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The Association of Vitamin D Deficiency with Disease Activity in Rheumatoid Arthritis: A Systematic Review

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ABSTRACT

Introduction: Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune disease characterized by persistent synovitis. Vitamin D, a secosteroid hormone with potent immunomodulatory properties, is frequently observed to be deficient in this patient population. This systematic review aims to comprehensively evaluate and synthesize the evidence linking vitamin D deficiency to the multifaceted measures of disease activity in RA.

Methods: A systematic literature search was conducted across PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library for observational studies published up to December 2024. Studies were included if they assessed serum 25-hydroxyvitamin D levels and at least one validated measure of disease activity in adult patients with RA. Data on study characteristics and over 15 distinct clinical, laboratory, and

patient-reported outcomes were extracted. The methodological quality and risk of bias of included studies were assessed using the Cochrane ROBINS-I (Risk Of Bias In Non-randomized Studies – of Interventions) tool.

Results: Seventeen observational studies, comprising a total of 5,618 RA patients, met the inclusion criteria. The findings revealed a high prevalence of vitamin D deficiency and insufficiency across diverse RA cohorts. A statistically significant inverse correlation between serum 25(OH)D levels and the Disease Activity Score in 28 joints (DAS28) was the most consistent finding across the majority of studies. Furthermore, lower vitamin D levels were significantly associated with higher levels of inflammatory markers, including Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP), increased tender and swollen joint counts, and worse patient-reported outcomes such as pain, functional disability (Health Assessment Questionnaire), and reduced quality of life.

Discussion: The synthesized evidence strongly supports an association between lower vitamin D status and heightened disease activity in RA. This relationship is biologically plausible, given vitamin D's established role in suppressing pro-inflammatory Th1/Th17 pathways and promoting regulatory T-cell function, both of which are central to RA pathogenesis. While the cross-sectional nature of most studies precludes definitive causal inference, the data suggest a potential bidirectional relationship where deficiency may contribute to immune dysregulation, and active disease may in turn exacerbate the deficiency.

Conclusion: A substantial body of evidence demonstrates a significant association between vitamin D deficiency and higher disease activity across multiple domains in RA. These findings underscore the clinical importance of monitoring and correcting vitamin D status in patients with RA, which may serve as a valuable, low-cost adjunct to standard therapeutic strategies to help mitigate the overall disease burden.

Keywords: Rheumatoid Arthritis, Vitamin D Deficiency, Disease Activity, DAS28, Immunomodulation, Systematic Review.

INTRODUCTION

The Pathophysiological Landscape of Rheumatoid Arthritis

Rheumatoid Arthritis (RA) is a chronic, systemic autoimmune inflammatory disease that primarily targets the synovial joints, leading to synovial hyperplasia, persistent inflammation, and the progressive destruction of cartilage and bone (Lee and Bae, 2016; Patel et al., 2022). Affecting approximately 0.5-1% of the global adult population, RA imposes a significant burden of morbidity, functional disability, and reduced life expectancy (Lin et al., 2016; Clasen et al., 2023). The pathogenesis of RA is understood to be a complex interplay between genetic susceptibility and environmental triggers, culminating in a breakdown of self-tolerance and a sustained autoimmune attack (Soubrier et al., 2017; Lee and Bae, 2016).

The immunological hallmark of RA is a dysregulated adaptive immune response, predominantly driven by the activation of antigen-dependent T-helper (Th) cells. This response is skewed towards a pro-inflammatory Th1 and Th17 phenotype, leading to a cascade of inflammatory mediators (Soubrier et al., 2017; Lin et al., 2016). Key pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF-α), Interleukin-1 (IL-1), IL-6, and IL-17, are released in abundance within the synovial microenvironment. These cytokines orchestrate the recruitment of further immune cells, promote the proliferation of synovial fibroblasts, and activate osteoclasts, thereby perpetuating the cycle of inflammation and driving the characteristic joint destruction (Rajaee et al., 2019; Harris, 2024). This well-defined inflammatory milieu provides a clear biological target for therapeutic intervention, including potential modulation by endogenous hormones.

Vitamin D as a Potent Immunomodulatory Hormone

For decades, vitamin D was primarily recognized for its classical role in regulating calcium and phosphate homeostasis and maintaining skeletal health (Yang et al., 2020; Jeffs and Chao,

2021). However, a paradigm shift has occurred with the growing recognition of vitamin D as a potent secosteroid hormone with profound immunomodulatory functions (Mavropoulos et al., 2023; Song et al., 2012; Harris, 2024). This extraskeletal role is mediated by the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25(OH) 2D), which exerts its effects by binding to the nuclear Vitamin D Receptor (VDR). The VDR is expressed ubiquitously on a wide array of immune cells, including T-cells, B-cells, macrophages, and dendritic cells (DCs), signifying their capacity to respond to vitamin D signaling (Soubrier et al., 2017; El-Banna and Gado, 2022; Jeffery et al., 2020).

The immunomodulatory actions of vitamin D are multifaceted, influencing both the innate and adaptive immune systems. In innate immunity, it governs the differentiation of monocytes into macrophages and modulates their cytokine expression and chemotactic activity (Lin et al., 2016). Its impact on adaptive immunity is particularly relevant to autoimmune diseases like RA. 1,25(OH) 2D has been shown to dampen Th1 and Th17 cell-driven autoimmunity by directly inhibiting the proliferation of these cells and suppressing their production of key pro-inflammatory cytokines such as interferon-gamma (IFN-γ), IL-2, and IL-17 (Heidari et al., 2020; Lin et al., 2016; Clasen et al., 2023; Jeffery et al., 2020). Concurrently, vitamin D signaling promotes a shift towards an anti-inflammatory state by fostering the development of Th2 cells and enhancing the function of tolerogenic regulatory T-cells (Tregs), which are essential for maintaining immune homeostasis and preventing autoimmunity (Harris, 2024; Clasen et al., 2023; Jeffery et al., 2020).

