European Journal of Nutrition (2023) 62:2827–2839
https://doi.org/10.1007/s00394-023-03196-8

ORIGINAL CONTRIBUTION

The Mediterranean diet, and not dietary inflammatory index, is associated with rheumatoid arthritis disease activity, the impact of disease and functional disability

Sofia Charneca[1] · Margarida Ferro[1] · João Vasques[1] · Elisabete Carolino[2] · Joana Martins-Martinho[3,4] · Ana Margarida Duarte-Monteiro[3,4] · Eduardo Dourado[3,4] · João Eurico Fonseca[3,4] · Catarina Sousa Guerreiro[1,5]

Received: 10 January 2023 / Accepted: 13 June 2023 / Published online: 24 June 2023

Abstract

Purpose To assess the relationship between adherence to the Mediterranean Diet (MD) /individual Dietary Inflammatory Index (DII) and disease activity, disease impact, and functional status in Rheumatoid Arthritis (RA) patients.

Methods RA patients followed at a hospital in Lisbon, Portugal, were recruited. DII was calculated using dietary intake data collected with a food frequency questionnaire (FFQ). Adherence to the MD was obtained using the 14-item Mediterranean Diet assessment tool. Disease Activity Score of 28 Joints (DAS28) and the DAS28 calculated with C-Reactive Protein (DAS28-CRP) were used to assess disease activity. Impact of disease and functional status were evaluated using the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire and the Health Assessment Questionnaire (HAQ), respectively.

Results 120 patients (73.3% female, 61.8 ± 10.1 years of age) were included. Patients with higher adherence to the MD had significantly lower DAS28-CRP (median 3.27(2.37) vs 2.77(1.49), p = 0.030), RAID (median 5.65(2.38) vs 3.51(4.51), p = 0.032) and HAQ (median 1.00(0.56) vs 0.56(1.03), p = 0.013) scores. Higher adherence to the MD reduced the odds of having a higher DAS28 by 70% (OR = 0.303, 95%CI = (0.261, 0.347), p = 0.003). Lower adherence to MD was associated with higher DAS28-CRP (β = − 0.164, p = 0.001), higher RAID (β = − 0.311, p < 0.0001), and higher HAQ scores (β = − 0.089, p = 0.001), irrespective of age, gender, BMI and pharmacological therapy. Mean DII of our cohort was not significantly different from the Portuguese population (0.00 ± 0.17 vs − 0.10 ± 1.46, p = 0.578). No associations between macronutrient intake or DII and RA outcomes were found.

Conclusions Higher adherence to the MD was associated with lower disease activity, lower impact of disease, and lower functional disability in RA patients.

Keywords Mediterranean diet · Rheumatoid arthritis · Disease activity · Disease impact · Functional disability

Abbreviations

ACR	American college of rheumatology
bDMARDs	Biological disease-modifying antirheumatic drugs
BMI	Body mass index
CRP	C-reactive protein
DAS28	Disease activity score in 28 joints
DAS28-CRP	Disease activity score in 28 joints calculated with C-reactive protein
DII	Dietary inflammatory index
DMARDs	Disease-modifying antirheumatic drugs
EULAR	European league against rheumatism
ESR	Erythrocyte sedimentation rate
FFQ	Food frequency questionnaire
HAQ	Health assessment questionnaire
hs-CRP	High-sensitivity C-reactive protein
MD	Mediterranean diet
PREDIMED	Prevención con dieta Mediterránea
RA	Rheumatoid arthritis
RAID	Rheumatoid arthritis impact of disease
RCT	Randomised clinical trial
RF	Rheumatoid factor
SD	Standard deviation
SCFA	Short-chain fatty acids
SJC	Swollen joint count
TJC	Tender joint count
VAS	Visual analogue scale

Extended author information available on the last page of the article

Introduction

Rheumatoid Arthritis (RA) is a chronic immune-mediated inflammatory disorder characterized by progressive joint damage, autoantibody production, cartilage and bone destruction, and systemic features ultimately causing disability, decreased quality of life and substantial morbidity [1–3]. Among other patient-related factors, treatment decisions in RA are based on disease activity [4]. Several RA disease activity measures have been developed for both regular clinical practice and clinical trials. The most used one is the Disease Activity Score of 28 Joints (DAS28), helping to apply a treat-to-target management strategy in clinical practice [5, 6].

The aetiology of RA is not yet fully understood, as it depends on a complex interaction between genetic and environmental factors [7, 8]. Dietary factors and dietary patterns are among the suggested environmental triggers that may contribute to RA development in genetically susceptible individuals [8–10]. Moreover, a substantial number of patients report that what they eat influences their RA symptoms, thus avoiding certain foods hoping to prevent the worsening of the disease [11]. Accordingly, changing dietary patterns have been suggested as nonpharmacological interventions that could be recommended to minimise the disease burden and optimise functioning in the daily life of established RA patients [12]. The Mediterranean Diet (MD) is one of those suggested strategies.

