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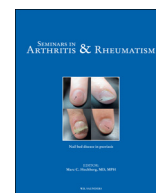
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The impact of rheumatoid arthritis on quality-of-life assessed using the SF-36: A systematic review and meta-analysis

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ABSTRACT

Objective: The assessment of health-related quality-of-life (HRQoL) in rheumatoid arthritis (RA) is becoming increasingly common in both research and clinical practice. One of the most widely used tools for measuring HRQoL is the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36). We conducted a systematic review examining the impact of RA on HRQoL, measured through the SF-36. **Methods:** MEDLINE and Embase were searched for observational studies reporting mean and standard deviation scores for each domain of the SF-36 in adult RA patients. Studies were reviewed in accordance with PRISMA guidelines, and a random-effects meta-analysis was performed.

Results: In total, 31 studies were eligible for inclusion in the meta-analysis, including 22,335 patients. Meta-analyses found that pooled mean HRQoL score for the SF-36 physical component summary was 34.1 (95% CI: 22.0–46.1) and mental component summary was 45.6 (95% CI: 30.3–60.8). Increased age was associated with reduced physical function and physical component summary (PCS) scores but improved mental health and mental component summary (MCS) scores. Female gender was associated with improved scores on role physical, bodily pain and PCS but reduced mental health and MCS scores. Longer disease duration was associated with improved MCS. Patients with RA have a substantially reduced HRQoL in comparison to both other physical illnesses and in comparison to normative datasets from UK and USA populations.

Conclusions: RA has a substantial impact on HRQoL. This supports recent NICE guidelines stipulating that RA patients should be regularly assessed for the impact their disease has on HRQoL and appropriate management provided.

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Introduction

Rheumatoid arthritis (RA) has major, diverse effects on patients' health-related quality-of-life (HRQoL), spanning both physical and mental domains of well-being [1]. However despite having been measured in many studies, there are currently no systematic reviews providing summary estimates and exploring the factors that are most strongly associated with HRQoL. Measurement of HRQoL is potentially useful for several reasons. Firstly, many patients value HRQoL more than disease-related variables such as inflammatory biomarkers or joint counts [2]; assessing clinical state exclusively in terms of narrow disease activity may not characterise the health outcomes of primary concern to patients.

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Secondly, reduced HRQoL in RA patients is associated with increased use of healthcare resources [3] and with increased levels of depression [4]. Therefore limiting the adverse effects of RA on HRQoL should be a key therapeutic goal.

The Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) [5] is a popular tool for assessing HRQoL and has been used in many physical health conditions and healthcare settings [6,7]. It defines HRQoL as the extent to which physical health impacts an individual's functional ability and perceived well-being in mental, social and physical aspects of life [5]. The SF-36 has 8 individual subscales divided across physical and psychological HRQoL domains: Physical Function (PF), Role Physical (RP), Bodily Pain (BP), and Global Health (GH), Vitality (V), Social Function (SF), Role Emotional (RE) and Mental Health (MH). Scores on these subscales can be combined to form 2 higher-order summary scores, the Physical Component Summary (PCS) and Mental Component Summary (MCS). The PCS is calculated by positively weighting the 4 subscales in the physical domain (PF, RP, BP and GH) and the remaining psychological domain subscales negatively. In contrast the MCS is calculated by positively weighting the 4 mental domain subscales (MH, V, SF and RE), and negatively weighting the 4 physical domain subscales.

The SF-36 has been found to be a reliable and valid measure in RA [8], correlating well with disease-specific measures like the Health Assessment Questionnaire (HAQ [9]) and the Arthritis Impact Measurement Scale (AIMS [10]). However, rather than providing a disease-specific assessment of HRQoL, as provided by the HAQ and AIMS, the SF-36 is a generic measure, applicable to both the normal population and other disease groups, thus providing a useful tool for comparison of HRQoL between diseases and in comparison to healthy populations.

Increased levels of pain, disease activity and reduced physical function have been shown to be associated with reduced HRQoL in RA [11,12]. The evidence from studies of other chronic diseases suggests that a number of other factors may be expected to have an impact, including gender, body mass index (BMI), disease severity and age [13–15]. Several of these associated variables provide possibilities for targeted intervention, with potential to improve both HRQoL and physical health. To date, there has been limited systematic assessment of the impact of RA on HRQoL, however a literature review assessing pain and HRQoL in older patients (≥ 75 years) with RA found that pain, increased age and functional limitation decreased HRQoL [16]. The present article aims to fill this gap in the literature. We aim (1) to systematically review the literature assessing the impact of RA on the 8 domains of the SF-36, (2) to provide a meta-analysed mean score for each SF-36 domain and Physical and Mental Component Summary scores, (3) to explore the impact of study characteristics on HRQoL scores and (4) to compare HRQoL in RA patients with HRQoL in the general population and in other health conditions.

Patients and methods

Search strategy and selection criteria

Data extraction forms were designed in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA [17]). MEDLINE and Embase were searched using the Ovid platform from 1992 (when the SF-36 was developed) to October 2012. The following search terms were used: *Rheumatoid Arthritis* or *RA* and *Quality of Life* or *SF-36*. The search was limited to articles only published in English.

Inclusion and exclusion criteria

Our target was populations of individuals with RA whether recruited from the general population, primary care or secondary care samples.

