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Socioeconomic Status and Medication Use in Rheumatoid Arthritis: A Scoping Review

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Objective. Socioeconomic status (SES) influences disease outcomes in rheumatoid arthritis (RA) patients. Differences in medication use may partly explain this association. A scoping review was used to identify research conducted on this topic and determine what knowledge gaps remain.

Methods. Medline, Embase, and PsychInfo were searched from their inception until February 2022 for studies that assessed SES and medication use as an outcome variable. Data was extracted on the use of specific SES measures, medication use, and whether differences in SES variables were associated with differences in medication use.

Results. We identified 2,103 studies, of which 81 were selected for inclusion. Included studies originated most frequently from the US (42%); the mean ± SD age of participants was 55.9 ± 6.8 years, and most were female (75%). Studies measured a median of 4 SES variables (interquartile range 3–6), with educational, area-level SES, and income being the most frequent measurements used. Patients' race and/or ethnicity were documented by 34 studies. Studies primarily assessed the likelihood of prescription of disease-modifying antirheumatic drugs or dispensation, medication adherence, or treatment delays. A majority of studies documented at least 1 SES measure associated with a difference in medication use.

Conclusion. There is some evidence that SES affects use of medications in patients with RA; however, multiple definitions of SES have been utilized, making comparisons between studies difficult. Prospective studies with consistently defined SES will be needed to determine whether differences in medication use accounts for the poorer outcomes experienced by patients of lower SES.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease with the potential to cause long-term disability secondary to irreversible joint damage if left untreated (1). The current paradigm of early treatment with disease-modifying antirheumatic drugs (DMARDs) and targeting specific levels of disease activity has been shown to increase the likelihood of disease remission (2,3). In addition to conventional synthetic DMARDs (csDMARDs), an increasing number of effective treatment options are now available to RA patients with the development of biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Despite these advances, disadvantageous socioeconomic status (SES) has been associated with poorer clinical outcomes, including disease activity, disability, and quality of life (4–6). Reasons for the association between socioeconomic factors and differences in RA outcomes remain uncertain (5) but may relate to differences in medication use. These differences are likely multifactorial, relating to delays in initiating DMARD treatment, choice of DMARD, and/or adherence to the prescribed treatment.

Evaluating individuals' SES is complex, as there is no gold standard, and SES varies throughout the life course (7). The utility of personal characteristics, such as highest educational achievement, employment status, or personal income in assessing SES varies as an individual ages. Area-level SES assessments, such as average neighborhood household income, risk misclassifying an individual patient's SES. There is poor overall agreement between area-level and personal SES

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SIGNIFICANCE & INNOVATIONS

- Low socioeconomic status (SES) has been associated with poorer disease outcomes in rheumatoid arthritis (RA) patients, although the reason for this observation is not known.
- Many studies in this review found disparities in medication use among patients with RA according to SES, including types of medications used, persistence with certain treatments, and delays in treatment.
- SES varies across the life course, and studies of SES in RA patients are inconsistent in their definitions of SES, making it difficult for between-study comparisons to be made.
- Work to standardize assessment and reporting of socioeconomic variables should be undertaken in consultation with patients, researchers, and clinicians, thus allowing for better comparisons in results from studies originating across different health care settings.

measures, indicating that they identify different population groups (8,9).

The overall aim of this study was to perform a literature review to establish what is known about the relationship between SES and medication use in RA patients. The primary aim was to determine whether there is an association between SES and medication use in RA. A secondary aim was to describe how studies define and record SES.

MATERIALS AND METHODS

Type of review. A scoping review may be used to examine how research has been conducted on a certain topic, to identify knowledge gaps, and to establish the types of literature available in a given field (10). Scoping reviews may be employed when the subject to be studied is too heterogeneous or complex to be summarized with a formal systematic review. Scoping review methodology is extensively reviewed elsewhere (11). Preliminary literature searches indicated significant heterogeneity between studies precluding the use of systematic review methodology, and so scoping review methodology was employed a priori.

Definitions. *SES.* For the purposes of this study, we have considered SES as "a broad concept that refers to the placement of persons, families, households and census tracts or other aggregates with respect to their capacity to create or consume goods that are valued in our society" (12). We used Cochrane's equity PROGRESS Plus tool (13) to prospectively define a framework for measures that would be considered SES by this definition, similar to the approach of the Cochrane Musculoskeletal Group in assessing health inequity (14). We anticipated that included studies would define an individual's SES through reference to personal factors, including stated gender and age, level of educational attainment, current employment, occupational class, personal income, marital status, and health insurance coverage status. We additionally recorded whether studies reported participants' race and/or ethnicity, as it is a component of the PROGRESS Plus equity framework and may assist in the identification of populations vulnerable to experiencing health care disparity. "Area-level" SES refers to an individual's SES based on aggregate data pertaining to their area of residence (e.g., average neighborhood household income).