The MD, defined by the United Nations Educational, Scientific and Cultural Organization, UNESCO, as an Intangible Cultural Heritage, is a health-promoting dietary pattern that emphasises non-dietary aspects such as culture, skills, knowledge and traditions [13]. The MD is characterised by the consumption of olive oil, whole grains, fruits and vegetables, a moderate amount of fish, dairy and meat, all seasoned with various condiments and spices, and accompanied by wine or infusions [14]. The health benefits of this dietary pattern are well documented. Higher adherence to the MD is associated with a reduction in the risk of chronic diseases and overall mortality [15].

In recent years, an increasing number of studies investigated the role of the MD in RA. There is preliminary evidence that this dietary pattern might reduce pain and increase physical function in RA patients [16]. Furthermore, the MD is an especially promising and sustainable diet intervention, as it is an overall healthy, well-balanced, non-restrictive dietary pattern with antioxidant and anti-inflammatory properties [17].

The Dietary Inflammatory Index (DII) is also of interest when considering diet and inflammation, as it is a dietary index developed to reflect the inflammatory potential of diet. A variety of health outcomes are associated with the DII, ranging from cardiovascular diseases [18] to cancer [19] and even all-cause mortality [20]. A recent case–control study reported that individuals with the highest DII scores, indicating the most pro-inflammatory diet, were about three times more likely to have RA than those with the lowest DII [21]. However, data regarding the association of the MD and DII with disease activity in RA is still lacking. Proving this association is a crucial first step to the future inclusion of dietary aspects in RA treatment recommendations.

Methods

Aims, study design and population

We conducted a single-centre cross-sectional observational study to assess the relationship between adherence to the MD and individual DII with disease activity, disease impact and functional status in RA patients. Patients who attended their regular follow-up consultation with a rheumatologist at the Rheumatology Department of Centro Hospitalar Universitário Lisboa Norte on Wednesdays, Thursdays and Fridays from December 2019 to July 2021 were recruited to participate in this study. Patients older than 18 years old complying with the European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) 2010 RA classification criteria [22] were included. Exclusion criteria included the inability to attend the nutritional assessment session or any physical or health condition that prevented data collection. Each patient who agreed to participate in the study voluntarily was adequately informed about the project and signed an informed written consent before enrolment. This study was approved by the Lisbon Academic Medical Center Ethical Committee (Ref. Nº 262/19).

Collected data

Dietary intake, adherence to the Mediterranean diet and dietary inflammatory index

Dietary intake was collected using a semi-quantitative food frequency questionnaire (FFQ), previously validated for the Portuguese population [23, 24]. Macro and micronutrient intake for the previous 12 months was obtained through the FFQ, which encompasses 82 food items and beverage categories and their frequency of consumption.

Individual scores of adherence to the MD were obtained using the *14-item Mediterranean Diet assessment tool* from the PREDIMED (*PRevención com dieta Mediterránea*) trial [25, 26]. The Portuguese version of this questionnaire was used [27]. Each of the 14 items is scored with 1 point if it meets the criteria defined for this dietary

pattern, achieving a final score of up to 14 points. Higher scores represent greater adherence to the MD. Adherence to the MD was classified as follows: 0–5 points, low adherence; 6–9 points, moderate adherence; ≥ 10 points, high adherence [26].

DII was calculated based on data collected from the Portuguese FFQ. This index considers diet as a whole, including macronutrients, micronutrients and bioactive compounds [28]. Higher DII scores represent a more pro-inflammatory diet. To calculate the DII of our sample, we used 28 of the 45 possible food parameters (alcohol, energy, fat, fibre, folic acid, iron, magnesium, mono-unsaturated fat, niacin, omega-3, omega-6, protein, polyunsaturated fat, riboflavin, saturated fat, selenium, thiamin, trans fat, vitamin A, vitamin C, vitamin D, vitamin E, zinc, vitamin B12, vitamin B6, caffeine, carbohydrates and cholesterol). We also calculated the DII of the Portuguese population using data from the National Food, Nutrition, and Physical Activity Survey of the Portuguese General Population 2015–2016 [29]. For the DII of the Portuguese population, only 24 nutrients were used due to missing information on omega-3, omega-6, selenium and caffeine intake.

