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RESEARCH ARTICLE

Seasonal climate variation, gut microbiota dysbiosis, and rheumatoid arthritis disease activity: A cross-sectional analysis of the gut–joint axis

Indra Sivakumar[1] | Jeevarathinam Thirumalai[2] | Vinodhkumar Ramalingam[3]
Hema Shree K[4] | Lavanya Ramanan[5] | Saravanan Sekaran[5]

[1]Department of Microbiology, Saveetha Institute of Basic Medical Sciences, Saveetha Institute of Medical and Technical Sciences, Chennai, India
[2]Department of Paediatric and Neonatal Sciences, Saveetha College of Physiotherapy, Saveetha Institute of Medical and Technical Sciences, Chennai, India
[3]Department of Sports Sciences, Saveetha College of Physiotherapy, Saveetha Institute of Medical and Technical Sciences, Chennai, India
[4]Department of Anatomy, Saveetha Institute of Basic Medical Sciences, Saveetha Institute of Medical and Technical Sciences, Chennai, India
[5]Department of Physiology, Saveetha Institute of Basic Medical Sciences, Saveetha Institute of Medical and Technical Sciences, Chennai, India

Abstract

Background: Seasonal environmental variation has been associated with fluctuations in rheumatoid arthritis (RA) disease activity, but the biological mechanisms underlying these changes remain unclear. Increasing evidence suggests that the gut-joint axis may mediate environmental effects on systemic inflammation. This study investigated whether seasonal environmental variation is associated with changes in gut inflammatory biomarkers, microbiota diversity, and RA disease activity.

Methods: A cross-sectional study was conducted among 1,080 patients with RA diagnosed according to the 2010 ACR/EULAR criteria. Participants were stratified by season into Winter (n=225), Pre-Monsoon (n=315), Monsoon (n=360), and Post-Monsoon (n=180). Climate parameters, serological markers (RF and anti-CCP), gut microbiota diversity (16S rRNA sequencing), inflammatory biomarkers (calprotectin and lactoferrin), disease activity indices (DAS28-CRP and CDAI), and patient-reported outcomes were assessed.

Results: Serological markers showed no seasonal variation. In contrast, disease activity indices, gastrointestinal symptoms, and faecal inflammatory biomarkers varied significantly across seasons (all $P<0.001$), with the highest levels observed during Pre-Monsoon and Monsoon periods. Faecal lactoferrin demonstrated strong positive associations with disease activity and functional disability (adjusted $\beta=0.75$, R^2 0.71), values markedly exceeding the predictive capacity of conventional serological markers (adjusted R^2 0.12).

Conclusion: Seasonal environmental variation is linked to changes in RA disease activity and intestinal inflammation. These findings support a climate-gut-inflammation pathway in which environmental stressors may influence RA manifestations via intestinal dysbiosis and gut-mediated inflammatory mechanisms. As this study was cross-sectional, these findings are hypothesis-generating and do not establish causal or temporal relationships; longitudinal studies are required to confirm.

Key messages

Seasonal environmental stress is associated with increased rheumatoid arthritis disease activity through gut microbiota dysbiosis and intestinal inflammation rather than changes in autoimmune serology. Gut-derived biomarkers, particularly lactoferrin, demonstrated stronger associations with current disease activity than conventional serological markers, which serve a diagnostic rather than activity-monitoring role, highlighting the gut-joint axis as a potential target for monitoring and climate-sensitive management of rheumatoid arthritis.

Correspondence
Indra Sivakumar
indrasivakumar51@gmail.com

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A: Iftekhar Hussain Bandhan
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Introduction

Rheumatoid arthritis (RA) is a systemic autoimmune condition affecting approximately 0.5-1% of the global population, characterised by symmetric polyarticular inflammation, progressive joint destruction, and substantial morbidity and mortality [1]. While RA pathogenesis fundamentally involves dysregulation of adaptive immunity manifested as autoantibody production and autoreactive T cell responses, the triggers initiating these processes and the factors modulating disease expression remain incompletely understood [2, 3]. Environmental factors including infections, dietary components, occupational exposures, and smoking have been implicated as putative risk factors for RA development and disease manifestation [4, 5]. However, growing evidence suggests that environmental factors exert continuous influence on disease activity throughout the disease course, not solely during initiation phases [4, 6].

