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DOI:

[10.1136/rmdopen-2021-002058](https://doi.org/10.1136/rmdopen-2021-002058)

*Document Version*

Publisher's PDF, also known as Version of record

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*Citation for published version (APA):*

Dey, M., Busby, A., Elwell, H., Lempp, H., Pratt, A., Young, A., Isaacs, J., & Nikiphorou, E. (2022). Association between social deprivation and disease activity in rheumatoid arthritis: a systematic literature review. *RMD Open*, 8(1), [e002058]. <https://doi.org/10.1136/rmdopen-2021-002058>

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## REVIEW

# Association between social deprivation and disease activity in rheumatoid arthritis: a systematic literature review

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**To cite:** Dey M, Busby A, Elwell H, *et al.* Association between social deprivation and disease activity in rheumatoid arthritis: a systematic literature review. *RMD Open* 2022;**8**:e002058. doi:10.1136/rmdopen-2021-002058

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/rmdopen-2021-002058>).

Received 10 November 2021  
Accepted 29 March 2022

## ABSTRACT

Physical and mental illnesses are driven by ethnicity, social, environmental and economic determinants. Novel theoretical frameworks in rheumatoid arthritis (RA) focus on links and adverse interactions between and within biological and social factors. This review aimed to summarise associations between socioeconomic status (SES) and RA disease activity, and implications for future research. Articles studying the association between SES and RA disease activity were identified, from 1946 until March 2021. The research question was: Is there an association between social deprivation and disease activity in people with RA? Articles meeting inclusion criteria were examined by one author, with 10% screened at abstract and full paper stage by a second author. Disagreements were resolved with input from a third reviewer. Information was extracted on definition/measure of SES, ethnicity, education, employment, comorbidities, disease activity and presence/absence of association between SES and disease activity. Initially, 1750 articles were identified, with 30 articles ultimately included. SES definition varied markedly—10 articles used a formal scale and most used educational attainment as a proxy. Most studies controlled for lifestyle factors including smoking and body mass index, and comorbidities. Twenty-five articles concluded an association between SES and RA disease activity; two were unclear; three found no association. We have demonstrated the association between low SES and worse RA outcomes. There is a need for further research into the mechanisms underpinning this, including application of mixed-methods methodology and consideration of syndemic frameworks to understand bio–bio and bio–social interactions, to examine disease drivers and outcomes holistically.

## INTRODUCTION

A growing body of evidence indicates that patients with rheumatoid arthritis (RA) and lower socioeconomic status (SES) have poorer disease outcomes compared with patients with higher SES. This situation includes greater levels of disease activity, as reflected by laboratory markers, composite scores (swollen and tender joint counts, Disease Activity Scores (DAS)), worse physical function, health-related quality of life and pain.<sup>1–3</sup> People with

## Key messages

### What is already known about this subject?

- There is a strong association between low socioeconomic status and worse outcomes in rheumatoid arthritis.

### What does this study add?

- There are complex relationships underpinning the association between low socioeconomic status and worse disease outcomes in rheumatoid arthritis, and this is an under-researched area.
- Novel theoretical frameworks and mixed-methods research may be useful in increasing our understanding of this association.

### How might this impact on clinical practice?

- An increased understanding of the multifactorial relationship between socioeconomic status and rheumatoid arthritis disease activity will facilitate a more holistic, and ultimately more effective, approach to patient care.

## Summary points

- Relationships underpinning the association between low socioeconomic status and worse outcomes in rheumatoid arthritis are complex and an under-researched area.
- Novel theoretical frameworks can increase our understanding of these bio–bio and bio–social interactions.
- Increased understanding of the complex association between socioeconomic status and disease activity may facilitate more holistic approaches to patient care.

lower SES also experience poorer clinical outcomes of comorbidities of RA, especially mental health.<sup>4</sup> Decreased levels of engagement or contact with healthcare professionals in this patient group, including allied healthcare, has further negative impacts on the RA disease trajectory, a pattern also observed in