Disease activity, the impact of disease and functional status

Disease activity, the impact of disease and functional status were evaluated according to validated assessment tools: the disease activity score of 28 joints calculated with erythrocyte sedimentation rate (DAS28) and with C-reactive protein (DAS28-CRP), the Rheumatoid Arthritis Impact of Disease (RAID) questionnaire and the Health Assessment Questionnaire (HAQ), respectively. DAS28 and DAS28-CRP are measures of disease activity in RA based on clinical and laboratory data: Tender Joint Count (TJC) and Swollen Joint Count (SJC) of 28 joints, erythrocyte sedimentation rate (ESR, in mm/hour) or C-reactive protein (CRP, in mg/dL) and global health (with 100 being the worst imaginable health state and 0 the best imaginable health state, as reported on a visual analogue scale, VAS). TJC and SJC were evaluated by a rheumatologist. Laboratory data were collected based on standard protocols. DAS28 was classified as: remission (DAS28 ≤ 2.6), low disease activity (2.6 < DAS28 ≤ 3.2), moderate disease activity (3.2 < DAS28 ≤ 5.1) and high disease activity (DAS28 > 5.1). The RAID questionnaire includes seven domains (pain, functional disability, fatigue, emotional well-being, sleep, coping and physical well-being), ultimately originating a patient-derived score of the impact of the disease [30]. The short version of HAQ was used to assess the patient's perception of functional status. This questionnaire includes the HAQ disability index and the HAQ's patient global and pain VAS [31].

Anthropometric, clinical, sociodemographic and lifestyle data

Height measurement was performed using a stadiometer (Tanita®, The Leicester Height Measure), and body weight was determined using a calibrated digital scale (SECA® Model 899). Registered dietitians performed all measurements. Body Mass Index (BMI) was calculated as weight/height squared (kg/m^2). Participants were classified as overweight or obese if BMI ≥ 25 kg/m^2 in individuals under 65 years old or BMI ≥ 27 kg/m^2 in individuals aged ≥ 65 years old. The patient's clinical history was recorded, including disease duration, current medication and associated comorbidities. Age, gender, educational level, menopausal status, physical activity, smoking status and family history of disease were also recorded using a structured questionnaire.

Statistical analysis

The Normal distribution of the variables was verified using the Kolmogorov–Smirnov or Shapiro–Wilk tests, depending on the sample size. Data from categorical variables were described as frequencies (percentages). Normally distributed continuous variables are presented as mean ± standard deviation (SD). The median (interquartile range) was presented when data from continuous variables were not normally distributed. Groups were created based on the patient's adherence to the MD, using previously mentioned cut-offs. Comparisons between groups were performed using the one-way ANOVA for normally-distributed data. When statistically significant differences between groups were identified the multiple comparisons HSD Tukey test was used. The non-parametric alternative (Kruskal–Wallis) was used when data were not normally distributed. When statistically significant differences were identified the Kruskal–Wallis multiple comparisons test was used. Chi-squared test was used for comparisons between categorical variables, and the Chi-squared test by Monte Carlo simulation was used when the conditions for the chi-squared test were not met. Multiple ordinal regression with a negative-log–log link function was used for the DAS28 analysis, controlled for multiple confounders. Multiple linear regression was used to identify DAS28-CRP, RAID and HAQ regressors. Regarding pharmacological therapy, we excluded sulfasalazine from this analysis due to its small sample size (n = 13). Statistical analysis was conducted using SPSS version 27.0 (SPSS® Inc., Chicago, IL). A p value of less than 0.05 was considered statistically significant.

Results

Sample characterisation

Of the 124 participants evaluated, four were excluded due to a change of diagnosis. In total, 120 patients with RA (73.3% female, mean age of 61.8 ± 10.1 years) with a median disease duration of 11.0(14.8) years were included. Overall, the median PREDIMED score was 8.0 (3.0). Most patients (65.5%) were above their ideal weight based on BMI. The mean BMI was 27.8 ± 4.5 kg/m^2 in men and 28.3 ± 5.1 kg/m^2 in women. Median DAS28 and DAS28-CRP were 3.1(1.4) and 2.4(1.3), respectively. A quarter of the patients (25.7%) were in remission (DAS28 ≤ 2.6), 31.0% had low disease activity (2.6 < DAS28 ≤ 3.2), 36.3% had moderate disease activity (3.2 < DAS28 ≤ 5.1) and 7.1% had high disease activity (DAS28 > 5.1). Regarding patient-reported outcomes, the mean RAID score was 4.4 ± 2.2, and the median HAQ score was 0.9(1.1). Most patients had comorbidities (81.7%). The most prevalent were dyslipidemia (39.2%), arterial hypertension (38.3%) and diabetes mellitus (17.5%).

Adherence to the Mediterranean diet

Within our sample, 12.5% of the participants had low (n = 15), 60.8% had moderate (n = 73), and 26.7% had high adherence to the MD (n = 32). Patients with higher adherence to the MD had significantly lower DAS28-CRP (p = 0.030), RAID (p = 0.032) and HAQ (p = 0.013) scores (Table 1). Median DAS28 was also lower among patients with higher adherence to the MD, but this was not statistically significant (p = 0.070). DAS28-CRP was significantly higher in patients with low adherence to the MD compared to patients with both moderate and high adherence to the MD (respectively, median 3.27(2.37) in the low adherence vs 2.27(1.26) in the moderate adherence to the MD groups, p = 0.042; median 3.27(2.37) in the low adherence vs 2.29(1.20) in the high adherence to the MD groups, p = 0.038). Differences in disease activity measures between groups of adherence to the MD are illustrated in Fig. 1. For RAID scores, significant differences were only found between the high and low adherence to the MD groups (median 5.65(2.38) in the low adherence vs 3.51(4.51) in the moderate adherence to the MD groups p = 0.034). HAQ scores were significantly lower in patients with high adherence to the MD compared to patients with both moderate and low adherence to the MD (respectively, median 0.56(1.03) in the high adherence vs 0.87(1.00) in the moderate adherence to the MD groups, p = 0.048; median 0.56(1.03) in the high adherence vs 1.00(0.56) in the low adherence to the MD groups, p = 0.027).

