Running head: Do we need distinct classification criteria for children with RMDs?

Notes From the Field

Do we need distinct paediatric classification criteria for rheumatic diseases that affect both children and adults?

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Rheumatic diseases (RMDs) represent a diverse group of conditions that can affect individuals of any age. While paediatric and adult rheumatologists develop specialized expertise in the recognition, diagnosis and management of these diseases, individuals diagnosed with RMDs at distinct stages in their life face age and developmentally distinct challenges, which necessitate a comprehensive approach to healthcare. This approach must encompass coordinated and integrated care, including effective transition protocols for adolescents, as well as access to high-quality research at every stage in life. Developmental factors play a key role in shaping the immune system, resulting in age-related differences in disease risk, outcomes, and treatment responses, emphasizing the necessity for age-tailored approaches in both research and clinical care. This is particularly crucial because genetic predispositions, environmental influences and socio-economic conditions can heavily impact RMD presentation and outcomes.

The need for improved evidence-based health care in rheumatology requires high quality, multi-centre studies with suitable geographical and ethnic representability across the lifespan. Accurate classification criteria help identify homogeneous disease populations, which is vital for advancing the understanding of the disease pathogenesis, and for the development and testing of tailored therapeutic strategies. Moreover, adequate classification criteria can enhance the identification of disease subtypes with different outcomes and treatment responses, paving the way for more individualized management approaches.

While there are similarities in the presentation and management of RMDs between distinct age groups, such as children and adults, or younger and older adults, significant differences in pathogenesis, clinical phenotype, disease progression and outcomes often necessitate age-specific classification criteria. However, this distinction has only been made for children vs. adults with certain RMDs, using an arbitrary age cut-off of 16 or 18 years of age.

Two main strategies have been employed in the classification of paediatric RMDs: one involves adapting adult classification criteria for use in paediatric populations with similar disease phenotypes, while the other focuses on developing and validating criteria specifically tailored to children.

A harmonised classification across the life span has practical implications, as clinicians recognise that epidemiological differences between RMDs affecting children and adults should not significantly impact the performance of shared classification criteria across the life span. However, epidemiological differences could be underpinned by unique genetic traits and immune characteristics of children compared to adults, reflected in distinct disease susceptibility, as well as more severe trajectories for RMDs that emerge in childhood, aspects which may not be optimally addressed by a harmonised classification and research approach across the life span.

Conversely, there are phenotypical similarities between children and adults that span arbitrary age boundaries - which should support the use of similar classification criteria, as well as differences in clinical phenotype and pathogenesis between younger and older individuals affected by the same disease - which may not be reflected in the existent adult classification criteria. These age-related variations can be attributed to factors beyond genetics or immune system maturation and aging, including alterations in the microbiome and environmental exposures that contribute to age-dependent RMD patterns, all relevant for the selection of homogeneous disease populations for research purposes.

As various approaches to classify RMDs in paediatric vs. adult rheumatology exist, we aim to evaluate their relevance and limitations, and propose, wherever possible, to promote classification criteria which reflect shared clinical presentation and pathogenic mechanisms across age-corresponding RMD phenotypes, while also accounting for developmental and immunological factors that may influence disease trajectories, where relevant.

Classification of chronic inflammatory arthritis across the lifespan

Using the same classification criteria for children and adults with RMDs could harmonize research across age groups and facilitate the inclusion of both paediatric and adult populations in clinical trials. This approach could potentially expedite the approval and availability of new therapeutic options. However, standardizing the classification of RMDs is highly dependent on the particularities of the diagnostic label used in children vs. adults, which may reflect more or less heterogeneous disease phenotypes. For example, rheumatoid arthritis (RA) reflects a relatively homogeneous inflammatory arthritis phenotype in adults, while juvenile idiopathic arthritis (JIA) is an umbrella diagnosis in children, encompassing several subtypes of childhood arthritis, characterised by heterogeneous pathogenesis and clinical presentation.