Seasonal climate variations represent a predictable environmental exposure with measurable intensity, offering an opportunity to systematically investigate environmental determinants [7]. Clinical observations across multiple decades and regions have reported seasonal variation in RA disease activity, including changes in symptom severity, disease activity indices, and inflammatory markers [8]. Mechanical hypotheses have emphasised barometric pressure changes, temperature fluctuations, and humidity effects on synovial fluid viscosity and joint compliance [9]. However, recent investigations have increasingly focused on biological mechanisms through which environmental stressors may modulate systemic inflammation, including effects on immune cell function, antimicrobial peptide production, and microbial ecology [10, 11].

Emerging evidence identifies the gut microbiota and the intestinal immune system as key regulators of systemic inflammation and autoimmunity in RA [12]. Microbiota dysbiosis, characterised by reduced Shannon diversity and altered Firmicutes/Bacteroidetes Ratios, is associated with increased disease activity and joint damage [13]. Gut barrier dysfunction, reflected by increased intestinal permeability and elevated faecal calprotectin and lactoferrin, has also been reported in RA [14], supporting the gut–joint axis hypothesis, whereby dysbiotic microbiota and barrier disruption promote bacterial translocation and systemic inflammation [15]. However, the role of seasonal environmental factors in modulating this pathway remains unclear. This study, therefore, investigated seasonal climate variation as a determinant of RA expression using an integrated framework combining climate parameters, serological markers, gut microbiota and faecal inflammatory markers, disease activity indices, and patient-reported outcomes. This study hypothesised that RA activity and gut dysbiosis show seasonal variation, climate variables have weak direct biomarker associations suggesting indirect mediation, and faecal biomarkers outperform conventional serology in predicting disease outcomes.

Methods

Study design and participants

This cross-sectional study included 1,080 patients with rheumatoid arthritis (RA) diagnosed according to the 2010 ACR/EULAR classification criteria [16]. Participants were recruited from a rheumatology outpatient clinic in Chennai, Tamil Nadu, India, over a 12-month period and stratified by season of assessment: Winter (December–February; n=225), Pre-Monsoon (March–May; n=315), Monsoon (June–September; n=360), and Post-Monsoon (October–November; n=180). Eligible participants were adults aged 18–80 years with RA duration ≥6 months who provided written informed consent. Exclusion criteria included recent acute infection (within 4 weeks), malignancy, pregnancy, coexisting autoimmune diseases, or use of immunosuppressive therapy other than conventional synthetic disease-modifying antirheumatic drugs (csDMARDs).

Environmental exposure assessment

Environmental variables were used to characterise climatic conditions at the time of patient assessment. Ambient temperature (°C) and relative humidity (%) corresponding to the study period were obtained from local meteorological records in Chennai. To represent combined climatic stress, a Climate Stress Factor (CSF) was calculated as temperature × humidity / 100. High humidity exposure was defined as relative humidity ≥80%. Environmental variables were matched to each participant based on the date of clinical assessment.

Clinical and laboratory assessment

Following a 12-hour overnight fast, venous blood samples were collected for laboratory measurements. Serological biomarkers included rheumatoid factor (RF) measured by nephelometry (positive ≥20 IU/mL), anti-cyclic citrullinated peptide antibodies (anti-CCP) measured by ELISA (Euroimmun, Germany), and C-reactive protein (CRP) assessed using high-sensitivity nephelometry (Abbott Diagnostics). Disease activity was evaluated using DAS28-CRP and the Clinical Disease Activity Index (CDAI); flare was defined as DAS28-CRP >5.1, low disease activity as DAS28-CRP >2.6 to 3.2, and remission as DAS28-CRP <2.6, per standard EULAR thresholds. Patient-reported outcomes included Health Assessment Questionnaire Disability Index (0-3), pain on a 100-mm visual analogue scale (VAS), morning stiffness duration, fatigue (0-10 scale), and gastrointestinal symptom score (0-12). Clinically significant symptoms were defined as pain VAS ≥40 mm, fatigue ≥5, and morning stiffness ≥60 minutes. Demographic and clinical data included age, sex, BMI, disease duration, and medication use.

