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EDITORIAL

Early Detection and Treatment Opportunities for Children With Subclinical Rheumatic Heart Disease

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Rheumatic heart disease (RHD) remains a leading cause of cardiovascular morbidity and mortality among children and young adults in low- and middle-income countries, affecting 1425985.76 (95% uncertainty interval [UI], 1729730.47–1158391.91) people worldwide, causing 388794.23 (95% UI, 554148.70–260877.33) deaths, and is responsible for 14474875.82 (95% UI, 19881741.34–10128789.97) disability-adjusted life years in 2023, according to the Global Burden of Disease study 2023.[1] (Figure 1) In addition, based on Global Burden of Disease 2023, Brazil had 1425985.8 (95% UI, 1158391.9–1729730.5) prevalent cases of RHD in 2023 and a prevalence age-standardized rate of 628.9 (95% UI, 504.6–755.4) per 100000, with an 8.1% increase in all-ages prevalence from 1990 to 2023. Also, based on Department of Informatics of the Unified Health System, Unified Health System spending on valve heart surgery totaled approximately US$ 21.5 million in 2008, rising to US$ 50.6 million in 2024, corresponding to an increase of 135.3%. These numbers highlight RHD relevance globally and in Brazil.[2]

See Article by Barros Branco et al.

Despite its preventable nature, RHD continues to impose a devastating burden on vulnerable populations, particularly in regions with limited health care access. The transition from acute rheumatic fever (ARF) to chronic RHD involves complex immunological mechanisms that remain incompletely understood, especially in early disease stages. The study by Branco et al. this issue of the *Journal of the American Heart Association* (*JAHA*) provides compelling evidence that inflammatory dysregulation occurs even at the borderline subclinical stage of RHD, offering important insights into pathogenesis and therapeutic targets.[3]

The introduction of standardized echocardiographic screening protocols, particularly the 2012 World Heart Federation criteria, has revolutionized our ability to detect RHD at its earliest stages.[4] These criteria distinguish between "borderline" and "definite" subclinical RHD, with borderline cases representing the most nascent form detectable by current imaging techniques.

However, the clinical significance of borderline subclinical RHD continues to be debated. Key questions persist: Does borderline disease represent true pathology or echocardiographic variation? What drives progression? Can we identify biological markers that predict disease trajectory?

Branco et al. address these questions through a prospective cohort investigation of 1026 children aged 5 to 15 years in disadvantaged areas of São Paulo, Brazil. By combining rigorous echocardiographic screening with comprehensive cytokine profiling, the investigators

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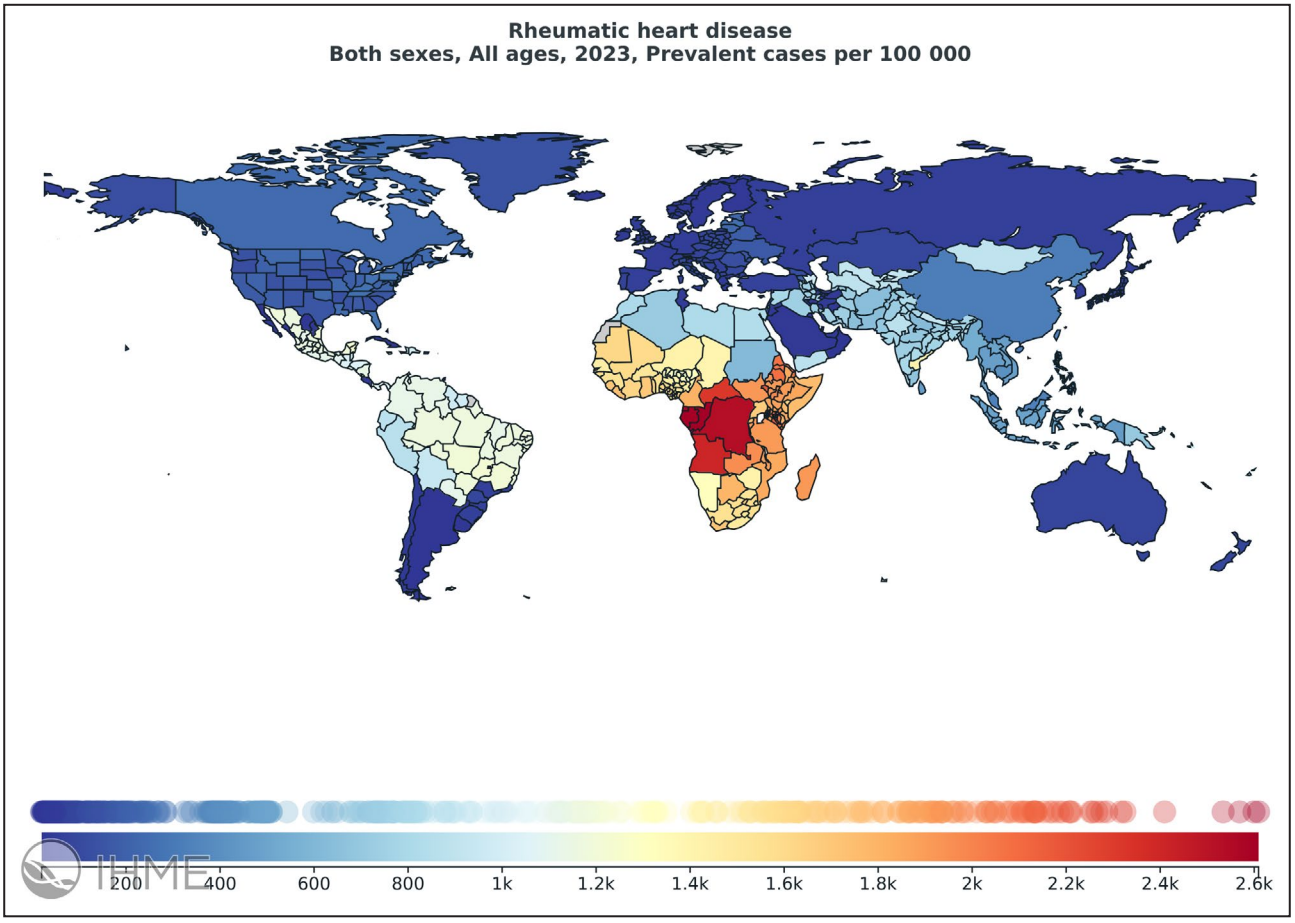