The International League of Associations for Rheumatology (ILAR) criteria, commonly used for classifying JIA, have several limitations. These include arbitrary age and joint count cut-offs, as well as mutually exclusive features that can complicate the classification of individuals who exhibit overlapping signs and symptoms. Moreover, the ILAR classification criteria do not address the genetic or molecular similarities between different JIA subtypes[1], which can impact the adequate treatment selection and accurate risk-stratification of individuals with JIA. The ILAR subgroup of non-systemic JIA that shares clear genetic and pathogenic mechanisms with their adult corresponding phenotype is the seropositive poly JIA group, which often affects adolescent girls and resembles seropositive RA. The pathogenesis of the early onset forms of the chronic arthritis we observe in childhood is less well-defined.

The Paediatric Rheumatology International Trials Organisation (PRINTO) proposed a novel classification system for JIA, categorizing the condition into four distinct subtypes[2]. This classification introduces the age cut-off of 18 years, in alignment with the World Health Organisation definition of childhood age-span, as well as an additional category for early-onset JIA with positive antinuclear antibodies (ANA), which the ILAR criteria do not cover. The PRINTO criteria also suggest renaming enthesitis-related arthritis as enthesitis/spondylitis related JIA, recognising its pathogenic similarities with ankylosing spondylitis. However, the exclusion of juvenile psoriatic arthritis (JPsA) from the PRINTO criteria poses challenges, especially since there are therapies specifically licensed for JPsA[3].

A study exploring the overlap between the ILAR and PRINTO criteria in a large UK cohort found that nearly 70% of young people with JIA could not be classified into any of the named PRINTO categories[4]. This significant discrepancy highlights the limitations of current JIA classification systems, and underscores the need for further refinement and validation across diverse populations.

Although anti-citrullinated peptide antibodies are important for diagnosing and predicting outcomes in RA, and despite its genetic and phenotypic similarities to seropositive polyarticular JIA, these antibodies are not included in either the ILAR or PRINTO JIA classification criteria.

The recent decision by the Paediatric Rheumatology European Society (PReS) and the European Associations and Alliances of Rheumatology (EULAR) to recognize systemic JIA and Adult-Onset Still's

Disease as manifestations of the same condition, now termed Still's disease, is a noteworthy development[5]. This consensus is based on shared pathogenic mechanisms, clinical presentations, and treatment strategies, underscoring the importance of a unified approach to disease classification.

Classification of systemic connective tissue diseases, vasculitides and autoinflammatory conditions across the life span

These RMDs share the same pathogenesis and have rather consistent features throughout the lifespan. Systemic lupus erythematosus (SLE), with the exception of monogenic lupus, is characterised by the same type of organ and systems involvement in children and adults, with recognised differences in the prevalence of certain manifestations: a higher proportion of individuals with childhood onset SLE (cSLE) experience systemic manifestations, lupus nephritis and central nervous system involvement compared to adults with SLE according to various cohort studies. These differences may reflect the increased genetic burden in children, as well as challenges in accessing adult SLE treatments worldwide and/or poorer compliance to medication in adolescence, as potential factors.

Distinct classification criteria for cSLE have not been deemed necessary. Differences in presentation and severity of cSLE were adequately captured at the disease onset by the adult criteria, as they are not underpinned by differences in pathogenesis between cSLE and adult-onset SLE. The American College of Rheumatology (ACR) and the Systemic Lupus International Collaborating Clinics (SLICC) criteria, commonly used to support SLE diagnosis, have been validated in both adult and paediatric populations, with recent updates improving their applicability across age groups[6]. ACR and EULAR proposed novel classification criteria in 2019, subsequently validated in adult SLE populations, were found to have satisfactory performance in cSLE as well[7].

