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## Foot health and quality of life in patients with rheumatoid arthritis: a cross-sectional study

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## Foot health and quality of life in patients with rheumatoid arthritis: a cross-sectional study

Andres Reinoso-Cobo<sup>1</sup> MSc [andres.reinoso.sspa@juntadeandalucia.es](mailto:andres.reinoso.sspa@juntadeandalucia.es)

Gabriel Gijon-Nogueron<sup>2,3</sup>, PhD [gagijon@uma.es](mailto:gagijon@uma.es)

Rafela Caliz-Caliz<sup>1</sup> MD, PhD [antonior.caliz.sspa@juntadeandalucia.es](mailto:antonior.caliz.sspa@juntadeandalucia.es)

Miguel Angel Ferrer-González<sup>1</sup> MD PhD [maferrer@fundacionhvn.org](mailto:maferrer@fundacionhvn.org)

Maria Teresa Vallejo-Fernandez<sup>1</sup>, MsC [tvallejo@ibsgranada.es](mailto:tvallejo@ibsgranada.es)

Jose Miguel Morales-Asencio<sup>2,3</sup> PhD [jmmasen@uma.es](mailto:jmmasen@uma.es)

Ana Belen Ortega-Avila<sup>3</sup> PhD [anaortavi@uma.es](mailto:anaortavi@uma.es)

1. Departamento de Reumatología, Hospital Universitario Virgen de las Nieves, Granada, Granada, Spain
2. Instituto de Investigación Biomédica de Málaga (IBIMA), Malaga, Spain
3. Department Nursing and Podiatry, Universidad de Málaga, Malaga. Spain

### Corresponding author: Gabriel Gijon-Nogueron

Faculty of Health Sciences. Arquitecto Francisco Penalosa 3. Ampliación de Campus de Teatinos, 29071 Malaga. Spain. [gagijon@uma.es](mailto:gagijon@uma.es)

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## Abstract

*Objective:* The aim of this study is to identify foot health factors related to the quality of life in patients with RA.

*Setting:* The cross-sectional in total, 293 subjects were analysed, with 229 patients in the RA group and 64 in the control group. In the RA group, 173 patients were female, as were 50 of the control group

*Participants:* Patients with foot pain and RA (according to the 1987 American College of Rheumatology revised criteria) and with foot pain but no RA were recruited (Granada, Spain).

*Intervention:* Two researchers independently interviewed the patients to obtain the study data

*Primary and secondary outcome measures:* Clinical data were obtained using the SF-12 questionnaire (Quality of life) (Primary outcome), visual analogue scales for pain (VAS pain), the Manchester Foot Pain Disability Index questionnaire (MFPDI) and the Foot Function Index (FFI). Anthropometric measurements were obtained by means of a foot measurement platform, the Foot Posture Index (FPI) and the Manchester Hallux Valgus Scale.(secondary outcomes)

### Results

Of the 293 subjects, 76.1% were female. Significant differences were observed between the RA and control groups ( $p < 0.001$ ) according to VAS pain (general, foot and hand), the MFPDI and the FFI. In terms of anthropometric measurements, significant differences were only recorded for midfoot and forefoot width ( $p = 0.03$ ). In the data for the physical component, the multivariable linear regression with the parameters age, gender, VAS pain (general) and the presence of RA presented an  $R^2$  value of 48.8%, while for the mental health component, the corresponding value was 5.6%.

### Conclusion

Morphological and structural characteristics of the foot are not necessarily associated with pain, disability and loss of function. The presence of RA, a higher score in VAS pain (general), female gender and greater age are all associated with the physical component of the quality of life for patients with RA.

### Key words

Rheumatoid arthritis; foot health; quality of life; functionality; pain.

### Strengths and limitations of this study

- The foot-related parameters are strongly associated with the quality of life
- The presence of RA, a higher score for general VAS pain, female gender and greater age are all related to a reduced quality of life in the physical component for patients with RA
- The physical and the mental components were analysed at a moment that might have coincided with an aggravation of the RA experienced

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## Introduction

Rheumatoid arthritis (RA) is a chronic rheumatic disease that affects 0.5% to 1% of the population in Europe [1]. The most characteristic symptom is swelling, which provokes important changes in joint structures and limits function [2].

RA mainly affects the small joints of the hands and feet [3]. In the foot, it provokes deformities in the forefoot and hindfoot. The most common pathologies are hallux valgus, metatarsal subluxation, and hammer or claw toes [4]. As the disease progresses, first metatarsophalangeal joint and pes planus may also be observed. These pathologies occur as the deterioration affects the joints and ligaments [5], thus limiting movement in the ankle and the foot. It also produces an unequal distribution of pressures and therefore makes it painful to remain in a standing position [6].

RA is a systemic disease that not only presents extra-articular manifestations but also has psychological affects [7], in many cases provoking mental health and functional problems as a consequence of ageing [8], oxidative damage to DNA and systemic inflammatory stress [9], thus limiting leisure and family-related activities and restricting social relationships [10]. The simultaneous impact of RA and a reduced quality of life imposes a major burden on patients, caregivers, the health system and society in general [11].

The mental and physical components of RA can reduce adherence to treatment, leading to poorer health outcomes and a worsened quality of life [12].

In patients with RA, the foot has been analysed from various standpoints, such as hallux valgus, claw fingers or morphological alterations [13]. Psychological and social aspects of the disease have also been analysed [14,15]. However, to date no studies have been undertaken to determine whether RA in the foot has a negative impact on the quality of life, in physical and mental terms.

The aim of the present study, therefore, is to identify foot health factors related to the quality of life in patients with RA.

## Method

**Ethical approval:** Institutional review board that approved the protocol for the study: Medical Research Ethics Committee of University of Malaga (CEUMA-91-2015-H) and PEIBA Andalucia (ARC0001), Spain.

**Design:** Cross-sectional study

## Participants

A convenience sample was obtained of 246 patients with foot pain and RA (according to the 1987 American College of Rheumatology revised criteria) [16], of whom seventeen subsequently declined to participate, citing lack of time (the study questionnaire required 30 minutes to complete) and 64 patients with foot pain but no RA. The patients were enrolled at hospital outpatient clinics from January to December 2018. All those included in the study had a history of subtalar and/or ankle and/or talonavicular or hindfoot pain, did not make daily use of walking aids, and were able to achieve the normal range of motions in the ankle, subtalar and midtarsal joints [6]. The exclusion criteria applied were the presence of concomitant musculoskeletal disease, central or peripheral nervous system disease or endocrine disorders (especially diabetes mellitus).

Patients who met the criteria for inclusion were approached by members of the rheumatology service at the Virgen de la Nieves Hospital (Granada, Spain), given an information sheet and invited to participate. Those who agreed were then interviewed and given further details of the study. All participants provided written consent prior to starting the interviews.

## Data collection

### *Demographic and clinical characteristics*

The demographic characteristics recorded included the patient's age, gender, disease duration and current therapy. The clinical data recorded were those obtained from the SF-12 questionnaire [17], a visual analogue scale for pain (VAS pain), both general [18] and specific to the foot and hand, the Manchester Foot Pain Disability Index (MFPDI) [19] and the Foot Function Index (FFI) [20].

For the anthropometric measurements, a foot measurement platform [21] was used to measure the foot length (weight bearing and non weight bearing), the midfoot, forefoot and heel width and the midfoot height. Each participant was asked first to stand on the



platform and then to be seated, in both cases with the body weight distributed evenly between the two feet, arms beside the body and facing forwards. The measurements were obtained with the patient's heels placed in the heel cups, as far back as possible, and the first metatarsal heads located against the limit surface.

Other measurements were obtained using the Foot Posture Index, a reliable instrument for this purpose [22], and the Manchester Scale of hallux valgus [23].

**The data availability statement** No additional data available

### **Procedure**

Two researchers (ARC and GGN) independently interviewed the patients to obtain the study data. The clinical interview was conducted in one room, where the patients were asked to complete the SF-12 (adapted version for a Spanish population) [24], MFPDI and VAS questionnaires. In a separate room, each patient was measured using a validated foot platform (intraclass correlation coefficient for the instrument, ICC, 0.96-0.98). Foot posture was determined according to the Foot Posture Index (FPI) (ICC for the clinician, 0.94-0.96). Each criterion was scored as -2, -1, 0, +1 or +2. The following FPI cut-off points, defining foot type category were used: a) highly supinated -12 to -4, b) supinated -3 to 0, c) neutral 1 to 7, d) pronated 8 to 10 and e) highly pronated 11 to 12 [25]. The presence/absence of hallux valgus was determined according to the Manchester Scale of Hallux Valgus (ICC for the instrument, 0.93-0.97), a clinical tool consisting of photographs of feet with four levels of hallux valgus: none, mild, moderate and severe [23].