Medication use. Medication use was defined as reported or documented prescription of a medicine, reported or documented dispensation of a medicine, reported or documented adherence with medicines, and delays in diagnosis leading to documented delay in medication prescription. Studies were deemed to have identified a difference in medication use if a statistically significant result was found when comparing medication use between socioeconomic groups. This result could be drawn from unadjusted or multivariable/adjusted analyses, and in some cases, from data that did not represent the study's primary outcome measure.

Search strategy. Two main searches were performed in undertaking this review in consultation with a research librarian. Medline, Embase, and PsychInfo databases were searched from inception to February 2022. Articles were selected if they included "rheumatoid arthritis," by subject heading or keyword, in addition to terms for medication use and SES (see Supplementary Tables 1–3, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25024).

The selection of articles to be included was performed using an online systematic literature review tool (Covidence). Initially, the titles and abstracts of the identified articles were screened by a single reviewer (OR) using a conservative approach for relevance to the research questions. A full-text review of the remaining articles was performed by 2 reviewers (OR and CLH), with articles selected according to predetermined inclusion and exclusion criteria. The inclusion criteria were: 1) written in English language; 2) studied RA patients; 3) original research type; 4) retrospective or prospective study design; 5) assessment of medication use; and 6) study included a comparison of medication use based on any marker of SES. The exclusion criteria were: 1) article is a review article or does not present original research; 2) markers of SES were not included as a comparator group for the purposes of assessing for differences in medication use; and 3) treatment addressed as preferences or in a theoretical sense only.

Finally, reference lists of included articles were reviewed for additional studies that had not been identified by the primary search. In doing this, additional studies recording medication adherence as a measure of medication use were identified. As multiple systematic reviews have been undertaken assessing

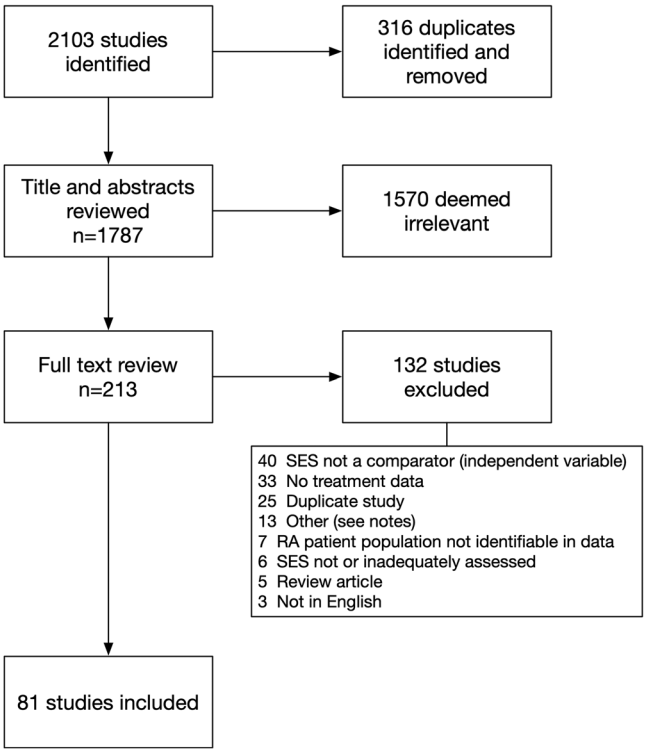

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. RA = rheumatoid arthritis; SES = socioeconomic status.

adherence in RA patients (15–17), studies that addressed only medication adherence as the studied measure of medication use were not included. Studies that were only published as abstracts from conference proceedings were included to assess the entirety of the available literature.

Data extraction. Demographic data were extracted for each study, including year of publication, country of origin, study type, aim, outcome measures, number of participants, proportion of female participants, and mean age of participants. Using the PROGRESS framework, each SES measure recorded by the study was extracted, even if not all measures were used in the comparison of medication use. The type of SES variable measurement was recorded as continuous, categorical, or dichotomous. Information about the medication classes studied was recorded. Analyses were broadly categorized as unadjusted, adjusted/multivariable analyses, or both, based on whether the analyses controlled for confounding variables, such as RA disease activity.