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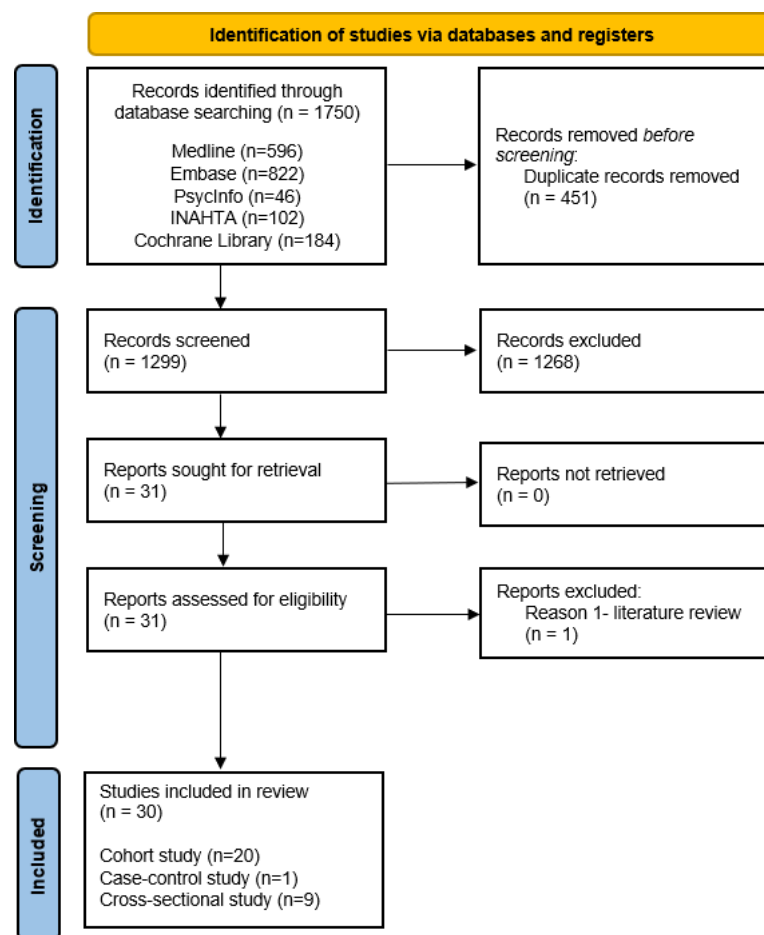
societies with both private and publicly funded health-care.<sup>4-6</sup>

Physical and mental illnesses are driven by social, environmental and economic determinants. Social deprivation, for example, was highlighted as a key factor for morbidity and mortality in people with long-term diseases in The Marmot Review.<sup>7</sup> People from socially deprived backgrounds are more likely to experience adverse health outcomes, including increased rates of hospitalisation and death as a result of long-term diseases, including RA. SES is also closely associated with lifestyle and other factors which affect disease outcomes in RA, such as smoking, body mass index (BMI), diet and comorbidities, for example, cardiovascular disease and diabetes.<sup>8</sup>

SES can be measured at the individual (eg, occupation, education), regional (such as the Index of Multiple Deprivation (IMD) in the UK) and national level (eg, gross domestic product). There are advantages and disadvantages to extrapolating these to determine SES, often dependent on the research question and population under study. The role of social determinants of health in driving significant levels of health inequity is widely accepted and, while some are driven in part by biological differences or lifestyle choices, others are

beyond the control of individuals or groups. Current research, using novel theoretical frameworks in RA, focuses on the study of potential links and adverse interactions among comorbidities. These are more likely in the context of specific social determinants such as low education, unemployment and low household income.<sup>9</sup> An example of such a theoretical framework is the syndemics framework, the study of links and adverse interactions among comorbidities that are more likely in the context of specific social determinants such as, low education attainment, unemployment, low household income and racial and ethnic discrimination (figure 1).<sup>9</sup> A syndemic is characterised by the presence of two or more disease states, adversely interacting with each other and negatively affecting the course of each disease trajectory. Such adverse interactions are exacerbated in the setting of increased multimorbidity and/or in specific social contexts.

This systematic literature review (SLR) aims to characterise the association between social deprivation and disease activity in RA, and inform future research methodologies in this area.



**Figure 1** Flow diagram of stages of systematic literature review. Cochrane Library encompasses library of: systematic reviews; systematic review protocols; controlled clinical trials. INAHTA, International Network of Agencies for Health Technology Assessment.

## METHODS

This SLR was conducted in accordance with the Cochrane Handbook<sup>10</sup> and reported as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>11</sup>

The protocol was developed by EN, MD and HE, and registered in the PROSPERO database of systematic reviews on 22 March 2021, CRD42021244007.<sup>12</sup> The research question is framed and structured using the 'Patients, Intervention, Comparator or Control and Outcome' (PICO) format<sup>13</sup>: Is there an association between social deprivation and disease activity in people with RA?

### Population

Target population was adult patients with established RA. Additionally, studies discussing inflammatory arthritis were also included, where it was stated explicitly that patients with RA were included within the cohort.

### Intervention

Social deprivation related terms and indices (and related indexing terms).