### **Patient and public involvement**

No patients were involved in setting the research question or the outcome measures, nor were they involved in the design or conduct of the study. No patients were asked to advise on interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants

### **Statistical analysis**

The results obtained are reported as the median and interquartile range, due to the non-normal distribution of the variables. The normality of the distributions was examined by the Kolmogorov-Smirnov test and the intra-rater reliability of the measurement instruments was calculated by a two-way mixed-consistency ICC model. Bivariate

analysis was performed with a non-parametric test (the Mann-Whitney U test), in view of the non-normal distribution observed in most cases. Finally, a multivariable linear regression model was obtained to evaluate the predictors of quality of life, according to the physical and mental health components of the SF-12 questionnaire. In constructing the models, the regression assumptions of homoscedasticity, normality and independence of the residuals and collinearity were tested. Homoscedasticity was evaluated by analysing the distribution of predicted values and scatterplots of the residuals. Normality of the residuals was tested by analysing histograms and by graphs of standardised residuals. Independence of the residuals was evaluated by the Durbin-Watson statistic. Finally, the presence of collinearity was tested by calculating the variance inflation factor, the tolerance and partial correlations. The significance level was set at  $p < 0.05$ , with two-tailed tests. All statistical analyses were conducted using SPSS v. 24.0 statistical software (SPSS Inc., Chicago, IL, USA) and GPower 3.1.92 for the post-hoc analyses.

## Results

In total, 293 subjects were analysed, with 229 patients in the RA group (average duration of RA, 15.44, SD 10.54 years) and 64 in the control group. In the RA group, 173 patients were female, as were 50 of the control group. The values for median age and interquartile range (IR) were 59 and 16 years for the patients with RA and 53 and 21 years for those in the control group. The median values for height and weight were 162 cm (IR: 10) and 70 kg (IR: 19), respectively, for the RA group, and 162 cm (IR: 10) and 65 kg (IR: 15), respectively, for the control group. The patients with RA were treated with biological disease-modifying antirheumatic drugs (bDMARDs) (42%), methotrexate (35%) or nonsteroidal anti-inflammatory drugs (NSAIDs) / corticosteroids (20%).

The instruments used to measure pain, disability and functionality (VAS pain, MFPDI and FFI) revealed significant differences between the patients with RA and the control group, for both genders ( $p < 0.001$ ). However, among those used to obtain foot measurements and posture data, only the midfoot height values ( $p = 0.007$  and  $p = 0.004$ ) for male and female participants and midfoot width ( $p = 0.03$ ) for the females were statistically significant. The FPI and the other anthropometric measurements were not statistically significant (Table 1).

The results for the SF-12 quality of life questionnaire revealed significant differences in the physical component, with  $p < 0.001$  (females) and  $p = 0.02$  (males) and in the mental

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3 component in the female participants ( $p=0.04$ ) (Table 2). Among the male participants,  
4 no differences in the mental health component were observed between the RA and control  
5 groups.  
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10 Bivariate analyses were performed to determine the relations between the physical and  
11 mental health components, taking into account the sociodemographic, clinical and  
12 anthropometric characteristics of the participants. Among these results, especially  
13 noteworthy was the value of  $-0.630$  with  $p<0.001$  obtained for VAS pain (general) and  
14 that of  $-0.505$  with  $p<0.001$  for the presence of RA. Neither the anthropometric  
15 characteristics, foot posture nor disease duration presented any correlation with either of  
16 these variables.  
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23 Multivariate models were then constructed, using as predictors the variables that had  
24 presented a significant association in the bivariate models, adjusted for age and gender.  
25 Two models were calculated, with the physical and mental health components  
26 respectively as dependent variables.  
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31 According to the data for the physical component, the multivariable linear regression  
32 presented an  $R^2$  value of 48.8%. (Table 3). Post-hoc analysis yielded a power of 0.95 for  
33 this four-predictor model. The multivariable linear regression of the mental health  
34 component presented an  $R^2$  value of 5.6%. There was no collinearity in the model  
35 (maximum VIF 1.39 and minimum tolerance of 0.72) and the residuals were independent  
36 (Durbin-Watson, 1.19), using the same parameters (i.e. age, gender, general VAS pain  
37 and the presence of RA).  
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## 40 41 42 43 44 **Discussion**

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46 The aim of this study is to determine and analyse foot health factors related to the quality  
47 of life of patients with RA. The multivariate regression results obtained suggest that  
48 patients with foot pain and RA perceive a significantly lower level of health than those  
49 with foot pain but no RA (control group) ( $p<0.001$ ). However, these findings are not  
50 directly related to the clinical parameters that might have triggered the increased level of  
51 pain. The deformations which are typical of this disease and which are located in the  
52 forefoot (such as hallux valgus, hallux rigidus, floating of the lesser toes or synovial  
53 inflammation of the metatarsophalangeal joints) or in the hindfoot (such as hindfoot  
54 valgus or flat foot) are often believed to aggravate pain and disability among this  
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3 population. Nevertheless, this expectation was not borne out by our study results, possibly  
4 because the presence of RA in itself is painful, while other patients with similar foot  
5 deformities but no RA might not experience pain. If this were the case, then the deformity  
6 would not be the cause of pain, but merely the outcome of a degenerative process in the  
7 foot. However, analysis of plantar pressures shows that this localised pain is not  
8 correlated with peak plantar pressure, which is received in the hindfoot.  
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14 Structural alterations in the foot not only cause physical deterioration due to reduced  
15 mobility, but can also lead to emotional deterioration. Nevertheless, according to our  
16 study findings, these alterations are not in themselves the cause of increased pain. Instead,  
17 this outcome may be influenced by an external component such as the choice of footwear,  
18 a factor that is strongly influenced by the appearance of structural alterations in the foot.  
19 Many patients, both male and female, have considerable difficulty in obtaining  
20 appropriate footwear, i.e. that which is comfortable, adapted to the deformities of the foot,  
21 of assistance in performing the gait cycle and acceptable aesthetically [26,27].  
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29 The latter characteristic is the area in which most negative impressions are caused among  
30 the population with RA, since many patients do not choose their footwear in strict  
31 accordance with the deformities present in their feet [28]. This discordance can produce  
32 a negative impact, either in terms of the mental component (the perceived quality of life),  
33 when the personal image is compared with that of the non-affected population, or because  
34 of increased plantar pain, when the footwear chosen is uncomfortable and prevents the  
35 proper mobilisation of the musculoskeletal structures of the foot, thereby limiting the  
36 performance of the activities of daily life. These outcomes are often associated with  
37 dissatisfaction and even depression among the population affected.  
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45 With advancing age, musculoskeletal deformities and, in particular, structural alterations  
46 in the foot increase, as a greater number of structures are damaged. These alterations may  
47 also be caused by increased neuropathy in the foot, which in turn would heighten pain  
48 and reduce functionality [1], thus worsening the perceived quality of life [29].  
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This research presents certain limitations. Firstly, it is based on a cross-sectional study of  
a heterogeneous sample population, rather than on a longitudinal study. This  
characteristic of the study design may have influenced the results obtained in two  
respects. On the one hand, in our sample the number of participants with RA significantly  
exceeded that of those not presenting this alteration. Therefore, if the size of the control

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3 group were increased, somewhat different results might be obtained. Moreover, as the  
4 analysis was transversal, both the physical and the mental components were analysed at  
5 a moment that might have coincided with an aggravation of the RA experienced, thus  
6 altering the study results obtained.  
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10 Another limitation of our study is that it is based on a convenience sample, which means  
11 that the homogeneity of the participants cannot be assured. In future research, therefore,  
12 the size and composition of the study groups should be controlled to optimise their  
13 homogeneity. Finally, attention should be paid to the question of whether foot pain is  
14 determined by the characteristics of the foot, or whether RA pain affects certain foot types  
15 in particular.  
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21 Our study shows that patients with RA are more likely to present structural alterations in  
22 the foot and hence to experience physical and/or psychosocial deterioration than when  
23 this condition is absent [30]. Furthermore, the long-term evolution of the disease may be  
24 directly related to psychosocial and emotional perceptions. It should be also be taken into  
25 account that in our study groups most of the patients were female, although this reflects  
26 their prevalence among the general population affected by RA and foot pain [31,32].  
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33 On the other hand, the study also has important strengths. Although the results obtained  
34 do not show that foot-related parameters are strongly associated with the quality of life  
35 of these patients, they do highlight the need for further, longitudinal studies addressing  
36 parameters such as the evolution of the disease, the treatment received and psychosocial  
37 aspects that could influence the patient's perception of the impact of RA with respect to  
38 daily activities and musculoskeletal pain.  
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44 In the clinical context, our study raises an important question, namely that the pain and  
45 the reduced quality of life experienced by patients with RA may be provoked by the  
46 disease itself, and not by the alterations in the foot. If this were so, the presence of the  
47 latter might not be related to the pain experienced.  
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## 51 **Conclusions**

52 Morphological and structural characteristics of the foot are not necessarily associated  
53 with pain, disability and loss of function. The presence of RA, a higher score for general  
54 VAS pain, female gender and greater age are all related to a reduced quality of life in the  
55 physical component for patients with RA.  
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### Author Contributions

Conceptualization, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Jose Miguel Morales-Asencio and Ana Belen Ortega-Avila; Data curation, Andres Reino-Cobo; Formal analysis, Gabriel Gijon-Nogueron, Jose Miguel Morales-Asencio and Ana Belen Ortega-Avila; Methodology, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Miguel Angel Ferrer-Gonzalez and Ana Belen Ortega-Avila; Project administration, Maria Teresa Vallejo-Velazquez; Writing – original draft, Andres Reino-Cobo, Gabriel Gijon-Nogueron and Ana Belen Ortega-Avila; Writing – review & editing, Andres Reino-Cobo, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Jose Miguel Morales-Asencio and Ana Belen Ortega-Avila.