Figure 1. Global distribution of rheumatic heart disease prevalence in 2023.
World map illustrating age-standardized prevalence rates of rheumatic heart disease per 100 000 population across all countries for both sexes and all ages in 2023, based on Global Burden of Disease Study 2023 data.[1] The color gradient represents disease burden intensity, with dark blue indicating the lowest prevalence rates (≤200 per 100 000) predominantly in high-income countries of North America, Western Europe, and Oceania. Intermediate rates (400–800 per 100 000, light blue to yellow) are evident in Eastern Europe, the Middle East, and parts of Asia. The highest prevalence rates (>2000 per 100 000, red to dark red) are concentrated in sub-Saharan Africa, particularly Central and East Africa, and parts of Oceania, reflecting persistent socioeconomic disparities and limited health care access. This geographic distribution underscores RHD as a disease of poverty and health inequity, with endemic regions bearing a disproportionate burden. Brazil demonstrates intermediate prevalence (628.9 per 100 000), highlighting RHD's continued relevance in middle-income countries. The map points up the urgent need for targeted screening programs, improved access to penicillin prophylaxis, and early detection strategies in high-burden regions. Source: Institute for Health Metrics and Evaluation, Global Burden of Disease Study 2023.[1] RHD indicates rheumatic heart disease. Figure created by the author from http://www.healthdata.org/gbd.

demonstrate that borderline subclinical RHD is associated with significantly elevated IL-6 (interleukin-6) levels compared with matched controls, with median IL-6 concentrations of 49.9 pg/mL versus 15.9 pg/mL (P=0.048). Furthermore, longitudinal follow-up over 2 years revealed persistent elevation of IL-6 without significant temporal changes, suggesting ongoing inflammatory activity rather than a transient response.[3]

The role of cytokines in RHD pathogenesis has been investigated in animal models and patients with established disease. This study represents the first prospective evaluation of cytokine profiles in borderline subclinical RHD.[5,6] The findings illuminate several important aspects of disease biology. First, the elevation of IL-6, a pleiotropic cytokine with both proinflammatory and regulatory functions, indicates that active immune processes occur even before significant valvular dysfunction develops. IL-6 plays a central role in the acute phase response, B-cell differentiation, and T-cell activation—all processes implicated in the autoimmune mechanisms underlying RHD.[7]

Second, the trend toward elevated TNF-α (tumor necrosis factor-alpha) levels, even though it has not reached statistical significance, suggests involvement of additional proinflammatory pathways. TNF-α is a key mediator of inflammation and tissue injury, and its potential elevation in borderline disease warrants further investigation.

Third, the study found no compensatory elevation in anti-inflammatory cytokines such as IL-4 and IL-10. This imbalance between proinflammatory and

anti-inflammatory mediators may represent a defect in immune regulation that predisposes certain individuals to disease progression. The absence of this regulatory response suggests either an intrinsic deficiency in anti-inflammatory pathways or active suppression of protective mechanisms.