### Comparator

Patients with RA, not categorised as socioeconomically deprived.

### Outcomes

The main outcome was disease activity, as defined by DAS (including DAS28, European Alliance of Associations for Rheumatology (EULAR) response and/or ACR responses), difficult-to-treat arthritis, inflammation and/or refractory disease. Relative risks and ORs of the effect of social deprivation on RA outcomes in quantitative studies were extracted, with qualitative outcomes recorded separately.

### Search strategy, databases searched and study selection

The search strategy (available in online supplemental material 1) was developed by two authors (MD and EN) with the help of a librarian expert in undertaking SLRs and clinical research (HE). The bibliographic databases Medline, Embase and PsycINFO were searched via the Ovid platform. Other databases examined were the International Network of Agencies for Health Technology Assessment and Cochrane Databases (Systematic Reviews, Register of Controlled Clinical Trials, Methodology Register). The search conducted had no time restriction and included articles in the databases searched between 1946 and 17 March 2021, when the search was carried out.

The search was limited to English-language articles due to nuances in describing socioeconomic factors in other languages and comparability across studies. Inclusion criteria for articles were: observational studies, qualitative studies and randomised controlled trials. Opinion

articles (including editorials), case reports and reviews were excluded.

Initial scoping reviews were performed on 11 March 2021 to optimise the search strategy and ensure relevant papers were captured, especially with regard to the exposure and outcome variables. The focus of the review was on the effect of 'SES' or similar database indexing terms, specifically on disease activity (and similar indexing terms).

All full-length articles were uploaded into EndNote V.X9 (Clarivate Analytics, Pennsylvania, USA), with duplicates removed (figure 1). Titles and abstracts were screened by MD, to assess eligibility. The full articles which met the inclusion criteria were then examined in detail by MD. For validation purposes, 10% of the articles were screened at the abstract and full paper stage by a second author, AB. There were two disagreements at the abstract screening stage (ie, 2/130, with 130 being 10% of 1299) which were resolved with input from a third reviewer (EN).

### Assessment of risk of bias, data extraction and synthesis

Risk of bias in each included study was assessed using the Newcastle-Ottawa Scale for observational studies.<sup>14</sup> Results for each article are provided in online supplemental material 1. Data extraction from the included articles was undertaken by MD, with 10% of articles also reviewed and the information extracted by AB for validation. No papers or additional data or online supplemental material 1 were required from authors.

For each selected article, in addition to basic information, the following information was extracted: definition and/or measure of social deprivation; ethnicity of sample (if available); education data (if available); comorbidities; disease activity measure; covariates; presence/absence of association between social deprivation and disease activity with a summary of authors' conclusions.

## RESULTS

In the initial search strategy, a total of 1750 articles and 797 conference abstracts were identified. After deduplication, this was reduced to 1299 full papers. After further screening of titles and abstracts, 1268 papers were excluded, with 31 proceeding to full-text screening. Finally, 30 articles were included in the SLR. At full-text screening, 100% concordance was achieved between the two reviewers (MD and AB) on a 10% validation check. Therefore, 30 articles were deemed eligible for data extraction. Figure 1 summarises the article numbers during the article retrieval process. Included articles were all observational studies, which comprised: 20 cohort studies, 9 cross-sectional studies and 1 case-control study. Twenty-six articles focused on patients with a diagnosis of RA, while the remaining four articles included patients with a diagnosis of inflammatory arthritis. Basic information for included articles are summarised in table 1. Information on exposures and outcomes is summarised

