op?			Interleukin-18 in pediatric rheumatic diseases.	https://www.ncbi.nlm.nih.gov/pubmed/31192813
			MicroRNAs in juvenile idiopathic arthritis: Can we learn more about pathophysiological mechanisms?	https://www.ncbi.nlm.nih.gov/pubmed/31176874
			MicroRNA-125b regulates Th17/Treg cell differentiation and is associated with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/31102153

			HLA associations in inflammatory arthritis: emerging mechanisms and clinical implications.	https://www.ncbi.nlm.nih.gov/pubmed/31092910
			Molecular signature characterisation of different inflammatory phenotypes of systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/31005900
			The role of microRNA-16 in the pathogenesis of autoimmune diseases: A comprehensive review.	https://www.ncbi.nlm.nih.gov/pubmed/30780103
			Autoantibodies in the Pathogenesis, Diagnosis, and Prognosis of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30693002
			The association of CAT-262C/T polymorphism with catalase activity and treatment response in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30680511
			The role of extracellular histones in systemic-onset juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30642364
			Gut microbiota in children and altered profiles in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30638708
			Low Serum IGF-1 in Boys with Recent Onset of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30622975
			NFIL3 mutations alter immune homeostasis and sensitise for arthritis pathology.	https://www.ncbi.nlm.nih.gov/pubmed/30552177
			Foxp3 Molecular Dynamics in Treg in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30333832
			Plasma interleukin-37 is increased and inhibits the production of inflammatory cytokines in peripheral blood mononuclear cells in systemic juvenile idiopathic arthritis patients.	https://www.ncbi.nlm.nih.gov/pubmed/30305171
			Recent advances in our understanding of the pathogenesis of juvenile idiopathic arthritis and their potential clinical implications.	https://www.ncbi.nlm.nih.gov/pubmed/30269617
			Insufficient IL-10 Production as a Mechanism Underlying the Pathogenesis of Systemic Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30266771
			The role of S100 proteins in the pathogenesis and monitoring of autoinflammatory diseases.	https://www.ncbi.nlm.nih.gov/pubmed/30255357
			T Cell Receptor-Independent, CD31/IL-17A-Driven Inflammatory Axis Shapes Synovitis in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30127787

			Systemic juvenile idiopathic arthritis and macrophage activation syndrome: update on pathogenesis and treatment.	https://www.ncbi.nlm.nih.gov/pubmed/29870499
			Systemic juvenile idiopathic arthritis: New insights into pathogenesis and cytokine directed therapies.	https://www.ncbi.nlm.nih.gov/pubmed/29773270
			Update on research and clinical translation on specific clinical areas from biology to bedside: Unpacking the mysteries of juvenile idiopathic arthritis pathogenesis.	https://www.ncbi.nlm.nih.gov/pubmed/29773267
			Associations between interleukin-10 polymorphisms and susceptibility to juvenile idiopathic arthritis: a systematic review and meta-analysis.	https://www.ncbi.nlm.nih.gov/pubmed/29748155
			Changes in thiol/disulfide homeostasis in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29569426
			Peripheral regulatory T cells and anti-inflammatory cytokines in children with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29494710
			Association of interferon regulatory factor 5 (IRF5) gene polymorphisms with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29423720
			TNF-alpha 863C > A promoter and TNFRII 196T > G exonic variationsmay be risk factors for juvenile idiopathic arthritis	https://www.ncbi.nlm.nih.gov/pubmed/29306244
			Single nucleotide polymorphism of Methyl-CpG-binding protein 2 gene associates with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29288368
			Neutrophil activation signature in juvenile idiopathic arthritis indicates the presence of low-density granulocytes.	https://www.ncbi.nlm.nih.gov/pubmed/29240923
			Risk Factors Associated with Juvenile Idiopathic Arthritis: Exposure to Cigarette Smoke and Air Pollution from Pregnancy to Disease Diagnosis.	https://www.ncbi.nlm.nih.gov/pubmed/29142039
			A multidimensional blood stimulation assay reveals immune alterations underlying systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28935693
			Genome-Wide Association Meta-Analysis Reveals Novel Juvenile Idiopathic Arthritis Susceptibility Loci.	https://www.ncbi.nlm.nih.gov/pubmed/28719732
			Early feeding and risk of Juvenile idiopathic arthritis: a case control study in a prospective birth cohort.	https://www.ncbi.nlm.nih.gov/pubmed/28549465
			Update on the pathogenesis and treatment of juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28538013