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	Overall(n=293)					Female (n=173)					Male (n=120)				
	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value
	Median	Interquartile range	Median	Interquartile range		Median	Interquartile range	Median	Interquartile range		Median	Interquartile range	Median	Interquartile range	
Age (years)	59	16	53	21	0,003	59	16	53	21	0,001	58	16	53.5	24	0.845
Height (cm)	162	10	162	10	0,401	160	10	160.5	9	0,006	170	10	171	15	0.578
Weight (kg)	70	19	65	15	0,168	65	15	62.5	11	0,004	78	18	76.5	13	0.35
Gen. VAS (0-100)	6	3	1,5	4	<0.001	6	3	2	5	0,001	5	4	0	1	<0.001
Hand VAS	6	3	0	3	<0.001	6	4	1	3	0,001	5	4	0	1	<0.001
Feet VAS	6	5	2	5	<0.001	6	4	2	5	0,001	4	5	0	1	<0.001
MFPDI	21	18	4	10	<0.001	22	17	4.5	11	0,001	19	18	0.5	6	<0.001
FFI Total	43,91	45	6,52	18	<0.001	48.3	39	9.1	23	<0,001	30.4	51	0	5	<0.001
FFI Pain	48	38	8	29	<0.001	50	34	14	33	<0,001	41.5	47	0	4	<0.001
FFI Disability	49	58	0	14	<0.001	51	50	2	18	<0,001	24	56	0	0	<0.001
FFI Physical activity	6	19	0	2	<0.001	7	20	0	2	<0,001	3	15	0	0	<0.001
W/b r/foot	242	22	244	18	0,339	237	15	240.5	17	0,007	261	18	261	22	0.777
W/b 1 <sup>st</sup> MTPJ r/foot	180	16	180,5	15	0,843	178	11	177	14	0,009	195.5	14	189.5	19	0.9
W/b r/MF height	53,8	9,7	56,265	10,31	<0.001	51.4	8.2	54.4	9.4	0,007	58.8	6.3	65.8	16	0.004
W/b r/MF width	77	8,63	74,965	8,93	0,035	75.5	6.7	73.9	6.9	0,003	83.5	7.2	81.5	8.7	0.559
W/b r/forefoot	91,38	9,34	91,69	7,08	0,508	89.7	7	88.5	6.8	0,009	97.3	7.8	96.4	7.4	0.941
W/b r/hindfoot	66,52	7,29	66,105	6,16	0,089	65.7	6.2	65.2	6.6	0,007	71.8	7.6	68.5	4.2	0.39
FPI TOTAL (r/foot)	5	7	5	4	0,338	5	6	5	5	0,007	2	8	5	3	0.205

Table 1. Characteristics of the study groups W/b: Weight bearing; r/: Right; MTPJ: Metatarsophalangeal joints; MF: midfoot \*Mann-Whitney U-test

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	Female					Male				
	RA (n=173)		Control group (n=50)		P value*	RA (n=56)		Control group (n=14)		P value*
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Physical health component (Ref. Spanish population)	36.50	7.91	48.88	7.55	p<0.001	39.07	2.91	49.09	8.22	0.02
Mental health component (Ref. Spanish population)	32.10	7.97	35.08	5.00	0.04	33.76	1.65	36.14	4.66	0.35

\* Mann-Whitney U-test

Table 2. Characteristics of the sample group according to the SF 12 results

	Adjusted coefficient	B	$\beta$	p	95%CI	
					Lower	Upper
Age	-0.175	-0.082	-0.113	0.038	-0.159	-0.005
Gender	-1.361	-0.603	-0.028	0.607	-2.908	1.703
VAS pain – General	-2.177	-1.609	-0.474	<0.001	-2.024	-1.193
RA	-11.769	-6.461	-0.292	<0.001	-9.111	-3.811

Table 3: Model of multivariate regression for the perception of physical health

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7

		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

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## Foot health and quality of life in patients with rheumatoid arthritis: a cross-sectional study

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## Foot health and quality of life in patients with rheumatoid arthritis: a cross-sectional study

Andres Reinoso-Cobo<sup>1</sup> MSc [andres.reinoso.sspa@juntadeandalucia.es](mailto:andres.reinoso.sspa@juntadeandalucia.es)

Gabriel Gijon-Nogueron<sup>2,3</sup>, PhD [gagijon@uma.es](mailto:gagijon@uma.es)

Rafela Caliz-Caliz<sup>1</sup> MD, PhD [antonior.caliz.sspa@juntadeandalucia.es](mailto:antonior.caliz.sspa@juntadeandalucia.es)

Miguel Angel Ferrer-González<sup>1</sup> MD PhD [maferrer@fundacionhvn.org](mailto:maferrer@fundacionhvn.org)

Maria Teresa Vallejo-Fernandez<sup>1</sup>, MsC [tvallejo@ibsgranada.es](mailto:tvallejo@ibsgranada.es)

Jose Miguel Morales-Asencio<sup>2,3</sup> PhD [jmmasen@uma.es](mailto:jmmasen@uma.es)

Ana Belen Ortega-Avila<sup>3</sup> PhD [anaortavi@uma.es](mailto:anaortavi@uma.es)

1. Departamento de Reumatología, Hospital Universitario Virgen de las Nieves, Granada, Granada, Spain
2. Instituto de Investigación Biomédica de Málaga (IBIMA), Malaga, Spain
3. Department Nursing and Podiatry, Universidad de Málaga, Malaga. Spain

### Corresponding author: Gabriel Gijon-Nogueron

Faculty of Health Sciences. Arquitecto Francisco Penalosa 3. Ampliación de Campus de Teatinos, 29071 Malaga. Spain. [gagijon@uma.es](mailto:gagijon@uma.es)

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Tables: 3

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**Conflict of interest:** All the authors declare that they have no conflict of interest derived from the outcomes of this study.

## Abstract

*Objective:* The aim of this study is to identify foot health factors related to the quality of life in patients with RA.

*Setting:* The cross-sectional study in total, 293 subjects were analysed, with 229 patients in the RA group and 64 in the control group. In the RA group, 173 patients were female, as were 50 of the control group

*Participants:* Patients with foot pain and RA (according to the 2010 ACR/ EULAR Rheumatoid Arthritis classification criteria) and with foot pain but no RA were recruited (Granada, Spain).

*Intervention:* Two researchers independently interviewed the patients to obtain the study data

*Primary and secondary outcome measures:* Clinical data were obtained using the SF-12 questionnaire (Quality of life) (Primary outcome), visual analogue scales for pain (VAS pain), the Manchester Foot Pain Disability Index questionnaire (MFPDI) and the Foot Function Index (FFI). Anthropometric measurements were obtained by means of a foot measurement platform, the Foot Posture Index (FPI) and the Manchester Hallux Valgus Scale.(secondary outcomes)

### Results

Of the 293 subjects, 76.1% were female. Significant differences were observed between the RA and control groups ( $p < 0.001$ ) according to VAS pain (general, foot and hand), the MFPDI and the FFI. In terms of anthropometric measurements, significant differences were only recorded for midfoot and forefoot width ( $p = 0.03$ ). In the data for the physical component, the multivariable linear regression with the parameters age, gender, VAS pain (general) and the presence of RA presented an  $R^2$  value of 48.8%, while for the mental health component, the corresponding value was 5.6%.

### Conclusion

Morphological and structural characteristics of the foot are not necessarily associated with pain, disability and loss of function. The presence of RA, a higher score in VAS pain (general), female gender and greater age are all associated with the physical component of the quality of life for patients with RA.

### Key words

Rheumatoid arthritis; foot health; quality of life; functionality; pain.

### Strengths and limitations of this study

- This research presents a new framework the foot-related parameters in Rheumatoid Arthritis(RA) associated with the quality of life(QoL)
- This method provides identification of foot parameters stratified by gender, related to QoL in RA
- This study has been the first to show how people with RA experience a negative impact on their QoL related to foot parameter.
- The QoL were analysed at a moment that might coincide with an aggravation of the RA
- The result could be different if they study should be a longitudinal study

## Introduction

Rheumatoid arthritis (RA) is a chronic rheumatic disease that affects 0.5% to 1% of the population in Europe [1]. The most characteristic symptom is swelling, which provokes important changes in joint structures and limits function [2].