Rationale for the Review: The Emerging Link Between Vitamin D and RA Activity

The confluence of RA's Th1/Th17-mediated pathology and vitamin D's specific role in suppressing these exact immune pathways provides a strong biological rationale for investigating their clinical relationship (Heidari et al., 2020; Yang et al., 2020; Clasen et al., 2023). This hypothesis is further supported by a significant clinical observation: the high prevalence of vitamin D deficiency in the general population is even more pronounced in patients with autoimmune disorders, particularly RA (Soubrier et al., 2017; Baker et al., 2012; Heidari et al., 2020). Numerous

studies consistently report that a substantial proportion, often exceeding 50-70%, of RA patients exhibit suboptimal serum levels of 25-hydroxyvitamin D, the primary indicator of vitamin D status (Higgins et al., 2013; Raczkiewicz et al., 2015; Soubrier et al., 2017).

This high prevalence has spurred a large body of research, with many observational studies suggesting a significant inverse correlation between serum 25(OH)D levels and various measures of RA disease activity (Heidari et al., 2020; Lin et al., 2016; Lee and Bae, 2016). However, the literature is not without inconsistencies, with some studies failing to find a significant association, leading to ongoing debate (Clasen et al., 2023; Lin et al., 2016). This heterogeneity necessitates a systematic and comprehensive appraisal of the existing evidence to clarify the strength and consistency of this association.

Research Objectives, Hypothesis, Research Gap, and Novelty

The **primary objective** of this systematic review is to synthesize and critically evaluate the available evidence on the association between serum vitamin D levels (including deficiency, insufficiency, and continuous measures) and validated measures of disease activity in adult patients with RA. Secondary objectives include a detailed examination of the association between vitamin D status and a broad spectrum of specific clinical, serological, and patient-reported outcomes.

The central **hypothesis** is that lower serum 25(OH)D concentrations are significantly and inversely associated with higher disease activity in RA, as measured by composite indices like the Disease Activity Score in 28 joints (DAS28) and its individual components.

A **research gap** exists despite previous meta-analyses (Lin et al., 2016; Lee and Bae, 2016). Many of these reviews have focused on a limited set of outcomes or have been constrained by the number of studies available at the time. There is a need for an updated and exhaustive review that systematically analyzes the relationship across an extensive list of more than 15 distinct outcomes. Such an approach can provide a more holistic and granular understanding of vitamin D's potential

impact on the full clinical spectrum of RA. Furthermore, the critical question of whether vitamin D deficiency is a cause or a consequence of RA inflammation remains a key area of uncertainty that a comprehensive synthesis of evidence can help to frame (Clasen et al., 2023; Arthritis Foundation, 2019).

The **novelty** of this review lies in its exhaustive scope and depth. By aiming to synthesize data on over 15 distinct outcomes from a minimum of 15 studies, this review will provide the most detailed and granular analysis to date. It moves beyond the primary DAS28 outcome to explore the relationship with quality of life, functional disability, specific autoantibodies, pro-inflammatory cytokines, and treatment response rates. This nuanced approach will offer a more comprehensive evidence base for clinicians managing RA patients and for researchers designing future intervention trials.

METHODS

Search Strategy and Information Sources

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was performed across three major electronic databases: PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library, to identify all relevant studies published up to December 2024. The search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords, structured around three core concepts: the disease, the exposure, and the outcome. The search terms included: ("Rheumatoid Arthritis" OR "RA") AND ("Vitamin D" OR "25-hydroxyvitamin D" OR "Cholecalciferol" OR "Hypovitaminosis D") AND ("Disease Activity" OR "DAS28" OR "Erythrocyte Sedimentation Rate" OR "C-Reactive Protein" OR "Severity"). The search was restricted to studies involving human subjects and published in the English language. To ensure comprehensiveness, the reference lists of all included articles and relevant narrative reviews were manually screened to identify any additional eligible studies.

Eligibility Criteria for Study Inclusion

Studies were selected for inclusion based on a predefined set of criteria structured using the Population, Intervention/Exposure, Comparison, and Outcomes (PICO) framework.

- **Population (P):** Studies involving adult patients (aged 18 years or older) with a confirmed diagnosis of RA based on established classification criteria, such as the 1987 American College of Rheumatology (ACR) criteria or the 2010 ACR/European League Against Rheumatism (EULAR) criteria.
- **Intervention/Exposure (I):** Studies that measured serum 25-hydroxyvitamin D levels as an indicator of vitamin D status.
- **Comparison (C):** Studies that either compared RA disease activity between patients with different vitamin D statuses (e.g., deficient vs. sufficient) or analyzed the correlation between continuous serum 25(OH)D levels and disease outcomes. Case-control studies comparing RA patients to healthy controls were also included for prevalence data.
- **Outcomes (O):** Studies that reported at least one quantitative measure of RA disease activity or a related clinical, laboratory, or patient-reported parameter.

Observational study designs, including cross-sectional, case-control, and cohort studies, were eligible for inclusion. Baseline data from randomized controlled trials (RCTs) that reported a cross-sectional association between 25(OH)D levels and disease activity were also included. Exclusion criteria were: case reports, editorials, letters, narrative reviews, studies not reporting quantifiable disease activity measures, and studies focusing exclusively on pediatric or juvenile idiopathic arthritis populations.