Childhood inflammatory myositis, scleroderma and Sjögren disease may be regarded within the spectrum of adult disease, because of similarities in pathogenesis between children and adults. The new harmonized classification criteria for inflammatory myopathies, proposed by EULAR/ACR, were derived and validated in both adult and juvenile cohorts [8]. However, these criteria have limitations, particularly related to the exclusion of features like calcinosis and certain myositis-specific autoantibodies, which are more prevalent in children.

The provisional classification criteria for juvenile systemic sclerosis, proposed by PReS/ACR/EULAR, overlap with the revised adult criteria, but also include additional features relevant to children[8]. The proposal to develop distinct criteria for juvenile systemic sclerosis, incorporating specific features, such as digital ulcers and periungual capillary abnormalities, is driven by the aim to improve their relevance for research, diagnostic and management of systemic sclerosis in children[9].

Childhood-onset Sjögren's disease is particularly challenging, as it is rare and lacks validated classification criteria. Although diagnostic algorithms and scoring systems have been proposed to support diagnosis and classification, these are not yet widely adopted[10]. The 2016 EULAR/ACR criteria for adult Sjögren's disease do not classify many paediatric cases, often because children exhibit less dryness, the cardinal clinical feature in adults[11].

Vasculitides present additional classification challenges because of the restriction of certain types of vasculitides to certain age groups. These diseases vary significantly in prevalence and presentation between children and adults, and need to be approached in a distinct manner. For instance, giant cell arteritis does not occur in children, while Kawasaki disease is virtually exclusively encountered in

paediatric populations; therefore, exploring classification criteria across the life course is less relevant for these two conditions. For other types of vasculitides affecting individuals of all ages, the main differences are in relation to the prevalence of various manifestations rather than disease pathogenesis. The EULAR/PRINTO/PReS-endorsed Ankara 2008 criteria for childhood vasculitides, validated and widely used, provide a basis for accurate classification[12]. Distinct paediatric classification criteria were proposed for IgA vasculitis (IgAV) (Henoch–Schoenlein purpura), granulomatosis with polyangiitis (GPA), Takayasu Arteritis (TA) and polyarteritis nodosa (PAN). However, recent ACR/EULAR adult classification criteria developed from the Diagnosis and Classification of Vasculitis Study (DCVAS) registry highlight the ongoing evolution of classification systems for adult vasculitides[13]. Interestingly, both the Ankara 2008 and the DCVAS - derived ACR/EULAR adult criteria had a similar performance in children with GPA[14], suggesting potential for harmonisation across the life span.

Autoinflammatory diseases (AIDs) primarily manifest in childhood and are characterized by recurrent systemic inflammation due to innate immune system dysfunction. The *Eurofever* initiative has been instrumental in gathering data on AIDs in children, leading to the proposal of shared classification criteria endorsed by both paediatric and adult experts. This collaborative approach underscores the potential for unified criteria that can be applied across age groups, as well as the expansion of large-scale research initiatives, including clinical trials, facilitating improved disease recognition across the life-span, high quality research and progress towards tailored therapies[15].

One size does not fit all: the value of expertise sharing and future research needs.

Classification criteria should be derived through methodologically-sound studies applied to age, sex/gender and ethnically diverse cohorts with a certain RMDs as well as corresponding disease mimickers. Although, shared classification criteria across children and adults with similar RMDs would be advantageous in terms of harmonising research across the life span, support transition of care and access to treatments, the impact of age at onset on RMD manifestations, reflecting both the genetic burden and exposome influences on disease pathogenesis, as well as differences in clinical presentation early vs. later in life, likely determine their performance and clinical utility.

In addition to harmonising research in RMDs, shared classification criteria could support innovative management strategies, if the disease is similar in children compared to both younger and older adults. The British Society of Rheumatology endorses evidence and consensus-based recommendations for management of various RMDs, co-produced by paediatric and adult rheumatologists allowing an ‘across the life course’ perspective. For conditions with similar pathogenesis, proposing new childhood-specific classification criteria may not be entirely appropriate, but this has to be balanced against differences in clinical presentation between children and adults with impact on identifying homogeneous disease groups.