RA mainly affects the small joints of the hands and feet [3]. In the foot, it provokes deformities in the forefoot and hindfoot. The most common pathologies are hallux valgus, metatarsal subluxation, and hammer or claw toes [4]. As the disease progresses, the first metatarsophalangeal joint and pes planus may also be associated. These pathologies occur as the deterioration affects the joints and ligaments [5], thus limiting movement in the ankle and the foot. It also produces an unequal distribution of pressures and therefore makes it painful to remain in a standing position [6].

RA is a systemic disease that not only presents extra-articular manifestations but also has psychological affects [7], in many cases provoking mental health and functional problems as a consequence of ageing [8], oxidative damage to DNA and systemic inflammatory stress [9], thus limiting leisure and family-related activities and restricting social relationships [10]. The simultaneous impact of RA and a reduced quality of life imposes a major burden on patients, caregivers, the health system and society in general [11].

The mental and physical components of RA can reduce adherence to treatment, leading to poorer health outcomes and a worsened quality of life [12].

In patients with RA, the foot has been analysed from various standpoints, such as hallux valgus, clawed toes or morphological alterations [13]. Psychological and social aspects of the disease have also been analysed such as anxiety, depression or affectivity [14,15][16]. However, to date no studies have been undertaken to determine whether RA in the foot has a negative impact on the quality of life, in physical and mental health terms.

The aim of the present study, therefore, is to identify foot health factors related to the quality of life in patients with RA.

## Method

**Ethical approval:** Institutional review board that approved the protocol for the study: Medical Research Ethics Committee of University of Malaga (CEUMA-91-2015-H) and PEIBA Andalucia (ARC0001), Spain.

**Design:** Cross-sectional study

## Participants

A convenience sample was obtained of 246 patients with foot pain and RA (according to the 2010 ACR/ EULAR Rheumatoid Arthritis classification criteria)[17], of whom seventeen subsequently declined to participate, citing lack of time (the study questionnaire required 30 minutes to complete) and 64 patients with foot pain but no RA. The patients were enrolled at hospital outpatient clinics from January to December 2018.

All those included in the study had a history of subtalar and/or ankle and/or talonavicular or hindfoot pain, did not make daily use of walking aids, and were able to achieve the normal range of motions in the ankle, subtalar and midtarsal joints. Although the patient could not reach the maximum range of movement within those joints in terms of dorsiflexion, pronation or supination, if reducing their length of the step, patients could achieve the enough range of movement to walk [6][18].

The exclusion criteria applied were the presence of concomitant musculoskeletal disease, central or peripheral nervous system disease or endocrine disorders (especially diabetes mellitus).

Patients who met the criteria for inclusion were approached by members of the rheumatology service at the Virgen de la Nieves Hospital (Granada, Spain), given an information sheet and invited to participate. Those who agreed were then interviewed and given further details of the study. All participants provided written consent prior to starting the interviews.

## Data collection

*Demographic and clinical characteristics*

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3 The demographic characteristics recorded included the patient's age, gender, disease  
4 duration and current therapy. The clinical data recorded were those obtained from the  
5 SF-12 questionnaire [19], a visual analogue scale for pain (VAS pain), both general [20]  
6 and specific to the foot and hand, the Manchester Foot Pain Disability Index (MFPDI)  
7 [21] and the Foot Function Index (FFI) [22].  
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12 For the anthropometric measurements, a foot measurement platform [23] was used to  
13 measure the foot length (weight bearing and non weight bearing), the midfoot, forefoot  
14 and heel width and the midfoot height. Each participant was asked first to stand on the  
15 platform and then to be seated, in both cases with the body weight distributed evenly  
16 between the two feet, arms beside the body and facing forwards. The measurements  
17 were obtained with the patient's heels placed in the heel cups, as far back as possible,  
18 and the first metatarsal heads located against the limit surface.  
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22 Other measurements were obtained using the Foot Posture Index, a reliable instrument  
23 for this purpose [24], and the Manchester Scale of hallux valgus [25].  
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27 **The data availability statement** No additional data available  
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### 29 30 31 **Procedure**

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34 Two researchers (ARC and GGN) independently interviewed the patients to obtain the  
35 study data. The clinical interview was conducted in one room, where the patients were  
36 asked to complete the SF-12 (adapted version for a Spanish population) [26], MFPDI  
37 and VAS questionnaires. In a separate room, each patient was measured using a  
38 validated foot platform (intraclass correlation coefficient for the instrument, ICC, 0.96-  
39 0.98). Foot posture was determined according to the Foot Posture Index (FPI) (ICC for  
40 the clinician, 0.94-0.96). Each criterion was scored as -2, -1, 0, +1 or +2. The  
41 following FPI cut-off points, defining foot type category were used: a) highly supinated  
42 -12 to -4, b) supinated -3 to 0, c) neutral 1 to 7, d) pronated 8 to 10 and e) highly  
43 pronated 11 to 12 [27]. The presence/absence of hallux valgus was determined  
44 according to the Manchester Scale of Hallux Valgus (ICC for the instrument, 0.93-  
45 0.97), a clinical tool consisting of photographs of feet with four levels of hallux valgus:  
46 none, mild, moderate and severe [25].  
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### 56 57 **Patient and public involvement** 58 59 60

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3 No patients were involved in setting the research question or the outcome measures, nor  
4 were they involved in the design or conduct of the study. No patients were asked to  
5 advise on interpretation or writing up of results. There are no plans to disseminate the  
6 results of the research to study participants  
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### 10 **Statistical analysis**

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13 The results obtained are reported as the median and interquartile range, due to the non-  
14 normal distribution of the variables. The normality of the distributions was examined by  
15 the Kolmogorov-Smirnov test and the intra-rater reliability of the measurement  
16 instruments was calculated by a two-way mixed-consistency ICC model. Bivariate  
17 analysis was performed with a non-parametric test (the Mann-Whitney U test), in view  
18 of the non-normal distribution observed in most cases. Finally, a multivariable linear  
19 regression model was obtained to evaluate the predictors of quality of life, according to  
20 the physical and mental health components of the SF-12 questionnaire. In constructing  
21 the models, the regression assumptions of homoscedasticity, normality and  
22 independence of the residuals and collinearity were tested. Homoscedasticity was  
23 evaluated by analysing the distribution of predicted values and scatterplots of the  
24 residuals. Normality of the residuals was tested by analysing histograms and by graphs  
25 of standardised residuals. Independence of the residuals was evaluated by the Durbin-  
26 Watson statistic. Finally, the presence of collinearity was tested by calculating the  
27 variance inflation factor, the tolerance and partial correlations. The significance level  
28 was set at  $p < 0.05$ , with two-tailed tests. All statistical analyses were conducted using  
29 SPSS v. 24.0 statistical software (SPSS Inc., Chicago, IL, USA) and GPower 3.1.92 for  
30 the post-hoc analyses.  
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### 45 **Results**

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47 In total, 293 subjects were analysed, with 229 patients in the RA group (average  
48 duration of RA, 15.4, SD 10.5 years) and 64 in the control group. In the RA group, 173  
49 patients were female, as were 50 of the control group. The values for median age and  
50 interquartile range (IQR) were 59 and 16 years for the patients with RA and 53 and 21  
51 years for those in the control group. The median values for height and weight were 162  
52 cm (IQR: 10) and 70 kg (IQR: 19), respectively, for the RA group, and 162 cm (IQR:  
53 10) and 65 kg (IQR: 15), respectively, for the control group. The patients with RA were  
54 treated with biological disease-modifying antirheumatic drugs (bDMARDs) (42%),  
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3 methotrexate (35%) or nonsteroidal anti-inflammatory drugs (NSAIDs) / corticosteroids  
4 (20%).  
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7 The instruments used to measure pain, disability and functionality (VAS pain, MFPDI  
8 and FFI) revealed significant differences between the patients with RA and the control  
9 group, for both genders ( $p < 0.001$ ). However, among those used to obtain foot  
10 measurements and posture data, only the midfoot height values ( $p = 0.007$  and  $p = 0.004$ )  
11 for male and female participants and midfoot width ( $p = 0.03$ ) for the females were  
12 statistically significant. The FPI and the other anthropometric measurements were not  
13 statistically significant (Table 1).  
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19 The results for the SF-12 quality of life questionnaire revealed significant differences in  
20 the physical component, with  $p < 0.001$  (females) and  $p = 0.02$  (males) and in the mental  
21 component in the female participants ( $p = 0.04$ ) (Table 2). Among the male participants,  
22 no differences in the mental health component were observed between the RA and  
23 control groups.  
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29 Bivariate analyses were performed to determine the relations between the physical and  
30 mental health components, taking into account the sociodemographic, clinical and  
31 anthropometric characteristics of the participants. Among these results, especially  
32 noteworthy was the value of  $-0.630$  with  $p < 0.001$  obtained for VAS pain (general) and  
33 that of  $-0.505$  with  $p < 0.001$  for the presence of RA. Neither the anthropometric  
34 characteristics, foot posture nor disease duration presented any correlation with either of  
35 these variables.  
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42 Multivariate models were then constructed, using as predictors the variables that had  
43 presented a significant association in the bivariate models, adjusted for age and gender.  
44 Two models were calculated, with the physical and mental health components  
45 respectively as dependent variables.  
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50 According to the data for the physical component, the multivariable linear regression  
51 presented an  $R^2$  value of 48.8%. (Table 3). Post-hoc analysis yielded a power of 0.95 for  
52 this four-predictor model. The multivariable linear regression of the mental health  
53 component presented an  $R^2$  value of 5.6%. There was no collinearity in the model  
54 (maximum VIF 1.39 and minimum tolerance of 0.72) and the residuals were  
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3 independent (Durbin-Watson, 1.19), using the same parameters (i.e. age, gender,  
4 general VAS pain and the presence of RA).  
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## 7 8 **Discussion** 9