Studies were included if they met the following criteria: (1) case–control, cohort, and cross-sectional design; (2) HRQoL assessed using the SF-36; (3) a sample size of 50 or more patients and (4) HRQoL must have all 8 SF-36 domains recorded as mean scores with standard deviations (SDs) or standard errors (SE).

Studies were excluded if they (1) were case-series, case-reports, expert opinion or consensus statements; (2) included fewer than 50 patients; (3) were duplicates using the same patient data; (4) did not record all 8 SF-36 domains with means and SDs or (5) used a sample in which patients were selected on the basis of their HRQoL scores (e.g., intervention trials). To maximise the external validity of our findings, we excluded interventions and randomised controlled trials (RCTs). RCTs tend to utilise rigorous eligibility criteria (such as high disease activity and low levels of comorbidity), limiting the eligibility of their results to the general RA population [18]. Studies that reported SF-36 domain scores normalised against the population were excluded from meta-analysis but were assessed in a narrative synthesis.

Data extraction and quality assessment

FM conducted the primary data extraction. In order to reduce bias, all articles were examined independently by a second reviewer (I.S.). Inter-rater disagreement was minimal; any disagreements were resolved through discussion and re-examination of the article. When multiple publications spanned the years of longitudinal studies, baseline levels of HRQoL were reported.

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [19] was referred to for the development of a purpose-built 8-point quality assessment tool (Appendix 1). This addressed aspects of methodology that could impact reported outcomes, and assessed the sampling method used, the sample size, participation rate and the eligibility criteria for participation in the studies. Articles were scored using the following scale: 0–2 = low quality, 3–5 = medium quality and 6–8 = high quality.

Statistical analyses

Heterogeneity was found to be high between studies, therefore random-effects meta-analyses with 95% confidence intervals (CI) were conducted with STATA (version 10.0), using the metan package [20]. To calculate PCS and MSC values, scores for each of the 8 domains were extracted and standardized using a z-score transformation. They were then multiplied by 10 and added to 50 to generate normalised scores for each domain and aggregated using factor score coefficients and creating normalised scores for each component summary [21]. PCS and MCS scores were meta-analysed using the standard errors provided for the Physical Function (PF) and Mental Health (MH) domains, respectively, as these domains represent the largest weighting within each component summary. Heterogeneity was assessed using I^2 , with values approximating 25%, 50% and 75% indicating low, moderate and high heterogeneity, respectively [22].

Spearman's correlation analyses with adjusted r^2 were used to assess the impact of linear study variables and sample characteristics on HRQoL scores. Additionally, the clinical variables associated with HRQoL in RA were discussed qualitatively; the wide range of measures used and methods used to analyse data limited meta-analytic possibilities.

Sensitivity analyses explored whether pooled mean SF-36 scores were influenced by study design. Planned sensitivity analyses included exclusion of studies with a participation rate $\geq 75\%$ or non-reported participation rate, exclusion of studies not stating a sampling strategy or using a convenience/non-randomised sampling strategy; exclusion of studies that did not state eligibility criteria for inclusion in the study; and exclusion of

studies using subsets of patients (e.g., a female-only sample or patients with limited disease duration). Subgroup analyses were planned by overall study quality, sample size, publication decade and version of SF-36 questionnaire used, if there was more than one study in the subgroup. A significant difference between primary and sensitivity and subgroup analyses was deemed present when confidence intervals did not overlap.

To make comparison with other health conditions, data from RA patients were plotted in a graph alongside data from patients with hypertension, congestive heart failure, type 2 diabetes, clinical depression and myocardial infarction collected from the SF-36 manual [23]. Normative datasets from UK [24] and the USA [23] were used to compare HRQoL in RA patients with the HRQoL of healthy individuals.

Results

Search results

We screened 3248 potentially relevant, non-duplicate articles (Fig. 1). Assessment of study titles and abstracts resulted in the exclusion of 2785 articles. The full texts of 463 articles were assessed for eligibility, and 427 were excluded due to not meeting eligibility criteria for inclusion. At data extraction, a further 3 were excluded, resulting in 33 articles being deemed eligible for inclusion. One of these articles was normalised against the general population, and another's norm-status could not be established. These 2 were therefore discussed in a narrative synthesis, while the remaining 31 articles were included in the meta-analysis.

Included studies

Table 1 presents the 33 articles included in the review; full references can be found for these studies in Appendix 2. The studies represented a total of 22,473 patients with RA; the median of mean ages was 53.9 years (IQR: 51.0–57.5 years), and the

median percentage of females represented in the sample was 78.3% (IQR: 73.4–81.8%). Sample sizes ranged from 50 to 13,722 participants, with a median of 156.0 (IQR: 86.0–297.0).

Quality assessment

Table 1 also shows the quality assessments for the 33 articles, according to the quality assessment tool. The average quality of the articles was low to moderate with a median quality score of 3.0/8.0 (IQR: 2.0–5.0). Three articles scored 0/8, and 23 (65.7%) of articles scored 4/8 or lower. One article achieved the maximum score of 8 [25] and 2 received 7 out of 8 [26,27]. Specifically, 24.2% of studies had a sample size larger than 300, only 39.4% stated a participation rate and of these, only 30.8% had a participation rate over 75%, and only 60.6% of studies reported participant eligibility criteria for entry into the study.