			Cow's Milk Allergy in Infancy and Later Development of Juvenile Idiopathic Arthritis: A Register-Based Case-Control Study.	https://www.ncbi.nlm.nih.gov/pubmed/28459985
			Alteration of Fecal Microbiota Profiles in Juvenile Idiopathic Arthritis. Associations with HLA-B27 Allele and Disease Status.	https://www.ncbi.nlm.nih.gov/pubmed/27833598
			Association of tumour necrosis factor-alpha G/A -238 and G/A -308 single nucleotide polymorphisms with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27753221
			Inflammatory Gene Expression Profile and Defective Interferon-γ and Granzyme K in Natural Killer Cells From Systemic Juvenile Idiopathic Arthritis Patients.	https://www.ncbi.nlm.nih.gov/pubmed/27696741
			The human microbiome and juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27650128
			Association of interleukin-6 single nucleotide polymorphisms with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27646136
			Gut microbiota-host interactions and juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27448997
			Network analysis and juvenile idiopathic arthritis (JIA): a new horizon for the understanding of disease pathogenesis and therapeutic target identification.	https://www.ncbi.nlm.nih.gov/pubmed/27411317
			Whole blood expression profiling from the TREAT trial: insights for the pathogenesis of polyarticular juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27388672
			Interleukin 10 and transforming growth factor beta 1 gene polymorphisms in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27215961
			Association of Interleukin-2, but not Interferon-Gamma, single nucleotide polymorphisms with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27040810
			Monocyte MicroRNA Expression in Active Systemic Juvenile Idiopathic Arthritis Implicates MicroRNA-125a-5p in Polarized Monocyte Phenotypes.	https://www.ncbi.nlm.nih.gov/pubmed/27014994
			Variants in CXCR4 associate with juvenile idiopathic arthritis susceptibility.	https://www.ncbi.nlm.nih.gov/pubmed/27005825
			Next-Generation Sequencing Reveals Restriction and Clonotypic Expansion of Treg Cells in Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/26815131

			Potential Effects of Interleukins on the Pathogenesis of Systemic Onset Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/26810447
			Altered signaling in systemic juvenile idiopathic arthritis monocytes.	https://www.ncbi.nlm.nih.gov/pubmed/26747737
			IL23R gene polymorphism with juvenile idiopathic arthritis and its association with serum IL-17A.	https://www.ncbi.nlm.nih.gov/pubmed/26016922
			Association of Increased Sun Exposure Over the Life-course with a Reduced Risk of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30378692
			Using the attract method to identify core pathways in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27525947
		Sys review	Association between Air Pollution and the Development of Rheumatic Disease: A Systematic Review.	https://www.ncbi.nlm.nih.gov/pubmed/27847517

Summary of findings	***see q44 for genetic factors*
Evaluation	The evidence is fragmented.
Is the question answered?	insufficiently answered

Q46

Question	Ref		Article name	Article link
Is er een verband tussen jeugdreuma en andere (auto-immuun) ziekten, en zo ja, hoe kunnen we dit beter begrijpen?	[55]	prospective study	Serological screening for coeliac disease in patients with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/31182344
	[56]	genetic screening	Genetic Screening of Mutations Associated with Fabry Disease in a Nationwide Cohort of Juvenile Idiopathic Arthritis Patients.	https://www.ncbi.nlm.nih.gov/pubmed/28299312
	[57]	intestine biopsy	Evaluation of screening for coeliac disease in children with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30265401
	[58]	retrospective	Pneumonia in children with juvenile idiopathic arthritis in Finland 1999-2014: a nationwide retrospective register linkage study.	https://www.ncbi.nlm.nih.gov/pubmed/29303705
	[59]	review	Macrophage activation syndrome as a complication of juvenile rheumatoid arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29077164