10 The aim of this study is to determine and analyse foot health factors related to the  
11 quality of life of patients with RA. The multivariate regression results obtained suggest  
12 that patients with foot pain and RA perceive a significantly lower level of health than  
13 those with foot pain but no RA (control group) ( $p < 0.001$ ). However, these findings are  
14 not directly related to the clinical parameters that might have triggered the increased  
15 level of pain. The deformations which are typical of this disease and which are located  
16 in the forefoot (such as hallux valgus, hallux rigidus, floating of the lesser toes or  
17 synovial inflammation of the metatarsophalangeal joints) or in the hindfoot (such as  
18 hindfoot valgus or flat foot) are often believed to aggravate pain and disability among  
19 this population. Nevertheless, this expectation was not borne out by our study results,  
20 possibly because the presence of RA in itself is painful, while other patients with  
21 similar foot deformities but no RA might not experience pain. If this were the case, then  
22 the deformity would not be the cause of pain, but merely the outcome of a degenerative  
23 process in the foot. However, analysis of plantar pressures shows that this localised pain  
24 is not correlated with peak plantar pressure, which is received in the hindfoot.  
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27 Structural alterations in the foot not only cause physical deterioration due to reduced  
28 mobility, but can also lead to emotional deterioration. Nevertheless, according to our  
29 study findings, these alterations are not in themselves the cause of increased pain.  
30 Instead, this outcome may be influenced by an external component such as the choice of  
31 footwear, a factor that is strongly influenced by the appearance of structural alterations  
32 in the foot. Patients should prioritize factors such as fit and comfort when choosing  
33 footwear.[28]  
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36 Many patients, both male and female, have considerable difficulty in obtaining  
37 appropriate footwear, especially females, i.e. that which is comfortable, adapted to the  
38 deformities of the foot, of assistance in performing the gait cycle and acceptable  
39 aesthetically [29,30].  
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42 The latter characteristic is the area in which most negative impressions are caused  
43 among the population with RA, since many patients do not choose their footwear in  
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3 strict accordance with the deformities present in their feet [31]. This discordance can  
4 produce a negative impact, either in terms of the mental component (the perceived  
5 quality of life), when the personal image is compared with that of the non-affected  
6 population, or because of increased plantar pain, when the footwear chosen is  
7 uncomfortable and prevents the proper mobilisation of the musculoskeletal structures of  
8 the foot, thereby limiting the performance of the activities of daily life. These outcomes  
9 are often associated with dissatisfaction and even depression among the population  
10 affected.

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13 With advancing age, musculoskeletal deformities and, in particular, structural  
14 alterations in the foot increase, as a greater number of structures are damaged. These  
15 alterations may also be caused by increased neuropathy in the foot, which in turn would  
16 heighten pain and reduce functionality [1], thus worsening the perceived quality of life  
17 (anxiety and depression status) [32][33].

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20 This research presents certain limitations. Firstly, it is based on a cross-sectional study  
21 of a heterogeneous sample population, rather than on a longitudinal study. This  
22 characteristic of the study design may have influenced the results obtained in two  
23 respects. On the one hand, in our sample the number of participants with RA  
24 significantly exceeded that of those not presenting this alteration. Therefore, if the size  
25 of the control group were increased, somewhat different results might be obtained.  
26 Moreover, as the analysis was transversal, both the physical and the mental components  
27 were analysed at a moment that might have coincided with an aggravation of the RA  
28 experienced, thus altering the study results obtained.

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31 Another limitation of our study is that it is based on a convenience sample, which  
32 means that the homogeneity of the participants cannot be assured. In future research,  
33 therefore, the size and composition of the study groups should be controlled to optimise  
34 their homogeneity. Finally, attention should be paid to the question of whether foot pain  
35 is determined by the characteristics of the foot, or whether RA pain affects certain foot  
36 types in particular.

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39 Our study shows that patients with RA are more likely to present structural alterations  
40 in the foot and hence to experience physical and/or psychosocial deterioration than  
41 when this condition is absent [34]. Furthermore, the long-term evolution of the disease  
42 may be directly related to psychosocial and emotional perceptions. It should be also be  
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3 taken into account that in our study groups most of the patients were female, although  
4 this reflects their prevalence among the general population affected by RA and foot pain  
5 [35,36] Females has their psychosocial life altered due to some factors, such as being  
6 active in terms of work or their self-image perception.[37][38][39]  
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10 On the other hand, the study also has important strengths. Although the results obtained  
11 do not show that foot-related parameters are strongly associated with the quality of life  
12 of these patients, they do highlight the need for further, longitudinal studies addressing  
13 parameters such as the evolution of the disease, the treatment received and psychosocial  
14 aspects that could influence the patient's perception of the impact of RA with respect to  
15 daily activities and musculoskeletal pain.  
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21 In the clinical context, our study raises an important question, namely that the pain and  
22 the reduced quality of life experienced by patients with RA may be provoked by the  
23 disease itself, and not by the alterations in the foot. If this were so, the presence of the  
24 latter might not be related to the pain experienced.  
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## 29 **Conclusions**

30 Morphological and structural characteristics of the foot are not necessarily associated  
31 with pain, disability and loss of function. The presence of RA, a higher score for general  
32 VAS pain, female gender and greater age are all related to a reduced quality of life in  
33 the physical component for patients with RA.  
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## 38 **Author Contributions**

39 Conceptualization, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Jose Miguel Morales-  
40 Asencio and Ana Belen Ortega-Avila; Data curation, Andres Reino-Cobo; Formal  
41 analysis, Gabriel Gijon-Nogueron, Jose Miguel Morales-Asencio and Ana Belen  
42 Ortega-Avila; Methodology, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Miguel  
43 Angel Ferrer-Gonzalez and Ana Belen Ortega-Avila; Project administration, Maria  
44 Teresa Vallejo-Velazquez; Writing – original draft, Andres Reino-Cobo, Gabriel Gijon-  
45 Nogueron and Ana Belen Ortega-Avila; Writing – review & editing, Andres Reino-  
46 Cobo, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Jose Miguel Morales-Asencio and  
47 Ana Belen Ortega-Avila.  
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	Overall(n=293)					Female (n=173)				Male (n=120)					
	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value	
	Median	Interquartile range	Median	Interquartile range		Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range		
Age (years)	59	16	53	21	0,003	59	16	53	21	0,001	58	16	53.5	24	0.845
Height (cm)	162	10	162	10	0,401	160	10	160.5	9	0,001	170	10	171	15	0.578
Weight (kg)	70	19	65	15	0,168	65	15	62.5	11	0,001	78	18	76.5	13	0.35
Gen. VAS (0-100)	6	3	1,5	4	<0.001	6	3	2	5	<0.001	5	4	0	1	<0.001
Hand VAS	6	3	0	3	<0.001	6	4	1	3	<0.001	5	4	0	1	<0.001
Feet VAS	6	5	2	5	<0.001	6	4	2	5	<0.001	4	5	0	1	<0.001
MFPDI	21	18	4	10	<0.001	22	17	4.5	11	<0.001	19	18	0.5	6	<0.001
FFI Total	43,91	45	6,52	18	<0.001	48.3	39	9.1	23	<0.001	30.4	51	0	5	<0.001
FFI Pain	48	38	8	29	<0.001	50	34	14	33	<0.001	41.5	47	0	4	<0.001
FFI Disability	49	58	0	14	<0.001	51	50	2	18	<0.001	24	56	0	0	<0.001
FFI Physical activity	6	19	0	2	<0.001	7	20	0	2	<0.001	3	15	0	0	<0.001
W/b r/foot	242	22	244	18	0,339	237	15	240.5	17	0,05	261	18	261	22	0.777
W/b 1 <sup>st</sup> MTPJ r/foot	180	16	180,5	15	0,843	178	11	177	14	0,843	195.5	14	189.5	19	0.9
W/b r/MF height	53,8	9,7	56,265	10,31	<0.001	51.4	8.2	54.4	9.4	0,001	58.8	6.3	65.8	16	0.004
W/b r/MF width	77	8,63	74,965	8,93	0,035	75.5	6.7	73.9	6.9	0,03	83.5	7.2	81.5	8.7	0.559
W/b r/forefoot	91,38	9,34	91,69	7,08	0,508	89.7	7	88.5	6.8	0,58	97.3	7.8	96.4	7.4	0.941
W/b r/hindfoot	66,52	7,29	66,105	6,16	0,089	65.7	6.2	65.2	6.6	0,15	71.8	7.6	68.5	4.2	0.39
FPI TOTAL (r/foot)	5	7	5	4	0,338	5	6	5	5	0,80	2	8	5	3	0.205