Impact of RA on HRQoL

Table 2 demonstrates the pooled mean scores for the 8 SF-36 subscales, with 95% confidence intervals (CI). The physical health domains (PF, RP, BP and GH) showed lower (worse) mean scores than the mental health domains (V, SF, RE and MH). Forest plots of each domain meta-analysis can be found in Appendix 3. The pooled scores for the physical health domains ranged between 36.1 and 49.0, with the lowest (worst) being RP and the highest (best) being PF. The pooled overall PCS score was 34.1 (Fig. 2). The pooled scores for the mental health domains ranged between 45.1 and 69.1, with V scoring the lowest (worst) and MH showing the highest (best) score. The pooled overall MCS score was 45.6 (Fig. 2).

Narrative synthesis of normalised studies

One study examined HRQoL in both early-stage and late-stage Norwegian RA patients, and normalised their data against the Norwegian population [28]. In early-stage RA, all physical domains (PF, RP, BP and GH) were substantially lower than in the general population. The overall mean PCS score was 37.7 (SD = 5.7), indicating a reduced overall physical HRQoL in comparison to the Norwegian population (M = 50.0, SD = 10.0). Mental HRQoL (V, SF, RE and MH) tended to not differ so greatly from population scores, with RE and MH domains scoring slightly higher than general population scores (51.1 and 51.2, respectively). The overall MCS score was slightly higher than MCS in the Norwegian population (52.7, SD = 7.9). In late-stage RA, a similar pattern of scores was found. Patients reported lower levels of PF (34.7), RP (40.8), BP (39.3) and GH (36.8) than the general population, and overall MCS score was substantially lower than the mean population score of 50.0 (32.5, SD = 8.0). Again, mental health scores were slightly higher, with V and SF scoring lower than the general population (44.7 and 45.6, respectively) and RE and MH scoring higher than the general population (50.7 and 53.6, respectively). Overall MCS score was slightly higher than MCS in the Norwegian population (55.6, SD = 6.4).

One study used the first version of the SF-36, although it could not be confirmed whether scores had been normalised against population scores or not, as although the scores seemed low, they had large standard deviations [29]. This study assessed HRQoL in Italian RA patients and reported lower levels of physical HRQoL than mental HRQoL. Patients reported low levels of PF (29.0, SD = 27.5), RP (15.0, SD = 35.1), BP (17.7, SD = 16.5) and GH (22.0, SD = 19.0) and low overall PCS (24.1, SD = 7.1). Patient-reported mental HRQoL was slightly higher: V (30.6, SD = 23.5), SF (41.5, SD = 31.6), RE (30.4, SD = 42.7) and MH (39.4, SD = 22.7). Overall MCS was also lower than PCS (36.1, SD = 11.7). Additionally, they looked at early RA patients and found substantially impaired HRQoL in the physical domains and mental domains. Overall PCS

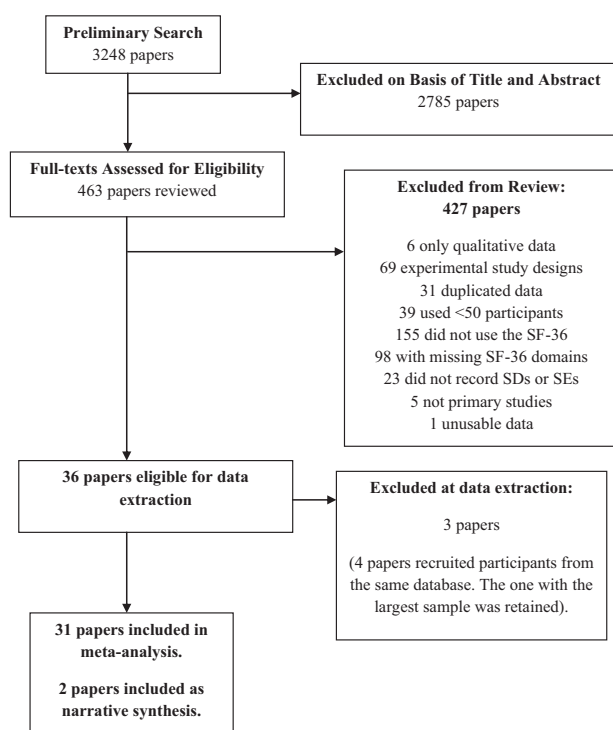


Fig. 1. Articles identified and screened for eligibility.

