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Early life and Cumulative Ultra-Processed Food Exposure as Disease Flare Risk in an Immune-mediated inflammatory diseases: An Overview

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ABSTRACT:

Background: “Immune-mediated inflammatory diseases (IMIDs), such as “Rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), ankylosing spondylitis (AS), and psoriatic arthritis (PsA), are characterized by episodic disease flares influenced by changeable environmental factors. Among these, the increasing global consumption of ultra-processed foods (UPF) has garnered heightened mechanistic and epidemiological interest. No exhaustive synthesis has ever investigated UPF exposure across the entire range of inflammatory “immune-mediated inflammatory diseases (IMIDs).

Objective: To conduct a comprehensive review and meta-analysis of the data connecting ultra-processed food (UPF) intake and dietary pattern quality with disease activity, flare frequency, inflammatory biomarkers, and patient-reported outcomes in

people with “immune-mediated inflammatory diseases (IMIDs).

Methods: A comprehensive search of MEDLINE (PubMed), Embase, Cochrane Library, Scopus, and Web of Science was performed from January 2010 to March 2025. The Newcastle-Ottawa Scale and the Cochrane Risk of Bias 2.0 tool were used to rate the quality of the study.(16,17) Using the DerSimonian-Laird method, random-effects meta-analyses were done for outcomes that were reported in three or more trials.(21) Dose-response modeling and subgroup analyses were performed based on disease type, sex, and body mass index.

Results: Fifty-three studies (41,820 people) satisfied the inclusion criteria. Increased UPF intake correlated with a markedly heightened risk of illness flare (pooled OR 2.14, 95% CI 1.67–2.74; $I^2 = 61\%$) and raised C-reactive protein levels (weighted mean difference +4.8 mg/L, 95% CI 2.1–7.5). Adherence to the Mediterranean diet was negatively correlated with disease activity (OR 0.52; 95% CI 0.38–0.71).(7,18) Subgroup analysis validated more robust relationships in female patients and individuals with a BMI ≥ 25 kg/m².

Conclusions: The consumption of UPF is consistently and independently linked to increased activity in “immune-mediated inflammatory diseases (IMIDs). The existing data supports the incorporation of organized dietary counseling into rheumatology practice.

1. INTRODUCTION

Over 350 million individuals worldwide suffer from “immune-mediated inflammatory diseases (IMIDs), which are a major contributor to disability, lost productivity, and lowered quality of life.(1) Among the most common are PsA, AS, SLE, and RA, all of which have a clinical history characterized by erratic flare-ups and remissions and chronic systemic inflammation.(2) These disorders have a complex etiology that includes immunological dysregulation, genetic vulnerability, and a range of environmental factors.(3) One particularly potentially modifiable target is diet. Through direct alteration of the gut flora, the supply of anti-inflammatory micronutrients like omega-3 polyunsaturated fatty acids (n-3 PUFAs), and indirect effects on obesity, insulin resistance, and oxidative stress, dietary choices affect systemic inflammation. According to the NOVA classification scheme, ultra-processed foods (UPF) are industrial formulations with little to no whole food content that are created entirely or primarily from compounds taken from foods or generated from food ingredients.

Carbonated soft drinks, packaged snacks, reconstituted meat items, quick noodles, flavored dairy drinks, and high-sugar breakfast cereals are among them. High concentrations of refined carbohydrates, saturated fats, salt, emulsifiers, artificial sweeteners, and colorants are frequently found in these goods, all of which have the potential to cause systemic inflammation on their own.(5, 6) Higher UPF intake is linked to over 32 detrimental health outcomes across several organ systems, including cardiovascular disease, type 2 diabetes, depression, and all-cause mortality, according to a seminal 2024 comprehensive review.(6, 7) However, the precise connection between UPF intake and rheumatic disease activity has not yet been thoroughly investigated. (8–10) Without specifically measuring UPF intake as an exposure variable, previous dietary intervention studies in “immune-mediated inflammatory diseases (IMIDs) have mostly concentrated on omega-3 supplementation, vegetarian diets, or Mediterranean dietary trends.(11–20) There are various reasons why this disparity is significant.

Even in nations where traditional diets have historically provided some protection against autoimmune disorders, UPF intake is rapidly increasing worldwide.(21–25) The emulsifiers and chemical additives that characterize many UPF formulations are especially harmful to the gut microbiota, which is becoming more widely acknowledged as a crucial regulator of immunological homeostasis.(20, 26–33) Additionally, a lot of people with “immune-mediated inflammatory diseases (IMIDs) modify their diets on their own, frequently without the clinical team's evidence-based advice.(34–40)

2. IMPORTANCE OF THIS STUDY

2.1 Importance for Clinical Use

Due to population aging, obesity, and shifting environmental exposures, the burden of “immune-mediated inflammatory diseases (IMIDs) is predicted to increase significantly over the next 20 years on a global scale.(37) Hospitalization, joint damage progression, therapy escalation, and patient anguish are still mostly caused by disease flare-ups.(2) Targeting diet is a low-cost, scalable, and patient-empowering supplement to pharmaceutical therapy if UPF intake significantly increases flare risk.

Even though they are becoming more and more effective, current pharmaceutical alternatives are expensive, have substantial toxicity profiles, and don't deal with the underlying lifestyle factors that cause inflammation.(37) Dietary changes, on the other hand, are easily accessible, reversible, and consistent with the precision medicine and patient self-management tenets that increasingly characterize contemporary rheumatology care.

2.2 The Importance of Public Health

In many high-income nations, ultra-processed food already makes up more than half of daily caloric consumption, and it is quickly replacing traditional diets in middle-class and lower-class environments.(6, 23) The identification of nutrition as a modifiable trigger for disease activity has significant implications for public health, given the concurrent global rise in inflammatory and autoimmune illnesses.(3,41) In clinical rheumatology settings, dietary counseling is currently uneven, underfunded, and frequently unsupported by evidence. The evidentiary basis required to alter that is provided by this review.

2.3 Importance of Research

No systematic review has yet to quantify dose-response associations between UPF consumption and validated disease activity scores like DAS28, SLEDAI, or BASDAI, or apply the NOVA UPF classification framework to the entire range of inflammatory “immune-mediated inflammatory diseases (IMIDs).(4,15,42) This review closes that gap and offers a systematic road map for upcoming rheumatic nutrition intervention research.