The persistence of elevated IL-6 over 2 years without spontaneous resolution raises important questions about the natural history of borderline subclinical RHD. Does this sustained inflammatory state inevitably lead to progression, or do some individuals maintain stable disease through compensatory mechanisms? Long-term follow-up studies with serial echocardiography and cytokine measurements will be essential to identify predictors of progression versus stability.

The identification of elevated IL-6 in borderline subclinical RHD has several important implications for clinical practice and research. From a diagnostic perspective, cytokine profiling might enhance risk stratification among individuals with borderline echocardiographic findings. Current guidelines provide limited guidance on the management of borderline disease, with recommendations ranging from watchful waiting to prophylactic antibiotics.[8] The addition of biomarkers such as IL-6 could help identify high-risk individuals who would benefit from more intensive monitoring or early intervention.

More provocatively, these findings suggest that anti-inflammatory therapies targeting specific cytokines might prevent or slow disease progression. The success of IL-6 inhibitors in other inflammatory conditions, including rheumatoid arthritis and systemic juvenile idiopathic arthritis, provides proof of concept for this approach.[9] Similarly, TNF-α inhibitors have demonstrated efficacy in various autoimmune diseases. Could such targeted biological therapies interrupt the progression from borderline to definite RHD? This hypothesis deserves rigorous evaluation in clinical trials.

However, several challenges exist. First, the cost of biological agents presents formidable barriers in resource-limited settings. Although more affordable through biosimilars, they remain expensive. Second, the long-term safety of immunomodulatory therapies in children requires careful consideration, particularly the risk of infection in regions with high tuberculosis burdens. Third, optimal timing, duration, and patient selection remain undefined.

Alternative approaches may prove more feasible in resource-constrained environments. Could conventional anti-inflammatory agents such as corticosteroids or NSAIDs provide benefit? Might nutritional interventions enhance anti-inflammatory mechanisms? These questions deserve investigation.

The findings reported by Branco et al. must be considered within the broader context of comprehensive RHD prevention strategies. Although biomarker-guided interventions hold promise, they represent only 1 component of a multifaceted approach that must include primary prevention of ARF through improved living conditions and health services, secondary prevention through antibiotic prophylaxis, and tertiary prevention through appropriate management of established disease.[10]

The high prevalence of subclinical RHD detected—7.6% overall, with 6.7% borderline and 0.9% definite—underscores its magnitude in endemic regions. These figures align with other screening studies and highlight the limitations of relying solely on clinical ARF detection.[11] Many RHD cases develop without recognized ARF episodes, suggesting subclinical infections or imperfect recall. Echocardiographic screening can identify these individuals, but cost-effectiveness remains a challenge.

The observation that inflammation persists in borderline disease has implications for secondary prevention. Current guidelines recommend benzathine penicillin prophylaxis for ARF history or established RHD, but recommendations for borderline disease vary.[8] If borderline disease represents active inflammation with possible risk progression, prophylactic antibiotics merit consideration. However, this must be balanced against antibiotic resistance, adherence challenges, and injection burdens.

The study by Branco et al.[8] opens several important avenues for future research. First, validation of these findings in independent cohorts from diverse geographic and ethnic backgrounds will be essential to establish the generalizability of IL-6 as a biomarker. Second, expansion of cytokine panels to include additional mediators, as well as markers of endothelial dysfunction and cardiac injury, may provide a more comprehensive picture of pathophysiological processes. Third, integrating cytokine data with genetic studies could identify individuals at the highest risk based on both inflammatory profiles and genetic susceptibility.

Longitudinal studies with extended follow-up will be crucial to determine whether cytokine levels predict disease progression. Ideally, such studies would include not only echocardiographic outcomes but also clinical end points such as symptom development, need for surgical intervention, and cardiovascular events. Advanced imaging techniques, including cardiac magnetic resonance imaging and strain echocardiography, might detect subtle changes in myocardial structure and function.

From a therapeutic perspective, proof-of-concept clinical trials of anti-inflammatory interventions in borderline subclinical RHD are urgently needed. Such trials should be designed with careful attention to safety monitoring, appropriate control groups, and clinically meaningful end points (Figure 2). Given the challenges of conducting trials in pediatric populations in resource-limited settings, innovative trial designs such