Table 1
Overview of studies reporting SF-36 QoL in rheumatoid arthritis patients

| References | Country | Study design | Sampling method ^a | Quality ^b | Sample size | Setting ^c | Participation rate (%) | Mean age (sd) | Mean disease duration (sd) | Women (%) |
|---------------------------------|-----------------|-----------------|------------------------------|----------------------|-------------|----------------------|------------------------|---------------|----------------------------|-----------|
| <i>Meta-analysis</i> | | | | | | | | | | |
| Aggarwal, 2006 | India | Cross-Sectional | 0 | 0 | 101 | 1 | – | 43.2 (11.7) | 8.1 (5.6) | 89.1 |
| Aktekin, 2011 | Turkey | Cross-Sectional | 1 | 3 | 166 | 0 | – | 52.5 (12.6) | 10.6 (8.1) | 78.3 |
| Alishiri, 2008 | Iran | Cross-Sectional | 1 | 5 | 411 | 1 | 9 | 46.8 (12.0) | 6.3 (5.7) | 87.3 |
| Bartlett, 2003 | USA | Cross-Sectional | 1 | 5 | 77 | 1 | 71.0 | 57.5 (13.0) | – | 80.5 |
| Campolina, 2010 | Brazil | Cross-Sectional | 0 | 2 | 200 | 1 | – | 49.2 (10.0) | 11.6 (8.4) | 78.0 |
| Chermond, 2008 | Brazil | Cross-Sectional | 1 | 3 | 100 | 1 | – | 51.0 (11.0) | 11.0 (8.0) | 92.0 |
| Dadoniene, 2003 | Lithuania | Cross-Sectional | 1 | 6 | 201 | 2 | 56.0 | 55.9 (10.0) | 11.9 (9.5) | 83.0 |
| de Souza, 2011 | Brazil | Cross-Sectional | 0 | 0 | 50 | 1 | – | 52.3 (7.7) | 11.1 (8.0) | 92.0 |
| Eser, 2012 | Turkey | Cross-Sectional | 0 | 1 | 150 | 0 | – | 53.3 (12.1) | 12.3 (8.3) | 84.0 |
| Geuskens, 2008 | The Netherlands | Cross-Sectional | 0 | 3 | 86 | 1 | 61.3 | 53.0 (14.0) | 16.0 (17.0) | 72.0 |
| Ibn Yacoub, 2011 | Morocco | Cross-Sectional | 1 | 3 | 185 | 1 | – | 46.6 (10.8) | – | 100.0 |
| Ibn Yacoub, 2012 | Morocco | Cross-Sectional | 0 | 2 | 248 | 1 | – | 47.5 (11.7) | 10.6 (8.1) | 79.0 |
| Kvien, 1998 | Norway | Cross-Sectional | 0 | 4 | 1030 | 2 | 66.4 | 62.3 (14.69) | 12.9 (11.4) | 79.0 |
| Laas, 2009 | Finland | Longitudinal | 0 | 1 | 97 | 1 | – | 52.0 (13.0) | 17.0 | 75.0 |
| Lapsley, 2002 | Australia | Longitudinal | 0 | 3 | 81 | 1 | 70.0 | 58.2 (11.2) | 15.6 (9.9) | 80.0 |
| Lempp, 2009 | UK | Cross-Sectional | 0 | 3 | 125 | 1 | – | 58.9 (13.5) | 12.2 (11.5) | 73.8 |
| Lie et al. [25] | Norway | Longitudinal | 1 | 8 | 1218 | 3 | 85.0 | 56.4 (13.7) | 4.2 (7.9) | 71.3 |
| Linde et al. [8] | Denmark | Cross-Sectional | 0 | 2 | 200 | 1 | – | Median 59.0 | Median 6.0 | 77.0 |
| Linde, 2008 (b) | Denmark | Longitudinal | 0 | 5 | 150 | 1 | 89.8 | Median 60.0 | – | 80.0 |
| Longford, 2011 | Spain | Cross-Sectional | 0 | 3 | 812 | 1 | – | 60.7 (14.2) | – | 78.8 |
| Mok et al. [26] | China | Cross-Sectional | 1 | 7 | 153 | 1 | 80.6 | 51.7 (10.8) | 6.2 (6.1) | 77.0 |
| Picavet, 2003 | The Netherlands | Cross-Sectional | 1 | 5 | 156 | 2 | 46.9 | – | – | – |
| Rupp, 2004 | The Netherlands | Longitudinal | 0 | 5 | 679 | 1 | 56.6 | 59.6 (13.8) | 8.7 (9.3) | 71.0 |
| Ruta, 1998 | UK | Cross-Sectional | 1 | 3 | 240 | 0 | – | 56.0 (14.0) | 13.0 (13.0) | 78.3 |
| Salaffi, 2002 | Italy | Cross-Sectional | 0 | 1 | 78 | 1 | – | 56.0 | 7.1 | 70.5 |
| Salaffi, 2010 | Italy | Cross-Sectional | 1 | 7 | 469 | 1 | 62.1 | 57.5 (14.3) | 6.1 (4.2) | 71.8 |
| Sivas, 2009 | Turkey | Cross-Sectional | 0 | 0 | 79 | 0 | – | 42.4 (9.0) | 8.6 (5.5) | 100 |
| Soderlin, 2007 | Sweden | Longitudinal | 0 | 4 | 724 | 2 | 73.0 | 64.0 | 15.0 | 73.0 |
| Thyberg, 2005 | Sweden | Longitudinal | 0 | 6 | 297 | 1 | 92.8 | 55.0 (15.0) | < 1 year | 68.0 |
| West, 2009 | Sweden | Longitudinal | 1 | 2 | 50 | 1 | – | 50.6 | < 1 year | 68.0 |
| Wolfe, 2010 | USA | Cross-Sectional | 0 | 2 | 13,722 | 2 | – | 61.2 | – | 77.0 |
| <i>Narrative synthesis</i> | | | | | | | | | | |
| Altinkesen and Gelecek [28] | Turkey | Cross-Sectional | 0 | 1 | 78 | 1 | – | 54.5 (9.1) | 10.3 (4.6) | 78.2 |
| Picchianti-Diamanti et al. [29] | Italy | Longitudinal | 1 | 2 | 60 | 1 | – | 53.0 (12.6) | 5.1 (9.1) | 75.0 |

For references see online Appendices.