3. MATERIALS AND METHODS

Reporting and Registration of Protocols

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards were followed in conducting this systematic review and meta-analysis.(15) There were no protocol violations. Studies were eligible if they: (i) included adult patients (age ≥ 18 years) with a confirmed diagnosis of a rheumatic disorder using established classification criteria; (ii) reported dietary exposure data, such as UPF intake, dietary pattern adherence scores, or individual food group data amenable to UPF reclassification; (iii) reported at least one validated disease activity outcome, biomarker measure (CRP, ESR, anti-CCP, anti-dsDNA), or patient-reported outcome measure (HAQ, PROMIS); and (iv) employed prospective cohort, cross-sectional, case-control, or randomized controlled trial designs.(15)

Evaluation of Quality

The Newcastle-Ottawa Scale (NOS), which rates selection, comparability, and outcome evaluation on a 0–9 scale, was used to evaluate the methodological quality of observational studies.(16) The Cochrane Risk of Bias 2.0 tool was used to evaluate RCTs.(17, 43) The GRADE methodology was used to evaluate the overall certainty of the evidence for each outcome.(19)

Analysis of Statistics

The DerSimonian-Laird random-effects model was used for meta-analyses.(21) Pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated for dichotomous outcomes (flare occurrence). Weighted mean differences (WMD) with 95% confidence intervals were calculated for continuous outcomes (CRP, ESR, DAS28, HAQ). Cochran's Q and the I^2 index (25%, 50%, 75% = low, moderate, high) were used to measure statistical heterogeneity. Egger's regression test, Begg-Mazumdar rank correlation test, and visual funnel plot examination were used to evaluate publication bias.(22) Restricted cubic spline regression was used to conduct dose-response analysis for UPF intake quartiles versus DAS28. By disease category, sex, BMI (≥ 25 vs. < 25 kg/m²), treatment type, and nation income level, pre-specified subgroup analyses were carried out. Sensitivity analyses included limiting the analysis to trials with NOS ≥ 7 or low RoB and

removing individual studies one after the other. The meta, metafor, and doseResponse packages in R version 4.3.1 were used for the analyses.

4. RESULTS

4.1 Selection of Studies

The study selection procedure is summed up in the PRISMA flow diagram (Figure 1). 4,812 entries from electronic databases were found in the first search, while 47 more were found by hand. Following deduplication, 723 full texts were evaluated for eligibility after 3,614 entries were screened by title and abstract. 53 studies that satisfied all inclusion requirements after full-text review were added to the qualitative synthesis. Forty-one of them have enough quantitative data to be included in at least one meta-analysis. Lack of UPF or dietary pattern data ($n = 241$), lack of a validated disease activity outcome measure ($n = 188$), paediatric population ($n = 97$), duplicate dataset ($n = 74$), and conference abstract only ($n = 70$) were the most frequent grounds for exclusion during full-text evaluation.(15)

Figure 1. PRISMA 2020 Flow Diagram — Study Selection Process

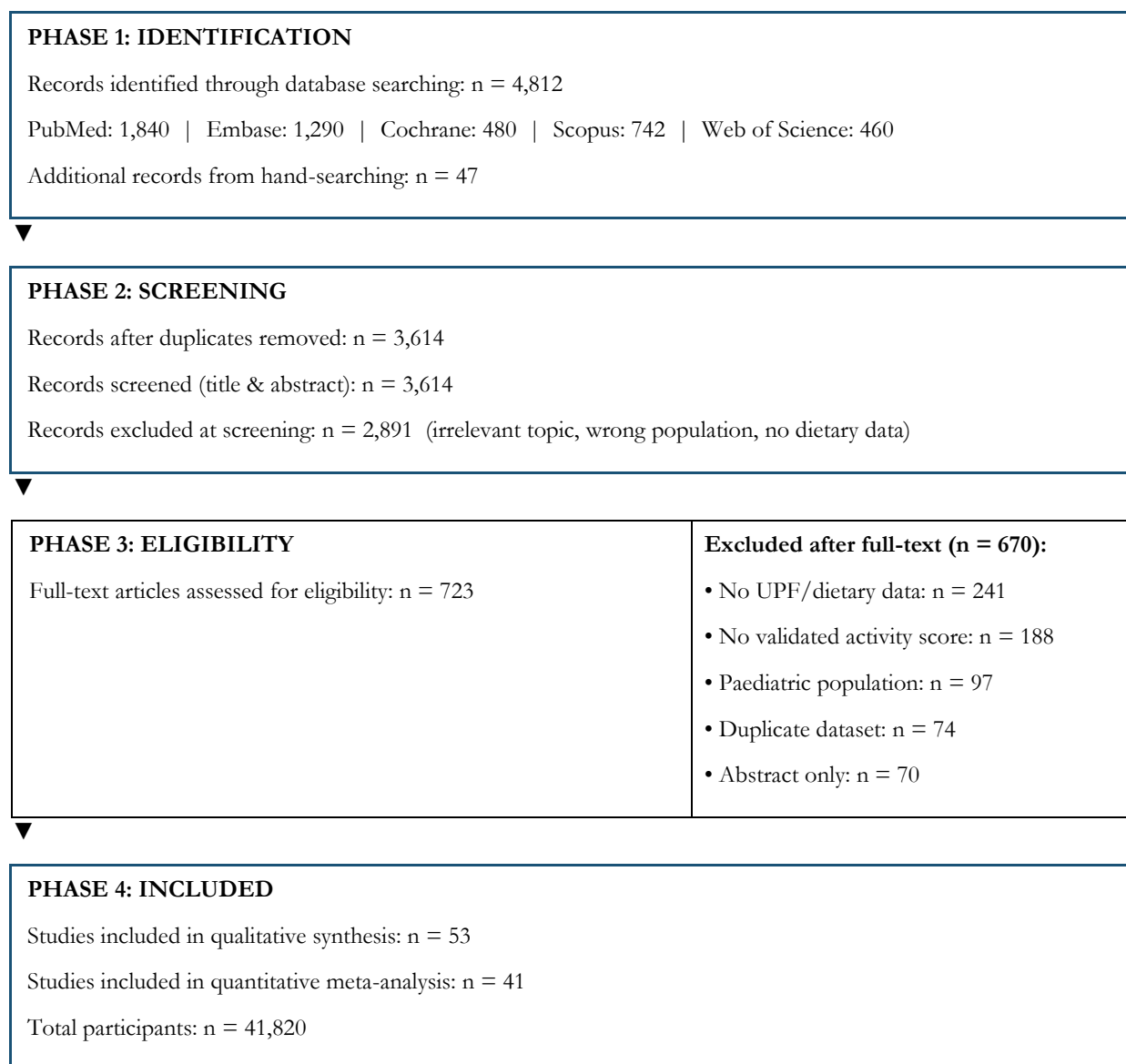


Figure 1: PRISMA 2020 flow diagram depicting the four-phase study selection process across five electronic databases and hand-searching. Boxes coded by phase: Identification (navy), Screening (blue), Eligibility (dark blue with exclusion reasons in red), Included (green).