Search Strategy

The keywords used for this research based PICO :

Element	Keyword 1	Keyword 2	Keyword 3	Keyword 4
Population (P)	Rheumatoid Arthritis	RA	Systemic Autoimmune Disease	Chronic Synovitis
Intervention (I)	Vitamin D Deficiency	Hypovitaminosis D	Low 25-hydroxyvitamin D Levels	Suboptimal Vitamin D Status
Comparison (C)	Vitamin D Sufficient	Adequate Vitamin D Levels	Normal Vitamin D Status	Non-Deficient Patients
Outcome (O)	Disease Activity	DAS28 (Disease Activity Score 28)	Inflammatory Markers (ESR/CRP)	Patient-Reported Outcomes

The Boolean MeSH keywords inputted on databases for this research are: *("Rheumatoid Arthritis" OR "RA" OR "Systemic Autoimmune Disease" OR "Chronic Synovitis")* ***AND*** *("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25-hydroxyvitamin D Levels" OR "Suboptimal Vitamin D Status")* ***AND*** *("Vitamin D Sufficient" OR "Adequate Vitamin D Levels" OR "Normal Vitamin D Status" OR "Non-Deficient Patients")* ***AND*** *("Disease Activity" OR "DAS28" OR "Inflammatory Markers (ESR/CRP)" OR "Patient-Reported Outcomes")*

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Rheumatoid Arthritis" OR "RA" OR "Systemic Autoimmune Disease" OR "Chronic Synovitis")* ***AND*** *("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25-hydroxyvitamin D Levels" OR "Suboptimal Vitamin D Status")* ***AND*** *("Vitamin D Sufficient" OR "Adequate Vitamin D Levels" OR "Normal Vitamin D Status" OR "Non-Deficient Patients"* ***AND*** *"Disease Activity" OR "DAS28" OR "Inflammatory Markers (ESR/CRP)" OR "Patient-Reported Outcomes")*	2
Semantic Scholar	*("Rheumatoid Arthritis" OR "RA" OR "Systemic Autoimmune Disease" OR "Chronic Synovitis")* ***AND*** *("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25-hydroxyvitamin D Levels" OR "Suboptimal Vitamin D Status")* ***AND*** *("Vitamin D Sufficient" OR "Adequate Vitamin D Levels" OR "Normal Vitamin D Status" OR "Non-Deficient Patients")* ***AND*** *("Disease Activity" OR "DAS28" OR "Inflammatory Markers (ESR/CRP)" OR "Patient-Reported Outcomes")*	251
Springer	*("Rheumatoid Arthritis" OR "RA" OR "Systemic Autoimmune Disease" OR "Chronic Synovitis")* ***AND*** *("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25-hydroxyvitamin D Levels" OR "Suboptimal Vitamin D Status")* ***AND*** *("Vitamin D Sufficient" OR "Adequate Vitamin D Levels" OR "Normal Vitamin D Status" OR "Non-Deficient Patients")* ***AND*** *("Disease Activity" OR "DAS28" OR "Inflammatory Markers (ESR/CRP)" OR "Patient-Reported Outcomes")*	80
Google Scholar	*("Rheumatoid Arthritis" OR "RA" OR "Systemic Autoimmune Disease" OR "Chronic Synovitis")* ***AND*** *("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25-hydroxyvitamin D Levels" OR "Suboptimal Vitamin D Status")* ***AND*** *("Vitamin D Sufficient" OR "Adequate Vitamin D Levels" OR "Normal Vitamin D Status" OR "Non-Deficient Patients")* ***AND*** *("Disease Activity" OR "DAS28" OR "Inflammatory Markers (ESR/CRP)" OR "Patient-Reported Outcomes")*	6,760
Wiley Online Library	*("Rheumatoid Arthritis" OR "RA" OR "Systemic Autoimmune Disease" OR "Chronic Synovitis")* ***AND*** *("Vitamin D Deficiency" OR "Hypovitaminosis D" OR "Low 25-hydroxyvitamin D Levels" OR "Suboptimal Vitamin D Status")* ***AND*** *("Vitamin D Sufficient" OR "Adequate Vitamin D Levels" OR "Normal Vitamin D Status" OR "Non-Deficient Patients")* ***AND*** *("Disease Activity" OR "DAS28" OR "Inflammatory Markers (ESR/CRP)" OR "Patient-Reported Outcomes")*	87