Table 1. Characteristics of the study groups W/b: Weight bearing; r/: Right; MTPJ: Metatarsophalangeal joints; MF: midfoot \*Mann-Whitney U-test



	Female					Male				
	RA (n=173)		Control group (n=50)			RA (n=56)		Control group (n=14)		
	Mean	SD	Mean	SD	P value*	Mean	SD	Mean	SD	P value*
Physical health component (Ref. Spanish population)	36.50	7.91	48.88	7.55	p<0.001	39.07	2.91	49.09	8.22	0.02
Mental health component (Ref. Spanish population)	32.10	7.97	35.08	5.00	0.04	33.76	1.65	36.14	4.66	0.35

\* Mann-Whitney U-test

Table 2. Characteristics of the sample group according to the SF 12 results

	Adjusted coefficient	B	$\beta$	p	95%CI	
					Lower	Upper
Age	-0.175	-0.082	-0.113	0.038	-0.159	-0.005
Gender	-1.361	-0.603	-0.028	0.607	-2.908	1.703
VAS pain – General	-2.177	-1.609	-0.474	<0.001	-2.024	-1.193
RA	-11.769	-6.461	-0.292	<0.001	-9.111	-3.811

Table 3: Model of multivariate regression for the perception of physical health

For peer review only

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7

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(b) Report category boundaries when continuous variables were categorized

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).

# BMJ Open

## Foot health and quality of life in patients with rheumatoid arthritis: a cross-sectional study

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<b>Primary Subject Heading</b>:	Rheumatology
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3 **Foot health and quality of life in patients with rheumatoid arthritis: a cross-**  
4 **sectional study**  
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8 Andres Reinoso-Cobo<sup>1</sup> MSc [andres.reinoso.sspa@juntadeandalucia.es](mailto:andres.reinoso.sspa@juntadeandalucia.es)

9 Gabriel Gijon-Nogueron<sup>2,3</sup>, PhD [gagijon@uma.es](mailto:gagijon@uma.es)

10 Rafael Caliz-Caliz<sup>1</sup> MD, PhD [antonior.caliz.sspa@juntadeandalucia.es](mailto:antonior.caliz.sspa@juntadeandalucia.es)

11 Miguel Angel Ferrer-González<sup>1</sup> MD PhD [maferrer@fundacionhvn.org](mailto:maferrer@fundacionhvn.org)

12 Maria Teresa Vallejo-Velazquez<sup>1</sup>, MsC [tvallejo@ibsggranada.es](mailto:tvallejo@ibsggranada.es)

13 Jose Miguel Morales-Asencio<sup>2,3</sup> PhD [jmmasen@uma.es](mailto:jmmasen@uma.es)

14 Ana Belen Ortega-Avila<sup>3</sup> PhD [anaortavi@uma.es](mailto:anaortavi@uma.es)

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21  
22 1. Departamento de Reumatología, Hospital Universitario Virgen de las Nieves, Granada,  
23 Granada, Spain  
24 2. Instituto de Investigación Biomédica de Málaga (IBIMA), Malaga, Spain  
25 3. Department Nursing and Podiatry, Universidad de Málaga, Malaga. Spain  
26  
27

28 **Corresponding author: Gabriel Gijon-Nogueron**

29  
30 Faculty of Health Sciences. Arquitecto Francisco Penalosa 3. Ampliación de Campus de  
31 Teatinos, 29071 Malaga. Spain. [gagijon@uma.es](mailto:gagijon@uma.es)  
32

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36 Tables: 3  
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46 **Conflict of interest:** All the authors declare that they have no conflict of interest  
47 derived from the outcomes of this study.  
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## Abstract

*Objective:* The aim of this study is to identify foot health factors related to the quality of life in patients with RA.

*Setting:* The cross-sectional study in total, 293 subjects were analysed, with 229 patients in the RA group and 64 in the control group. In the RA group, 173 patients were female, as were 50 of the control group

*Participants:* Patients with foot pain and RA (according to the ACR/EULAR 2010 rheumatoid arthritis classification criteria) and with foot pain but no RA were recruited (Granada, Spain).

*Intervention:* Two researchers independently interviewed the patients to obtain the study data

*Primary and secondary outcome measures:* Clinical data were obtained using the SF-12 questionnaire (Quality of life) (Primary outcome), visual analogue scales for pain (VAS pain), the Manchester Foot Pain Disability Index questionnaire (MFPDI) and the Foot Function Index (FFI). Anthropometric measurements were obtained by means of a foot measurement platform, the Foot Posture Index (FPI) and the Manchester Hallux Valgus Scale.(secondary outcomes)

### Results

Of the 293 subjects, 76.1% were female. Significant differences were observed between the RA and control groups ( $p < 0.001$ ) according to VAS pain (general, foot and hand), the MFPDI and the FFI. In terms of anthropometric measurements, significant differences were only recorded for midfoot and forefoot width ( $p = 0.03$ ). In the data for the physical component, the multivariable linear regression with the parameters age, gender, VAS pain (general) and the presence of RA presented an  $R^2$  value of 48.8%, while for the mental health component, the corresponding value was 5.6%.

### Conclusion

Morphological and structural characteristics of the foot are not necessarily associated with pain, disability and loss of function. The presence of RA, a higher score in VAS pain (general), female gender and greater age are all associated with the physical component of the quality of life for patients with RA.

### Key words

Rheumatoid arthritis; foot health; quality of life; functionality; pain.



## Strengths and limitations of this study

- The foot-related parameters are strongly associated with QoL.
- RA, higher score for VAS pain, female sex and age are all related to the physical component of QoL.
- Neither FPI nor any other anthropometric measurements are related to QoL.
- QoL was analysed at a moment that might coincide with an aggravation of RA.
- A longitudinal study might obtain different results.

## Introduction

Rheumatoid arthritis (RA) is a chronic rheumatic disease that affects 0.5% to 1% of the population in Europe [1]. The most characteristic symptom is swelling, which provokes important changes in joint structures and limits function [2].

RA mainly affects the small joints of the hands and feet [3]. In the foot, it provokes deformities in the forefoot and hindfoot. The most common pathologies are hallux valgus, metatarsal subluxation, and hammer or claw toes [4]. As the disease progresses, the first metatarsophalangeal joint and pes planus may also be associated. These pathologies occur as the deterioration affects the joints and ligaments [5], thus limiting movement in the ankle and the foot. It also produces an unequal distribution of pressures and therefore makes it painful to remain in a standing position [6].

RA is a systemic disease that not only presents extra-articular manifestations but also has psychological affects [7], in many cases provoking mental health and functional problems as a consequence of ageing [8], oxidative damage to DNA and systemic inflammatory stress [9], thus limiting leisure and family-related activities and restricting social relationships [10]. The simultaneous impact of RA and a reduced quality of life imposes a major burden on patients, caregivers, the health system and society in general [11].

The mental and physical components of RA can reduce adherence to treatment, leading to poorer health outcomes and a worsened quality of life [12].

In patients with RA, the foot has been analysed from various standpoints, such as hallux valgus, clawed toes or morphological alterations [13]. Psychological and social aspects of the disease have also been analysed such as anxiety, depression and affectivity, have

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3 also been analysed [14,15][16]. However, to date no studies have been undertaken to  
4 determine whether RA in the foot has a negative impact on the quality of life, in  
5 physical and mental health terms.  
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8 The aim of the present study, therefore, is to identify foot health factors related to the  
9 quality of life in patients with RA.  
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## 20 **Method**

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22 **Ethical approval: Institutional review board that approved the protocol for the**  
23 **study:** Medical Research Ethics Committee of University of Malaga (CEUMA-91-  
24 2015-H) and PEIBA Andalucia (ARC0001), Spain.  
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27 **Design:** Cross-sectional study  
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## 30 **Participants**

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32 A convenience sample was obtained of 246 patients with foot pain and RA (according  
33 to the ACR/EULAR rheumatoid arthritis classification criteria)[17], of whom seventeen  
34 subsequently declined to participate, citing lack of time (the study questionnaire  
35 required 30 minutes to complete) and 64 patients with foot pain but no RA. The patients  
36 were enrolled at hospital outpatient clinics from January to December 2018.  
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41 All those included in the study had a history of subtalar and/or ankle and/or  
42 talonavicular or hindfoot pain, did not make daily use of walking aids, and were able to  
43 perform the normal range of motions in the ankle, subtalar and midtarsal joints. Even if  
44 maximum dorsiflexion, pronation or supination in these joints could not be produced, a  
45 sufficient range of motion was achieved by adjusting the dynamics, for example by  
46 reducing stride length[6][18].  
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51 The exclusion criteria applied were the presence of concomitant musculoskeletal  
52 disease, central or peripheral nervous system disease or endocrine disorders (especially  
53 diabetes mellitus).  
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3 Patients who met the criteria for inclusion were approached by members of the  
4 rheumatology service at the Virgen de la Nieves Hospital (Granada, Spain), given an  
5 information sheet and invited to participate. Those who agreed were then interviewed  
6 and given further details of the study. All participants provided written consent prior to  
7 starting the interviews.  
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## 10 11 12 **Data collection**