Whether a study recorded a statistically significant difference in medication use between groups of patients with different a SES was recorded. This finding may have been drawn from results separate to the study's primary outcome. The threshold of statistical significance was defined by the methodology of each study.

RESULTS

Literature search. The above search strategy identified 2,103 unique studies (Figure 1). After title and abstract screening, 213 studies were selected for full-text review. Ultimately, 132 were excluded for the following reasons: no SES measure used as a comparator variable (40 studies), no medication use recorded (33 studies), duplicate study (25 studies), results from RA patient group not identifiable (7 studies), SES not sufficiently assessed (6 studies), review article (5 studies), not in English (3 studies), and 13 for other reasons.

Characteristics of included documents. The 81 studies included for full-text review were published between 1994 and 2021, with 79% published since 2010. Of the included studies, almost three-fourths were published articles, with the remainder being conference abstracts (Table 1). Most studies (65%) were retrospective analyses of established observational cohorts or RA registries, followed by cross-sectional analyses (21%), with prospective observational cohort studies being the least frequent (11%). The median number of participants was 1,045.5 (interquartile range [IQR] 269–3,961), and the majority (75%) were female, with a mean ± SD age of 55.9 ± 6.8 years. Studies primarily originated from the US (42% of studies), followed by Canada (12%), and the UK (6%). The main outcome measures included likelihood of prescription or supply of a certain

Table 1. Characteristics of included studies and conference abstracts*

Characteristic	Total (n = 81)
Median year of publication (IQR)	2014 (2011–2017)
Median no. of participants (IQR)	1,045.5 (269–3,961)
Age, mean ± SD years	55.9 ± 6.8
Female, mean ± SD %	75 ± 10
Study origin	
US	34 (42)
Canada	10 (12)
UK	5 (6.2)
Others	32 (40)
Study type	
Cross-sectional	17 (21)
Retrospective cohort	53 (65)
Observational cohort	9 (11)
Other†	2 (2)
Published as a conference abstract	23 (28)
Statistical methodology used	
Unadjusted	17 (21)
Multivariate	54 (67)
Not reported	10 (12)
Category of outcome measure	
Delay to visit or treatment	14 (17)
Medication adherence/persistence	21 (26)
Likelihood of prescription/supply	34 (42)
Access/cost	3 (4)
Disease activity/function	9 (11)

* Values are the number (%) unless indicated otherwise. IQR = interquartile range.
† One study was a cross-cultural study, and the other was a case–control study.

medication or medication class, adherence to or persistence with therapy, delay in treatment, disease activity, function, or access to and/or cost of treatments.

Studies recorded a median of 4 SES variables (IQR 3–6) (Table 2). Aside from age and sex (reported by 88% and 86% of studies, respectively), SES was most commonly assessed by highest level of education achieved (59%), area-level SES (48%), and income (38%).

Area-level SES alone was recorded in 11 studies (14%), whereas personal-level SES (other than age and sex) alone was reported in almost half of studies (40 studies, 49%). Measurement of both area- and personal-level SES occurred in 27 studies (33%), and the nature of SES measurement could not be determined in 3 conference abstracts. Aside from education, all other SES variables were most commonly dichotomized as high or low SES.

Almost all (96%) studies recorded data about DMARD use. Use of csDMARDs was reported by 49 studies (61%), and bDMARD use was assessed in 57 studies (70%). Glucocorticoid use was recorded in 40 studies (49%), use of nonsteroidal antiinflammatory drugs in 17 studies (21%), and opioid use was recorded in only 4 studies (5%). Findings from the included studies are summarized below, and the data extracted from the included studies and abstracts are listed in Supplementary Table 4, available on the *Arthritis Care & Research* website at http://onlinelibrary.wiley.com/doi/10.1002/acr.25024.