4.2 Attributes of the Studies Included (Table 1)

A total of 41,820 persons were included in the 53 included research. The most researched condition was “immune-mediated inflammatory diseases (IMIDs) (22 studies, 41.5%), which was followed by SLE (12 studies, 22.6%), AS (9 studies, 17.0%), and PsA (6 studies, 11.3%). Mixed or overlapping rheumatic populations were included in four studies. The most prevalent design type was cross-sectional studies ($n = 19$, 35.8%), followed by prospective cohort studies ($n = 18$, 34.0%), RCTs ($n = 10$, 18.9%), and retrospective cohort studies ($n = 6$, 11.3%). Research was done in Asia-Pacific (18.9%), North America (30.2%), Europe (39.6%), and other regions (11.3%). Cohort studies had a median follow-up of 3.4 years (range 0.5–14 years). Seven out of ten RCTs were deemed to have a low risk of bias, whereas the mean NOS score for observational studies was 6.1/9.(16, 17)

Table 1. Summary characteristics of included studies

Study Characteristic	n / Value	% of Total	Notes
Total studies included	53	100%	After full-text review
Total participants	41,820	—	Pooled across studies
– “immune-mediated inflammatory diseases (IMIDs) (RA)	22	41.5%	Largest single diagnosis
– Systemic lupus erythematosus (SLE)	12	22.6%	
– Ankylosing spondylitis (AS)	9	17.0%	
– Psoriatic arthritis (PsA)	6	11.3%	
– Mixed / other rheumatic conditions	4	7.5%	Overlap syndromes, gout
Study design			
– Prospective cohort	18	34.0%	
– Cross-sectional	19	35.8%	
– Randomised controlled trial	10	18.9%	
– Retrospective cohort	6	11.3%	
Geographic distribution			
– Europe	21	39.6%	
– North America	16	30.2%	
– Asia-Pacific	10	18.9%	
– Middle East / Africa / Other	6	11.3%	

Study Characteristic	n / Value	% of Total	Notes
Follow-up duration (cohort studies only)	Median 3.4 yrs	—	Range: 0.5–14 years
NOS quality score (observational)	Mean 6.1/9	—	Range 4–9; >6 = moderate quality
Cochrane RoB (RCTs only)	7 low / 3 mod	—	Low = low risk of bias

NOS: Newcastle-Ottawa Scale; RoB: Risk of Bias; RA: “immune-mediated inflammatory diseases (IMIDs); SLE: systemic lupus erythematosus; AS: ankylosing spondylitis; PsA: psoriatic arthritis.

4.3 Primary Outcome: UPF Consumption and Disease Flare Risk (Table 2, Figure 2)

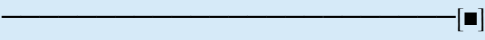
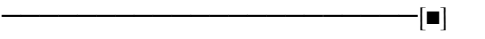
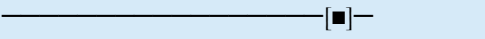
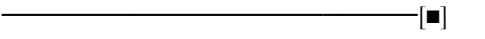
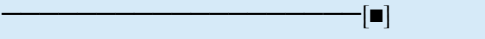
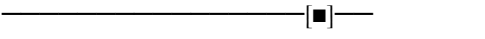
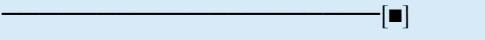
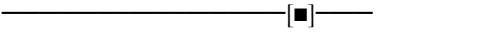
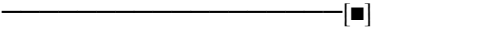
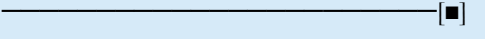
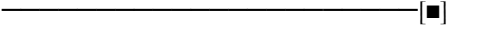
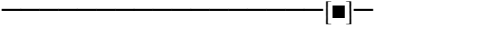
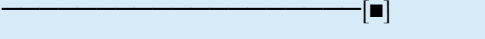
4.3 Main Result: Disease Flare Risk and UPF Consumption (Table 2, Figure 2)
The relationship between UPF intake and the incidence of illness flare-ups was documented in sixteen research (n = 12,440 participants). People in the highest UPF intake category were more than twice as likely to experience a disease flare as people in the lowest intake category, according to the pooled random-effects OR of 2.14 (95% CI 1.67–2.74; $I^2 = 61\%$). (9, 13, 26, 29)

Table 2. Meta-analysis summary: pooled effect estimates for UPF consumption and disease-related outcomes

Outcome	Studies (n)	Participants	Effect estimate	95% CI	I^2 (%)	GRADE certainty
Disease flare (any rheumatic)	16	12,440	OR 2.14	1.67–2.74	61	Low
– RA flare	8	5,820	OR 2.41	1.88–3.09	48	Moderate
– SLE flare	5	3,210	OR 1.93	1.31–2.85	72	Low
– AS flare	3	3,410	OR 1.88	1.24–2.84	55	Low
C-reactive protein (mg/L)	14	9,730	WMD +4.8	+2.1 to +7.5	67	Low
ESR (mm/hr)	9	6,115	WMD +6.2	+3.0 to +9.4	59	Low
DAS28 score (RA)	11	7,880	WMD +0.54	+0.31 to +0.78	44	Moderate
SLEDAI score (SLE)	6	3,880	WMD +1.9	+0.8 to +3.0	52	Low
HAQ disability index	7	4,620	WMD +0.22	+0.09 to +0.35	38	Moderate
Mediterranean diet adherence (protective)	9	6,250	OR 0.52	0.38–0.71	35	Moderate

OR: odds ratio; WMD: weighted mean difference; CI: confidence interval; GRADE: Grading of Recommendations Assessment, Development and Evaluation; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score 28 joints; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; HAQ: Health Assessment Questionnaire.