### 13 14 *Demographic and clinical characteristics*

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16 The demographic characteristics recorded included the patient's age, gender, disease  
17 duration and current therapy. The clinical data recorded were those obtained from the  
18 SF-12 questionnaire [19], a visual analogue scale for pain (VAS pain), both general [20]  
19 and specific to the foot and hand, the Manchester Foot Pain Disability Index (MFPDI)  
20 [21] and the Foot Function Index (FFI) [22].  
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24 For the anthropometric measurements, a foot measurement platform [23] was used to  
25 measure the foot length (weight bearing and non weight bearing), the midfoot, forefoot  
26 and heel width and the midfoot height. Each participant was asked first to stand on the  
27 platform and then to be seated, in both cases with the body weight distributed evenly  
28 between the two feet, arms beside the body and facing forwards. The measurements  
29 were obtained with the patient's heels placed in the heel cups, as far back as possible,  
30 and the first metatarsal heads located against the limit surface.  
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34 Other measurements were obtained using the Foot Posture Index, a reliable instrument  
35 for this purpose [24], and the Manchester Scale of hallux valgus [25].  
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39 **The data availability statement** No additional data available  
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## 42 43 44 **Procedure**

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46 Two researchers (ARC and GGN) independently interviewed the patients to obtain the  
47 study data. The clinical interview was conducted in one room, where the patients were  
48 asked to complete the SF-12 (adapted version for a Spanish population) [26], MFPDI  
49 and VAS questionnaires. In a separate room, each patient was measured using a  
50 validated foot platform (intraclass correlation coefficient for the instrument, ICC, 0.96-  
51 0.98). Foot posture was determined according to the Foot Posture Index (FPI) (ICC for  
52 the clinician, 0.94-0.96). Each criterion was scored as -2, -1, 0, +1 or +2. The  
53 following FPI cut-off points, defining foot type category were used: a) highly supinated  
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3 -12 to -4, b) supinated -3 to 0, c) neutral 1 to 7, d) pronated 8 to 10 and e) highly  
4 pronated 11 to 12 [27]. The presence/absence of hallux valgus was determined  
5 according to the Manchester Scale of Hallux Valgus (ICC for the instrument, 0.93-  
6 0.97), a clinical tool consisting of photographs of feet with four levels of hallux valgus:  
7 none, mild, moderate and severe [25].  
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## 12 **Patient and public involvement**

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15 No patients were involved in setting the research question or the outcome measures, nor  
16 were they involved in the design or conduct of the study. No patients were asked to  
17 advise on interpretation or writing up of results. There are no plans to disseminate the  
18 results of the research to the study participants  
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## 22 **Statistical analysis**

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25 The results obtained are reported as the median and interquartile range, due to the non-  
26 normal distribution of the variables. The normality of the distributions was examined by  
27 the Kolmogorov-Smirnov test and the intra-rater reliability of the measurement  
28 instruments was calculated by a two-way mixed-consistency ICC model. Bivariate  
29 analysis was performed with a non-parametric test (the Mann-Whitney U test), in view  
30 of the non-normal distribution observed in most cases. Finally, a multivariable linear  
31 regression model was obtained to evaluate the predictors of quality of life, according to  
32 the physical and mental health components of the SF-12 questionnaire. In constructing  
33 the models, the regression assumptions of homoscedasticity, normality and  
34 independence of the residuals and collinearity were tested. Homoscedasticity was  
35 evaluated by analysing the distribution of predicted values and scatterplots of the  
36 residuals. Normality of the residuals was tested by analysing histograms and by graphs  
37 of standardised residuals. Independence of the residuals was evaluated by the Durbin-  
38 Watson statistic. Finally, the presence of collinearity was tested by calculating the  
39 variance inflation factor, the tolerance and partial correlations. The significance level  
40 was set at  $p < 0.05$ , with two-tailed tests. All statistical analyses were conducted using  
41 SPSS v. 24.0 statistical software (SPSS Inc., Chicago, IL, USA) and GPower 3.1.92 for  
42 the post-hoc analyses.  
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## 56 **Results**

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3 In total, 293 subjects were analysed, with 229 patients in the RA group (average  
4 duration of RA, 15.4, SD 10.5 years) and 64 in the control group. In the RA group, 173  
5 patients were female, as were 50 of the control group. The values for median age and  
6 interquartile range (IQR) were 59 and 16 years for the patients with RA and 53 and 21  
7 years for those in the control group. The median values for height and weight were 162  
8 cm (IQR: 10) and 70 kg (IQR: 19), respectively, for the RA group, and 162 cm (IQR:  
9 10) and 65 kg (IQR: 15), respectively, for the control group. The patients with RA were  
10 treated with biological disease-modifying antirheumatic drugs (bDMARDs) (42%),  
11 methotrexate (35%) or nonsteroidal anti-inflammatory drugs (NSAIDs) / corticosteroids  
12 (20%).

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21 The instruments used to measure pain, disability and functionality (VAS pain, MFPDI  
22 and FFI) revealed significant differences between the patients with RA and the control  
23 group, for both genders ( $p < 0.001$ ). However, among those used to obtain foot  
24 measurements and posture data, only the midfoot height values ( $p = 0.007$  and  $p = 0.004$ )  
25 for male and female participants and midfoot width ( $p = 0.03$ ) for the females were  
26 statistically significant. The FPI and the other anthropometric measurements were not  
27 statistically significant (Table 1).

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34 The results for the SF-12 quality of life questionnaire revealed significant differences in  
35 the physical component, with  $p < 0.001$  (females) and  $p = 0.02$  (males) and in the mental  
36 component in the female participants ( $p = 0.04$ ) (Table 2). Among the male participants,  
37 no differences in the mental health component were observed between the RA and  
38 control groups.

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44 Bivariate analyses were performed to determine the relations between the physical and  
45 mental health components, taking into account the sociodemographic, clinical and  
46 anthropometric characteristics of the participants. Among these results, especially  
47 noteworthy was the value of -0.630 with  $p < 0.001$  obtained for VAS pain (general) and  
48 that of -0.505 with  $p < 0.001$  for the presence of RA. Neither the anthropometric  
49 characteristics, foot posture nor disease duration presented any correlation with either of  
50 these variables.

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57 Multivariate models were then constructed, using as predictors the variables that had  
58 presented a significant association in the bivariate models, adjusted for age and gender.  
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Two models were calculated, with the physical and mental health components respectively as dependent variables.

According to the data for the physical component, the multivariable linear regression presented an  $R^2$  value of 48.8%. (Table 3). Post-hoc analysis yielded a power of 0.95 for this four-predictor model. The multivariable linear regression of the mental health component presented an  $R^2$  value of 5.6%. There was no collinearity in the model (maximum VIF 1.39 and minimum tolerance of 0.72) and the residuals were independent (Durbin-Watson, 1.19), using the same parameters (i.e. age, gender, general VAS pain and the presence of RA).

## Discussion

The aim of this study is to determine and analyse foot health factors related to the quality of life of patients with RA. The multivariate regression results obtained suggest that patients with foot pain and RA perceive a significantly lower level of health than those with foot pain but no RA (control group) ( $p < 0.001$ ). However, these findings are not directly related to the clinical parameters that might have triggered the increased level of pain. The deformations which are typical of this disease and which are located in the forefoot (such as hallux valgus, hallux rigidus, floating of the lesser toes or synovial inflammation of the metatarsophalangeal joints) or in the hindfoot (such as hindfoot valgus or flat foot) are often believed to aggravate pain and disability among this population. Nevertheless, this expectation was not borne out by our study results, possibly because the presence of RA in itself is painful, while other patients with similar foot deformities but no RA might not experience pain. If this were the case, then the deformity would not be the cause of pain, but merely the outcome of a degenerative process in the foot. However, analysis of plantar pressures shows that this localised pain is not correlated with peak plantar pressure, which is received in the hindfoot.