**Table 1** Basic information and characteristics of included studies

Author/year	Country (ies)	Geographic region (if in UK)	Type of study	Total sample size	% female	Mean age (years)	Comorbidities (where studied in the cohort)	Average duration of rheumatoid arthritis (months/years, as specified)
Alarcón <sup>32</sup> 2014	Chile	.	Cross-sectional	189	90.5	54.3	.	.
Andersson <sup>19</sup> 2013	Sweden	.	Cohort	1460	68	54.2	.	6.7 months
Baldassarri <sup>65</sup> 2014	USA	.	Cross-sectional	937	86.6	54.6	Clinical Comorbidity Index based on 23 doctor-diagnosed conditions	111 months (within eRA 6.6)
Barton <sup>27</sup> 2011	USA	.	Cross-sectional	498	84	54	.	10 years
Berkanovic <sup>66</sup> 1996	USA	.	Cross-sectional	118	75	51.7	Mean no of comorbidities 1.05, range 0–5	.
Brekke <sup>20</sup> 1999	Norway	.	Cross-sectional	247 (respondents); 133 assessed in clinic	78.7 in respondents; 82.4 in clinic sample	63.2 in respondents; 67.8 in clinic sample	Mean 1.1 in respondents	12.7 months in respondents; 14.5 months in clinic sample
Callhoff <sup>21</sup> 2017	Germany	.	Cross-sectional	1492	81.6	54.9	.	14 years
Camacho <sup>15</sup> 2012	UK	.	Cohort (Norfolk Arthritis Register; NOAR)	553	62.8	57.2	.	5 months
Chandrashekhara <sup>36</sup> 2018	India	.	Cross-sectional	1990	83.3	48.65	Recorded as either present or absent: bronchial asthma, chronic heart failure, diabetes mellitus, hypertension, hypercholesterolaemia and thyroid illness. Occurrence of any one of the comorbidities was classified as 'presence of comorbidity'	.
Glave-Testino <sup>33</sup> 1994	Mexico	.	Case-control	128	.	45	Patients with severe comorbidity excluded. Defined as: systemic arterial HTN, chronic renal failure, CHF, chronic liver disease, DM	12 years
Gamboa-Cárdenas <sup>34</sup> 2019	Peru	.	Cohort	498	85.1	45.9	.	5.3 months (symptom duration)
Gong <sup>37</sup> 2016	China	.	Cross-sectional	207	85.5	49	Persons with cognitive impairment or current severe diseases, such as cancer and stroke, were excluded. About one quarter of the participants (24.6%) had at least one comorbid disease, such as hypertension (5.8%), digestive system disorders (3.9%), heart disease (2.4%) and anaemia (1.9%).	9.3 years

Continued

Table 1 Continued

Author/year	Country (ies)	Geographic region (if in UK)	Type of study	Total sample size	% female	Mean age (years)	Comorbidities (where studied in the cohort)	Average duration of rheumatoid arthritis (months/years, as specified)
Haller <sup>22</sup> 2015	Sweden	.	Cohort	Cohort 1 (1996–98): 317; Cohort 2 (2006–9) 436	67%; 68%	56; 58	.	.
Harrison <sup>16</sup> 2009	UK	.	Cohort (NOAR)	1393	67	55	.	5 months
Harrison <sup>1</sup> 2005	UK	Stoke on Trent; Cannock Chase; Truro; King's College Hospital, London; and Macclesfield	RCT	466	68	62.1	Comorbidity information collected at baseline. Conditions grouped according to body system: cardiovascular disease including hypertension, psychiatric including depression, respiratory, endocrine, gastrointestinal, nervous system.	11 years
Jacobi <sup>4</sup> 2003	The Netherlands	.	Cohort	869	71	59.5	.	8.7 years
Jiang <sup>40</sup> 2015	Sweden	.	Cohort	3021	72	54.5	.	6.5 months
Kearsley-Fleet <sup>17</sup> 2018	UK	BSRBR-RA	Cohort	13 502	76	57	Categorised as 1, 2, 3+	10 years
Linde <sup>23</sup> 2009	Denmark	.	Cohort	3156	75	64.5	Categorised as 1, 2, 3+	7.5 months
Massardo <sup>35</sup> 2012	Chile	.	Cohort	1093; 1059 when excluding those with missing ethnic data	85.5	45.6	.	6 months
McEntegart <sup>5</sup> 1997	UK	Scotland (divided whole and west), England, Wales	Cohort	440 in 1980s cohort; 374 in 1993 cohort	.	57.5	.	.
Molina <sup>29</sup> 2015	USA	.	Cohort	1209	75.8	58	.	10.7 months (average of the three SES categories)
Moufarrej <sup>30</sup> 2015	USA	.	Cross-sectional	182	76.3	45.6 (DAS28 $\leq$ 3.2); 48.5 (DAS28 $>$ /=3.2)	.	.
Putrik <sup>39</sup> 2016	Multinational	Multinational cohort	Cohort	3920	82	56	RDCI based on: ischaemic cardiovascular disease (myocardial infarction, stroke), cancer (colon, skin, lung, breast and uterus for women, prostate for men and lymphoma), gastrointestinal diseases (diverticulitis, ulcers), infections (hepatitis), lung disease (chronic obstructive pulmonary disease and asthma) and psychiatric disorders (depression)	.