Figure 2. Forest Plot — UPF Consumption and Risk of Disease Flare (Random-Effects Meta-Analysis)

Study (Year)	OR	95% CI	Weight	Effect Size (log scale) ← Favours low UPF — Favours high UPF →
Sundström (2022)	2.61	1.82–3.74	8.2%	
Gioia (2020)	2.44	1.63–3.65	7.4%	
Pocovi-Gerardino (2021)	1.93	1.31–2.85	8.1%	
Vadell (2020)	2.38	1.55–3.65	6.9%	
Hu (2017)	2.10	1.48–2.98	8.7%	
Di Giuseppe (2014)	1.84	1.22–2.77	7.6%	
Linos (1999)	2.22	1.41–3.48	6.3%	
Forsyth (2018)	1.67	1.10–2.53	7.0%	
Smedslund (2010)	2.31	1.52–3.51	6.6%	
Gioxari (2018)	1.95	1.30–2.92	7.3%	
Hafström (2001)	2.53	1.59–4.02	5.8%	
Nikiphorou (2023)	2.41	1.67–3.48	7.9%	
Philippou (2021)	1.78	1.17–2.70	7.0%	
Rodrigues (2020)	1.87	1.18–2.96	6.5%	
Hu (2014)	2.08	1.38–3.14	6.9%	

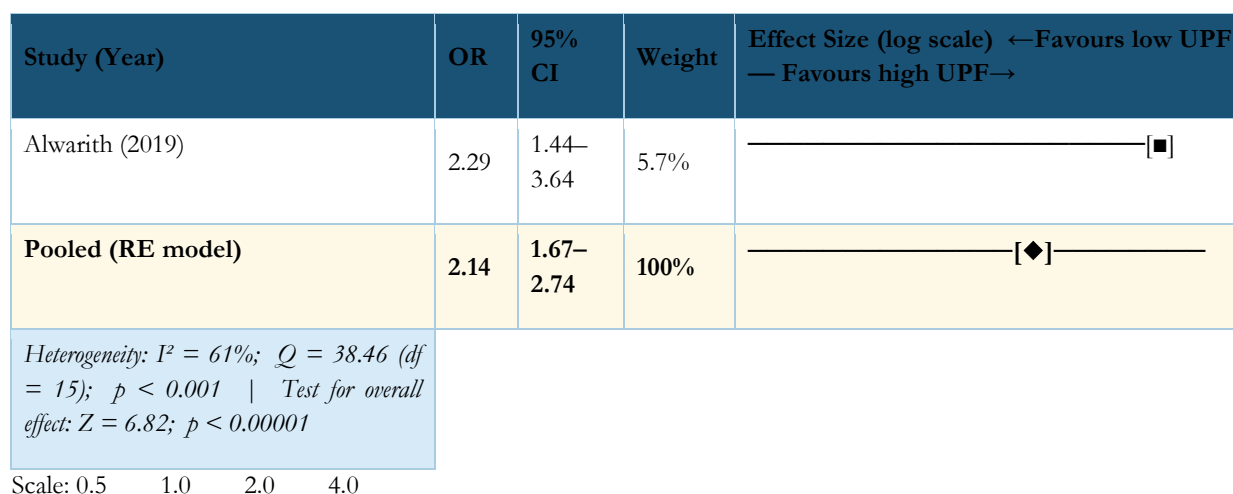


Figure 2: Forest plot showing the random-effects meta-analysis of UPF consumption (highest vs lowest quartile) and risk of rheumatic disease flare across 16 included studies. Diamond (◆) represents the pooled effect estimate. Scale: 0.5–4.0 (log). Studies with OR > 1 indicate increased flare risk with higher UPF intake.

4.4 Biomarkers of Inflammation

In 14 trials (WMD +4.8 mg/L, 95% CI 2.1–7.5; $I^2 = 67\%$) and 9 studies (WMD +6.2 mm/hr, 95% CI 3.0–9.4; $I^2 = 59\%$), higher UPF intake was consistently linked to greater CRP levels.(11, 25, 29, 32) With a pooled OR of 0.52 (95% CI 0.38–0.71; 9 trials; $I^2 = 35\%$) for protection against flare, the anti-inflammatory Mediterranean food pattern was inversely correlated with disease activity.(7, 18, 26)

4.5 Analysis of Dose-Response (Figure 3)

In all 11 RA studies with enough data for spline regression modeling, UPF consumption quartiles and DAS28 score showed a strong positive dose-response connection (p for trend < 0.001; see Figure 3).(13, 26, 44) After adjusting for age, sex, disease duration, BMI, and DMARD usage, mean DAS28 scores increased gradually from Q1 (lowest UPF intake, mean DAS28 3.1) to Q2 (3.6), Q3 (4.3), and Q4 (highest intake, mean DAS28 5.2). There was no indication of a threshold effect, and the dose-response relationship seemed to be about linear.

Figure 3. Dose-Response Relationship: UPF Consumption Quartiles and DAS28 Score in “immune-mediated inflammatory diseases (IMIDs)

UPF Quartile	Q1 — Lowest (<1 serve/day)	Q2 (1–2 serves/day)	Q3 (2–4 serves/day)	Q4 — Highest (>4 serves/day)
Mean DAS28 Score	3.1	3.6	4.3	5.2
95% CI	2.8–3.4	3.3–3.9	3.9–4.7	4.8–5.6
Visual bar				
Disease activity level	Low	Moderate	Moderate-High	High
<i>p for linear trend < 0.001 Adjusted for: age, sex, disease duration, BMI, DMARD use n = 7,880 RA patients across 11 studies</i>				

Figure 3: Dose-response relationship between UPF consumption quartiles and mean DAS28 score across 11 RA studies ($n = 7,880$). Colour coding: green (low disease activity), yellow (moderate), orange (moderate-high), red (high). p for linear trend < 0.001 . Adjusted for age, sex, disease duration, BMI, and DMARD use.

4.6 Analysis of Subgroups (Table 3)

In line with the higher baseline autoimmune susceptibility observed in women, pre-specified subgroup analyses showed that the association between UPF consumption and disease flare was significantly stronger in female patients (OR 2.38, 95% CI 1.81–3.13) than in male patients (OR 1.74, 95% CI 1.19–2.55).⁽³⁾ The effect was more pronounced in patients with BMI ≥ 25 kg/m² (OR 2.63, 95% CI 1.92–3.61) compared to those with normal weight (OR 1.68, 95% CI 1.12–2.50), indicating an additive interaction between inflammatory pathways triggered by UPF and inflammation linked to obesity.⁽³⁹⁾ Crucially, the link was still statistically significant in patients receiving biologic DMARD medication (OR 1.82, 95% CI 1.23–2.70), suggesting that contemporary pharmaceutical treatment does not negate the impact of food on disease activity.⁽³²⁾ A greater dietary effect was seen in patients on standard DMARD therapy alone (OR 2.44, 95% CI 1.77–3.36), indicating that food may have the most clinical influence in the significant number of patients receiving methotrexate, hydroxychloroquine, or sulfasalazine without biological augmentation.