Table 2. Level of measurement of socioeconomic status (SES) and race/ethnicity variables in included studies and abstracts*

	Result
Median no. of types of SES measurement (IQR)	4 (3–6)
Level of measurement of participants' age	
Not assessed	10 (12)
Age assessed	71 (88)
Ordinal	13 (16)
Continuous	53 (65)
Other	5 (6)
Participants' sex measured	
Not assessed	11 (14)
Assessed	70 (86)
Level of measurement of participants' educational attainment	
Not assessed	33 (41)
Education assessed	48 (59)
Dichotomous	8 (10)
Ordinal	20 (25)
Continuous	14 (17)
Other	6 (7)
Level of measurement of participants' income	
Not assessed	50 (62)
Income assessed	31 (38)
Dichotomous	14 (17)
Ordinal	11 (14)
Continuous	1 (1)
Other	5 (6)
Level of measurement of participants' occupation	
Not assessed	77 (95)
Occupation assessed	4 (5)
Ordinal	2 (2)
Other	2 (2)
Level of measurement of participants' employment status	
Not assessed	63 (78)
Employment assessed	18 (22)
Dichotomous	10 (12)
Ordinal	6 (7)
Other	2 (2)
Level of measurement of participants' health insurance coverage	
Not assessed	55 (68)
Health insurance assessed	26 (32)
Dichotomous	15 (19)
Ordinal	8 (10)
Other	3 (4)
Level of measurement of participants' marital status	
Not assessed	62 (77)
Marital status assessed	19 (23)
Dichotomous	10 (12)
Categorical	6 (7)
Other	3 (4)
Level of measurement of participants' area-level SES	
Not assessed	42 (52)
Area-level SES assessed	39 (48)
Dichotomous	13 (16)
Ordinal	12 (15)
Continuous	7 (9)
Other	7 (9)
Level of measurement of participants' race or ethnicity	
Not assessed	47 (58)
Race/ethnicity assessed	34 (42)
Dichotomous	11 (14)
Categorical	21 (26)
Other	2 (2)

* Values are the number (%) unless indicated otherwise. IQR = interquartile range.

Effect of education on medication use. Although 41 studies (55%) reported education level, only 29 analyzed its effect on medication use (70% of those studies reporting on education). In those that did, the results were not always drawn from the primary outcome of the study or they were not adjusted for the effects of potential confounding factors.

Increased use of both csDMARD and bDMARDs for participants with greater years of education was demonstrated in numerous studies (18–21). Similarly, participants with lower educational attainment had a lower likelihood of starting a bDMARD in a Norwegian study, although in a time-varying analysis this was only significant for older patients (22). Greater educational attainment was also linked with reduced use of glucocorticoids in unadjusted analyses (18,23). There was no association, however, between education and opioid use in the only study included to assess this (24). Education was associated with differences in the choice of initial bDMARD and also influenced subsequent bDMARD choice at the time of switching, with lower educational attainment associated with the use of non–tumor necrosis factor inhibitors and infliximab at time of switching (25).

Studies examining the impact of education on medication adherence had conflicting results. Studies from the US (26), UK (27), and China (28) found that greater educational attainment was associated with better medication adherence, and conversely, studies from Estonia, Mexico, and Canada found that adherence was poorer in patients with greater educational attainment (29–31). Furthermore, other studies also found no significant difference in adherence according to patients' educational attainment (32–36). Years of education was associated with reduced delay in first rheumatology visit, and ≥13 years of education predicted DMARD prescription in a Spanish study (37).

Effect of income on medication use. Thirty-one studies (38%) recorded participants' income, and 25 studies (30%)

examined the impact of income on medication use. Only 1 study reported income as a continuous variable with high precision, with the remainder using dichotomous (14 studies) or categorical variables (11 studies) to group patients' income status.

Studies from the US found an association between income and likelihood of DMARD use (38) as well as visits to a rheumatologist (39). Lower income and lack of a rheumatologist visit were linked with higher likelihood of glucocorticoid monotherapy (40). Regardless of rheumatologist visits, low income was a predictor of stopping DMARDs in another US study (41). Patients in the US with greater annual personal income had higher likelihood of bDMARD initiation (42), whereas Medicare beneficiaries without a low-income subsidy (and who therefore have a higher out-of-pocket cost for medications) had a lower likelihood of initiating subcutaneously administered (Part D) bDMARDs (43). However, an association between income and medication use was not demonstrated in the 2 non-US originating studies from Canada (44,45).

There was no consistent association between income and medication adherence across studies. Low income was found to be associated with better medication adherence in studies from the US (35) and Estonia (29), whereas other studies from China (28), Canada (31), Pakistan (46), and Austria (33) supported an inverse relationship.

Effect of area-level SES measurements. Thirty-nine studies (48%) assessed area-level SES. There was significant heterogeneity between studies in defining area-level SES measures. Some studies dichotomously defined disadvantaged areas as those areas having a certain percentage of individuals under a particular poverty threshold, whereas others applied composite population-level data using localized indexes such as the Index of Multiple Deprivation, the Carstairs Deprivation Index (both used in the UK), or the Socioeconomic Index for Areas (SEIFA; Australia) or categorically based on different counties/regions. When defined using the Townsend Index based on postal code, area-level disadvantage was found to be associated with greater RA disease activity and disability in a prospective cohort from the UK (47), with no effect on medication use seen, although this was not the primary outcome of this study.