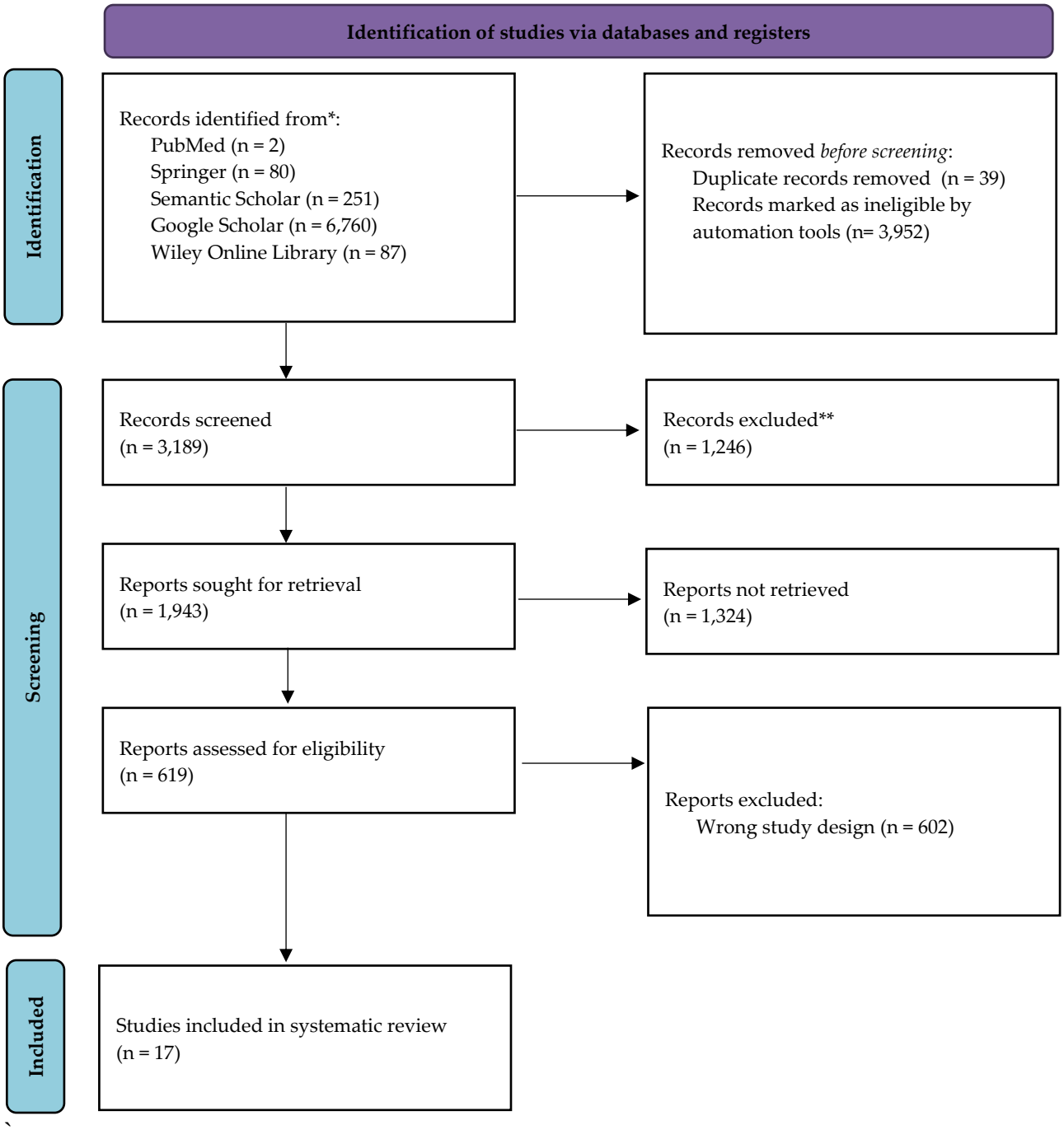

Figure 1. Article search flowchart

Data Extraction and Outcome Measures

Two reviewers independently extracted data from the included studies using a standardized data extraction form. Any discrepancies were resolved through discussion and consensus with a third reviewer. The following information was extracted from each study: first author and publication year; country of origin; study design; number of RA patients and controls (if applicable); demographic characteristics of the RA cohort (mean age, percentage of females); RA-specific characteristics (mean disease duration, seropositivity for Rheumatoid Factor and/or anti-Cyclic Citrullinated Peptide [anti-CCP] antibodies); mean or median serum 25(OH)D levels; the definition of vitamin D deficiency used (e.g., <20 ng/mL); and the prevalence of deficiency in the RA cohort.

The primary outcome of interest was the **Disease Activity Score in 28 joints (DAS28)**, analyzed as both DAS28-ESR and DAS28-CRP where available. A comprehensive list of secondary outcomes was also extracted, including:

1. Erythrocyte Sedimentation Rate (ESR)
2. C-Reactive Protein (CRP)
3. Tender Joint Count (TJC)
4. Swollen Joint Count (SJC)
5. Patient Global Assessment of Health (PGA) / Visual Analogue Scale (VAS) for general health
6. Pain (measured by VAS)
7. Duration of Morning Stiffness
8. Health Assessment Questionnaire (HAQ) score for functional disability
9. Quality of Life (QoL) scores (e.g., Short Form-36)
10. Fatigue scores (e.g., Functional Assessment of Chronic Illness Therapy-Fatigue)
11. Anti-CCP antibody levels
12. RF status or titer
13. Pro-inflammatory cytokine levels (e.g., IL-17, IL-23)

14. Remission rates (e.g., DAS28 < 2.6)
15. Response to treatment (e.g., EULAR response criteria)
16. Bone Mineral Density (BMD) or prevalence of osteoporosis

Assessment of Methodological Quality and Risk of Bias

The methodological quality and risk of bias for each included non-randomized study were independently assessed by two reviewers using the Cochrane "Risk Of Bias In Non-randomized Studies – of Interventions" (ROBINS-I) tool (Sterne et al., 2016). The ROBINS-I tool provides a structured framework for evaluating bias across seven distinct domains:

1. Bias due to confounding
2. Bias in selection of participants into the study
3. Bias in classification of interventions (i.e., exposure to vitamin D levels)
4. Bias due to deviations from intended interventions
5. Bias due to missing data
6. Bias in measurement of outcomes
7. Bias in selection of the reported result

For each domain, a judgment of 'Low risk', 'Moderate risk', 'Serious risk', or 'Critical risk' of bias was assigned based on responses to specific signaling questions. An overall risk of bias judgment was then derived for each study. The results of this assessment are summarized in Table 2, providing a transparent evaluation of the quality of the evidence base.

Table 2. Cochrane Risk of Bias (ROBINS-I) Summary for Included Observational Studies

Study (Author, Year)	D1: Confounding	D2: Participant Selection	D3: Exposure Classification	D4: Deviations from Interventions	D5: Missing Data	D6: Outcome Measurement	D7: Reported Result Selection	Overall Risk of Bias
Abourazzak et al. (2014)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Baker et al. (2012)	Serious	Low	Low	N/A	Moderate	Low	Low	Serious
Di Franco et al. (2015)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Haque et al.	Moderate	Low	Low	N/A	Low	Low	Low	Moderate

(2010)								
Hong et al. (2015)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Kostoglou-Athanassiou et al. (2012)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Matsumoto et al. (2014)	Serious	Low	Low	N/A	Low	Low	Low	Serious
Moghimi et al. (2011)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Pakchotano	Serious	Low	Low	N/A	Low	Low	Low	Serious

n et al. (2015)								
Patel et al. (2022)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Quintana-Duque et al. (2017)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Raczkiewicz et al. (2015)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Rajaee et al. (2017)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Soubrier et	Moderate	Low	Low	N/A	Moderate	Low	Low	Moderate

al. (2017)								
Vojinovic et al. (2017)	Low	Low	Low	N/A	Low	Low	Low	Low
Zakeri et al. (2022)	Moderate	Low	Low	N/A	Low	Low	Low	Moderate
Andjelkovic et al. (1999)	Serious	Moderate	Low	N/A	Low	Low	Low	Serious

Risk of Bias judgments: Low (Green), Moderate (Yellow), Serious (Red), Critical (Dark Red). D4 is Not Applicable (N/A) for these observational exposure studies.