^a 0 = convenience/non-randomised or undefined sampling strategy, 1 = consecutive/randomised sampling strategy.

^b Quality rated out of 8: 0–2 = low quality, 3–5 = medium quality and 6–8 = high quality.

^c 0 = not stated, 1 = outpatient clinic, 2 = database/register and 3 = outpatient clinic/database.

was 25.6 (SD = 3.9), and overall MCS was 29.5 (SD = 9.0), suggesting that people with early RA have lower mental HRQoL than patients with more established RA but comparable overall physical HRQoL.

Associated study variables

Spearman's correlation analyses with adjusted r^2 were used to assess the associations between linear variables and HRQoL

Table 2
Meta-analysed SF-36 scores and associated study variables

| | SF-36 sub-group and summary scores | | | | | | | | | |
|-----------------------------------|------------------------------------|-------------------|--------------------|-----------|------------------------------|--------------------|-----------|-----------|--------------------|----------------------------|
| | PF | RP | BP | GH | PCS | V | SF | RE | MH | MCS |
| <i>Meta-analysis results</i> | | | | | | | | | | |
| Pooled mean | 49.0 | 36.1 | 46.6 | 48.3 | 34.1 | 45.1 | 66.0 | 59.6 | 69.1 | 45.6 |
| 95% CI | 48.7–49.4 | 35.8–36.5 | 46.3–46.9 | 48.0–48.6 | 22.0–46.1 | 44.8–45.4 | 65.7–66.4 | 59.0–60.1 | 68.8–69.3 | 30.3–60.8 |
| Heterogeneity I^2 (%) | 94.6 | 97.4 | 98.7 | 98.0 | 0.0 | 97.6 | 98.6 | 96.9 | 99.1 | 0.0 |
| <i>Associated study variables</i> | | | | | | | | | | |
| Study quality | –0.05 | –0.15 | –0.25 | 0.05 | – 0.23 | –0.30 | –0.04 | –0.02 | 0.12 | 0.06 |
| Sample size | –0.31 | –0.03 | –0.19 | –0.20 | – 0.19 | –0.44 [†] | –0.23 | –0.07 | –0.10 | – 0.13 |
| Mean age | –0.49 ^{**} | –0.23 | –0.23 | –0.16 | – 0.60 ^{***} | –0.36 | 0.15 | 0.20 | 0.47 ^{**} | 0.42 [†] |
| Mean disease duration | –0.22 | –0.16 | 0.09 | 0.08 | – 0.26 ^{***} | –0.01 | 0.27 | 0.39 | 0.39 | 0.47 [†] |
| % Female | 0.25 | 0.36 [†] | 0.53 ^{**} | 0.09 | 0.60 ^{***} | 0.24 | –0.14 | –0.10 | –0.43 [†] | – 0.42 [†] |
| Publication year | 0.32 | 0.24 | 0.24 | –0.02 | 0.40 [†] | 0.18 | 0.07 | –0.14 | –0.22 | – 0.28 |
| Participation rate | 0.05 | –0.31 | –0.17 | 0.40 | – 0.02 | –0.25 | 0.04 | –0.27 | –0.01 | – 0.13 |

Note: Bold numbers denote summary scores of physical (PCS) and mental (MCS) components.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

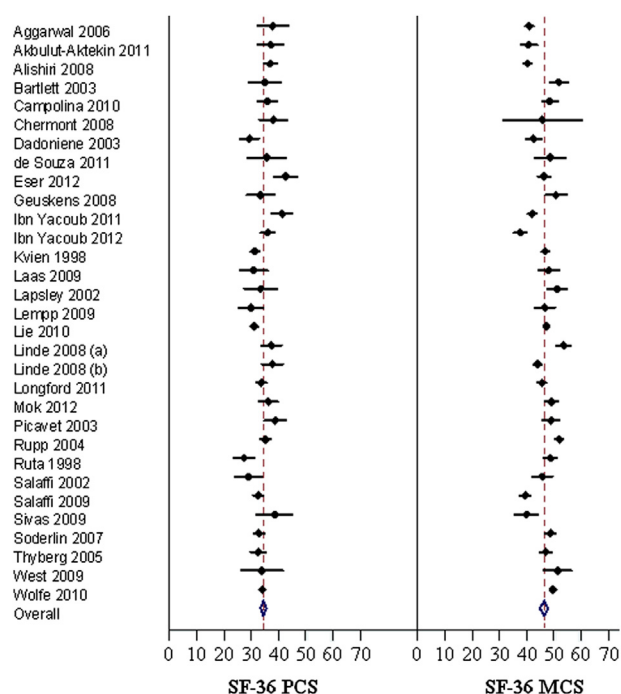


Fig. 2. The impact of RA on SF-36 Mental and Physical Component Summaries; meta-analysed SF-36 scores in rheumatoid arthritis patients by random-effects meta-analysis.

