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Review Article

Prevalence and Risk Factors of rheumatoid arthritis in pediatric rheumatology patients

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Abstract

Background: Chronic arthritis of childhood, gathered under the term juvenile idiopathic arthritis (JIA), is the pediatric analogue most often loosely described as rheumatoid arthritis in children, yet only a minority of affected children carry the seropositive, adult-like phenotype.

Objective: This review synthesizes published evidence on the prevalence and distribution of JIA subtypes, including rheumatoid-factor-positive polyarticular disease, among children seen in pediatric rheumatology settings, and summarizes the genetic, immunological, environmental, and demographic risk factors associated with subtype susceptibility.

Methods: We synthesized population-based epidemiological studies, multicenter registry cohorts including CARRA and the Nordic JIA cohort, immunogenetic association studies, and case-control literature addressing environmental and perinatal exposures in JIA.

Findings: Oligoarticular disease is consistently the largest referral category, rheumatoid-factor-positive polyarticular disease the smallest but most continuous with adult seropositive rheumatoid arthritis, HLA-DRB1*04 and shared non-HLA loci link that subtype to adult disease, and uveitis risk, sex distribution, and age at onset vary systematically by subtype.

Conclusions: JIA prevalence and risk factors differ by ILAR subtype rather than forming one disease continuum, and subtype- and serology-aware stratification remains the most actionable tool for anticipating uveitis risk, erosive disease, and long-term outcome in pediatric rheumatology populations.

Keywords: juvenile idiopathic arthritis; pediatric rheumatology; prevalence; risk factors; seropositivity

1. Introduction

Chronic arthritis beginning before the sixteenth birthday is not a single disease but a family of related syndromes gathered, since the late 1990s, under the umbrella term juvenile idiopathic arthritis (JIA), the pediatric analogue most often discussed loosely as "rheumatoid arthritis in children" even though the adult rheumatoid factor-positive phenotype accounts for only a small minority of affected children [1]. The International League of Associations for Rheumatology (ILAR) classification divides JIA into seven categories on the basis of joint involvement pattern in the first six months, extra-articular features, and serology, replacing the older, partly overlapping juvenile rheumatoid arthritis and juvenile chronic arthritis nomenclatures [1,2]. JIA is among the most common chronic rheumatic diseases of childhood worldwide, with incidence estimates of roughly 2-20 per 100,000 children per year and point prevalence of roughly 16-150 per 100,000, a spread wide enough that geography, case ascertainment, and classification era each explain meaningful variance [3,4].

Pediatric rheumatology referral cohorts, where children are seen by a specialist rather than identified through population screening, show which JIA subtypes actually fill clinics, how seropositive disease clusters, and which features track with more persistent courses. This review synthesizes the literature on the prevalence and distribution of JIA subtypes, including the rheumatoid-factor-positive polyarticular phenotype that most directly parallels adult rheumatoid arthritis, and summarizes the genetic, immunological, infectious, and sociodemographic risk factors associated with disease susceptibility and phenotype. Understanding this distribution matters clinically because subtype at presentation shapes both prognosis and extra-articular surveillance, most visibly for uveitis risk, and because risk-factor research offers the clearest current route toward earlier recognition and, eventually, prevention.

2. Classification and prevalence of JIA subtypes

The seven ILAR categories, oligoarticular (persistent and extended), rheumatoid-factor-negative polyarticular, rheumatoid-factor-positive polyarticular, systemic, psoriatic, enthesitis-related, and undifferentiated, are not evenly represented in pediatric rheumatology practice [1]. Oligoarticular JIA, affecting four or fewer joints in the first six months, is consistently the largest single category in North American and European cohorts, typically 40-50% of referred children, followed by rheumatoid-factor-negative polyarticular disease at roughly 20-25% [5,6]. Systemic JIA, mechanistically distinct and now understood as autoinflammatory rather than classically autoimmune, makes up 4-17% of cohorts depending on region, with a higher relative share in some Asian referral series [7,8]. Rheumatoid-factor-positive polyarticular JIA, the subtype most directly analogous to adult seropositive rheumatoid arthritis, is consistently the smallest ILAR category, generally 2-7% of referred children, but carries disproportionate clinical weight because it behaves most like adult disease: earlier erosive damage, female predominance, and later onset within childhood, typically after age eight to ten [7,9].