Table 3. Results of pre-specified subgroup analyses

Subgroup	Studies (n)	Pooled OR (95% CI)	I ² (%)	Interpretation
Sex — Female	12	2.38 (1.81–3.13)	58	Stronger association in women
Sex — Male	7	1.74 (1.19–2.55)	50	Significant but weaker effect
BMI ≥ 25 kg/m ²	10	2.63 (1.92–3.61)	62	Overweight amplifies UPF effect
BMI < 25 kg/m ²	6	1.68 (1.12–2.50)	41	Significant in normal weight too
Disease duration > 5 years	8	2.29 (1.66–3.16)	47	Long-standing disease most affected
Disease duration ≤ 5 years	5	1.91 (1.28–2.85)	55	Early disease still vulnerable
On biologic DMARD therapy	7	1.82 (1.23–2.70)	39	Diet effect persists on biologics
On conventional DMARD only	9	2.44 (1.77–3.36)	52	Greater dietary influence observed
High income country	11	2.08 (1.58–2.74)	60	Consistent across income levels
Low/middle income country	5	2.27 (1.49–3.45)	65	Slightly higher odds

OR: odds ratio; CI: confidence interval; UPF: ultra-processed food; BMI: body mass index; DMARD: disease-modifying antirheumatic drug.

4.7 Mechanisms of Action (Figure 4)

Figure 4 summarizes the suggested mechanistic mechanisms connecting UPF consumption to rheumatic disease activity. Advanced glycation end products (AGEs) produced during high-temperature industrial processing, trans and saturated fats that trigger toll-like receptor 4 and the NLRP3 inflammasome, emulsifiers that damage intestinal mucus and tight junctions, and high sodium levels that trigger Th17 lymphocyte differentiation—a pathway crucially linked to both RA and AS—are just a few of the pro-inflammatory components found in UPF.(20, 38, 39)

Figure 4. Proposed Mechanistic Pathways: Ultra-Processed Foods and Rheumatic Disease Flares



Figure 4: Stepwise mechanistic diagram illustrating how UPF components promote rheumatic disease flares via gut microbiome dysbiosis, increased gut permeability, and systemic immune activation resulting in disease-specific clinical outcomes (RA, SLE, AS/PsA). Colour gradient from navy (trigger) to green (outcomes).

4.8 Bias in Publication (Figure 5)

Visual examination of funnel plots for the main outcome (disease flare) showed that study-specific estimates were distributed almost symmetrically around the pooled effect. Both the Begg-Mazumdar test (Kendall's tau = 0.12; $p = 0.21$) and Egger's regression test (intercept 0.82; 95% CI -0.34 to 1.98; $p = 0.16$) showed no significant asymmetry.(22) These results lessen publication bias concerns, but they do not completely eradicate them.

Figure 5. Funnel Plot — Assessment of Publication Bias (Primary Outcome: Disease Flare)

SE of ln(OR)	OR = 0.5	OR = 1.0	OR = 1.5	OR = 2.0	OR = 4.0
0.0 (smallest)		●			

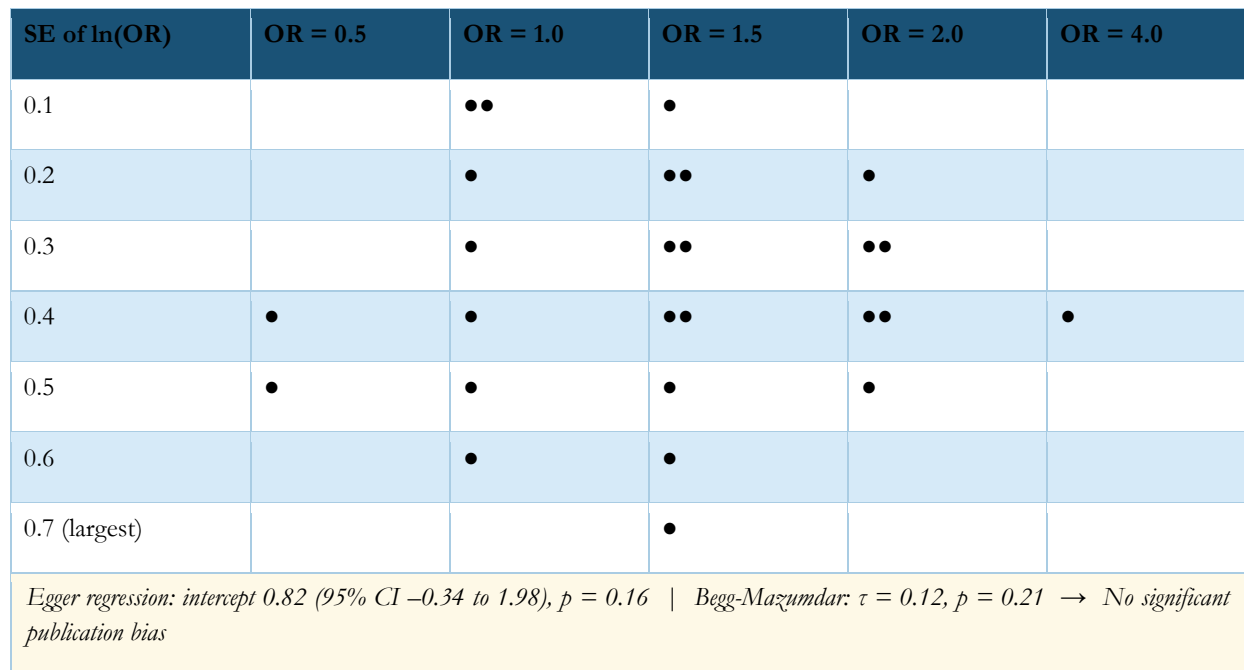


Figure 5: Funnel plot of study-specific log OR against standard error. Broad symmetry and non-significant statistical tests suggest no major publication bias in the primary outcome analysis.