Higher adherence to the MD [OR = 0.303, 95% CI = (0.261, 0.347), p = 0.003] and higher glucocorticoid dose [OR = 0.427, 95% CI = (0.375, 0.479), p = 0.026] independently decreases the chance of increased disease activity evaluated by DAS28, irrespective of age, gender, BMI and pharmacological therapy (methotrexate, hydroxychloroquine, glucocorticoids or biological disease-modifying antirheumatic drugs) (Table 2). Adherence to MD (β = − 0.164, p = 0.001) and glucocorticoid dose (β = 0.174, p = 0.003) were also independently associated with DAS28-CRP. Lower adherence to MD and higher glucocorticoid doses were associated with higher values of DAS28-CRP, irrespective of age, gender, BMI, disease duration, and pharmacological therapy (Table 3, Model 1). Adherence to MD (β = − 0.311, p < 0.0001), gender (β = 1.605, p < 0.0001), BMI (β = 0.141, p = 0.0011), use of MTX (β = − 1.610, p = 0.029) and the dose of glucocorticoids (β = 0.299, p = 0.008) were independently associated with RAID. Lower adherence to MD, being female, having a higher BMI, not taking MTX, and taking higher doses of glucocorticoids were associated with higher RAID scores, irrespective of age and disease duration (Table 3, Model 2). Finally, adherence to MD (β = − 0.089, p = 0.001), gender (β = 0.468, p < 0.0001), BMI (β = 0.044, p = 0.001), use of glucocorticoids (β = 0.299, p = 0.008), and dose of glucocorticoids (β = 0.117, p < 0.0001) were independently associated with HAQ. Lower adherence to MD, being female, having a higher BMI, and taking higher doses of corticoids were associated with higher HAQ scores, irrespective of age and disease duration (Table 3, Model 3).

Overall, higher adherence to the DM was associated with lower DAS28 (p = 0.003), lower DAS28-CRP (p < 0.0001), lower RAID scores (p = 0.002) and lower HAQ scores (p = 0.011) irrespective of age, gender, BMI and pharmacological therapy.

Dietary intake and dietary inflammatory index

The dietary intake of the different MD adherence groups was not significantly different, except for dietary fibre (Table 4). The dietary fibre intake of patients with low adherence to the MD was lower than that of patients with moderate (p = 0.024) and high (p = 0.002) adherence to the MD.

There were no associations between single macronutrients and RA disease outcomes in our cohort. The mean DII of our cohort (0.00 ± 0.17) was not significantly different from the mean DII of the Portuguese population (− 0.10 ± 1.46, p = 0.578). The DII was not associated with DAS28 (p = 0.311), DAS28-CRP (p = 0.163), RAID score (p = 0.415) or HAQ score (p = 0.562) in our cohort.

When inquired about dietary restrictions, a quarter of the patients (n = 30, 25.0%) reported that they excluded certain foods from their diet because they believed it would benefit RA disease activity or symptom management. Alcoholic

Table 1 Clinical and sociodemographic characteristics of the study participants according to adherence to the MD