	[60]	review	When a patient suspected with juvenile idiopathic arthritis turns out to be diagnosed with an infectious disease - a review of Lyme arthritis in children.	https://www.ncbi.nlm.nih.gov/pubmed/28482848
	[61]	cross sectional	Joint hypermobility and oligoarticular juvenile idiopathic arthritis: What relationship?	https://www.ncbi.nlm.nih.gov/pubmed/28052441
	[62]		LACC1 polymorphisms in inflammatory bowel disease and juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27098602
	[63]	cross sectional	Epidemiology and risk of juvenile idiopathic arthritis among children with allergic diseases: a nationwide population-based study.	https://www.ncbi.nlm.nih.gov/pubmed/26965056
	[252]	Sys review & meta analysis	Association of PTPN22 1858C/T Polymorphism with Autoimmune Diseases: A Systematic Reviewand Bayesian Approach.	https://www.ncbi.nlm.nih.gov/pubmed/30871019

Summary of findings	No relation between Celiac disease and JIA has been found. [55] There is no indication that all JIA patients should be screened for CD. [57] No relation between Fabry disease and JIA. [56] JIA patients had a higher rate of pneumonia. [58] MAS is a life threatening complication of JIA. [59] Jojnt hypermobility syndrome is associated with oligoarticular JIA. [61] The LACC1 gene is linked to several inflammatory disease (UC, Crohn's, JIA). [62] Children with onset of allergic diseases were at increased risk of developing JIA. [63] PTPN22's association with multiple autoimmune diseases might indicate a common mechanism underlying the development of autoimmune disease. PTPN22 encodes a protein tyrosine phosphatase that inhibits antigen-receptor signaling in T cells and promotes pattern-recognition receptor-induced type I interferon production by myeloid cells. Zheng et al. proposed that PTPN22 has stronger associations with autoimmune disorders in which auto-antibodies have a major role in pathogenesis. The effect of PTPN22 depends on the respective tissue affected by autoimmunity. [252] *Lyme arthritis may have the same clinical picture as JIA. [60]
Evaluation	One mechanism of underlying association proposed. Validation of this finding needed.
Is the question answered?	Insufficiently answered

Q47

Question	Ref		Article name	Article link

Hoe komt het dat niet alle patiënten met jeugdreuma dezelfde symptomen en klachten hebben (bijv. klachten van de ogen en gewrichten)?				

Summary of findings	
Evaluation	
Is the question answered?	no relevant literature

DIAGNOSE

Q48

Question	Ref		Article name	Article link
Hoe kunnen we jeugdreuma beter en sneller herkennen?	[131]	retrospective	Comparative study of Interleukin-18 (IL-18) serum levels in adult onset Still's disease (AOSD) and systemic onset juvenile idiopathic arthritis (sJIA) and its use as a biomarker for diagnosis and evaluation of disease activity.	https://www.ncbi.nlm.nih.gov/pubmed/30886992
	[132]	review	Autoantibodies in the Pathogenesis, Diagnosis, and Prognosis of Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30693002
	[133]	retrospective	Features distinguishing juvenile idiopathic arthritis among children with musculoskeletal complaints.	https://www.ncbi.nlm.nih.gov/pubmed/30498888
	[134]	review	The role of imaging in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29972659
	[135]	review	Imaging in juvenile idiopathic arthritis - international initiatives and ongoing work.	https://www.ncbi.nlm.nih.gov/pubmed/29332166
	[136]	lab	Peptide-based electrochemical biosensor for juvenile idiopathic arthritis detection.	https://www.ncbi.nlm.nih.gov/pubmed/29031228
	[137]	lab	Extremely elevated IL-18 levels may help distinguish systemic-onset juvenile idiopathic arthritis from other febrile diseases.	https://www.ncbi.nlm.nih.gov/pubmed/28225869
	[138]	review	Juvenile Idiopathic Arthritis: Diagnosis and Treatment.	https://www.ncbi.nlm.nih.gov/pubmed/27747582