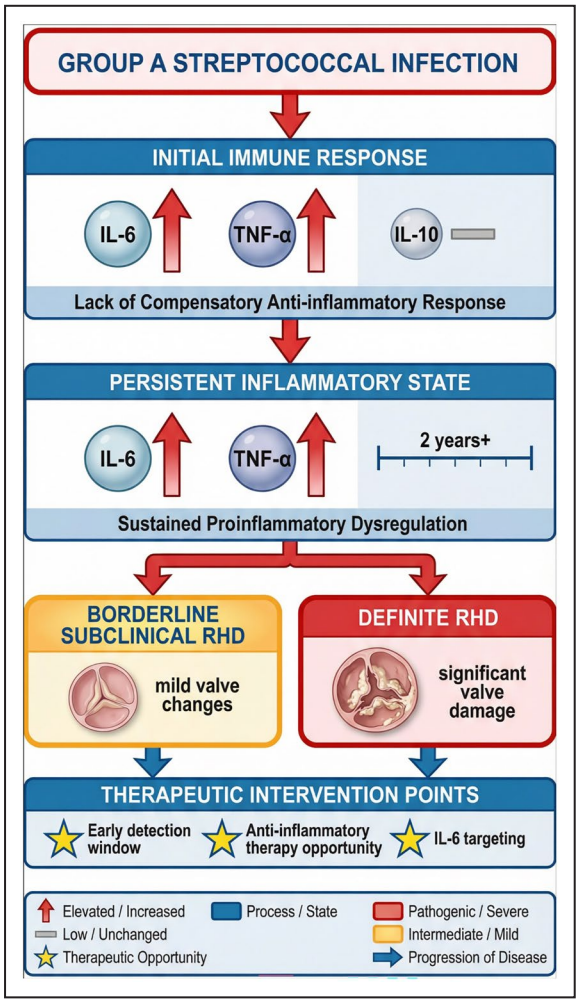

Figure 2. Inflammatory cascade in subclinical rheumatic heart disease.
Pathophysiological pathway from Group A streptococcal infection to subclinical RHD. Following infection, elevated pro-inflammatory cytokines (IL-6, TNF-α) occur without compensatory anti-inflammatory response (IL-10 unchanged), as demonstrated by Branco et al. This inflammatory imbalance persists for ≥2 years, leading to progressive valve damage: borderline subclinical RHD (mild changes, orange) or definite RHD (significant damage, red). Valve illustrations show anatomical progression from normal to pathological states. Bottom panel highlights 3 therapeutic intervention opportunities: early detection via screening, anti-inflammatory therapy, and IL-6 targeting. Color legend: red arrows=elevated cytokines; blue boxes=processes/states; red boxes=severe disease; orange boxes=mild disease; blue arrows=progression; yellow stars=therapeutic opportunities. Data derived from Branco et al.[3] IL-6 indicates interleukin-6; IL-10, interleukin-10; RHD, rheumatic heart disease; and TNF-α, tumor necrosis factor-alpha.

as adaptive platforms and pragmatic trials embedded within screening programs may be necessary.

Finally, mechanistic studies to elucidate the cellular and molecular basis of the inflammatory imbalance observed will be important. Why do some individuals with borderline disease exhibit elevated IL-6 whereas others do not? What prevents the expected compensatory anti-inflammatory response? Are there defects in regulatory T-cell function? Answering these questions may reveal additional therapeutic targets and deepen our understanding of RHD pathogenesis.

The implementation of family screening for individuals with borderline subclinical RHD, especially in vulnerable settings, holds promise as a tool for targeted case-finding strategies. When associated with IL-6 measured as a biomarker, it may provide a biological rationale for early intervention. These findings indicate that subclinical RHD remains common in endemic settings, but careful phenotyping is essential to avoid its overestimation.

Clinical cohort studies further elucidate the downstream burden of RHD in Brazil. Despite progressive reductions in periprocedural mortality, studies reveal substantial residual morbidity, including high rates of atrial fibrillation, need for anticoagulation, and repeat interventions during long-term follow-up. More than one third of patients required ongoing specialist care or reintervention within 10 years, underscoring the chronic nature of RHD. Brazil shows declining mortality coexisting with persistent disease burden, underscoring the importance of primary and secondary prevention, timely referral, and structured care pathways.[12,13]

The demonstration by Branco et al. that borderline subclinical RHD is associated with elevated IL-6 and persistent inflammatory dysregulation represents an important advance in our understanding of early RHD pathogenesis. These findings validate the clinical significance of borderline echocardiographic findings and provide a biological rationale for early intervention strategies. Although many questions remain, this study opens a window of opportunity for preventing the progression of the world's most common acquired heart disease in young people.

As we move forward, the cardiovascular community must embrace a comprehensive approach that combines continued efforts in primary prevention, expanded implementation of screening programs, rigorous evaluation of biomarker-guided risk stratification, and carefully designed trials of targeted interventions. Children with borderline subclinical RHD deserve more than watchful waiting—they deserve evidence-based strategies to prevent the devastating consequences of progressive valvular disease. The work by Branco et al. provides an important foundation for developing such strategies, highlighting that the earliest stages of disease, though subclinical, are far from silent at the molecular level.

ARTICLE INFORMATION

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Disclosures

None.

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