(Table 2) including mean age of participants, proportion of female participants, sample size, overall study quality, participation rate, publication year and mean duration of illness.

Sample size was not associated with HRQoL, except for V, which was found to be higher in smaller sample sizes ($r = -0.44$, $p < 0.05$). Mean age was significantly associated with PF, overall PCS, MH and MCS. A lower mean age was significantly associated with improved PF ($r = -0.49$, $p < 0.01$) and higher PCS scores ($r = -0.60$, $p < 0.001$); a higher mean age was associated improved MH ($r = 0.47$, $p < 0.01$) and improved overall MCS scores ($r = 0.42$, $p < 0.05$).

Mean disease duration was associated with overall MCS score; a longer disease duration was significantly associated with improved MCS scores (0.47 , $p < 0.05$).

Significant associations were found between the proportion of female participants and levels of RP, BP, PCS, MH and MCS. Having a higher proportion of female participants was significantly associated with improved RP ($r = 0.36$, $p < 0.05$), BP ($r = 0.53$, $p < 0.01$) and overall PCS ($r = 0.60$, $p < 0.001$), with poorer MH ($r = -0.43$, $p < 0.05$), and poorer overall MCS ($r = -0.42$, $p < 0.05$). Publication year was significantly associated with improved PCS scores ($r = 0.40$, $p < 0.05$), with more recent publication years relating to improved PCS scores.

Sensitivity and subgroup analyses

Appendix 4 shows the pooled mean SF-36 domain scores according to each sensitivity and subgroup analysis in comparison to the primary analysis.

Planned sensitivity analyses included the exclusion of with unreported participation rates (PR) or PR lower than 75%; excluding convenience, non-randomised or unreported sampling methods; excluding studies with no eligibility criteria reported; excluding studies using subset of patients and the exclusion of studies recruiting non-secondary care patients.

The exclusion of studies with low or unreported participation rates significantly reduced RP, BP, PCS, V, SF, RE and MCS scores.

Excluding studies using non-randomised, convenience or with unspecified recruitment strategies significantly lowered RP, BP, GH, PCS, V, SF, RE, MH and MCS scores. Excluding studies not reporting eligibility criteria significantly reduced RE and MH scores, whilst excluding studies with subsets of patients increased RP scores. Excluding studies using SF-36 version 2 did not significantly alter the findings.

The subgroup analyses were performed according to overall study quality, sample size, decade of publication and area of origin. Reduced study quality (0–2) tended to yield higher scores on RP, BP, GH, PCS, SF, RE, MH and MCS domains. Moderate study quality (3–5) significantly lowered BP scores whilst higher study quality (6–8) reduced RP scores and increased PCS and RE scores.

Studies with smaller sample sizes (50–149) found reduced levels of RP, PCS, RE, MH and MCS but increased V. Moderate sample sizes (150–399) showed reduced levels of MH, whilst studies with larger sample sizes (>400) found reduced levels of SF and MH. When dividing the articles up into publication decade, studies published in the 1990s showed reduced levels of RP, GH, PCS, V and MCS, whereas publications post-2010 indicated improvements in RP, GH, PCS, SF, RE, MH and MCS.

Finally, data from Scandinavian patients indicated reduced RP, PCS, V, SF, RE and MCS but improved GH in comparison to the overall pooled scores. Studies using patients from non-Scandinavian Europe show lower levels of PF, RP, BP, GH, PCS, SF, MH and MCS in comparison to overall pooled scores. Asian studies report lower levels of PF, BP, GH, SF, RE, MH and MCS but increased RP and V. Data from American/South American studies report higher levels of RP, BP, GH, PCS, SF, RE, MH and MCS but reduced V. Studies from Africa show higher levels of BP, GH and PCS but lower levels of V, SF, RE, MH and MCS.

Comparison of RA patients with other long-term conditions and normal controls

Un-standardized data from patients with hypertension, congestive heart failure, type 2 diabetes, myocardial infarction and clinical depression were obtained from the SF-36 manual [23] and plotted in a graph against the un-standardized RA SF-36 scores (Fig. 3). The results of this comparison demonstrate that RA patients show consistently lower levels of physical HRQoL components PF, RP, BP and GH than patients with hypertension, type 2 diabetes, myocardial infarction and clinical depression. PF, RP and GH levels are comparable in patients with RA and congestive heart failure. Regarding mental HRQoL, RA patients score substantially lower than patients with hypertension, type 2 diabetes and myocardial infarction. RA and congestive heart failure patients score similarly on levels of V, SF, RE and MH, whereas clinically depressed patients score lower on all domains of mental HRQoL.

Figure 4 shows the pooled mean un-standardized SF-36 scores in the RA population in comparison to scores from the UK [24] and from the USA [23]. The figure shows that RA patients have considerably lower HRQoL than the normal population, particularly on the physical HRQoL components. A comparison between normed SF-36 scores and normed population scores is shown in Appendix 5.

Discussion

This systematic review aimed to examine the impact of RA on HRQoL assessed by the SF-36, to assess the variables associated with HRQoL, and to compare HRQoL in RA with that of the general population and patients with other health conditions.