Registry-based and multicenter cohort data reinforce this distribution while highlighting real between-population variation. The Nordic JIA cohort, following children across Denmark, Finland, Norway, and Sweden, found oligoarticular disease dominant at diagnosis but noted substantial category drift over eight years, with many children initially classified as oligoarticular later meeting criteria for the extended subtype, underscoring that subtype prevalence is partly a function of the observation window [10]. The CARRA registry in North America, the largest prospective pediatric rheumatology cohort assembled to date, reported broadly similar proportions to European series but found regional and racial variation in enthesitis-related and psoriatic JIA proportions tracking population differences in HLA-B27 carriage and psoriasis prevalence [11,12]. Adult-onset rheumatoid arthritis

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registries, for comparison, show a case-mix almost entirely composed of seropositive polyarticular disease, precisely the JIA subtype least represented in pediatric cohorts [13].

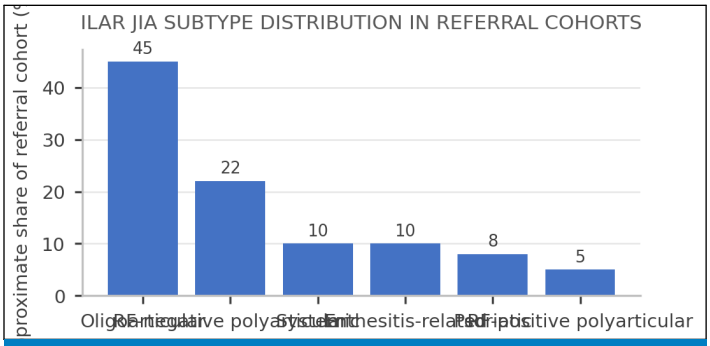


Figure 1: Approximate distribution of ILAR juvenile idiopathic arthritis categories among children in pediatric rheumatology referral cohorts, with oligoarticular disease the largest single category and rheumatoid-factor-positive polyarticular disease the smallest [7,5,11].

3. Genetic and immunogenetic risk factors

The strongest and most consistently replicated genetic risk factors for JIA, as for adult rheumatoid arthritis, lie within the human leukocyte antigen (HLA) region on chromosome 6, though the alleles implicated differ by subtype. HLA-A*02 and class II alleles including DRB1*08 and DRB1*11/13 are enriched in oligoarticular and early-onset polyarticular disease, while HLA-DRB1*04, the shared-epitope allele most strongly associated with adult seropositive rheumatoid arthritis, is specifically enriched in rheumatoid-factor-positive polyarticular JIA rather than across JIA broadly [14,15]. This subtype-specific architecture supports reading RF-positive polyarticular JIA as early-onset adult-type rheumatoid arthritis occurring within a pediatric age window, consistent with its course and treatment response mirroring adult disease more closely than any other subtype [14,9].

Genome-wide association studies beyond the HLA region have identified non-HLA loci shared with adult rheumatoid arthritis, including variants near PTPN22, STAT4, and the IL2/IL21 region, again tracking subtype: RF-positive and, to a lesser extent, RF-negative polyarticular disease share the most architecture with adult disease, while systemic JIA is now considered genetically and mechanistically closer to autoinflammatory syndromes such as adult-onset Still's disease [16,17]. Twin and family studies provide complementary evidence for a substantial heritable component across JIA, with sibling recurrence-risk ratios of roughly 12-15, though the specific subtype transmitted within families is not fully concordant, suggesting shared susceptibility operates partly at the level of a broader arthritis-prone immune phenotype [15,18].

Table 1: Genetic loci associated with juvenile idiopathic arthritis subtypes and their overlap with adult seropositive rheumatoid arthritis [14,15,16,17].