Gut microbiota and fecal biomarker analysis

Stool samples (≥2 g) were collected in sterile containers, transported on ice within 2 hours, and stored at -80°C until analysis. Bacterial DNA was extracted using the QIAamp PowerFecal DNA Kit (Qiagen, Germany) following manufacturer protocols. The V3-V4 hypervariable region of bacterial 16S rRNA gene was amplified using primers 341F (5'-

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CCTACGGGNGGCWGCAG-3') and 805R (5'-GACTACHVGGGTATCTAATCC-3') and sequenced on the Illumina MiSeq platform (2×300 bp paired-end).

Sequencing reads were processed using Quantitative Insights Into Microbial Ecology 2 (version 2023.5). Raw reads were quality-filtered, denoised, and clustered into amplicon sequence variants (ASVs) using Divisive Amplicon Denoising Algorithm 2 with default parameters. Taxonomic assignment was performed using the SILVA database (v138). Mean sequencing depth was 48,327 reads/sample (standard deviation 6,214; range 12,450-78,932); samples with <10,000 reads were excluded (n=18, 1.6% of initial 1,098 samples). The final dataset included 1,080 samples (98.4% retention). Shannon diversity index and Firmicutes/Bacteroidetes ratio were calculated using the phyloseq package in R.

Faecal calprotectin and lactoferrin were measured by enzyme-linked immunosorbent assay (ELISA; Immunodiagnostik AG, Bensheim, Germany) using kits K6927 and K6928, respectively. Lower limits of quantification were 10 μg/g for both biomarkers. Values below lower limits of quantification were imputed as lower limits of quantification/√2 (7.07 μg/g). Intra-assay coefficients of variation were 4.2% (calprotectin) and 3.8% (lactoferrin); inter-assay CVs were 7.1% and 6.5%, respectively. All samples were analysed in duplicate, and means were used for analysis.

Statistical analysis

Statistical analyses were conducted to examine seasonal variation and associations between gut biomarkers and rheumatoid arthritis outcomes. Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), and categorical variables as frequencies and percentages. Seasonal differences across the four climate periods were evaluated using the Kruskal-Wallis H test. Associations between gut biomarkers, microbiota diversity, and clinical outcomes were assessed using Spearman rank correlation coefficients. To identify independent predictors of disease activity and functional disability, multivariable linear regression models were constructed with DAS28-CRP and HAQ-DI as dependent variables and adjusted for age, sex, BMI, disease duration, and DMARD use. Statistical significance was defined as $P<0.05$. All analyses were performed using IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY, USA). This study is reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for cross-sectional studies.

Results

Study population characteristics

The study cohort comprised 1,080 patients with RA, with a mean age of 52.1 (10.8) years (range 29-80 years). Female patients constituted 68.9% (n=744) of the cohort. The mean disease duration was 7.8 (7.10) years, and the mean body mass index (BMI) was 25.5 (4.0) kg/m^2 (Table 1).

Table 1 Demographic and clinical characteristics of rheumatoid arthritis patients (n=1080)

Variables	Results
Mean (standard deviation)	
Age (years)	52.1 (10.8)
Disease duration (years)	7.8 (7.1)
Body mass index (kg/m²)	25.5 (4.0)
Number (%)	
Sex: female	744 (68.9)
Rheumatoid factor positive	816 (75.6)
Anti-cyclic citrullinated peptide positive	552 (51.1)
csDMARD use	
Methotrexate	964 (89.2)
Leflunomide	526 (48.7)
Hydroxychloroquine	824 (76.3)

DMARDs indicate disease-modifying antirheumatic drugs

Serological markers were common in the cohort, with rheumatoid factor (RF) positivity observed in 75.6% (n=816) and anti-cyclic citrullinated peptide (anti-CCP) positivity in 51.1% (n=552) of patients. All participants were receiving csDMARDs. Methotrexate was the most frequently prescribed agent (89.2%), followed by hydroxychloroquine (76.3%) and leflunomide (48.7%).

Stability of serological autoimmune markers across seasons

Serological markers reflecting underlying autoimmune status remained stable across seasons. The prevalence of RF and anti-CCP positivity showed no detectable seasonal variation, indicating that environmental stressors did not influence baseline autoimmune serological status.

Seasonal variation in disease activity and intestinal inflammation

In contrast to stable serological profiles, disease activity indices and intestinal inflammatory biomarkers demonstrated substantial seasonal fluctuations (Table 2).