	Low adherence to the MD (n = 15)	Moderate adherence to the MD (n = 73)	High adherence to the MD (n = 32)	p value
Sociodemographic and lifestyle characteristics				
Age (years), mean ± SD	60.87 ± 7.34	62.78 ± 9.98	59.94 ± 11.20	0.385[a]
Caucasian, n (%)	14 (93.33)	68 (93.15)	30 (93.75)	1.000[b]
Female, n (%)	10 (66.67)	54 (73.97)	24 (75.00)	0.818[c]
Menopause, n (%)	9 (90.00)	48 (88.89)	21 (87.50)	1.000[b]
Comorbidities, n (%)	11 (73.33)	63 (86.30)	24 (75.00)	0.260[c]
Never smoked, n (%)	6 (40.00)	45 (61.64)	20 (62.50)	0.271[c]
BMI classification*				0.237[b]
Underweight, n (%)	1 (6.67)	6 (8.70)	0 (0.00)	
Normal weight, n (%)	2 (13.33)	19 (27.54)	12 (37.50)	
Overweight or obese, n (%)	12 (80.00)	44 (63.77)	20 (62.50)	
Educational status				0.074[b]
No formal education, n (%)	0 (0.00)	1 (1.37)	0 (0.00)	
Primary school, n (%)	4 (26.67)	34 (46.58)	5 (15.63)	
Middle school, n (%)	7 (46.67)	15 (20.55)	12 (37.50)	
High school	3 (20.00)	13 (17.81)	7 (21.88)	
University, n (%)	1 (6.67)	10 (13.70)	8 (25.00)	
Occupational status				0.052[b]
Employed, n (%)	4 (26.67)	32 (43.84)	14 (43.75)	
Retired, n (%)	6 (40.00)	35 (47.95)	16 (50.00)	
Unemployed, n (%)	5 (33.33)	6 (8.22)	2 (6.25)	
Clinical characteristics				
RA disease duration (years), median(IQR)	5.50 (11.00)	10.50 (13.25)	11.50 (14.75)	0.589[d]
RF positive*, n (%)	1280.00)	44 (63.77)	19 (63.33)	0.460[c]
CRP (mg/L)*, median(IQR)	8.60 (16.68)	2.35 (4.27)	2.40 (4.82)	**0.047[d]**
ESR (mm/hour)*,, median(IQR)	28.50 (66.00)	22.00 (28.00)	22.50 (29.00)	0.536[d]
TJC (0–28)*, median(IQR)	2.00 (11.00)	0.00 (1.00)	0.00 (2.00)	0.094[d]
SJC (0–28)*, median(IQR)	0.00(1.25)	0.00 (0.75)	0.00 (0.00)	0.276[d]
Global Health VAS, median(IQR)	50.00(26.25)	50.00 (20.00)	30.00 (31.25)	0.115[d]
Pain VAS, median(IQR)	55.00(10.00)	40.00 (30.00)	40.00(51.25)	0.189[d]
DAS28*, median(IQR)	3.50 (3.00)	3.13 (1.18)	2.77 (1.49)	0.070[d]
DAS28-CRP*, median(IQR)	3.27 (2.37)	2.27 (1.26)	2.29 (1.20)	**0.030[d]**
HAQ*, median(IQR)	1.00(0.56)	0.87 (1.00)	0.56 (1.03)	**0.013[d]**
RAID*, median(IQR)	5.65(2.38)	4.45(2.92)	3.51 (4.51)	**0.032[d]**
Pharmacological therapy				
Methotrexate, n (%)	14 (93.33)	54 (73.97)	25(80.65)	0.236[c]
Current weekly dose of methotrexate (mg), median(IQR)	17.50 (10.00)	12.50 (15.00)	17.50(14.50)	0.121[d]
Hydroxychloroquine, n (%)	2 (13.33)	9 (12.33)	7(22.58)	0.412[b]
Sulfasalazine, n (%)	0 (0.00)	9 (12.33)	4(12.90)	0.361[b]
bDMARDs, n (%)	2 (13.33)	16 (21.92)	5(16.13)	0.649[c]
Glucocorticoids, n (%)	12 (80.00)	40 (54.79)	19(61.29)	0.189[c]
Current daily dose of glucocorticoids (mg of prednisolone), median(IQR)	2.50 (2.50)	2.50 (10.00)	2.50(5.00)	0.537[d]
NSAIDs, n (%)	5 (33.33)	23 (31.51)	13 (41.94)	0.589[c]

*Missing data: 4 patients had no information on BMI, 6 on RF, 2 on CRP and ESR, 4 on TJC and SJC, 7 on DAS-28 and DAS28-CRP, 2 on RAID score and 1 on Pharmacological therapy; p-values presented in bold are statistically significant ($p < 0.05$); [a]One-Way ANOVA; [b]Monte Carlo Simulation; [c]Chi-squared test; [d]Kruskal-Wallis Test

bDMARDs biological disease-modifying antirheumatic drugs, *BMI* body mass index (kg/m^2), *CRP* C-Reactive protein, *DAS28* disease activity score in 28 joints, DAS28-CRP disease activity score in 28 joints calculated using C-reactive protein, *ESR* erythrocyte sedimentation rate, global health *VAS* visual analog scale for global health, *HAQ* health assessment questionnaire, *NSAIDs* non-steroidal anti-inflammatory drugs, *Pain VAS* visual analog scale for pain, *RAID* rheumatoid arthritis impact of disease questionnaire, *RF* rheumatoid factor, *SJC* swollen joint count, *TJC* tender joint count