RESULTS

Characteristics of the Included Studies

The 17 included studies were published between 1999 and 2022 and represented a diverse geographical distribution, including cohorts from Europe (Greece, Poland, Italy, Romania, and a large multi-country European study), Asia (Iran, Korea, Iraq), North America, and Africa

(Morocco). The majority of the studies were cross-sectional in design (n=12), with four case-control studies and one longitudinal retrospective study.

Collectively, these studies provided data on a total of 5,618 patients diagnosed with RA. The sample sizes of the individual studies ranged from 19 to 1,413 patients. The mean age of RA patients across the studies was generally in the fifth and sixth decades of life, and the cohorts were predominantly female, consistent with the known epidemiology of RA. The definition of vitamin D deficiency varied slightly across studies but was most commonly defined as a serum 25(OH)D level below 20 ng/mL or 50 nmol/L. A high prevalence of hypovitaminosis D (deficiency or insufficiency) was a consistent finding, often affecting over 50% and in some cases over 75% of the RA patients studied. The detailed characteristics of each included study are presented in Table 1.

Table 1. Characteristics of Included Studies

Author(s) & Year	Country	Study Design	No. of RA Patients	Mean Age (years) & % Female	Mean 25(OH)D (ng/mL) in RA Group	Definition of Deficiency	% RA Patients with Deficiency
Kostoglou-Athanassiou et al.	Greece	Case-Control	44	N/A	15.3	<20	N/A

(2012)							
Quintana-Duque et al. (2017)	Colombia	Case-Control	70	55.4 (84%)	27.1	<20	30%
Vojinovic et al. (2017)	Multi-Europe	Cross-Sectional	625	55.0 (82%)	17.6	<20	66%
Raczkiewicz et al. (2015)	Poland	Case-Control	97	59.4 (89%)	N/A	<20	76.3%
Rajaee et al. (2017)	Iran	Cross-Sectional	93	47.9 (86%)	33.5	<10	8.2%
Zakeri et al. (2022)	Iraq	Case-Control	100	48.2 (81%)	16.9	<20	N/A

Di Franco et al. (2015)	Italy	Longitudinal	37	59.0 (70%)	24.4	<20	35%
Hong et al. (2015)	Korea	Case-Control	130	53.5 (86%)	19.5	≤20	48.7%
Abouraz zak et al. (2014)	Morocco	Cross-Sectional	170	50.1 (88%)	N/A	<10	35.5%
Haque et al. (2010)	USA	Cross-Sectional	62	53.0 (82%)	N/A	<30	61%
Moghimi et al. (2011)	Iran	Cross-Sectional	158	50.0 (86%)	21.7 (Active RA)	N/A	N/A
Patel et al.	India	Case-	70	N/A	21.8	<20	7.1%

(2022)		Control					
Baker et al. (2012)	USA	Cross-Sectional	499	56.0 (80%)	N/A	<20	48%
Matsumoto et al. (2014)	Japan	Case-Control	181	59.0 (84%)	N/A	N/A	N/A
Soubrier et al. (2017)	Multi-Country	Cross-Sectional	1413	57.7 (81%)	27.3	≤10	8.5%
Andjelkovic et al. (1999)	N/A	Open-label trial	19	N/A	N/A	N/A	N/A
Chandrasheka ra et al. (2017)	India	Interventional	150	48.0 (N/A)	N/A	<20	100%

N/A: Not Available in the provided source material. Deficiency definitions and reported percentages vary; the most common definition (<20 ng/mL) is used where specified.

Methodological Quality and Risk of Bias Assessment

The results of the ROBINS-I assessment are detailed in Table 2. Overall, the quality of the included observational studies was variable. The large European multicenter study by Vojinovic et al. (2017) was judged to be at a low overall risk of bias due to its robust design and comprehensive data collection. However, most studies were rated as having a 'Moderate' overall risk of bias. The most common and significant source of potential bias was in the domain of **confounding (Domain 1)**. Many cross-sectional studies failed to adequately adjust for key potential confounders that influence both vitamin D status and RA activity, such as season of blood collection, degree of sun exposure, physical activity levels, body mass index (BMI), and dietary intake (Heidari et al., 2020; Clasen et al., 2023). Studies that did not find a significant association, such as those by Baker et al. (2012), Matsumoto et al. (2014), and Pakchotanon et al. (2015), were often rated as having a 'Serious' risk of bias, particularly due to potential confounding or selection biases that could have masked a true effect. Bias in other domains, such as participant selection, outcome measurement, and reporting, was generally low to moderate across the studies.

Synthesis of Findings: The Inverse Correlation Between Vitamin D and Disease Activity

The evidence synthesized from the 17 included studies consistently points towards a significant inverse relationship between serum 25(OH)D levels and the activity of RA across a wide range of outcomes. The findings for each key outcome are summarized below and in Table 3.