Locus / region	JIA subtype most associated	Overlap with adult RA
HLA-DRB1*04 (shared epitope)	RF-positive polyarticular	Strong -- same allele implicated in adult seropositive RA
HLA-A*02, DRB1*08, DRB1*11/13	Oligoarticular, early-onset polyarticular	Weak -- largely JIA-specific association
PTPN22, STAT4, IL2/IL21 region	RF-positive and RF-negative polyarticular	Moderate to strong -- shared non-HLA susceptibility loci
Systemic-JIA-specific autoinflammatory loci	Systemic JIA	Minimal -- closer to autoinflammatory disease architecture

4. Environmental, infectious, and perinatal risk factors

Genetic susceptibility alone does not explain JIA incidence, and case-control and cohort literature has examined environmental exposures that might trigger disease in susceptible children. Maternal smoking during pregnancy has been associated with increased JIA risk in several but not all case-control studies, strongest for oligoarticular and RF-negative polyarticular disease [19]. Breastfeeding duration has been examined as a potentially protective exposure, with some Scandinavian cohort data suggesting a modest inverse association with subsequent JIA risk, though the effect size is small and not fully consistent across cohorts [20,19].

Infection has long been proposed as an environmental

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trigger for JIA, paralleling the reactive-arthritis literature in adults, with several studies reporting temporal clustering of new diagnoses following common childhood infections in the months preceding onset [21,20]. Enthesitis-related JIA shares much of its immunogenetic and clinical profile with adult spondyloarthritis, including HLA-B27 association and a plausible gut-microbiome-mediated trigger; several studies report altered gut microbial diversity in children with new-onset JIA relative to controls, though causality versus consequence of early disease and its treatment remains unresolved [22,23]. Socioeconomic and geographic factors also modulate observed prevalence: registries in higher-resource settings with better access to pediatric rheumatology consistently report higher measured JIA prevalence, a pattern likely reflecting both ascertainment differences and true underlying variation [3,4].

5. Sex, age at onset, and seropositivity

Sex distribution varies substantially across JIA subtypes and tracks with the degree of overlap with adult rheumatoid arthritis. Oligoarticular JIA, particularly the antinuclear-antibody-positive, early-onset form most strongly associated with chronic anterior uveitis, shows the strongest female predominance, with female-to-male ratios of 3:1 to 5:1 in referral cohorts [5,6]. RF-positive polyarticular JIA shows a comparably strong female predominance, while systemic JIA shows near-equal sex distribution and enthesitis-related JIA a male predominance, consistent with its shared biology with spondyloarthritis [7,9]. Age at onset likewise differs systematically: oligoarticular and early-onset ANA-positive polyarticular disease peak in the toddler and preschool years, systemic JIA peaks somewhat later across early-to-middle childhood, and RF-positive polyarticular JIA is disproportionately a disease of later childhood and early adolescence, rarely presenting before age eight, functionally pediatric-onset adult rheumatoid arthritis [9,7].

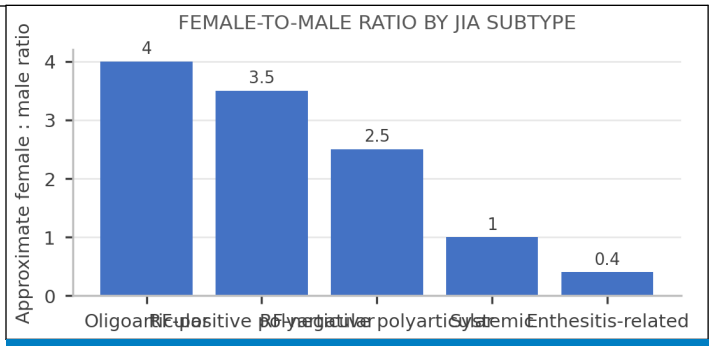


Figure 2: Female-to-male ratio and typical age-at-onset window by juvenile idiopathic arthritis subtype, showing the strongest female predominance and earliest onset in oligoarticular and rheumatoid-factor-positive polyarticular disease and the latest onset in rheumatoid-factor-positive polyarticular disease specifically [9,6,7].

Seropositivity is an important prognostic feature within pediatric rheumatology cohorts independent of ILAR category. Anti-cyclic citrullinated peptide (anti-CCP) antibody positivity in polyarticular JIA correlates strongly with rheumatoid factor positivity and a more erosive, treatment-refractory course, and several cohorts find anti-CCP a better predictor of radiographic progression than rheumatoid factor status alone [24,25]. Seropositive polyarticular JIA cohorts followed into adulthood show disease persistence well above 50%, against substantially better remission for oligoarticular disease, reinforcing that subtype and serology at presentation carry real prognostic weight [11,26].