Disease activity increased markedly during warmer and more humid periods. DAS28-CRP rose approximately 1.5-fold from Winter to Pre-Monsoon/Monsoon, and HAQ-DI nearly doubled over the same period, indicating a parallel rise in functional disability during high-stress seasons.

Intestinal inflammatory biomarkers exhibited even greater seasonal variation than disease activity measures. Fecal calprotectin and lactoferrin increased 2.8-fold and 3.4-fold, respectively, from Winter to Monsoon, while gastrointestinal symptom scores showed the most pronounced seasonal variation, increasing 2.4-fold from Winter to Pre-Monsoon, suggesting increased intestinal stress during periods of high temperature and humidity.

Gut inflammatory biomarkers strongly predicted disease activity

Gut-derived inflammatory biomarkers demonstrated substantially stronger associations with disease activity compared with conventional serological markers (Table 3). Faecal lactoferrin showed a very

Table 2 Seasonal variation in climate parameters, disease activity, patient-reported outcomes, and gut inflammatory biomarkers

Variables	Winter (n=225)	Pre-monsoon (n=315)	Monsoon (n=360)	Post-monsoon (n=180)	*P*
Climate variables					
Temperature (°C)	28.2 (26.5–30.1)	35.2 (33.8–36.9)	31.8 (30.2–33.5)	29.7 (28.1–31.4)	<0.001
Humidity (%)	65.2 (60.8–70.5)	72.4 (68.1–77.2)	88.5 (85.0–92.0)	68.7 (64.2–73.5)	<0.001
Climate stress factor	18.4 (16.1–21.3)	25.5 (23.1–28.4)	28.1 (25.7–30.9)	20.4 (18.1–23.2)	<0.001
Disease activity					
DAS28-CRP	3.1 (2.4–4.2)	4.8 (3.9–5.7)	4.7 (3.8–5.6)	3.5 (2.7–4.5)	<0.001
CDAI	12.5 (8.2–18.7)	24.3 (18.5–31.2)	23.8 (17.9–30.5)	14.2 (9.5–20.1)	<0.001
HAQ-DI (0-3)	0.85 (0.5–1.4)	1.6 (1.2–2.1)	1.5 (1.1–2.0)	1.0 (0.6–1.5)	<0.001
Patient-reported outcomes					
Visual analogue scale Pain (0-100 mm)	38 (25–55)	65 (48–78)	63 (46–76)	42 (28–59)	<0.001
Morning stiffness (min)	35 (20–60)	75 (50–105)	72 (48–102)	40 (25–68)	<0.001
Gastrointestinal symptoms (0-12)	2.5 (1.0–4.5)	6.2 (4.5–8.5)	6.0 (4.2–8.2)	2.8 (1.2–5.0)	<0.001
Gut microbiota and inflammation					
Faecal calprotectin (µg/g)	85 (58–124)	218 (165–285)	242 (178–315)	102 (68–145)	<0.001
Fecal lactoferrin (µg/g)	28 (18–42)	88 (65–115)	96 (71–128)	35 (22–52)	<0.001

Values are median [interquartile range]. Differences across the four seasonal groups were assessed using the Kruskal-Wallis test; only the resulting (FDR-corrected) P-value is reported. All *P* are FDR-corrected for multiple comparisons using the Benjamini-Hochberg procedure. Climate Stress Factor calculated as (Temperature × Humidity)/100. DAS28-CRP = Disease Activity Score in 28 joints with C-reactive protein; CDAI = Clinical Disease Activity Index; HAQ-DI = Health Assessment Questionnaire Disability Index; min = minutes.

strong positive association with DAS28-CRP (β=0.78) and, after adjustment for age, sex, BMI, disease duration, and medication use, explained 71% of the variance in disease activity (adjusted R^2=0.71). Similarly, faecal calprotectin was strongly associated with disease activity (β=0.69) and accounted for 65% of the variance in DAS28-CRP.

In contrast, microbial diversity demonstrated an inverse relationship with disease activity. A higher Shannon diversity index was negatively correlated with DAS28-CRP (β=0.78) and explained 68% of the variance in disease activity, indicating that greater microbial diversity may confer a protective effect against disease severity.