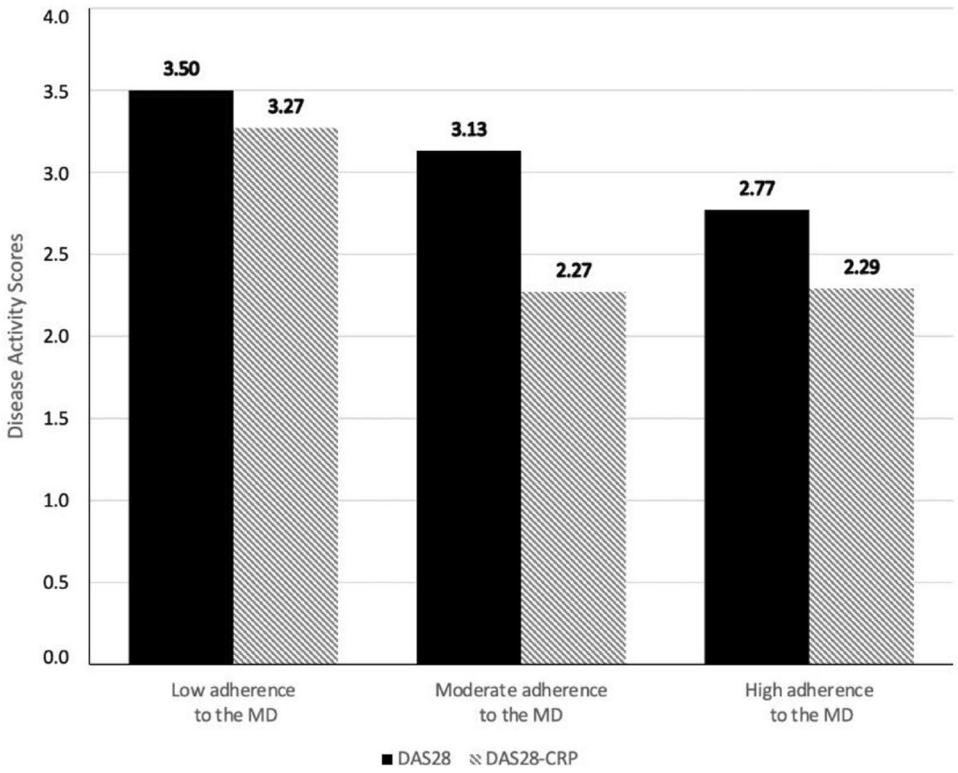

Fig. 1 Disease activity scores according to adherence to the MD. *DAS28* disease activity score in 28 joints, *DAS28-CRP* disease activity score in 28 joints calculated with C-reactive protein

beverages and shellfish were the most common dietary restrictions, reported by seven patients each. Other foods/dietary compounds mentioned were sugar/refined grains (n = 6), red meat/charcuterie (n = 5), citric fruits (n = 4) and gluten (n = 2).

Discussion

Our cohort had a higher proportion of patients with a high adherence to the MD than the general Portuguese population, according to the data from the National Food, Nutrition, and Physical Activity Survey of the Portuguese General Population 2015–2016 [29]. In our sample, adherence to the MD was significantly associated with RA disease activity using either DAS28 or DAS28-CRP scores. Adherence to the MD was also significantly associated with the impact of disease and functional disability, assessed by RAID and HAQ scores, respectively. Overall, higher levels of adherence to the MD were associated with lower disease activity, lower impact of disease and lower functional disability in RA patients. These data are concordant with previously published results. For example, in an Italian cohort, higher adherence to the MD was associated with a lower RAID total score [32], although it was not significantly associated with lower disease activity. Of interest, disease activity indexes in the Italian cohort were low (median DAS28-CRP was 2.08, q1–q3: 1.48 – 2.98), which could explain the lack of association [32]. In addition, in another Italian cohort, RA patients with high adherence to the MD had a significantly lower DAS28, a lower level of systemic inflammation (expressed by CRP serum concentration), and a healthier gut microbiota composition than patients with low/moderate adherence to the MD [33].

Fibre, one of the parameters evaluated by DII, was the only single nutrient intake found different between groups, which gives the chance to speculate whether the health promoting effects of the MD may be attributed to its impact on gut microbiota. Diet can shape our gut microbes, affect their composition and function, and different dietary components will influence the gut bacterial communities in a specific manner [34]. The MD richness in dietary fibre is one of the main characteristics linking this dietary pattern to gut microbiota modulation and increased short-chain fatty acids (SCFA) production. In turn, the SCFA reduce systemic inflammation and improve intestinal barrier function [35]. Moreover, we found that dietary fibre intake was significantly higher in patients with higher adherence to the MD. Fibre intake has been shown to be negatively associated with high-sensitivity CRP (hs-CRP) and RA risk, proposing that fibre might potentially influence the progression of RA by mitigating systemic inflammation [36]. Furthermore, a prospective study using a dietary intervention with high-fibre bars or cereals in RA patients for 28 days showed an improvement in patient-related outcomes, including quality of life and functional disability [37]. RA pathophysiology