Continued

Table 1 Continued

Author/year	Country (ies)	Geographic region (if in UK)	Type of study	Total sample size	% female	Mean age (years)	Comorbidities (where studied in the cohort)	Average duration of rheumatoid arthritis (months/years, as specified)
Roodenrijs <sup>24</sup> 2020	The Netherlands		Cohort	152 (52 D2T)	72.5	60.2 D2T; 64.5 non-D2T	EULAR comorbidity domains and Charlson Comorbidity Index	17 years D2T; 14 years non-D2T
Vliet Vlieland <sup>25</sup> 1994	The Netherlands		Cohort/ cross-sectional	127	100	35.9 (disease onset)		1.5 year (at diagnosis)
Yang <sup>31</sup> 2015	Canada		Cohort	2023	73	52.86		6.1 months
Yates <sup>18</sup> 2021	UK	NE/AA	Cohort	7455	62.3	56.7	40.2% $\geq 1$ comorbidity	
Young <sup>3</sup> 2000	UK	Multiple	Cohort	869	65.1	56 (median)		6 months (median)
Zou <sup>38</sup> 2020	Singapore		Cohort	213	73.2	51.3	Charlson Comorbidity Index, mean 1.1	1.8 months

CHF; Congestive Heart Failure; DAS, Disease Activity Score; DM, Diabetes Mellitus; EULAR, European Alliance of Associations for Rheumatology; HTN, Hypertension; RCT, Randomised Controlled Trial; RDCl, Rheumatic Disease Comorbidity Index; SES, Socioeconomic Status.

in online supplemental table 2. Risk of bias findings are summarised in online supplemental table 1. Overall, studies were judged to be of medium-to-high quality.

All included articles reported results of quantitative observational studies. Of note, there were no qualitative or mixed-methods studies.

With regard to country of origin from where the study population was drawn, 7 were from the UK,<sup>1-3 15-18</sup> 10 from the rest of Europe (3 the Netherlands, 3 Sweden, 1 Norway, 1 Germany, 1 Denmark),<sup>4 19-25</sup> 6 from USA and Canada,<sup>26-31</sup> 4 from South America (2 Chile, 1 Mexico, 1 Peru)<sup>32-35</sup> and 3 from Asia (1 India, 1 China, 1 Singapore).<sup>36-38</sup> One study included multinational data.<sup>39</sup> Sample sizes varied from 118 to 13502.

### Definitions and measures of social deprivation

There was variation in the way in which social deprivation was defined between included articles. In ten (33%) articles, a formal scale or measure was used, including: Carstairs deprivation score<sup>2 3</sup>; Graffar scale<sup>34 35</sup>; Townsend index score<sup>1</sup>; IMD<sup>15-18</sup>; Nam and Powers score.<sup>29</sup> One article based social inequality on the results of the ADIMARK survey in Chile,<sup>32</sup> while another based this on the ability or inability to afford biologic medications.<sup>30</sup>

The majority of articles included educational achievement in their definition of SES, either alone or in combination with other factors. Educational attainment alone was used as a proxy for SES in eight (27%) of the included articles,<sup>4 23-25 33 38-40</sup> while a further eight combined education with factors including employment status, occupation, income, race and area of residence.<sup>21 22 26-28 31 36 37</sup> Finally, one article categorised SES according to the area of the city in which patients were resident,<sup>20</sup> and another article used type of occupation.<sup>19</sup>

### Association with disease activity outcomes

Most articles reported a combination of DAS, the most common being the DAS28 (22 of 30 articles, 73%), usually erythrocyte sedimentation rate (ESR) based. Health Assessment Questionnaire scores (HAQ) were also commonly described (24 of 30 articles, 80%),<sup>1-4 15-17 19 20 23 25-35 37 38 40</sup> usually along with multiple other measures including DAS and/or a biochemical marker of inflammation such as ESR. Three articles reported only patient-reported outcomes (HAQ).<sup>23 28 37</sup> These studies were still deemed worthy of inclusion alongside articles reporting objective measures of disease as they form a key component of a patient's overall experience of their disease. Other disease activity measures such as Rheumatoid Arthritis Impact of Disease<sup>21</sup> and Ritchie score,<sup>25</sup> as well as individual symptoms of stiffness, pain scores and erosion scores were also reported as outcomes of importance.

With regard to methodologies used to assess the association between SES and RA disease activity outcomes, most studies applied multivariable linear and/or logistic regression models. Other methodologies employed to test this association included Poisson regression, hierarchical

regression, structural equation modelling, generalised least-squares random effects model, Cox regression and non-parametric statistical analyses.