	[139]	cross-sectional ?	Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/26417716
	[140]	lab	S100A12 and vascular endothelial growth factor can differentiate Blau syndrome and familial Mediterranean fever from systemic juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30406853
	[141]	lab	90K immunostimulatory glycoprotein in children with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/29157059
	[142]	lab	Interleukin-17A Levels Increase in Serum of Children With Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30375522
	[143]	lab	Serum ferritin levels as a useful diagnostic marker for the distinction of systemic juvenile idiopathic arthritis and Kawasaki disease.	https://www.ncbi.nlm.nih.gov/pubmed/27433933
	[144]	sys review	Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks?	https://www.ncbi.nlm.nih.gov/pubmed/27411444
	[145]	lab	Diagnostic performance of anti-citrullinated protein/peptide antibodies in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27323035
	[146]	lab	Plasma miR-26a as a Diagnostic Biomarker Regulates Cytokine Expression in Systemic Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/27252421
	[147]	lab	Differential plasma microRNAs expression in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/26054419
	[253]	longitudinal	Developing a Predictive Score for Chronic Arthritis among a Cohort of Children with Musculoskeletal Complaints—The Chronic Arthritis Score Study	https://www.sciencedirect.com/science/article/pii/S0022347615013207
	[AL]	Sys review	EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice -2015	https://ard.bmj.com/content/74/11/1946.long
	[AM]	Sys review	Juvenile Idiopathic Arthritis of the Axial Joints: A Systematic Review of the Diagnostic Accuracy and Predictive Value of Conventional MRI -2014	https://www.ajronline.org/doi/full/10.2214/AJR.12.10475
	[AN]	Sys review	Is ultrasound a validated imaging tool for the diagnosis and management of synovitis in juvenile idiopathic arthritis? A systematic literature review	https://onlinelibrary.wiley.com/doi/full/10.1002/acr.21644

Summary of findings	**Biomarkers:** A systematic review identified 68 candidates for potentially useful biomarker in diagnosing sJIA, however, few were validated, and further validation studies are needed to ascertain the role of these biomarkers. [144] Systemic JIA shows extremely high levels of IL-18. [131] [137] A cut-off value of 10,000 pg/ml is proposed for the diagnosis of sJIA. [131] The ANA test is useful in predicting risk of uveitis. The presence of ACPA in polyarticular RF+ JIA has been shown by numerous studies to confer a greater risk of more aggressive and erosive disease (but is not a diagnostic factor). [132] Peptide-based electrochemical biosensor may be a promising analytical tool for JIA diagnosis. [136] Measuring both serum S100A12 and VEGF levels may be useful in differentiating patients with Blau syndrome and FMF from those with sJIA. In active patients with sJIA, serum S100A12 protein and VEGF levels are over 2000 ng/ml and 1000 pg/ml but not patients with Blau syndrome. [140] 90K glycoprotein levels are increased in JIA children compared to healthy controls. [141] Serum levels of IL-17A in children with JIA were significantly higher in comparison to control group. [142] Serum ferritin levels were significantly elevated in s-JIA patients compared with Kawasaki Disease patients. [143] ACPA measurement can aid in diagnosing RF-positive polyarticular JIA. [145] Another study identified miR-26a as a potential biomarker for the diagnosis as well as differential diagnosis of sJIA. [146] Plasma miR-16 and miR-146a also have potential diagnostic value. [147] **Examination:** Standard diagnosis recommendations are available. [138] The following characteristics differentiate JIA among children with musculoskeletal complaints: duration of morning stiffness lasting at least 15 minutes, limping, joint swelling on MSK examination, and duration of MSK complaints exceeding 6 weeks. [133] One study identified 4 variables statistically associated with the final diagnosis of chronic arthritis. Joint swelling pattern (b1), precipitating factors of pain (b2), morning stiffness duration (b3), and pain frequency (b4). These are incorporated into a regression model. [253] **Imaging:** Imaging may be useful for diagnosis of JIA but standardised guidelines are lacking. [134]Ongoing initiatives are presented. [135] Characteristics of FDG-PET findings in the diagnosis of systemic juvenile idiopathic arthritis are presented. [139] Medical imaging techniques, including MRI, ultrasound, and conventional radiology, are superior to clinical examination and exclusion criteria alone for the diagnosis of JIA and accurate detection of joint inflammation. The joints to look out for