Our results show that RA negatively impacts HRQoL: in particular, pooled scores for the physical domains for the SF-36 are

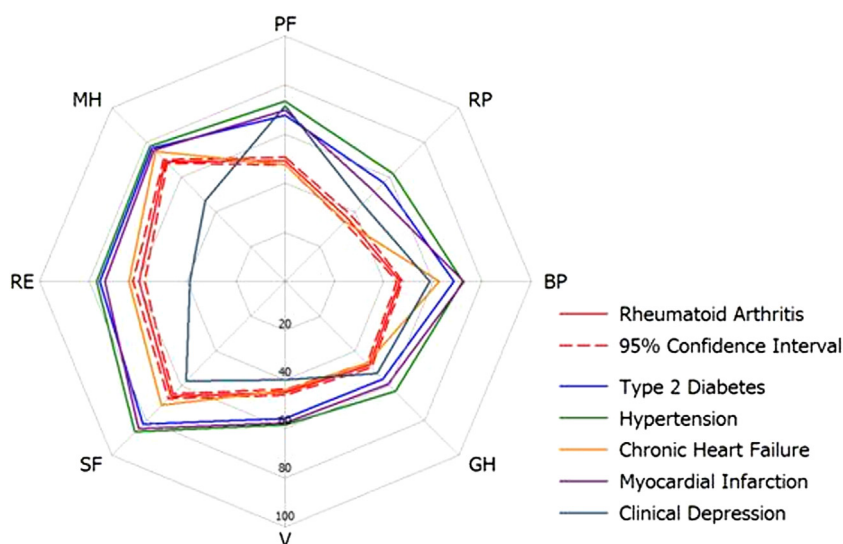


Fig. 3. Comparison of QoL in RA patients to patients with hypertension, congestive heart failure, type 2 diabetes, myocardial infarction and clinical depression, provided in the SF-36 handbook.

somewhat lower than the mental health domains, suggesting that RA has a greater impact on physical HRQoL than mental well-being. Furthermore, patients with RA have notably reduced levels of physical function, role physical and bodily pain in comparison to other health conditions (hypertension, congestive heart failure, type 2 diabetes, myocardial infarction and clinical depression). Mental HRQoL is lower in RA patients than in patients with congestive heart failure, hypertension, myocardial infarction and type 2 diabetes. We chose to make comparisons between HRQoL in RA and the illnesses provided in the SF-36 manual, which does not include a condition with a similar pain experience to RA. Until similar reviews are conducted in conditions with chronic pain, more reasonable between-illness comparisons are limited.

In comparison to both the UK and the USA general population, RA patients have lower levels of all 8 SF-36 domains. The differences between population and RA scores are particularly notable in the physical domains: physical function, role physical, bodily pain and global health. However RA patients also have substantially lower levels of vitality, social functioning and role emotional. These findings support previous research evidencing lower levels

of HRQoL in musculoskeletal conditions in comparison to healthy controls [30].

Notable associations were found between age, disease duration and proportion of female patients and SF-36 domains. A higher mean age was associated with reduced physical functioning, and overall PCS, which is unsurprising given that physical function declines with age [31]. More noteworthy was the positive association between mean age and the Mental Health domain: a higher mean age was associated with improved levels of Mental Health. This finding, although contradicting a previous literature review that concluded that increased age reduced HRQoL in RA patients aged over 75 years [16], supports the results of a recent meta-analysis, which found a similar negative association between depression prevalence and age in RA [32]. While there is a trend for depression levels to increase with age in the general population [33,34], being young may actually increase risk of poor mental well-being in RA. A similar relationship has been reported in other long-term conditions, including cancer [35,36], chronic obstructive pulmonary disease (COPD) [37] and diabetes [38]. Chronic conditions impact various aspects of life including employment, self-esteem, plans for the future and developing and maintaining

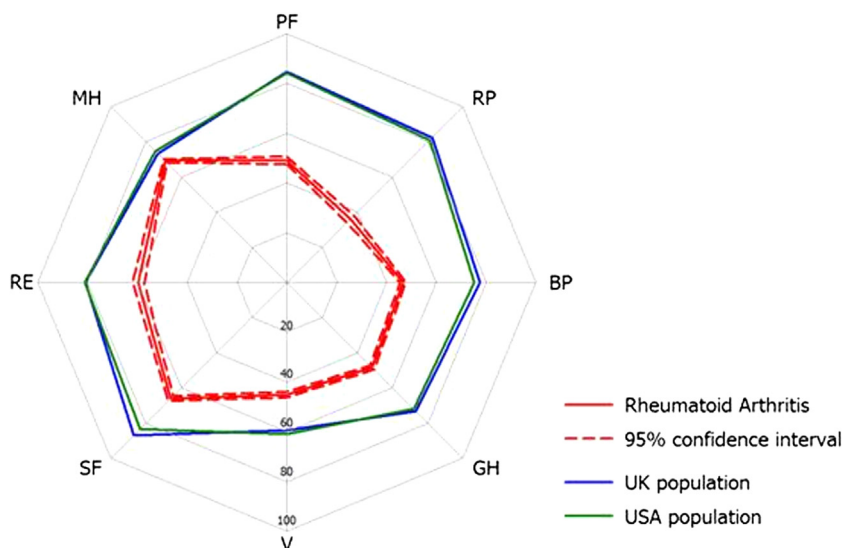


Fig. 4. QoL in RA patients in comparison to the general population scores for USA and UK.

relationships. It may be more mentally debilitating to experience these life impacts as a younger adult than as an older patient [39].