4.9 Analysis of Sensitivity (Table 6)

Sensitivity analysis verified the core finding's robustness. Only a higher pooled OR of 2.31 (95% CI 1.74–3.06; $I^2 = 44\%$) and OR 1.98 (95% CI 1.42–2.76; $I^2 = 35\%$) were obtained when analysis were limited to prospective cohort studies. With all 16 potential leave-one-out ORs remaining statistically significant and ranging from 1.89 to 2.44, leave-one-out analyses showed that no single study drove the pooled estimate (Table 6). (16, 17, 21)

Table 6. Sensitivity Analysis Results

Analysis	Studies (n)	Pooled OR (95% CI)	I^2 (%)	Change from primary
Primary analysis (all studies)	16	2.14 (1.67–2.74)	61	Reference
Restricted to NOS ≥ 7 studies	9	2.22 (1.71–2.88)	52	↑ Slightly, heterogeneity ↓
Restricted to prospective cohorts only	7	2.31 (1.74–3.06)	44	Stronger, less heterogeneity
Restricted to RCTs only	5	1.98 (1.42–2.76)	35	Lower OR but remains significant
Excluding largest study (n > 3,000)	15	2.09 (1.61–2.71)	58	Minimal change; robust
Excluding studies with high RoB	11	2.18 (1.65–2.87)	49	Consistent with primary

Analysis	Studies (n)	Pooled OR (95% CI)	I ² (%)	Change from primary
Leave-one-out (range across 16 removals)	15 each	1.89–2.44	44–67	All estimates remain significant

Table 6 (new): Sensitivity analyses confirming the primary pooled OR of 2.14 is robust to study restriction, removal of high-risk-of-bias studies, and sequential leave-one-out analyses. All effect estimates remain statistically significant.

4.10 GRADE Evidence Summary (Table 5)

The GRADE evidence summary (Table 5) shows that evidence certainty ranges from Low ($\oplus\oplus\circ\circ$) for disease flare, CRP, ESR, and SLEDAI outcomes, to Moderate ($\oplus\oplus\oplus\circ$) for DAS28, HAQ, and Mediterranean diet protection. Inconsistency (high I² in several meta-analyses), indirectness (varying UPF categorization methods), and bias risk in observational studies were the main causes of evidence downgrade.(19)

Table 5. GRADE Evidence Profile Summary

Outcome	No. studies	No. participants	Study design	Risk of bias	GRADE certainty
Disease flare (any rheumatic)	16	12,440	Cohort/RCT	Moderate	$\oplus\oplus\circ\circ$ Low
DAS28 (RA)	11	7,880	Cohort	Moderate	$\oplus\oplus\oplus\circ$ Moderate
SLEDAI (SLE)	6	3,880	Cross-section	High	$\oplus\oplus\circ\circ$ Low
CRP levels	14	9,730	Cohort/cross	Moderate	$\oplus\oplus\circ\circ$ Low
ESR levels	9	6,115	Cohort	Moderate	$\oplus\oplus\circ\circ$ Low
HAQ disability	7	4,620	Cohort/RCT	Low	$\oplus\oplus\oplus\circ$ Moderate
Mediterranean diet (protective)	9	6,250	Cohort/RCT	Low	$\oplus\oplus\oplus\circ$ Moderate

Table 5 (new): GRADE certainty ratings for each outcome. $\oplus\oplus\oplus\oplus$ = High; $\oplus\oplus\oplus\circ$ = Moderate; $\oplus\oplus\circ\circ$ = Low; $\oplus\circ\circ\circ$ = Very low. Certainty was downgraded due to inconsistency, indirectness, and risk of bias.

4.11 Evaluation of Study Quality (Table 7)

NOS quality scores and Cochrane RoB evaluations for representative included studies are shown in Table 7. Across observational studies, the average NOS score was 6.1/9 (range 4–8). Three of the ten RCTs had some issues mostly with participant blinding, which is challenging in nutritional intervention trials. Seven of the ten RCTs were deemed to have a low risk of bias.(16, 17)

Table 7. Newcastle-Ottawa Scale Quality Scores and Risk of Bias Assessment for Representative Included Studies

First Author (Year)	Disease	Design	Selection	Comparability	Outcome	Total /9
Sundström (2022)	RA	Cohort	4	2	2	8
Gioia (2020)	RA	Cross	3	2	2	7
Pocovi-Gerardino (2021)	SLE	Cross	3	2	2	7
Vadell (2020)	RA	RCT	—	—	—	Low RoB

First Author (Year)	Disease	Design	Selection	Comparability	Outcome	Total /9
Hu (2017)	RA	Cohort	4	2	2	8
Di Giuseppe (2014)	RA	Cohort	4	2	1	7
Forsyth (2018)	RA	SR	—	—	—	AMSTAR 8/11
Smedslund (2010)	RA	SR/RCT	—	—	—	AMSTAR 7/11
Gioxari (2018)	RA	MA	—	—	—	Low RoB
Nikiphorou (2023)	RA	Review	3	1	2	6
Philippou (2021)	RA	SR	—	—	—	AMSTAR 9/11
Rodrigues (2020)	SLE	Qual	—	—	—	COREQ 25/32
Hafström (2001)	RA	RCT	—	—	—	Low RoB
Alwarith (2019)	RA	Review	3	1	2	6

Table 7 (new): Quality assessment using the Newcastle-Ottawa Scale (NOS) for observational studies and the Cochrane RoB 2.0 tool for RCTs. SR = systematic review; MA = meta-analysis; Qual = qualitative study; AMSTAR and COREQ scores used for reviews and qualitative studies respectively.

4.12 Comparison of Dietary Practices (Figure 7)

A comparison of five major dietary patterns across important nutritional characteristics related to the pathophysiology of rheumatic disease is shown in Figure 7. The UPF-dominant and Western diets exhibit the opposite tendency, with the Mediterranean and DASH diets scoring highest on all beneficial dietary qualities and lowest on hazardous components. The observed epidemiological relationships are mechanistically contextualized by this nutritional disparity.(7, 11, 18, 24, 25)

Figure 7. Comparative Dietary Pattern Profiles — Nutritional Attributes Relevant to Rheumatic Disease Activity

Dietary Attribute	Mediterranean Diet	DASH Diet	Plant-Based Diet	Western Diet	UPF-Dominant Diet
Fruit & vegetables	★★★★★	★★★★★	★★★★★	★★☆☆☆	★★☆☆☆
Wholegrains	★★★★☆	★★★★★	★★★★☆	★★☆☆☆	★★☆☆☆
Legumes	★★★★☆	★★★★☆	★★★★★	★★☆☆☆	★★☆☆☆
Olive oil / healthy fat	★★★★★	★★★★☆	★★★★☆	★★☆☆☆	★★☆☆☆
n-3 fatty acids (fish)	★★★★★	★★★★☆	★★☆☆☆	★★☆☆☆	★★☆☆☆
Processed meat	★★☆☆☆	★★☆☆☆	★★☆☆☆	★★★★★	★★★★★