	assessment are mainly the knees and wrists, based on evidence of most commonly observed changes in joint inflammation [AL]. here is fair evidence that MRI is an accurate diagnostic tool for detecting JIA in temporomandibular joint, but insufficient evidence that it's an accurate diagnostic tool for detecting JIA in spinal and sacroiliac joint [AM]. Ultrasound is a valuable tool for detecting synovitis in JIA, and demonstrated higher sensitivity in assessing synovitis as compared to clinical examination [AN]
Evaluation	The evidence is highly fragmented. The evidence needs to be systematised. Imaging and biomarkers are a promising tool for faster JIA diagnosis.
Is the question answered?	insufficiently answered

Q49

Question	Ref		Article name	Article link
Hoeveel mensen in Nederland hebben jeugdreuma?				

Summary of findings	
Evaluation	
Is the question answered?	no relevant literature

TOEKOMST

Q50

Question	Ref		Article name	Article link
Wat is de invloed van jeugdreuma op toekomstmogelijkheden als het gaat om school, werk en relaties?	[125]	cross-sectional	Disability and health-related quality of life are associated with restricted social participation in young adults with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30270708
	[121]	observational cohort	The majority of patients with newly diagnosed juvenile idiopathic arthritis achieve a health-related quality of life that is similar to that of healthy peers: results of the German multicenter inception cohort (ICON).	https://www.ncbi.nlm.nih.gov/pubmed/29848349
	[122]	cross-sectional	The burden of systemic juvenile idiopathic arthritis for patients and	https://www.ncbi.nlm.nih.gov/pubmed/29600940

			caregivers: an international survey and retrospective chart review.	
	[123]	longitudinal cohort	Physical Functioning, Pain, and Health-Related Quality of Life in Adults With Juvenile Idiopathic Arthritis: A Longitudinal 30-Year Followup Study.	https://www.ncbi.nlm.nih.gov/pubmed/28732134
	[124]	cross-sectional	Education and employment in patients with juvenile idiopathic arthritis - a standardized comparison to the German general population.	https://www.ncbi.nlm.nih.gov/pubmed/28532479
	[130]	prospective cohort	Factors associated with preterm delivery among women with rheumatoid arthritis and juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/30133181
	[126]	prospective	Disease Activity of Juvenile Idiopathic Arthritis during and after Pregnancy: A Prospective Multicenter Study.	https://www.ncbi.nlm.nih.gov/pubmed/29196380
	[127]	cohort study	Juvenile onset arthritis and pregnancy outcome: a population-based cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/28663309
	[128]	retrospective	Postpartum complications in new mothers with juvenile idiopathic arthritis: a population-based cohort study.	https://www.ncbi.nlm.nih.gov/pubmed/28460079
	[129]	retrospective	Maternal juvenile rheumatoid arthritis may be associated with preterm birth but not poor fetal growth.	https://www.ncbi.nlm.nih.gov/pubmed/26675002

Summary of findings	A German study found that after 3 years in rheumatologic pediatric care JIA patients on average achieved similar psychosocial health levels to healthy peers, and a slightly lower physical health level. [121] A study assessed the impact of sJIA on everyday life of both patients and carers, finding functional limitation, requirement of assistive devices, & lower QoL for patients, and impaired mental health & work absenteeism for carers. [122] Another study found that compared to healthy controls, JIA patients had impaired physical but not mental HRQoL. During the longitudinal followup 15, 23, and 30 years after disease onset, patients' well-being and physical HRQoL deteriorated, whereas patients' experience of pain and mental HRQoL did not worsen. Almost half of the patients reported some form of disability. [123] A German study found that JIA patients on average achieved a lower education level and were more likely to be unemployed that the average German person. The authors mention that their results are in line with some other, but not all similar previous studies, and mention that the difference may be attributable to the country under examination and its insurance public education laws. [124] A Finnish study found that the majority of the patients (83%) were participating actively in everyday life; however, every sixth patient