Table 2 Ordinal regression results regarding DAS28

	Estimate	Std. error	Wald	df	Sig	95% confidence interval		Odds ratio	95% confidence interval for odds ratio	
						Lower bound	Upper bound		Lower bound	Upper bound
Threshold										
DAS28 = Remission	1.607	1.391	1.336	1	0.248	− 1.118	4.333			
DAS28 = Low disease activity	2.581	1.403	3.384	1	0.066	− 0.169	5.330			
DAS28 = Moderate disease activity	4.780	1.454	10.805	1	0.001	1.930	7.630			
Location										
PREDIMED score	− 0.177	0.060	8.542	1	**0.003**	− 0.295	− 0.058	0.303	0.261	0.347
Duration of RA	0.003	0.012	0.083	1	0.773	− 0.020	0.027	0.369	0.361	0.378
Glucocorticoids dose	0.163	0.073	4.982	1	**0.026**	0.020	0.306	0.427	0.375	0.479
Methotrexate dose	0.029	0.026	1.278	1	0.258	− 0.021	0.080	0.379	0.360	0.397
Age	0.023	0.013	2.898	1	0.089	− 0.003	0.049	0.376	0.367	0.386
BMI	0.002	0.028	0.007	1	0.933	− 0.052	0.057	0.369	0.349	0.389
Gender = Male	− 0.353	0.278	1.610	1	0.204	− 0.898	0.192	0.241	0.086	0.438
Gender = Female	0[a]			0						
Methotrexate = No	0.572	0.504	1.288	1	0.256	− 0.416	1.561	0.569	0.220	0.811
Methotrexate = Yes	0[a]			0						
Hydroxychloroquine = No	0.670	0.377	3.158	1	0.076	− 0.069	1.408	0.599	0.343	0.783
Hydroxychloroquine = Yes	0[a]			0						
Glucocorticoides = No	0.489	0.431	1.283	1	0.257	− 0.357	1.334	0.542	0.240	0.769
Glucocorticoides = Yes	0[a]			0						
bDMARDs = No	0.163	0.326	0.249	1	0.618	− 0.476	0.801	0.427	0.200	0.638
bDMARDs = Yes	0[a]			0						
NSAIDs = No	0.206	0.293	0.492	1	0.483	− 0.369	0.781	0.443	0.235	0.632
NSAIDs = Yes	0[a]			0						

Link function: negative log–log

a. This parameter is set to zero because it is redundant

p-values presented in bold are statistically significant ($p < 0.05$)

bDMARDs biological disease-modifying antirheumatic drugs, *BMI* body mass index (kg/m^2) *DAS28* disease activity score in 28 joints, *NSAIDs* non-steroidal anti-inflammatory drugs

Table 3 Ordinal regression results regarding DAS28

	Unstandardized coefficients		t	Sig	95,0% confidence Interval for B	
	B	Std. error			Lower bound	Upper bound
Model 1: dependent variable: DAS28-CRP						
(Constant)	3.062	0.883	3.467	0.001	1.308	4.817
Gender	0.135	0.213	0.634	0.528	− 0.287	0.557
Age	0.001	0.010	0.070	0.944	− 0.019	0.020
PREDIMED score	− 0.164	0.046	− 3.608	**0.001**	− 0.255	− 0.074
BMI	0.027	0.022	1.226	0.223	− 0.017	0.070
Duration of RA	0.010	0.009	1.022	0.310	− 0.009	0.028
Use of methotrexate	− 0.239	0.388	− 0.614	0.541	− 1.010	0.533
Methotrexate dose	− 0.003	0.020	− 0.151	0.880	− 0.042	0.036
Use of glucocorticoids	− 0.470	0.329	− 1.428	0.157	− 1.123	0.184
Glucocorticoids dose	0.174	0.056	3.085	**0.003**	0.062	0.286
Use of hydroxychloroquine	− 0.221	0.264	− 0.837	0.405	− 0.745	0.303
Use of bDMARDs	− 0.376	0.250	− 1.501	0.137	− 0.872	0.121
Use of NSAIDs	− 0.086	0.221	− 0.389	0.698	− 0.526	0.354
Model 2: dependent variable: RAID score						
(Constant)	− 0.424	1.659	− 0.256	0.799	− 3.716	2.869
Gender	1.605	0.409	3.925	**0.000**	0.793	2.417
Age	0.030	0.019	1.568	0.120	− 0.008	0.067
PREDIMED score	− 0.311	0.085	− 3.655	**0.000**	− 0.480	− 0.142
BMI	0.141	0.041	3.459	**0.001**	0.060	0.222
Duration of RA	0.028	0.018	1.514	0.133	− 0.009	0.064
Use of methotrexate	− 1.610	0.728	− 2.210	**0.029**	− 3.055	− 0.164
Methotrexate dose	0.065	0.038	1.729	0.087	− 0.010	0.140
Use of glucocorticoids	− 0.692	0.630	− 1.100	0.274	− 1.943	0.558
Glucocorticoids dose	0.299	0.109	2.730	**0.008**	0.081	0.516
Use of hydroxychloroquine	0.107	0.517	0.206	0.837	− 0.919	1.133
Use of bDMARDs	− 0.574	0.477	− 1.204	0.231	− 1.521	0.372
Use of NSAIDs	0.192	0.418	0.460	0.647	− 0.637	1.021
Model 3: dependent variable: HAQ score						
(Constant)	− 0.496	0.488	− 1.016	0.312	− 1.464	0.473
Gender	0.468	0.124	3.776	**0.000**	0.222	0.714
Age	0.008	0.006	1.460	0.148	− 0.003	0.019
PREDIMED score	− 0.089	0.026	− 3.444	**0.001**	− 0.140	− 0.038
BMI	0.044	0.012	3.580	**0.001**	0.020	0.069
Duration of RA	0.010	0.006	1.813	0.073	− 0.001	0.021
Use of methotrexate	− 0.210	0.221	− 0.950	0.345	− 0.649	0.229
Methotrexate dose	− 0.001	0.011	− 0.082	0.934	− 0.024	0.022
Use of Glicocorticoids	− 0.418	0.188	− 2.225	**0.028**	− 0.791	− 0.045
Glucocorticoids dose	0.117	0.032	3.673	**0.000**	0.054	0.180
Use of hydroxychloroquine	− 0.102	0.153	− 0.669	0.505	− 0.406	0.201
Use of bDMARDs	− 0.211	0.145	− 1.457	0.148	− 0.499	0.076
Use of NSAIDs	0.113	0.127	0.894	0.373	− 0.138	0.364