Even if a need for better classification criteria is identified, these criteria can only be derived from optimally designed prospective longitudinal cohorts with controls groups including key disease mimickers, robust methodological approaches, as well as adequate RMD population representability. This will require collaborative work across paediatric, transition and adult care specialists, and critical input from patient-experts of all ages. We identified several challenges for optimising classification criteria for RMDs across the lifespan and proposed future research strategies, which we included in **Table 1**.

Classification criteria will require periodic review to incorporate advances in medical technologies and discoveries, as well as changes in research priorities to facilitate early disease classification and timely management interventions, for the overall aim to improve disease outcome and preserve quality of life at any age.

We advocate for good performance classification criteria, reflecting shared pathogenic mechanism across age-distinct RMD phenotypes, which should be feasible and easy to implement. This will facilitate adequate dissemination of knowledge related to various disease processes, as well as innovation in RMD management, ultimately aiming to support wider and fairer access to research for diverse populations of all ages.

Table 1: Challenges in optimising the classification of RMDs across the life span and future research needs.

Challenges for optimising classification criteria across the life course	**Examples of RMDs for which these challenges are relevant**	**Future research needs**
Lack of correspondence between the diagnostic labels used in children and adults with inflammatory arthritis with similar pathogenesis and clinical presentation.	JIA vs. adult inflammatory arthritides.	Expert consensus studies to review the available literature data to propose and refine the nomenclature used for distinct sub-categories of inflammatory arthritis to reflect similarities across paediatric and adult phenotypes.
Scarcity of high-quality studies with geographic representability across the life span to define homogeneous RMD clinical phenotypes in children and adults.	Lack of studies in JIA in adulthood to enable phenotype correlations with adult inflammatory arthritides; Lack of initiatives/studies in SLE, inflammatory myositis, scleroderma, antiphospholipid syndrome, and rare types of vasculitides, etc. across the life span. Recent progress has been achieved in harmonising the longitudinal data collection across geographically-diverse cohorts in some conditions (SLE, myositis, autoinflammatory	More collaborative, high quality, prospective clinical studies with long-term follow-up, involving paediatric and adult rheumatologists, and patient populations across the life span to define shared clinical phenotypes as well as epidemiological differences at disease presentation to support future development/refinement of classification criteria. Initiation of harmonised national registries linked together across various geographical areas, capturing data and samples from individuals with RMDs across the life span.

	diseases) but not across the life course.	
Scarcity of high-quality studies focused on defining the pathogenesis of RMDs affecting both children and adults.	There are almost no studies exploring in parallel the pathogenesis of similar RMDs in children vs. adults	High-quality studies across the life span including genetic/molecular/tissue diagnosis to define commonalities and differences in the disease pathogenesis in children vs. adults, and their clinical correlates. Linked-in paediatric and adult RMD-specific registries.
Use of existent classification criteria across the life span without being validated in both children and adults.	Particularly relevant for rare RMDs, such as antiphospholipid syndrome, some vasculitides, IgG4-RD, etc., but also for inflammatory arthritides, which are classified completely differently in children vs. adults.	High-quality studies to cross-validate the existent classification criteria in both children and adult cohorts, to evaluate whether there is any need to revise the available criteria.
Timely incorporation of advances in medical technologies and discoveries in classification criteria for RMDs across the life span.	e.g. inclusion of imaging as classification item for Sjögren's Disease (salivary gland ultrasound) or myositis (magnetic resonance imaging for assessment of muscle inflammation).	Periodic refinement and testing of existent classification criteria to reflect advances in diagnostic tests or incorporate new emerging phenotypes.

Legend: IgG4-RD – Immunoglobulin G4-related disease; JIA – juvenile idiopathic arthritis; SLE – systemic lupus erythematosus; RMDs- rheumatic diseases.

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