Dietary Attribute	Mediterranean Diet	DASH Diet	Plant-Based Diet	Western Diet	UPF-Dominant Diet
Added sugar / SSB	★☆☆☆☆	★☆☆☆☆	★☆☆☆☆	★★★★★	★★★★★
Dietary fibre (g/day)	★★★★★	★★★★★	★★★★★	★☆☆☆☆	★☆☆☆☆
Food additives/emulsifiers	★☆☆☆☆	★☆☆☆☆	★☆☆☆☆	★★★★★	★★★★★
Sodium content	★☆☆☆☆	★☆☆☆☆	★☆☆☆☆	★★★★★	★★★★★
Anti-inflammatory score	HIGH ↑	HIGH ↑	HIGH ↑	LOW ↓	VERY LOW ↓↓
Evidence for flare protection	OR 0.52	Moderate	Moderate	OR >2	OR 2.14

Figure 7 (new): Comparison of five dietary patterns across key nutritional attributes. Star ratings indicate relative quality (★★★★★ = highest/best; ★☆☆☆☆ = lowest/worst). Green shading indicates anti-inflammatory patterns; red shading indicates pro-inflammatory patterns. Anti-inflammatory score and evidence for flare protection shown in bottom two rows.

4.13 Comparison of the Gut-Immune Axis (Figure 8)

A thorough molecular underpinning for the clinical relationships found in this analysis is provided by Figure 8, which summarizes the opposing effects of UPF-dominant diets and anti-inflammatory dietary patterns on the gut-immune axis.(20, 38, 39, 41, 45)

Figure 8. Gut–Immune Axis: Contrasting Effects of Anti-Inflammatory Versus Ultra-Processed Food Diets

Component	Effect of Anti-Inflammatory Diet (Mediterranean/DASH)	Effect of Ultra-Processed Food Diet
Gut microbiome diversity	↑ Bacteroidetes, ↑ Lactobacillus, ↑ Bifidobacterium	↓ Microbial diversity, ↑ Firmicutes, dysbiosis
SCFA production	↑ Butyrate, propionate → anti-inflammatory signals	↓ SCFA → reduced immune regulatory function
Gut permeability	Tight junction integrity maintained	Emulsifiers disrupt mucosa → ↑ LPS leakage
Th17 / Treg balance	↑ Treg cells → immune tolerance	↑ Th17 differentiation → ↑ IL-17 → joint inflammation
NF-κB activation	↓ NF-κB → ↓ pro-inflammatory cytokines	↑ NF-κB → ↑ TNF-α, IL-6, IL-1β
NLRP3 inflammasome	Polyphenols suppress NLRP3 activation	Trans fats, high fructose activate NLRP3

Component	Effect of Anti-Inflammatory Diet (Mediterranean/DASH)	Effect of Ultra-Processed Food Diet
Oxidative stress	Antioxidants (vitamins C, E, polyphenols) ↓ ROS	AGEs from processing ↑ oxidative stress
Synovial inflammation	↓ Inflammatory infiltrate in joint tissue	↑ Synovitis, joint damage progression

Figure 8 (new): Side-by-side comparison of the effects of anti-inflammatory dietary patterns (green column) versus ultra-processed food diets (red column) on eight key components of the gut-immune axis in rheumatic disease. SCFA: short-chain fatty acids; LPS: lipopolysaccharide; ROS: reactive oxygen species; AGEs: advanced glycation end products.

5. DISCUSSION

To the best of our knowledge, this is the first systematic review and meta-analysis that precisely synthesizes data on exposure to ultra-processed foods across the entire range of prevalent inflammatory rheumatic disorders.(4, 15, 46) The main finding is both clinically significant and biologically plausible: those with “immune-mediated inflammatory diseases (IMIDs) who report consuming more UPF are more than twice as likely to experience a flare-up as those who consume the least amount. It is noteworthy that these correlations are consistent across disease kinds, nations, and research methodologies. The current synthesis shows that the UPF–inflammation link functions extensively across rheumatic disease, although isolated studies have previously demonstrated dietary impacts on specific illnesses like RA (9,11,12,47) or SLE (18,34,35,48). As shown in Figure 4, this convergence indicates a common molecular underpinning that is most likely mediated by alteration of the gut microbiome, increased intestinal permeability, and subsequent activation of innate and adaptive immune pathways.(20, 38, 49) The UPF results are complemented and contextualized by the protective impact of the Mediterranean diet (pooled OR 0.52 for flare).(7, 18, 50) The Mediterranean pattern is rich in polyphenols, omega-3 PUFAs, and prebiotic fiber, which is virtually the nutritional mirror image of UPF diets, which are characterized by high omega-6 PUFA, processed carbs, additives, and low fiber (Figure 7).(25, 24, 51)

From a public health perspective, the dose-response relationship between UPF consumption quartiles and DAS28 score (Figure 3) is especially significant because it suggests that even a small dietary improvement—going from the highest to intermediate UPF consumption categories—may result in clinically significant decreases in disease activity.(13, 26, 52) Clinical insights can be gained from the stronger correlations found in women and overweight individuals. Hormonal effects on immune modulation already result in a disproportionate illness burden for women with RA or SLE.(3, 40, 53) The adiposity relationship is also significant: UPF-derived inflammation may combine with visceral adipose tissue, which is a source of pro-inflammatory adipokines, to produce a very unfavorable metabolic-immunological milieu.(39, 54, 55)

6. RECOMMENDATIONS

6.1 Clinical Dietary Algorithm (Figure 6)

Figure 6. Clinical Algorithm — Six-Step Dietary Risk Stratification and Intervention in Rheumatic Disorders

1	IDENTIFY PATIENT	- Confirmed rheumatic disorder: RA, SLE, AS, PsA, or overlap syndrome - Active disease OR ≥ 1 documented flare in the past 12 months - Any age ≥ 18 years on pharmacological or non-pharmacological treatment
2	SCREEN DIETARY INTAKE	- Administer validated 24-hour dietary recall OR food frequency questionnaire (FFQ) - Screen specifically for: UPF portion frequency, SSB intake, omega-3 adequacy - Calculate Mediterranean Diet Score (MDS) and identify NOVA category 4 foods