6. Comorbidities and disease burden

Uveitis is the extra-articular complication most closely tied to JIA subtype and the single highest-stakes reason accurate early classification matters in practice. Chronic anterior uveitis, often asymptomatic and detectable only through scheduled slit-lamp screening, complicates oligoarticular and, to a lesser extent, RF-negative polyarticular JIA at rates of roughly 10-20%, with ANA positivity and young age at onset as the strongest predictors, while RF-positive polyarticular and systemic JIA carry substantially lower uveitis risk [27,5]. This differential risk underlies the subtype- and ANA-stratified ophthalmologic screening intervals recommended by pediatric rheumatology and ophthalmology societies [27].

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Table 2: Reported uveitis risk and principal predictors by juvenile idiopathic arthritis subtype [27,5,29].

JIA subtype	Approx. uveitis prevalence	Strongest predictors
Oligoarticular (ANA-positive)	10-20%	Young age at onset, ANA positivity
RF-negative polyarticular	Lower, still elevated	ANA positivity, young age at onset
RF-positive polyarticular	Low	Not a major screening priority
Systemic JIA	Low; macrophage activation syndrome is the dominant acute risk	Sustained systemic inflammation

Growth impairment, reduced bone mineral density, and psychosocial burden are reported across JIA subtypes but are most pronounced in systemic and polyarticular disease, where sustained inflammation and, in earlier treatment eras, prolonged corticosteroid exposure compounded direct effects on growth plates and bone accrual [28]. Macrophage activation syndrome, a life-threatening hyperinflammatory complication, occurs almost exclusively in systemic JIA and is the most acute mortality risk within the pediatric rheumatology population, giving systemic JIA outsized clinical urgency despite its smaller share of cases [29]. Health-related quality of life measures across subtypes consistently show meaningful impairment relative to healthy peers, correlating more strongly with disease activity, joint count, and pain than with ILAR category itself [26,30].

7. Treatment landscape and its bearing on observed prevalence

The therapeutic era in which a cohort is assembled materially affects measured disease persistence and, indirectly, apparent subtype prevalence in referral populations, because more effective treatment shortens the window during which a child remains actively symptomatic and counted in point-prevalence snapshots. Widespread adoption of methotrexate as first-line therapy from the 1990s onward, followed by tumor necrosis factor inhibitors and, for systemic JIA specifically, interleukin-1 and interleukin-6 pathway antagonists, has measurably improved remission rates and reduced progression to erosive, treatment-refractory disease across nearly every category [31,32,33]. Etanercept and subsequent biologics produced substantial improvement in polyarticular JIA outcomes in randomized trials, and IL-1/IL-6 pathway therapy transformed systemic JIA management specifically, converting a subtype historically associated with high rates of chronic arthritis and growth failure into one with meaningfully better long-term joint outcomes in the biologic era [32,33,34]. Because treatment response differs by subtype and seropositivity, contemporary cohorts assembled in the biologic era show somewhat different apparent subtype proportions among children with active disease than older cohorts, complicating direct comparison of prevalence estimates across treatment eras [11,12].

8. Conclusion

Rheumatoid arthritis in the pediatric rheumatology setting is best understood not as a single disease but as a family of ILAR-defined subtypes with distinct genetic architecture, demographic distribution, and clinical trajectory, among which RF-positive polyarticular JIA stands out as most immunogenetically and clinically continuous with adult seropositive rheumatoid arthritis, despite representing a minority of referred children [1,14]. Oligoarticular disease remains the largest single category across most studied populations, carries the strongest association with sight-threatening uveitis, and shows the most female-skewed sex distribution, while systemic JIA, genetically and mechanistically distinct as an autoinflammatory syndrome, carries disproportionate acute risk through macrophage activation syndrome despite its smaller share of cases [7,29]. Genetic susceptibility, concentrated in the HLA region but extending to shared non-HLA loci with adult rheumatoid arthritis, interacts with environmental and perinatal exposures, including maternal smoking, breastfeeding duration, and antecedent infection, though no single environmental factor has emerged as a dominant,

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modifiable trigger across subtypes [14,19,21]. Continued investment in multicenter registries such as CARRA and the Nordic JIA cohort, paired with deeper immunogenetic and microbiome characterization, offers the clearest path toward refining subtype-specific risk prediction, earlier recognition of children likely to progress to erosive or sight-threatening disease, and more individualized treatment strategies for the heterogeneous group of children currently gathered under a single diagnostic umbrella [10,11].

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