Limited predictive value of conventional serological markers

Traditional serological markers demonstrated minimal predictive capacity for current disease activity (Table 3). RF positivity showed a weak inverse association with DAS28-CRP (β=−0.11) and explained only 2% of the variance. Similarly, anti-CCP positivity explained only 2% of CDAI variance (β=−0.12).

Overall, the explanatory power of faecal lactoferrin (71%) compared with RF positivity (2%) represents an approximately 35-fold difference, highlighting the substantially greater relevance of gut inflammatory biomarkers as indicators of active disease processes, compared with stable serological markers, which serve a distinct diagnostic rather than activity-monitoring role.

Discussion

This multi-domain investigation provides evidence for a climate-gut-inflammation cascade influencing seasonal RA expression. By integrating within-season correlations, between-season variations, and cross-domain analyses, the study identifies a mechanistic framework linking environmental stressors to RA manifestations. Importantly, serological autoimmune markers remained unchanged across seasons, indicating that climate factors do not alter underlying autoimmunity but instead modulate disease expression through gut-mediated inflammatory pathways, shifting the understanding of seasonal RA exacerbation toward microbiota-immune mechanisms.

Serological stability as evidence for downstream environmental modulation

The complete temporal invariance of RF and Anti-CCP seropositivity represents a key mechanistic finding. It contradicts hypotheses that environmental stressors directly alter autoimmune activation via T- or B-cell regulation, indicating instead that seasonal climate effects occur downstream of autoimmune initiation. This interpretation aligns with evidence that environmental factors primarily influence innate inflammatory pathways rather than adaptive immunity [17-19]. These findings extend this concept to climate stressors, suggesting that seasonal factors amplify pre-existing autoantibody-mediated pathology through enhanced innate inflammatory responses rather than initiating new autoimmune activity.

The gut–joint axis as central mechanism for environmental modulation

Strong biomarker-disease relationships were observed for gut inflammatory markers faecal lactoferrin and calprotectin showed markedly stronger associations with disease activity and functional disability than RF positivity, consistent with their differing intended clinical applications (diagnostic versus activity-monitoring). Similar associations were observed for faecal calprotectin and Shannon diversity index,

Table 3 Adjusted β estimates (95% confidence intervals) for gut biomarkers, serological markers, and climate variables in relation to disease activity and functional disability

Predictor variable	Outcome variable	Adjusted β (95% Confidence interval)	Adjusted R^2
Gut biomarkers			
Faecal lactoferrin (per 100 µg/g)	DAS28-CRP	0.8 (0.7 to 0.8)[a]	0.71
Faecal lactoferrin (per 100 µg/g)	HAQ-DI	0.8 (0.8 to 0.9)[a]	0.68
Faecal calprotectin (per 100 µg/g)	DAS28-CRP	0.7 (0.6 to 0.7)[a]	0.65
Faecal calprotectin (per 100 µg/g)	HAQ-DI	0.7 (0.7 to 0.8)[a]	0.58
Shannon diversity index	DAS28-CRP	−0.7 (−0.8 to −0.6)[a]	0.68
Shannon diversity index	HAQ-DI	−0.2 (−0.3 to −0.1)	0.03
Serological markers			
Rheumatoid factor positivity	DAS28-CRP	−0.1 (−0.2 to −0.0)[a]	0.02
Anti-cyclic citrullinated peptide positivity	CDAI	−0.1 (−0.2 to −0.0)[a]	0.02
Climate-biomarker associations			
Temperature → Shannon diversity	-	−0.1 (−0.2 to 0.0)	0.01
Humidity → Rheumatoid factor positivity	-	0.1 (−0.0 to 0.2)	<0.01
Climate stress factor → Faecal lactoferrin	-	0.1 (−0.0 to 0.1)	<0.01

DAS28-CRP indicate disease activity score28-C-reactive protein; HAQ-DI, health assessment questionnaire-disability index ; CDAI, clinical disease activity index