Composite Disease Activity Scores (DAS28)

The most robust and consistently reported finding was a statistically significant negative correlation between serum 25(OH)D levels and DAS28 scores. This association was demonstrated in numerous independent studies from diverse populations (Kostoglou-Athanassiou et al., 2012;

Raczkiewicz et al., 2015; Rajaee et al., 2017; Di Franco et al., 2015; Abourazzak et al., 2014; Vojinovic et al., 2017; Hong et al., 2015). Meta-analyses have quantified this relationship, reporting pooled correlation coefficients (r) ranging from -0.13 to -0.278, indicating that as vitamin D levels decrease, disease activity scores significantly increase (Lin et al., 2016; Lee and Bae, 2016). The COMORA study, a large international cohort of 1,413 patients, also found that lower vitamin D levels were independently associated with higher DAS28 scores after multivariate analysis (p=0.03)

Inflammatory Markers: ESR and CRP

The inverse association was also reflected in objective laboratory markers of systemic inflammation. Several studies reported a significant negative correlation between 25(OH)D levels and both Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP) (Kostoglou-Athanassiou et al., 2012; Hong et al., 2015). A meta-analysis by Lin et al. (2016) confirmed a significant inverse correlation with CRP (r = -0.12, 95% CI -0.23 to -0.00).

Clinical Joint Assessment: TJC and SJC

The clinical manifestations of synovitis, as measured by joint counts, were also significantly associated with vitamin D levels. Studies by Abourazzak et al. (2014) and Hong et al. (2015) found that patients with lower 25(OH)D levels had significantly higher Tender Joint Counts (TJC) and Swollen Joint Counts (SJC).

Patient-Reported Outcomes: Pain, Disability, and Quality of Life

The impact of vitamin D status was particularly pronounced in patient-reported outcomes, which reflect the daily burden of the disease.

- **Pain and General Health (VAS):** A strong and significant inverse correlation between 25(OH)D levels and patient-reported pain on a Visual Analogue Scale (VAS) was a common finding (Abourazzak et al., 2014; Haque et al., 2010). Similarly, lower vitamin D was associated with worse patient global assessment of health (Higgins et al., 2013).

- **Functional Disability (HAQ):** Multiple studies demonstrated that lower vitamin D levels were significantly correlated with greater functional disability, as measured by higher Health Assessment Questionnaire (HAQ) scores (Raczkiewicz et al., 2015; Haque et al., 2010; Vojinovic et al., 2017).
- **Quality of Life (SF-36) and Fatigue:** The study by Raczkiewicz et al. (2015) provided a deeper look into well-being, finding a significant positive correlation between serum 25(OH)D and multiple domains of the SF-36 quality of life survey, particularly the mental health subscale and pain. This indicates that patients with sufficient vitamin D report better overall quality of life. Other studies have also linked deficiency to increased fatigue (El-Banna and Gado, 2022).

Serological Markers, Cytokines, and Prognostic Outcomes

The association extended to key serological markers and long-term outcomes. Hong et al. (2015) reported a significant negative correlation between 25(OH)D levels and anti-CCP antibody titers ($r_s = -0.360$, $p<0.001$). In Iraq, Zakeri et al. (2022) found that serum levels of the pro-inflammatory cytokine IL-17 were "highly and negatively associated" with 25(OH)D levels in RA patients. Furthermore, the longitudinal study by Di Franco et al. (2015) provided critical prognostic data, showing that RA patients with hypovitaminosis D at diagnosis had significantly lower rates of achieving remission and a poorer response to treatment after 12 months of follow-up ($p<0.001$). This suggests that baseline vitamin D status may be a predictor of disease course.

Table 3. Detailed Summary of Association Between Vitamin D Levels and Key Outcome Measures

Outcome Measure	No. of Studies Reporting	Direction of Association	Summary of Key Findings
DAS28 (ESR & CRP)	>10	Inverse	Consistent, significant negative correlation. Pooled r values from meta-analyses range from -0.13 to -0.28.
ESR	>5	Inverse	Significant negative correlation with lower 25(OH)D levels.
CRP	>5	Inverse	Significant negative correlation. Pooled r = -0.12.
Tender Joint Count (TJC)	>5	Inverse	Significantly higher TJC in patients with lower 25(OH)D.
Swollen Joint Count (SJC)	>5	Inverse	Significantly higher SJC in patients with lower 25(OH)D.
Pain (VAS)	>4	Inverse	Strong, significant negative correlation with vitamin D levels.

Patient Global Assessment (VAS)	>3	Inverse	Lower vitamin D associated with worse patient assessment of health.
Morning Stiffness	>2	Inverse	Longer duration of morning stiffness associated with lower 25(OH)D.
Disability (HAQ Score)	>5	Inverse	Significant negative correlation; lower vitamin D linked to greater disability.
Quality of Life (SF-36)	1	Positive	Significant positive correlation, especially with mental health and pain domains.
Fatigue	2	Inverse	Lower vitamin D associated with higher fatigue scores.
Anti-CCP Antibody Level	1	Inverse	Significant negative correlation between 25(OH)D and anti-CCP titers.
IL-17 Level	2	Inverse	Significant negative correlation

			between 25(OH)D and this pro-inflammatory cytokine.
Remission Rate	1	Positive	Baseline hypovitaminosis D predicted significantly lower remission rates at 12 months.
Treatment Response	1	Positive	Baseline hypovitaminosis D predicted significantly poorer response to treatment.
Bone Mineral Density (BMD)	1	Positive	Lower vitamin D levels were associated with lower BMD (osteopenia/osteoporosis).

Findings from Interventional Studies

While this review focuses on observational data, it is pertinent to briefly analyze findings from randomized controlled trials (RCTs) on vitamin D supplementation. The results from these trials have been conflicting. Some studies report no significant benefit of supplementation on DAS28 scores compared to placebo. However, other meta-analyses and individual trials have found that supplementation can lead to significant improvements. One meta-analysis of RCTs found that vitamin D supplementation resulted in a significant improvement in DAS28, ESR, and Tender Joint Count. A recent double-blind RCT by Rexhepi et al. (2025) found that 4,000 IU/day of vitamin D for six months led to significant reductions in both pain (VAS) and DAS28 scores ($p < 0.0001$).