Living in localities with lower average personal incomes was associated with less DMARD (inclusive of csDMARD and bDMARD) use in a US study (38), and living in areas with more federally qualified health centers (another surrogate for disadvantage) was found to be associated with lower likelihood of initiating bDMARD therapy in another (48). Area-level SES did not consistently predict bDMARD use in RA patients from the US, and bDMARD initiation was not associated with differences in average area-level income (49). A Romanian study found that RA patients in urban areas and regions with a greater gross domestic product (GDP) or numbers of physicians had greater access to bDMARDs (50).

At a country level, the impact of GDP on access to treatments for RA was highlighted by Sokka et al, who found that more csDMARDs were used per capita in countries with a high GDP than in countries with a lower GDP, and that disease activity improved with increases in a country's GDP (51). Other studies found that country GDP was inversely proportional to bDMARD and tsDMARD affordability (52) and to bDMARD retention, even after adjustment for disease activity (53).

Area-level disadvantage in Australia, defined using the SEIFA's Index of Relative Socioeconomic Advantage and Disadvantage, conferred a risk of delay in RA diagnosis (54). Median household income was inversely associated with odds of delays in diagnosis and treatment in a US study (55). In Canada, the Marginalisation Index Composite score was not associated with differences in first bDMARD prescription (56).

Effect of race/ethnicity on medication use. Thirty-four studies (42%) assessed race or ethnicity, with 26 (84% of those reporting on race/ethnicity) assessing its impact on medication use. Most studies that assessed race/ethnicity originated in the US (25 studies, 81%). Studies that included this variable found that African American patients had greater disease activity (57), pain (58), and disability (59), with similar disparities also seen for Hispanic patients (60), when compared with White patients.

African American RA patients experienced reduced receipt of DMARDs (38,61) and increased use of glucocorticoid monotherapy (40) in studies using Medicare data. Studies using registry data found reduced self-reported DMARD use in African American (57,62) and non-White patients (63) and greater use in Hispanic patients (41,48,62). The effect of contact with a rheumatologist was found to be an important covariate in some of these studies, and visiting a rheumatologist in the past year was found to be the strongest predictor of DMARD use despite adjustment for race/ethnicity in one study (39).

Assessment of medication adherence is highly dependent on the instrument used to measure adherence. Nonetheless, 3 studies found significant differences in adherence based on patients' race/ethnicity. Two cross-sectional studies from the US identified lower adherence to DMARDs in African American patients compared with White patients based on Compliance Questionnaire Rheumatology (26) or Medication Adherence Report Scale (MARS) scores (34). The other study from the UK found that South Asian RA patients had significantly lower adherence, using either a dichotomous or continuous definition of adherence based on MARS score, than white British patients. More negative views of DMARDs in the Beliefs about Medicines Questionnaire were also found in this patient group (27).

DISCUSSION

This review has found evidence of an association between SES and medication use in patients with RA. However, there

was significant heterogeneity between studies in how both SES and medication use were defined, making it difficult to draw conclusions from the existing literature.

In RA patients, lower SES is associated with increased prevalence (64), poorer outcomes in terms of pain and function (65), greater disease activity (4,66), and premature mortality (67), while patients with a greater socioeconomic background have a reduced time to diagnosis (68). These differences may be driven by variations in medication use, and this review sought to explore the existing literature in order to better understand this association and identify the knowledge gaps in the area.

All studies included in this review were observational, and most were retrospective cohort studies (65%) or cross-sectional studies (21%). Such data are limited in their ability to determine causality from any demonstrated associations between independent and dependent variables. This is relevant, as pain or disability from RA may itself prevent patients from being able to work or study, leading to changes in patients' socioeconomic position (5). This example of reverse causality represents an alternative paradigm in which disadvantageous changes to patients' social circumstances may themselves influence medication use.

Individuals' SES, in addition to the best means of measuring it, may vary through the life course. Additionally, the validity and discriminant ability of SES measures relative to one another may change over time; income inequality has increased internationally over the last 3 decades (69), while the proportion of adults without postsecondary education is declining (70). These factors may be problematic when attempting to understand an SES measure's effect over many years in longitudinal cohorts (7). Choosing to define SES exclusively at the area level, without reference to the individual's personal SES, represents a possible source of bias; the ecological fallacy states that an individual can be misclassified when using only an area-level assessment to define their SES (9).