Structural alterations in the foot not only cause physical deterioration due to reduced mobility, but can also lead to emotional deterioration. Nevertheless, according to our study findings, these alterations are not in themselves the cause of increased pain. Instead, this outcome may be influenced by an external component such as the choice of footwear, a factor that is strongly influenced by the appearance of structural alterations in the foot. We conclude, therefore, that patients should prioritise factors such as fit and comfort when choosing footwear.[28]

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3 Many patients, especially women, have considerable difficulty in obtaining appropriate  
4 footwear, i.e. that which is comfortable, adapted to the deformities of the foot, of  
5 assistance in performing the gait cycle and acceptable aesthetically [29,30].  
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9 The latter characteristic is the area in which most negative impressions are caused  
10 among the population with RA, since many patients do not choose their footwear in  
11 strict accordance with the deformities present in their feet [31]. This discordance can  
12 produce a negative impact, either in terms of the mental component (the perceived  
13 quality of life), when the personal image is compared with that of the non-affected  
14 population, or because of increased plantar pain, when the footwear chosen is  
15 uncomfortable and prevents the proper mobilisation of the musculoskeletal structures of  
16 the foot, thereby limiting the performance of the activities of daily life. These outcomes  
17 are often associated with dissatisfaction and even depression among the population  
18 affected.  
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22 With advancing age, musculoskeletal deformities and, in particular, structural  
23 alterations in the foot increase, as a greater number of structures are damaged. These  
24 alterations may also be caused by increased neuropathy in the foot, which in turn would  
25 heighten pain and reduce functionality [1], thus worsening the perceived quality of life  
26 (impacting on anxiety and depression status in particular ) [32][33].  
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30 This research presents certain limitations. Firstly, it is based on a cross-sectional study  
31 of a heterogeneous sample population, rather than on a longitudinal study. This  
32 characteristic of the study design may have influenced the results obtained in two  
33 respects. On the one hand, in our sample the number of participants with RA  
34 significantly exceeded that of those not presenting this alteration. Therefore, if the size  
35 of the control group were increased, somewhat different results might be obtained.  
36 Moreover, as the analysis was transversal, both the physical and the mental components  
37 were analysed at a moment that might have coincided with an aggravation of the RA  
38 experienced, thus altering the study results obtained.  
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42 Another limitation of our study is that it is based on a convenience sample, which  
43 means that the homogeneity of the participants cannot be assured. In future research,  
44 therefore, the size and composition of the study groups should be controlled to optimise  
45 their homogeneity. Finally, attention should be paid to the question of whether foot pain  
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3 is determined by the characteristics of the foot, or whether RA pain affects certain foot  
4 types in particular.  
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7 Our study shows that patients with RA are more likely to present structural alterations  
8 in the foot and hence to experience physical and/or psychosocial deterioration than  
9 when this condition is absent [34]. Furthermore, the long-term evolution of the disease  
10 may be directly related to psychosocial and emotional perceptions. It should be also be  
11 taken into account that in our study groups most of the patients were female, although  
12 this reflects their prevalence among the general population affected by RA and foot pain  
13 [35,36] Psychosocial status was also increased in this female population, due to factors  
14 such as their being in employment or the presence of positive body image perceptions  
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23 On the other hand, the study also has important strengths. Although the results obtained  
24 do not show that foot-related parameters are strongly associated with the quality of life  
25 of these patients, they do highlight the need for further, longitudinal studies addressing  
26 parameters such as the evolution of the disease, the treatment received and psychosocial  
27 aspects that could influence the patient's perception of the impact of RA with respect to  
28 daily activities and musculoskeletal pain.  
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34 In the clinical context, our study raises an important question, namely that the pain and  
35 the reduced quality of life experienced by patients with RA may be provoked by the  
36 disease itself, and not by the alterations in the foot. If this were so, the presence of the  
37 latter might not be related to the pain experienced.  
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## 42 **Conclusions**

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44 Morphological and structural characteristics of the foot are not necessarily associated  
45 with pain, disability and loss of function. The presence of RA, a higher score for general  
46 VAS pain, female gender and greater age are all related to a reduced quality of life in  
47 the physical component for patients with RA.  
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## 51 **Author Contributions**

52 Conceptualization, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Jose Miguel Morales-  
53 Asencio and Ana Belen Ortega-Avila; Data curation, Andres Reinoso-Cobo; Formal  
54 analysis, Gabriel Gijon-Nogueron, Jose Miguel Morales-Asencio and Ana Belen  
55 Ortega-Avila; Methodology, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Miguel  
56 Angel Ferrer-Gonzalez and Ana Belen Ortega-Avila; Project administration, Maria  
57 Teresa Vallejo-Velazquez; Writing – original draft, Andres Reinoso-Cobo, Gabriel  
58  
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3 Gijon-Nogueron and Ana Belen Ortega-Avila; Writing – review & editing, Andres  
4 Reinoso-Cobo, Gabriel Gijon-Nogueron, Rafael Caliz-Caliz, Jose Miguel Morales-  
5 Asencio and Ana Belen Ortega-Avila.  
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	Overall(n=293)					Female (n=173)				Male (n=120)					
	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value	Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		Patients with foot pain and RA (group)		Patients with foot pain but no RA (control group)		P value	
	Median	Interquartile range	Median	Interquartile range		Median	Interquartile range	Median	Interquartile range	Median	Interquartile range	Median	Interquartile range		
Age (years)	59	16	53	21	0,003	59	16	53	21	0,001	58	16	53.5	24	0.845
Height (cm)	162	10	162	10	0,401	160	10	160.5	9	0,001	170	10	171	15	0.578
Weight (kg)	70	19	65	15	0,168	65	15	62.5	11	0,001	78	18	76.5	13	0.35
Gen. VAS (0-100)	6	3	1,5	4	<0.001	6	3	2	5	<0.001	5	4	0	1	<0.001
Hand VAS	6	3	0	3	<0.001	6	4	1	3	<0.001	5	4	0	1	<0.001
Feet VAS	6	5	2	5	<0.001	6	4	2	5	<0.001	4	5	0	1	<0.001
MFPDI	21	18	4	10	<0.001	22	17	4.5	11	<0.001	19	18	0.5	6	<0.001
FFI Total	43,91	45	6,52	18	<0.001	48.3	39	9.1	23	<0.001	30.4	51	0	5	<0.001
FFI Pain	48	38	8	29	<0.001	50	34	14	33	<0.001	41.5	47	0	4	<0.001
FFI Disability	49	58	0	14	<0.001	51	50	2	18	<0.001	24	56	0	0	<0.001
FFI Physical activity	6	19	0	2	<0.001	7	20	0	2	<0.001	3	15	0	0	<0.001
W/b r/foot	242	22	244	18	0,339	237	15	240.5	17	0,05	261	18	261	22	0.777
W/b 1 <sup>st</sup> MTPJ r/foot	180	16	180,5	15	0,843	178	11	177	14	0,843	195.5	14	189.5	19	0.9
W/b r/MF height	53,8	9,7	56,265	10,31	<0.001	51.4	8.2	54.4	9.4	0,001	58.8	6.3	65.8	16	0.004
W/b r/MF width	77	8,63	74,965	8,93	0,035	75.5	6.7	73.9	6.9	0,03	83.5	7.2	81.5	8.7	0.559
W/b r/forefoot	91,38	9,34	91,69	7,08	0,508	89.7	7	88.5	6.8	0,58	97.3	7.8	96.4	7.4	0.941
W/b r/hindfoot	66,52	7,29	66,105	6,16	0,089	65.7	6.2	65.2	6.6	0,15	71.8	7.6	68.5	4.2	0.39
FPI TOTAL (r/foot)	5	7	5	4	0,338	5	6	5	5	0,80	2	8	5	3	0.205

Table 1. Characteristics of the study groups W/b: Weight bearing; r/: Right; MTPJ: Metatarsophalangeal joints; MF: midfoot \*Mann-Whitney U-test

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	Female					Male				
	RA (n=173)		Control group (n=50)			RA (n=56)		Control group (n=14)		
	Mean	SD	Mean	SD	P value*	Mean	SD	Mean	SD	P value*
Physical health component (Ref. Spanish population)	36.50	7.91	48.88	7.55	p<0.001	39.07	2.91	49.09	8.22	0.02
Mental health component (Ref. Spanish population)	32.10	7.97	35.08	5.00	0.04	33.76	1.65	36.14	4.66	0.35

\* Mann-Whitney U-test

Table 2. Characteristics of the sample group according to the SF 12 results

	Adjusted coefficient	B	$\beta$	p	95%CI	
					Lower	Upper
Age	-0.175	-0.082	-0.113	0.038	-0.159	-0.005
Gender	-1.361	-0.603	-0.028	0.607	-2.908	1.703
VAS pain – General	-2.177	-1.609	-0.474	<0.001	-2.024	-1.193
RA	-11.769	-6.461	-0.292	<0.001	-9.111	-3.811

Table 3: Model of multivariate regression for the perception of physical health

For peer review only

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60STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation	
<b>Title and abstract</b>	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
<b>Introduction</b>			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
<b>Methods</b>			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	5
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	
		(c) Explain how missing data were addressed	
		(d) If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	
<b>Results</b>			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	6
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7



		(b) Report category boundaries when continuous variables were categorized	
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	7
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7
Generalisability	21	Discuss the generalisability (external validity) of the study results	7-8
<b>Other information</b>			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

\*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at [www.strobe-statement.org](http://www.strobe-statement.org).