	with JIA was either unemployed or on a disability pension. The latter were at a higher risk of negative outcomes such as worse emotional well-being. [125] One study found that disease activity 6 weeks postpartum increased. The study also found a significant improvement in reported mental health 6 weeks after delivery. In general, pregnant women experience low and stable disease activity. [126] Women with JIA were at increased risk of preterm birth [127][129] and pre-eclampsia. [127] Preterm delivery was associated with corticosteroid use, use of NSAIDs in the 1st trimester. [130] Mothers with JIA appear to be at higher risk for complications attributable to anaesthesia, postpartum haemorrhage and thromboembolism. However, mothers with JIA were at lower risk for obstetrical trauma and for developing depression in the period 1 year postpartum compared with mothers without JIA.[128]
Evaluation	The evidence is highly fragmented or inconclusive. Systematic research into the topic is required for meaningful conclusion to be drawn.
Is the question answered?	partially answered

PREVENTIE

Q51

Question	Ref		Article name	Article link
Kan jeugdreuma voorkomen worden, en zo ja hoe?	[64]	longitudinal	Methotrexate treatment may prevent uveitis onset in patients with juvenile idiopathic arthritis: experiences and subgroup analysis in a cohort with frequent methotrexate use.	https://www.ncbi.nlm.nih.gov/pubmed/27385618

Summary of findings	*Patients treated with MTX had a lower risk of developing uveitis. [64]
Evaluation	
Is the question answered?	No relevant literature

VOORZIENINGEN

Q52

Question	Ref		Article name	Article link

Hoe kunnen we de zorg en begeleiding voor patiënten met jeugdreuma zoveel mogelijk afstemmen op de behoeften van de patiënt?	[65]	qualitative	Development of a national audit tool for juvenile idiopathic arthritis: a BSPAR project funded by the Health Care Quality Improvement Partnership.	https://www.ncbi.nlm.nih.gov/pubmed/29069424
	[66]	qualitative	Harnessing interactive technologies to improve health outcomes in juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28511689
	[67]	qualitative	Young people's experiences of persistent musculoskeletal pain, needs, gaps and perceptions about the role of digital technologies to support their co-care: a qualitative study.	https://www.ncbi.nlm.nih.gov/pubmed/27940635
	[68]	qualitative	Promoting participation in healthcare situations for children with JIA: a grounded theory study.	https://www.ncbi.nlm.nih.gov/pubmed/27172512
	[69]	qualitative	Trends in paediatric rheumatology referral times and disease activity indices over a ten-year period among children and young people with Juvenile Idiopathic Arthritis: results from the childhood arthritis prospective Study.	https://www.ncbi.nlm.nih.gov/pubmed/27016664
	[250]	Sys review	Telemedicine for patients with rheumatic diseases: Systematic review and proposal for research agenda.	https://www.ncbi.nlm.nih.gov/pubmed/28420491
	[256]	Cross sectional, surveys	Information needs in parents of children with a rheumatic disease	https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-2214.2008.00870.x?casa_token=MNDShCOMGZcAAAAA:N4RCO9UF188gsRPSPEL9MY9CRI-Lvz7eskNNw0QNC6_K1S3LypqcT-wd80UcRk-9a5xE-s8eUxRbxj8

Summary of findings	The GP remains the most important source of information apart from the specialty clinic, but ratings of helpfulness are modest, only. The contribution of self-help groups and charities should not be overestimated, in as much as professional advice (verbal or written) is perceived as paramount. Irrespective of prior education, the parents' interest in further information remains high, both in medical core aspects, as well as complementary

	medicine. The Internet appears to be an increasingly important source of information as well, and its consequences on the doctor-patient-relationship should be target of further studies. [256] A national audit tool for assessment of patient satisfaction is proposed. [65] Interactive technologies may be used to involve the patient in their own care, allow for constant monitoring of the disease, [66] and to provide accessible resources for disease management. [67] A more trusting and secure relationship needs to be established between the patient and the health practitioners, allowing the patient to be involved in their own healthcare. [68] "Clinical networks improve equity of access to care, delivered as close to home as possible, and may improve local awareness of JIA, particularly if delivered in conjunction with an education programme." [69] Although proved having a high feasibility and patient satisfaction rates, the evidence for a superior or equal effectiveness of tele-rheumatology compared to the standard face-to-face approach was weakened by some methodological biases and wide heterogeneity of interventions, preventing to draw definitive conclusions. [250]
Evaluation	Multiple suggestions available, however, implementation of these needs to be improved.
Is the question answered?	Partially answered