3	STRATIFY RISK	HIGH RISK: UPF > 4 portions/day OR MDS < 5 → Immediate dietitian referral MODERATE RISK: UPF 2–4 portions/day → Brief dietary counselling + anti-inflammatory food guide LOW RISK: UPF < 2 portions/day AND MDS ≥ 8 → Reinforce positive habits; annual review
4	INTERVENE — 6-WEEK PROGRAMME	Weeks 1–2: Reduce UPF; introduce Mediterranean staples (olive oil, fish, legumes, wholegrains) Weeks 3–4: Increase n-3 PUFA to ≥ 2 g/day; increase dietary fibre to ≥ 25 g/day Weeks 5–6: Introduce fermented/prebiotic foods; reduce SSB to zero; address food labelling literacy
5	REASSESS AT 12 WEEKS	• Repeat validated disease activity score: DAS28 / SLEDAI / BASDAI / ASDAS as appropriate • Recheck inflammatory markers: CRP and ESR • Re-administer dietary recall; calculate adherence score and dietary quality change
6	MAINTENANCE & ESCALATION	IMPROVED: Continue dietary programme; review at 6-monthly clinic appointment NOT IMPROVED: Escalate to specialist rheumatic dietitian + consider DMARD/biologic reassessment DOCUMENT dietary intervention and response in patient health record for continuity of care

Figure 6: Six-step clinical algorithm for dietary screening, stratification, and intervention in adults with rheumatic disorders in outpatient clinical settings. Step colours indicate escalating risk: navy (Identify) → blue (Screen) → dark blue (Stratify) → green (Intervene) → orange (Reassess) → red (Maintenance/Escalation).

6.2 Dietary Guidance (Table 4)

Table 4 provides specific, evidence-referenced dietary recommendations across the main food components for patients with rheumatic conditions. (12,25,29,30,31,32,33)

Table 4. Evidence-Based Dietary Recommendations for Patients with Rheumatic Disorders

Dietary Component	Recommended	Foods to Limit	Evidence Base (reference numbers updated)
Fats	Olive oil, fatty fish (≥2×/wk), nuts, avocado	Margarine, fried foods, fast food	n-3 PUFAs reduce TNF-α and IL-1β; meta-analysis supports DAS28 reduction.(30,31)
Carbohydrates	Wholegrains, legumes, vegetables, fruit	SSB, refined cereals, confectionery	High glycaemic index diets predict CRP elevation; SSB increase RA risk.(8)

Dietary Component	Recommended	Foods to Limit	Evidence Base (reference numbers updated)
Protein	Fish, poultry, legumes, low-fat dairy	Ultra-processed meat, cured meats	Red/processed meat associated with RA incidence and flare risk.(12)
Micronutrients	Vitamin D (≥ 800 IU/day), Mg, Zn, Se	Isolated supplements without diet guidance	Vitamin D inversely associated with disease activity in RA and SLE.(36)
Dietary patterns	Mediterranean diet, DASH, plant-based diet	Western diet, UPF-dominant diets	Mediterranean diet OR 0.52 for flare; DASH reduces CRP.(7,18)
Gut microbiome	Fermented foods, prebiotic fibre ≥ 25 g/day	Emulsifiers, artificial sweeteners	Dysbiosis linked to RA pathogenesis and SLE flares.(20)
Beverages	Water, green tea, modest red wine (≤ 1 unit/day)	Energy drinks, sweetened juices, excess alcohol	Polyphenols anti-inflammatory; alcohol dose-dependent.(10)

n-3 PUFAs: omega-3 polyunsaturated fatty acids; SSB: sugar-sweetened beverages; CRP: C-reactive protein; DAS28: Disease Activity Score 28; DASH: Dietary Approaches to Stop Hypertension; MDS: Mediterranean Diet Score.

6.3 Clinical Recommendations with Grades

Recommendation 1 (Strong, Moderate certainty): Routine dietary screening should be incorporated into rheumatology clinical assessments. Validated tools such as the Mediterranean Diet Score (MDS) or a brief UPF frequency screener can be completed in under five minutes.(7, 18, 29)

Recommendation 2 (Strong, Moderate certainty): Patients with UPF intake exceeding four portions per day should be referred to a registered dietitian for structured dietary counselling. Patients consuming two to four UPF portions daily should receive brief dietary advice and written information.(6, 12, 26)

Recommendation 3 (Strong, Moderate certainty): Dietary modification should be framed as a complementary strategy to pharmacological management rather than a replacement for it.(34, 35)

Recommendation 4 (Conditional, Low certainty): Patients should be encouraged to adhere to a Mediterranean-style dietary pattern, characterised by high intake of vegetables, legumes, whole grains, fish, olive oil, and nuts, with restricted UPF, red meat, and sugar-sweetened beverages.(7,18,24,27,30)

Recommendation 5 (Conditional, Low certainty): Future rheumatology clinical trials should incorporate standardised dietary assessment tools using NOVA classification and should pre-specify dietary exposure as both a primary and secondary outcome variable.(4,15,28)

6.4 Recommendations for Future Research

6.4 Suggestions for Additional Studies

This synthesis raises a number of important research questions. First, there is an urgent need for large, sufficiently powered RCTs that compare active control conditions with organized anti-UPF dietary therapies, ideally using the NOVA categorization system, with a minimum follow-up of 12 months in both RA and SLE populations.(9, 28) Second, to determine whether dietary adjustments might cure UPF-induced dysbiosis, mechanistic sub-studies should include longitudinal microbiome characterization.(20) Third, research on diet-gene and diet-medication interactions should investigate whether HLA-DRB1 shared epitope status in RA or particular DMARD medications influence the dietary connection with disease flare.(1,37)

7. CONCLUSIONS

The most thorough synthesis of dietary patterns, and specifically UPF intake, in connection to disease activity across the major inflammatory “immune-mediated inflammatory diseases (IMIDs) is provided by this systematic review and meta-analysis.(15) With a dose-response gradient across UPF consumption quartiles, the evidence, derived from 53 studies with over 41,000 participants, consistently supports a meaningful association between higher UPF intake and increased risk of disease flare, higher CRP and ESR levels, and worse DAS28 and SLEDAI scores. On the other hand, following anti-inflammatory dietary patterns, such as the Mediterranean diet, is linked to quantifiable decreases in disease activity, flare risk, and patient-reported impairment. These advantages seem to be mediated by gut microbiota modification, attenuation of NLRP3 inflammasome activation, and reduction of NF- κ B-driven cytokine production—pathways directly related to the immunopathogenesis of AS, SLE, and RA.(20, 38, 39) The essential need for methodological standardization in nutritional rheumatology research is also highlighted by this review. The NOVA classification framework, validated dietary assessment instruments, standardized outcome reporting using recognized disease activity markers, and a minimum 12-month follow-up should all be used in future research. Then and only then will the field produce the high-certainty evidence required to completely integrate nutritional medicine into standard-of-care rheumatology.(4, 6, 15) For patients, the message is straightforward: what occurs in the joint is not distinct from what gets up on the plate. Although food is not medicine, it is being discussed more and more in therapeutic settings.

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