Of additional interest is the positive association found between disease duration and overall MCS score. Patients experiencing symptoms for a longer duration may have a greater level of acceptance of their condition than patients with recent onset disease. Although this is yet to be demonstrated in an RA population, research in other inflammatory conditions has found a significant association between disease duration and increased disease acceptance [40]. Acceptance of illness has been found to predict both anxiety and depressive outcomes in patients with RA [41] and acceptance of pain has been associated with decreased levels of depression and improved well-being [42,43]; therefore patients with longer disease duration may have had more time to come to terms with their condition.

It is likely that the negative association found between sample size and vitality represents issues of study quality. Smaller sample sizes may represent convenience sampling methods, which would mean results may represent only patients who present themselves for research participation, who in turn, would usually represent a healthier patient group [44].

A final noteworthy association was found between the proportion of females and various domains of the SF-36. Studies with a higher preponderance of females were found to have increased RP, BP and MCS scores but lower MH and PCS scores. As the RA patient-population represents a largely female population, this negative association between female gender and MH may reflect the increased risk of depression found in the female general population [45]. However, it appears that being female may be protective against poor physical HRQoL, a finding which has been previously reported in studies with palliative care patients [46], although it is contradictory to findings in RA patients, which suggest that females report higher levels of pain and reduced physical functioning [47].

Sensitivity analyses reveal that our results are sensitive to aspects of study methodology. With the exception of excluding studies using the SF-36 version 2, every sensitivity analysis manipulation notably altered many results. As exclusion of the SF-36 version 2 scores did not significantly alter results, it appears that the refinement of the item wording and response categories from version 1 to create version 2 supports previous research findings that the 2 measures yield comparable results [48].

Of particular note, participation rates and sampling methods seemed to make the most consistent impact on scores, with these sensitivity analyses both significantly reducing domains in both mental and physical HRQoL. The subgroup analyses reveal different patterns of results for different publication decades and area of origin. Data collected post-2010 showed a significant improvement in many domains of both physical and mental HRQoL. This also shows a marked improvement from studies published in both the 1990s and the 2000s. These findings would suggest that developments made in the care of RA in the past 20 years may have had a beneficial impact on HRQoL for patients. Furthermore, the country or area in which a patient lives may impact their HRQoL; patients in the Americas tended to show higher levels of physical and mental well-being. However, it is important to acknowledge that these comparisons are based on questionnaires with different translations; mean scores may not be comparable due to different cultural variation in both phrasings of items and responses and in interpretation of the concept of HRQoL [49].

We decided to exclude RCTs from our analysis in order to maximise the generalisability of our findings to the wider RA population. A previous unsystematic assessment of baseline SF-36 domain scores in RCTs reported substantially lower scores across all SF-36 domains in comparison to the findings from this review [50]. This discrepancy is likely to be due to the selective

recruitment of patients into RCTs, with eligibility criteria often selecting patients with higher disease activity and who have previously failed first-line treatment. This also supports our justification for the exclusion of such studies.

This systematic review used rigorous and reproducible methods. We used a broadly inclusive approach in our eligibility criteria, with data representing a large number of patients worldwide. However, as low socio-economic status (SES) patients are often under-represented in research samples [51], the results of this systematic review may not reflect lower SES patients. This can be problematic, as low SES is associated with increased susceptibility to RA [52] and reduced HRQoL [53]. SES was not adequately addressed in most studies included in this review, with only single measures of education level or monthly income commonly used to represent patient SES. Due to this heterogeneity, the representativeness of SES of the samples was impossible to establish. Furthermore, the majority of studies included in this review recruited patients from hospital outpatient clinics, which may represent the most morbid RA patients. Therefore our results may not fully represent the RA population. Furthermore, the comparisons made with other physical conditions are restricted, as data from comparator conditions are from small sample sizes and are not pooled estimates. Therefore conclusions about the impact of RA on HRQoL in comparison to other conditions are limited.

The SF-36 has been criticised for its conceptualization of the higher-order summary scores as independent constructs, despite the scoring algorithm for them involving negative weighting of all subscale items, thus assuming dependence [21]. This limitation of the SF-36 is thought to make interpretation of the PCS and MCS challenging. It is recommended, however, that the component summary scores be interpreted in conjunction with the individual domain scores. By providing pooled SF-36 summary scores alongside individual domain, this review can provide useful information pertaining to this well-validated measure, which is likely to continue to be widely used by researchers and clinicians in rheumatological populations.

Conclusion

This article attempted to systematically quantify the impact of RA on SF-36-measured HRQoL; the impact is substantial in both physical and mental domains, confirming HRQoL as a crucial target for intervention [54]. Recent National Institute of Clinical Excellence (NICE) guidelines stipulate that RA patients should be periodically assessed for the impact of their disease on their lives, including HRQoL and mood, and that access to a multidisciplinary team is essential for the assessment and management of these aspects of their condition [55]. The results of this systematic review and meta-analysis support this recommendation.

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Appendix. Supplementary Information

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.semarthrit.2014.05.001>.

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