Of the 30 articles, 25 (83%) reported a clear association between SES and disease activity, with lower SES predicting more active disease or worse clinical outcomes.<sup>1-4 15-18 20 21 24-33 35-39</sup> Of these, 13 quantified the association as an OR.<sup>3 4 15 16 18 21 24-26 32 33 36 39</sup> ORs for an association between SES and disease activity (ie, poorer SES associated with poorer disease outcomes) ranged from 1.06 to 3.15. One study described outcomes HR, with a value of 1.2 (95% CI 1.0 to 1.4) for refractory disease in the lowest IMD quintile group compared with patients in all other IMD quintiles.<sup>17</sup> Another study reported relative risk ratios (RRRs). Patients with higher levels of education had lower relative risk of having poorer disease trajectories, with RRR of 0.33–0.56.<sup>38</sup> Five of the 25 studies stated only p values for the associations,<sup>1 27 29 31 37</sup> while a further three studies reported outcomes as beta (regression) coefficients.<sup>20 28 35</sup> One study described results as percentage of patients with treatment-resistant disease who were unable to afford biologics (which was the study's definition of low SES),<sup>30</sup> and the remaining study reported only raw numbers of years after diagnosis until biologics required.<sup>29</sup>

Three articles (10%) did not find an association between SES and disease activity.<sup>19 23 40</sup> A Swedish cohort study<sup>19</sup> defined SES according to blue-collar and other occupations, as well as studying disease activity outcomes in immigrants and non-immigrants. They found that while immigrants scored worse for pain, function and tender joint scores over a 2-year period of follow-up, the data did not differ from non-immigrants in relation to objective measures of inflammation or EULAR outcome.<sup>19</sup> The authors concluded that socioeconomic class had no effect on disease outcomes, citing the 'relatively egalitarian' Swedish society as one possible reason.<sup>19</sup> A second article, also in a Swedish cohort, found those with higher educational attainment experienced less pain and functional disability compared with those with lower educational attainment, but no difference was seen in disease activity or treatment.<sup>40</sup> Finally, a Danish study cohort found no significant association between SES (defined according to educational level) and HAQ.<sup>23</sup> Two studies (7%) had unclear clinical outcomes, with one providing no comment on the association between SES and disease activity and the second comparing clinical findings between two cohorts recruited in 1996–1998 and 2006–2009, respectively, but providing no comment on impact of SES on disease activity.<sup>22 34</sup>

Some studies provided additional valuable insights (summarised in online supplemental table 2, final column) which, although not directly answering the research question under study, have high relevance in the broader sense of the impact of SES and RA.

### Covariates and comorbidities

Of the 30 included articles, 23 (77%) reported details of covariates adjusted for in the analyses of the association of SES and RA disease outcome.<sup>1 3 4 15-21 23 25-29 33-36 38-40</sup> (online supplemental table 3). These comprised age and gender, as well as RA disease duration and baseline values for outcomes of interest, for example, HAQ. Most articles controlled for one or more comorbidities or lifestyle factors, including smoking status, BMI and comorbidities.<sup>1 16-21 26-28 36 38 40</sup>

Comorbidity status was reported in 13 (43%) of the included articles.<sup>1 17 18 20 23 24 26 28 33 36-39</sup> A comorbidity index was used in four of these—Clinical Comorbidity Index<sup>26</sup>; Rheumatic Disease Comorbidity Index<sup>39</sup>; Charlson Comorbidity Index<sup>24 38</sup>; EULAR comorbidity domains.<sup>24</sup> The remaining nine articles presented the mean number of comorbidities per participant, and/or number of comorbidities by ordinal category (ie, one, two or three or more).