Adjusted β = standardized multivariable regression coefficient for the predictors listed, adjusted for age, sex, BMI, disease duration, and csDMARD use; Biomarker concentrations were scaled per 100 µg/g for clinical interpretability. Variance inflation factors were <3.0 for all models, indicating absence of multicollinearity. Residual diagnostics confirmed model assumptions. Adjusted R^2 is the overall (model-level) adjusted R^2 for each regression model as a whole, not a partial R^2 attributable to the single predictor shown. [a]$P<0.05$

highlighting the gut-joint axis as a potential intermediary through which environmental stressors may influence rheumatoid arthritis outcomes and supporting the role of intestinal barrier dysfunction and microbiota dysbiosis in RA pathogenesis [20, 21]. Studies by Scher *et al.*, Maeda *et al.*, and Vaahtovuo *et al.* reported RA-associated dysbiosis characterised by reduced Faecalibacterium prausnitzii, decreased Shannon diversity, and altered Firmicutes/Bacteroidetes ratios [22, 23]. These findings extend previous evidence by demonstrating pronounced seasonal increase in gut inflammatory biomarkers, with faecal calprotectin and lactoferrin rising markedly during Pre-Monsoon and Monsoon seasons alongside peaks in disease activity. Moreover, gut-derived biomarkers showed substantially stronger predictive capacity for disease activity and functional disability than conventional serological markers, supporting the role of the gut-joint axis as a key pathway linking environmental stress to rheumatoid arthritis outcomes.

The inverse association between microbial diversity and disease activity (Shannon diversity index vs. DAS28-CRP) suggests that greater microbial richness may exert a protective influence on rheumatoid arthritis disease activity. Mechanistically, diverse microbiota promote SCFA production (butyrate), supporting intestinal barrier integrity and Treg differentiation via GPR43/GPR109A signalling, enhance metabolic resilience, and limit expansion of pro-inflammatory taxa such as Prevotella and Bacteroides fragilis [24, 25]. Seasonal reductions in diversity during Pre-Monsoon and Monsoon likely reflect environmental conditions favouring dysbiotic microbial profiles.

Environmental mechanisms and hygiene-related hypotheses

Weak climate-biomarker correlations ($|r|\leq 0.13$, with only the temperature-Shannon diversity association reaching statistical significance) despite pronounced seasonal variation in gut biomarkers and disease activity suggest that environmental stress may influence rheumatoid arthritis through indirect biological pathways rather than direct linear associations. One likely mechanism is seasonal humidity influencing environmental microbiology, food preservation, and diet, with Pre-Monsoon/Monsoon periods associated with increased fungal food contamination, greater consumption of carbohydrate-rich preserved foods, and reduced intake of probiotic fermented foods, potentially altering gut microbiota composition [26, 27]; heat stress physiology, where elevated temperature and hormonal responses increase intestinal permeability through heat shock proteins and tight-junction alterations [28]; and reduced physical activity during hot seasons, which may influence intestinal motility and microbial transit, promoting dysbiotic microbial profiles.

Differential clinical utility of faecal versus serological biomarkers in tracking disease activity

Faecal biomarkers demonstrated substantially stronger predictive capacity for current disease activity than conventional serological markers (**Table 3**). Faecal lactoferrin showed a strong positive association with disease activity and functional disability, whereas RF and anti-CCP positivity showed only weak associations with DAS28-CRP and CDAI, respectively. This difference reflects the distinct clinical roles of these biomarker classes: RF and anti-CCP are diagnostic markers of autoimmune status not

expected to track fluctuating disease activity, whereas lactoferrin and calprotectin reflect intestinal neutrophil activity and mucosal inflammation that vary with current inflammatory burden. Comparable findings in autoimmune and inflammatory bowel diseases similarly show greater predictive value of calprotectin than serum markers for monitoring active inflammation [29, 30], supporting the use of markers as a complementary, activity-sensitive monitoring tool rather than a replacement for diagnostic serology.

Preserved symptom architecture across seasons: Quantitative versus qualitative changes

Despite significant seasonal variation in disease activity and symptoms, strong associations between clinical outcomes and gut inflammatory biomarkers remained consistent, suggesting that environmental stressors amplify disease intensity without altering underlying inflammatory pathways in rheumatoid arthritis. This supports a multiplicative amplification model, where pre-Monsoon and Monsoon represent periods of disease amplification with parallel increases in pain, stiffness, fatigue, disability, and gastrointestinal symptoms, reflecting systemic inflammatory amplification via the gut-joint axis rather than pathway-specific changes [15, 31].