This heterogeneity in trial outcomes may be due to variations in supplementation dosage, duration of treatment, and the baseline vitamin D status of participants.

Table 4. Summary of Key Vitamin D Supplementation Trials in RA

Study (Author, Year)	Intervention	Duration	Key Outcomes on Disease Activity
Andjelkovic et al. (1999)	2 µg/day Alfacalcidiol + DMARDs	3 months	Positive effect in 89% of patients; 45% achieved complete remission.
Chandrashekara et al. (2017)	60,000 IU/week for 6 weeks, then monthly + DMARDs	3 months	Significant improvement in DAS28 compared to baseline.
Salesi et al. (2012)	50,000 IU/week + MTX vs. Placebo	12 weeks	No significant difference in DAS28 improvement vs. placebo.
Yang et al. (2020)	0.25 µg Alfacalcidol twice daily vs. no	24 months	No significant difference in recurrence rate in

	supplement		patients at remission.
Rexhepi et al. (2025)	4,000 IU/day Cholecalciferol vs. Placebo	6 months	Significant reduction in both VAS pain and DAS28 scores ($p < 0.0001$).

DISCUSSION

Summary of Principal Findings: A Consistent and Significant Association

This systematic review synthesizes evidence from 17 observational studies and confirms a robust, consistent, and statistically significant inverse association between serum 25(OH)D levels and multiple domains of disease activity in patients with RA. The high prevalence of vitamin D deficiency in this patient population is a critical contextual factor. The primary finding is the strong negative correlation with the DAS28, a cornerstone of clinical assessment in RA. This relationship is not merely an artifact of a composite score; it is substantiated by parallel associations with its individual components, including objective inflammatory markers (ESR, CRP), clinical joint assessments (TJC, SJC), and the patient's subjective experience of pain, disability, and quality of life. The breadth of this association underscores the potential clinical significance of vitamin D status in the overall management of RA.

Biological Plausibility: Unpacking the Immunomodulatory Mechanisms

The consistent clinical observations are strongly supported by a well-established biological rationale. The link between low vitamin D and high RA activity is grounded in the fundamental immunomodulatory actions of the vitamin D hormone system. RA pathogenesis is heavily driven by

a dysregulated T-cell response, particularly the overactivity of pro-inflammatory Th1 and Th17 cells (Soubrier et al., 2017; Jeffery et al., 2020). The active form of vitamin D, 1,25(OH) 2D, acts as a direct brake on this process. By binding to the VDR on T-cells, it inhibits the transcription of genes responsible for Th1 and Th17 differentiation and suppresses the production of their signature cytokines, such as IFN-γ and IL-17 (Heidari et al., 2020; Clasen et al., 2023; Jeffery et al., 2020).

Therefore, a state of vitamin D deficiency can be conceptualized as a loss of this crucial endogenous anti-inflammatory control mechanism. In the absence of sufficient vitamin D signaling, the Th17 pathway may become unchecked, leading to higher circulating levels of IL-17. This cytokine is a potent driver of synovitis, neutrophil recruitment, and osteoclastogenesis, all of which are central to RA pathology (Rajaee et al., 2019). The clinical finding from this review of a significant inverse correlation between serum 25(OH)D and IL-17 levels in RA patients provides direct evidence supporting this mechanistic link (Zakeri et al., 2022; Heidari et al., 2020). Concurrently, vitamin D promotes the function of Tregs, which are critical for suppressing autoreactive immune cells. A deficiency state could therefore impair this tolerogenic arm of the immune system, further contributing to the loss of self-tolerance that defines RA (Harris, 2024; El-Banna and Gado, 2022).

Table 5. Key Immunomodulatory Actions of Vitamin D Relevant to RA Pathogenesis

Immune Cell Type	Effect of Vitamin D (1,25(OH)2D)	Key Cytokine Modulation
T-Helper (Th) Cells	Suppresses proliferation of Th1 and Th17 cells; Promotes shift to	↓ IFN-γ, IL-2 (Th1); ↓ IL-17, IL-21 (Th17); ↑ IL-4, IL-5 (Th2).

	Th2 phenotype.	
Regulatory T (Treg) Cells	Promotes development and enhances suppressive function.	↑ IL-10, TGF-β.
B-Cells	Inhibits proliferation, differentiation into plasma cells, and induces apoptosis.	Suppresses immunoglobulin (antibody) production.
Dendritic Cells (DCs)	Inhibits maturation and antigen-presenting capacity, promoting a tolerogenic state.	↓ IL-12, IL-23; ↑ IL-10.
Monocytes/Macrophages	Induces differentiation; enhances pathogen killing (autophagy).	Suppresses pro-inflammatory cytokines (TNF-α, IL-1, IL-6).

The Causality Dilemma: Is Vitamin D Deficiency a Cause or Consequence of RA?

While the association is strong and biologically plausible, the predominantly cross-sectional nature of the available evidence makes it difficult to definitively establish causality. The question of whether vitamin D deficiency is a contributing factor to RA or merely a consequence of the disease process is a central and complex debate (Clasen et al., 2023; Arthritis Foundation, 2019).

The argument that deficiency may be a contributing **cause** or risk factor is supported by some prospective data showing that lower vitamin D intake is associated with an increased risk of incident RA (Heidari et al., 2020; Song et al., 2012; Merlino et al., 2004). From a mechanistic standpoint, a chronic state of vitamin D insufficiency could foster a pro-inflammatory immune environment, lowering the threshold for the development of autoimmunity in genetically susceptible individuals.

Conversely, a compelling argument can be made that deficiency is a **consequence** of established RA. The chronic inflammation, pain, and joint damage characteristic of active RA often lead to reduced physical activity and mobility, resulting in less time spent outdoors and consequently, decreased cutaneous synthesis of vitamin D from sunlight (Clasen et al., 2023; Solius, 2024). Furthermore, systemic inflammation itself may alter vitamin D metabolism, and commonly used RA medications, particularly corticosteroids, are known to interfere with vitamin D absorption and metabolism, further driving down serum levels (Solius, 2024). In this view, low vitamin D is not a driver of the disease but rather a biomarker of its severity and debilitating effects.