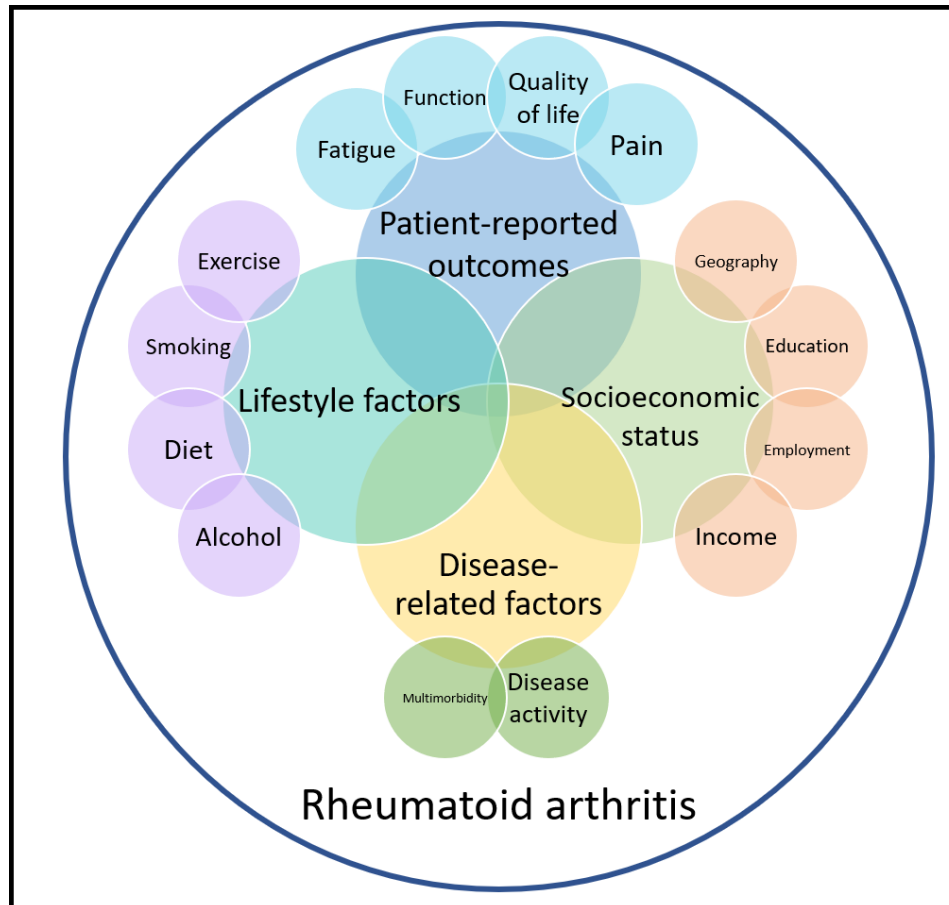
### DISCUSSION

Overall, studies were judged to be of medium-to-high quality. The results of our review indicate that there is an association between low SES and poorer disease outcomes in patients with RA. In referring to 'disease outcomes', we refer to disease activity, the studied outcome in our SLR protocol and PICO framework. Details on comorbidities and covariates were also extracted as these are relevant to this topic, especially when considering a syndemics approach to studying SES in patients with RA; however, it was not possible to draw conclusions on these particular outcomes from the data available.

Previous studies on this topic have suggested factors within SES, including education, geographical location, employment and income, as key predictors of RA disease activity. Looking more broadly, factors both directly and indirectly associated with SES, including comorbidity status, smoking, diet and BMI, also play a role.<sup>2 3 8</sup> Poor disease outcomes in turn influence factors such as comorbidities, making them more difficult to manage, both by clinicians and self-management by patients<sup>4 24</sup> (although, it is difficult to explicitly conclude this association with comorbidities from the data available to us in this review). This reinforces the negative influences of SES. Given these complex bio–bio and bio–psychosocial relationships which influence clinical outcomes, our results indicate that novel syndemics frameworks in this field may be an effective way of studying these factors (figure 2).<sup>9</sup>

There are numerous reasons for the association between SES and disease activity in RA, with comorbidities being key. SES, especially domains such as education, social environment and employment, link with lifestyle choices (smoking, diet, alcohol consumption) and other factors, such as mental health issues including stress, anxiety and depression, are highly prevalent in RA.<sup>41</sup> These in turn can lead to poor medication adherence,





**Figure 2** Example of a theoretical framework of drivers of clinical outcomes in rheumatoid arthritis. As demonstrated by the results of this review, socioeconomic status (SES), lifestyle factors, patient-reported outcomes and disease-related factors are closely associated. These relationships can be demonstrated using a theoretical framework—an example is the ‘syndemics’ framework. SES encompasses factors including geography (eg, postcode, rural vs urban location), education, employment and income, as well as others not described in this diagram such as race and ethnicity. Lifestyle factors encompass, but are not limited to, exercise and physical activity, smoking and diet. Only some examples of patient-reported outcomes are shown in the schematic diagram, and include fatigue, function, quality of life and pain. All of these are closely related to disease-related factors, including multimorbidity and active disease (inflammation). Components of each of lifestyle, SES, patient-reported factors and disease-related factors may be individually interrelated and some may be part of other categories, for example, SES and lifestyle factors have a large amount of overlap. Together, all four main components contribute to the patient experience of rheumatoid arthritis.

increased levels of chronic pain and fatigue and decreased overall health and well-being, leading to increased levels of disease activity. This situation is exemplified in several of the included articles but particularly in the study by Roodenrijs *et al*, detailing factors associated with difficult-to-treat arthritis, which has subsequently laid the basis of formalised guidelines on its management recently published by EULAR.<sup>24 42</sup> Novel syndemic frameworks can shed light on the crucial interplay between drivers of difficult-to-treat disease and poor outcomes in patients with RA.<sup>9</sup>

Our results raise the question as to how best to study the association between SES and disease outcomes, given this complex relationship between multiple biological, psychological and socioeconomic factors. It is interesting to note that all 30 studies included in this review applied quantitative analyses. One may expect, due to the multifaceted interplay between SES and RA disease activity,

qualitative or mixed-methods analyses may provide a richer insight about the underlying reasons for this association directly from patients and/or clinicians.