We found that studies measured relatively few SES variables, and only one-third recorded both a personal- and an area-level SES variable. This is important, as assessment of both area- and personal-level SES was found to strengthen the relationship between disadvantageous SES and reduced DMARD use by one study included here (38). Area-level and personal SES measures have independent effects on outcomes and combine to modify an individual's RA disease course (71).

Our results are similar to previous findings from meta-analyses of published research, including a review of articles featured in a systematic review that looked at whether health equity is considered in systematic reviews of the Cochrane Musculoskeletal Group (14). Those authors found that primary studies of interventions for RA patients generally reported insufficient variables necessary to address questions about health inequalities. Similarly, it was noted by an Outcome Measures in Rheumatology (OMERACT) special interest group in 2019 that few longitudinal RA outcome studies or registries report sufficient collection of variables to determine SES (72).

In studying health care disparities, the "understanding" phase of inquiry describes attempts to explain the presence of disparities identified in vulnerable populations (73). This includes weighing the relative contribution of both patient and nonpatient factors in contributing to a particular outcome. In our review, of the outcome measures assessed, nonpatient factors included clinician prescribing behavior, which was assessed by 42% of studies through assessment of variation in medication prescription or dispensation; the majority of these studies found evidence of variation in medication use according to the SES measure utilized.

To our knowledge this is the first scoping review to consider the impact of SES on the overall concept of medication use in RA patients. This is also one of only a few studies to collect data on the number of socioeconomic variables measured in RA studies and how they were measured (dichotomous, categorical, or continuous).

Another strength of this review was the use of the PROGRESS Plus framework to prospectively assess measurement of socioeconomic variables by included studies, ensuring robust data extraction. This tool requires consideration of patients' race and/or ethnicity in assessing equity, although we do not suggest that race and/or ethnicity represents a measure of SES, and thus, there was not a specific search term for this in our search strategy. This may have led to underascertainment of such articles in our search. Nonetheless, 34 studies examined patients' race and/or ethnicity, and we therefore felt it was therefore appropriate to highlight the impact of this factor in modifying patients' medication use. Assessment of study quality is not typically undertaken in scoping reviews (74), however, we incorporated information about the type of statistical analyses undertaken as a measure of the quality of the statistical analyses used. Additionally, the inclusion of studies published as conference abstracts has broadened the scope of this review.

There are notable differences between countries' health care systems, including differences in health insurance system, out-of-pocket payments, and reimbursement mechanisms. This is of particular relevance to our study because of the differences in prescription rules for bDMARDs and how these regulations may influence patients' medication use beyond the effects of individual patient or clinician factors. These differences should be noted when comparing results from studies from different countries, and further studies, like that of Bergstra et al (75), are needed. We did not limit our search for articles to any one country or type of health care system, but the majority of our results came from middle and high GDP countries, which limits the generalizability of our findings.

As demonstrated in this review, there is marked diversity in the approach to defining SES in studies of RA patients assessing medication use. We advocate for future studies to use both personal- and area-level SES measures in their analyses, recognizing that 1 single variable is unlikely to be adequate in characterizing an individual patient's SES. Considering the impact of

country-level factors, including health care coverage and bDMARD prescription rules, is also important in interpreting studies' results. A formal Delphi process, involving clinicians, researchers, and patients, may be needed to generate formal recommendations for the assessment of socioeconomic variables in future studies. We note the recent equity extension to the Consolidated Standards of Reporting Trials (CONSORT) statement (76); a similar extension could subsequently be proposed for the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) observational trials framework.

This scoping review is the first to summarize the existing literature regarding the association between SES and medication use in RA patients. While it found some evidence that SES is associated with differences in medication use among RA patients, the heterogeneity of the studies and variability in the definitions used for both predictor SES variables and outcome medication use variables highlighted that there is still much work to be done to better understand the impact of SES on this disease. This finding was demonstrated despite the lack of a standardized approach to the measurement of SES across studies and acknowledging the complex, bidirectional relationship between SES and disability from RA. Future studies should utilize well-defined SES measures, including both personal- and area-level variables, to contribute to the understanding phase of this health disparity. Further insight into the relative contribution of patient and nonpatient factors will ultimately improve the efficacy of interventions at both the local and country level to improve disparities in outcomes for RA patients.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Mr. Russell had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Analysis and interpretation of data. Russell.

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