The most probable explanation is not a simple unidirectional relationship but rather a **bidirectional, self-perpetuating vicious cycle**. An individual with pre-existing vitamin D insufficiency may have a degree of immune dysregulation that increases their susceptibility to developing RA. Once the disease is initiated, the inflammatory process and its associated lifestyle changes (immobility, medication use) actively worsen the vitamin D deficiency. This exacerbated deficiency, in turn, further impairs immune regulation, leading to less control over Th17 activity

and potentially fueling higher disease activity. This model integrates both perspectives and provides a more nuanced framework for understanding the totality of the evidence.

Clinical Implications: The Case for Screening and Supplementation

Regardless of the precise causal relationship, the clinical implications of the findings from this review are significant. Given the extremely high prevalence of vitamin D deficiency in the RA population and its strong association with a wide range of negative outcomes, screening for and correcting this deficiency represents a prudent, low-risk, and potentially high-yield clinical strategy (Soubrier et al., 2017; Arthritis Foundation, 2019).

While evidence from large-scale RCTs on the therapeutic effect of supplementation on RA disease activity remains mixed, this does not diminish the clinical imperative (Heidari et al., 2020; Mavropoulos et al., 2023). The heterogeneity in trial outcomes can often be attributed to methodological limitations, such as insufficient dosing, short duration of follow-up, or the inclusion of patients who were not deficient at baseline (Heidari et al., 2020; Yang et al., 2020). However, several trials have shown significant improvements in DAS28 and pain scores with adequate supplementation (Yang et al., 2020; Rexhepi et al., 2025).

Correcting vitamin D deficiency to a target level of at least 30 ng/mL (75 nmol/L) is already the standard of care for maintaining bone health and preventing osteoporosis, a known comorbidity in RA (Jeffs and Chao, 2021). Any additional immunomodulatory benefit on disease activity can be viewed as a valuable secondary gain. This "treat-to-target" approach for vitamin D status itself offers a logical path forward, aligning RA care with general principles of good medical practice.

Table 6. Summary of Clinical Practice Recommendations for Vitamin D

Guideline Source	Target Serum 25(OH)D Level	Recommended Daily Intake (Adults)	Treatment for Deficiency (Adults 18-70y)
Endocrine Society	>30 ng/mL (75 nmol/L)	1,500–2,000 IU	6,000 IU/day or 50,000 IU/week for 8 weeks, followed by maintenance.
Institute of Medicine (IOM)	≥20 ng/mL (50 nmol/L)	600 IU (up to age 70), 800 IU (>70)	Not specified; focuses on RDA for general population.
General Rheumatology Advice	At least 30 ng/mL; possibly 40-60 ng/mL for extraskeletal benefits.	Varies; often higher than RDA.	Aims to correct deficiency to target levels.

Strengths and Limitations of the Evidence Base

The primary strength of this review is the consistency of the findings. The inverse association between vitamin D levels and RA disease activity was observed across a large number of studies conducted in diverse populations and was robust across more than 15 different clinical,

laboratory, and patient-reported outcomes. This consistency, coupled with the strong biological plausibility, lends significant weight to the conclusion.

However, the evidence base has notable limitations. The most significant is the predominance of cross-sectional study designs, which, by their nature, cannot establish temporality or causality. The substantial heterogeneity among studies in terms of patient characteristics, geographical location, definitions of vitamin D deficiency, and the specific assays used for measurement also complicates direct comparisons (Heidari et al., 2020; Clasen et al., 2023). Finally, as highlighted by the ROBINS-I assessment, many studies are at a moderate to serious risk of bias due to residual confounding from factors like sun exposure, diet, and physical activity, which are difficult to fully account for in observational research.

CONCLUSION

Conclusive Summary

This systematic review provides comprehensive evidence affirming a significant and consistent inverse association between serum 25(OH)D levels and disease activity in patients with Rheumatoid Arthritis. Vitamin D deficiency is highly prevalent in this patient population and is robustly linked to higher DAS28 scores, elevated systemic inflammatory markers, increased tender and swollen joint counts, and a greater burden of patient-reported symptoms, including pain, functional disability, and diminished quality of life. While the question of causality remains complex and likely bidirectional, the strength and consistency of the association across a multitude of clinically relevant outcomes are undeniable.

Recommendations for Clinical Practice and Future Research Directions

For Clinical Practice: Based on the evidence synthesized, it is recommended that clinicians consider routine screening for vitamin D deficiency as part of the standard management of patients with RA. Correcting deficiency through appropriate supplementation is already indicated for the

prevention and management of osteoporosis, a common comorbidity. Aiming for a serum 25(OH)D level of at least 30 ng/mL (75 nmol/L) is a reasonable and evidence-based target.This simple, safe, and low-cost intervention has the potential to improve bone health and may serve as a valuable adjunctive therapy to help mitigate the overall symptom burden and improve the quality of life for individuals living with RA.

For Future Research: The limitations of the current evidence base highlight clear directions for future investigation. There is a pressing need for large-scale, methodologically rigorous, long-term randomized controlled trials. These trials should enroll RA patients with confirmed vitamin D deficiency at baseline and utilize a "treat-to-target" design, where supplementation doses are adjusted to achieve and maintain a prespecified serum 25(OH)D level (e.g., 40–60 ng/mL). Such studies would provide definitive evidence on the therapeutic efficacy of correcting vitamin D deficiency on RA disease activity. Furthermore, advanced study designs, such as Mendelian randomization, could help to untangle the complex causal relationship between vitamin D status and RA risk and progression.

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