Syndemic frameworks are one way in which this may be explored further, enabling the study of diseases using a mixed-methods approach to value the association between disease outcomes and multiple biological, psychological, social and other aspects, as demonstrated in the results of this review<sup>9 43</sup> (figure 2).

Health opportunities, as well as assessments and outcomes, such as the relationships explored in this SLR between SES and RA disease activity, can also be studied using the PROGRESS and PROGRESS-PLUS frameworks. PROGRESS refers to the following domains: place of residence; race/ ethnicity/ culture/ language; occupation; gender; religion; education; SES; social capital.<sup>44 45</sup> PROGRESS-PLUS includes a further three domains: personal characteristics associated with

discrimination (eg, age, disability); features of relationships (eg, exclusion from school); time-dependent relationships (eg, temporary negative change in circumstances such as just after hospital admission). These provide a broad framework which can be applied to ensure equity in conduct and reporting of research into SES factors, not only in RA but also other long-term conditions. Interestingly, the publications included marked variations for the definition of SES in this SLR. Indices such as the IMD,<sup>46</sup> used in the UK, is an effective way by which to capture many of the domains described by PROGRESS, comprising the components: income; employment; education; health; crime; barriers to housing and services; living environment (with some dissimilarities between the four UK regions).<sup>46</sup> The use of other indices, such as the Townsend and Graffar scale, can also make certain that multiple contributors to SES are accounted for. The majority of included studies applied education as a proxy for SES,<sup>4 23–25 33 38–40</sup> and in some cases combined this with other contributors to SES including employment status, occupation, income, race and area of residence.<sup>21 22 26–28 31 36 37</sup> Race and ethnicity were defined in 11 studies.<sup>18 26–30 32 34 35 38 39</sup> The importance of these social domains for disease outcomes more broadly has been highlighted during the COVID-19 pandemic, including in patients with long-term conditions such as RA.<sup>47</sup>

### Strengths and limitations of the SLR

Our review has several strengths. The authors agreed on a targeted search strategy to identify studies that focused on the association of SES with RA disease outcomes. With regard to the outcome under study, we paid attention to objective clinical measures of disease activity to allow comparison between articles. Both of these aspects, however, also limited our review, in that the scope of the search strategy may have excluded articles that have highlighted additional social factors, such as marital status, migration and religion. Nevertheless, the final search strategy included many domains that are commonly included as measures of deprivation in long-term conditions, including RA, such as the IMD. The emphasis on objective measures of disease activity may have also indirectly excluded qualitative studies. This lack of qualitative studies may have in turn have prevented more nuanced associations between SES and RA outcomes from being identified. However, this narrow focus enabled comparability between studies, as well as highlighting the potential lack of (and need for) mixed-methods studies in this field. It is possible that such methodologies may have been used in studies not ultimately included, due to not meeting our inclusion criteria. It is also important to acknowledge potential reporting bias in the included studies, and indeed in data which may not be published. Authors and publishers may be biased towards only positive associations. Similarly, given the few studies reporting on magnitude of association, this may only be stated where it is significant or sufficiently large. While

screening of all articles was conducted by one author, excellent concordance was achieved at all stages on 10% validation. Finally, due to the large heterogeneity in the reporting of outcomes (eg, OR, HR), and between the outcomes themselves, it was not possible to conduct a meta-analysis, including direct comparisons.

In conclusion, our review emphasises the association between low SES and worse disease outcomes in patients with RA. We have highlighted the complex multifaceted relationships giving rise to this association. There is a need for increased use of mixed-methods methodologies and consideration of tools such as PROGRESS and syndemic frameworks to understand bio–bio and bio–social interactions, to study drivers of disease and poor outcomes more holistically. These frameworks take a concentrated approach on how best to measure and finally tackle social deprivation, not just in RA, but across long-term conditions.

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**Contributors** All authors were involved in developing the idea and content. MD, AB, EN and HE developed the search and conducted data extraction. MD drafted the script. All authors provided input to the manuscript and were involved in finalising the paper.

**Funding** This work is funded by the British Medical Association Doris Hillier Grant (awarded to EN).

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

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