Q53

Question	Ref		Article name	Article link
Wat kunnen we doen om de overstap naar de volwassen zorg zo goed mogelijk te laten verlopen?	[111]	review	Patients with juvenile idiopathic arthritis become adults: the role of transitional care.	https://www.ncbi.nlm.nih.gov/pubmed/29652654
	[112]	prospective cohort study	Disease activity and dropout in young persons with juvenile idiopathic arthritis in transition of care: a longitudinal observational study.	https://www.ncbi.nlm.nih.gov/pubmed/29461957
	[113]	sys review (of qualitative literature only)	The transition of adolescents with juvenile idiopathic arthritis or epilepsy from paediatric health-care services to adult health-care services: A scoping review of the literature and a synthesis of the evidence.	https://www.ncbi.nlm.nih.gov/pubmed/29355024
	[114]	survey	Development of a clinical transition pathway for adolescents in the Netherlands.	https://www.ncbi.nlm.nih.gov/pubmed/29115764
	[115]	longitudinal cohort study	Transition to adult rheumatology care is necessary to maintain DMARD therapy in young people with juvenile idiopathic arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28583690

	[116]	reflective report	The most important needs and preferences of patients for support from health care professionals: A reflective practice on (transitional) care for young adults with Juvenile Idiopathic Arthritis.	https://www.ncbi.nlm.nih.gov/pubmed/28363359
	[117]	expert panel + systematic review	EULAR/PReS standards and recommendations for the transitional care of young people with juvenile-onset rheumatic diseases.	https://www.ncbi.nlm.nih.gov/pubmed/27802961
	[118]	systematic review	Systematic review and critical appraisal of transitional care programmes in rheumatology.	https://www.ncbi.nlm.nih.gov/pubmed/27496195
	[119]	mixed methods	The clinical impact of a brief transition programme for young people with juvenile idiopathic arthritis: results of the DON'T RETARD project.	https://www.ncbi.nlm.nih.gov/pubmed/26320142
	[120]	focus groups and interviews	Transitional care in clinical networks for young people with juvenile idiopathic arthritis: current situation and challenges.	https://www.ncbi.nlm.nih.gov/pubmed/25920453

Summary of findings	*A German study emphasized the need for a successful transition and potential consequences of patients falling into a "care gap" (but did not provide solutions for the issue). [115] A Dutch study found that the process of transition did not have an impact on disease activity, but patients win transition were more likely to drop out (especially those with low disease activity). [112] A review of transitional care for JIA patients proposes several methods of improving transitional care and provides examples of medical centres which have implemented various options. However, it also states that there is a lack of research into the impact of transition programmes on outcomes. [111] Another systematic review lists key processes considered central to a successful transition (early transition planning, accessible information, etc). It also states that the literature regarding outcomes of various transition programmes is scarce. [113] A study recognised that in the Netherlands transition care for JIA patients is inadequate, and presented guidelines on transition care (e.g. early start, individual transition plan, etc). [114] A subsequent reflective report on the redevelopment of the transition care in the same medical centre presented the experience of clinicians. [116] A systematic review identified existing transition care programmes, however not all of these reported the effect of the transition programme on disease outcomes. [118] One of the programmes that did report outcomes is the DON'T RETARD project which presented beneficial effects as measure by primary

	and secondary outcomes. [119] Another qulitative study presented the issues patients think exist in current transition care programmes and what can be done about these. [120] An expert panel has made 12 specific recommendations for transitional care of children with JIA. [117]
Evaluation	There appears to be plenty of literature on the topic. The issue lies in the lack of implementation of proposed policies. Furthermore, there needs to be a systematic assessment of various programmes in order to establish which one has the best effects on disease, QoL, and other outcomes.
Is the question answered?	partially answered