Gastrointestinal symptoms as leading indicator of environmental stress response

Gastrointestinal symptoms showed the greatest seasonal variation, with scores during Pre-Monsoon and Monsoon more than twice those in Winter and Post-Monsoon. This variation exceeded systemic disease activity, suggesting intestinal responses may be highly sensitive to environmental stressors. Possible mechanisms include seasonal pathogen exposure [32], heat-induced barrier dysfunction [33, 34], diet-related microbiota changes affecting SCFA production [35], and humidity-driven environmental microbiology shifts [36]. The temporal association between GI symptoms, inflammatory markers, and disease activity suggests GI complaints may act as early indicators of RA exacerbation [37].

Clinical implications and therapeutic targets

These findings highlight the gut microbiota and inflammatory markers as potential therapeutic targets in RA. Interventions aimed at improving microbiota diversity and reducing intestinal inflammation may be particularly beneficial during high-stress seasons (Pre-Monsoon/Monsoon) [38]. Strategies may include probiotic supplementation with diversity-promoting strains (Faecalibacterium prausnitzii, Roseburia, Akkermansia muciniphila), prebiotic intake (inulin, resistant starch) to enhance SCFA production, seasonal dietary optimisation, gut-barrier support (L-glutamine, zinc carnosine, collagen), and targeted antimicrobial approaches. Monitoring biomarkers (calprotectin, lactoferrin) may improve disease assessment and prediction of seasonal exacerbations [39, 40]. Additionally, environmental modifications (heat avoidance, air conditioning) and season-specific therapeutic intensification during Pre-Monsoon and Monsoon may help reduce disease burden [34].

Strengths and limitations

This study has several strengths, including a large sample (n=1,080) with balanced seasonal distribution, comprehensive assessment integrating climate, serology, gut microbiota, inflammatory markers, disease activity, and symptoms, and appropriate statistical analyses for non-normal data. The preservation of within-season correlation patterns despite seasonal variation supports robust mechanistic relationships and highlights the integration of environmental, immunological, microbiological, and clinical domains. However, limitations include the cross-sectional design limiting causal inference, restriction to a tropical/subtropical setting affecting generalisability, lack of systematic dietary assessment, limited medication stratification beyond DMARDs, and unmeasured mediating factors such as heat stress physiology, dietary shifts, and occupational exposures. Because participants were sampled once and different individuals contributed to each seasonal stratum rather than the same cohort being followed longitudinally across all four seasons, the observed seasonal differences could partly reflect inter-individual or genetic variability rather than a true within-person seasonal effect; repeated-measures or longitudinal designs are required to disentangle these possibilities. In addition, several clinically relevant confounders including glucocorticoid and, NSAIDs use, dietary patterns, physical activity levels, and socioeconomic conditions were not systematically measured or adjusted for in the regression models, despite their potential to influence both gut biomarkers and disease activity; these factors should be incorporated in future prospective studies.

Conclusion

This study demonstrates a climate-gut-inflammation cascade influencing seasonal RA expression. The Pre-Monsoon and Monsoon periods, characterised by higher humidity and temperature, were associated with increased disease activity, symptom burden, intestinal inflammation, and microbiota dysbiosis, while serological markers remained unchanged, suggesting that environmental effects may occur downstream of autoimmune initiation. However, as a cross-sectional study, it cannot establish temporal sequence or causality. Gut-derived biomarkers showed far greater predictive capacity (71% variance) than traditional serology (2%), highlighting the gut-joint axis as a key mechanism. Weak direct climate-biomarker associations suggest indirect pathways, such as heat stress, seasonal diet, and environmental microbiology. Overall, these findings emphasise gut-microbiota-immune interactions in seasonal RA exacerbation and support season-specific therapeutic strategies, with future prospective studies needed to confirm causal mechanisms.

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Author contributions

Concept or design of the work; or the acquisition, analysis, or interpretation of data for the work: IS, JT. *Drafting the work or reviewing it critically for important intellectual content:* JT. *Final approval of the version to be published:* IS, JT, VR, HS, LR, SS. *Accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved:* IS, JT.

Conflict of interest

We do not have any conflict of interest.

Data availability statement

We confirm that the data supporting the findings of the study will be shared upon reasonable request.

AI disclosure

The authors used QuillBot AI solely to assist with language editing and improving the clarity of the manuscript, as English is not the authors' native language. All scientific content, interpretation, and final approval of the manuscript were the sole responsibility of the authors.

Supplementary file

None

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