p-values presented in bold are statistically significant ($p < 0.05$)

bDMARDs biological disease-modifying antirheumatic drugs, *BMI* body mass index (kg/m^2), *DAS28-CRP* disease activity score in 28 joints calculated with C-reactive protein, *NSAIDs* non-steroidal anti-inflammatory drugs

Table 4 Overall caloric and macronutrient intake, and according to adherence to the MD

	Full sample (n = 120)	Low adherence to the MD (n = 15)	Moderate adherence to the MD (n = 73)	High adherence to the MD (n = 32)	p value
Energy (kcal), mean ± SD	2141.93 ± 532.91	2223.91 ± 687.75	2124.63 ± 528.74	2142.96 ± 472.52	0.808[a]
Energy per kilogram (kcal/kg)*, median(IQR)	28.61 (12.33)	30.52 (12.19)	28.25 (12.45)	30.07 (13.26)	0.847[b]
Protein (g), mean ± SD	92.90 ± 25.06	95.58 ± 27.68	92.09 ± 25.69	93.51 ± 22.94	0.877[a]
Protein per kilogram (g/kg)*, mean ± SD	1.33 ± 0.43	1.26 ± 0.31	1.32 ± 0.45	1.37 ± 0.44	0.719[a]
Carbohydrates (g), median(IQR)	222.23 (84.00)	222.49 (152.69)	225.36 (78.63)	214.30 (73.77)	0.900[b]
Sugar (g), median(IQR)	94.99 (51.23)	100.62 (109.05)	90.36 (42.84)	99.76 (49.04)	0.731[b]
Dietary fibre (g), median(IQR)	23.46 (10.31)	16.68 (8.88)	23.64 (10.28)	25.56 (8.91)	**0.002**[b]
Total fat (g), median(IQR)	92.19 (51.70)	110.50 (50.74)	89.11 (47.60)	102.15 (49.19)	0.398[b]
Saturated fat (g), median(IQR)	23.07 (11.30)	30.18 (15.16)	22.67 (12.51)	23.45 (10.10)	0.051[b]
Mono-unsaturated fat (g), median(IQR)	46.23 (24.95)	45.83 (29.97)	43.64 (24.14)	51.78 (27.76)	0.378[b]
Polyunsaturated fat (g), median(IQR)	14.15 (7.11)	14.65 (9.26)	13.77 (6.99)	14.23 (8.51)	0.543[b]
Cholesterol (mg), median(IQR)	316.16 (187.51)	363.41 (178.57)	308.88 (185.38)	312.21 (151.89)	0.407[b]
Alcohol (g), median(IQR)	0.10 (4.97)	0.77 (4.97)	0.00 (4.97)	0.70 (5.72)	0.883[b]

*Missing data: 4 patients had no information on actual body weight, which prevented the calculation of energy and protein per kilogram of body weight; p-values presented in bold are statistically significant ($p < 0.05$); [a]One-Way ANOVA, [b]Kruskal-Wallis Test

includes a state of chronic inflammation that might be provoked and aggravated by dysbiosis [38–40]. Therefore, microbiome-based therapeutics, where dietary interventions may be included, have been suggested as a potential new class in the RA armamentarium. There are compositional and functional alterations in the gut microbiota of RA patients, which may partially resolve after RA treatment [38]. The modulation of gut microbiota and intestinal barrier integrity and function are among the proposed mechanisms by which dietary interventions may improve RA-related outcomes [41, 42].

The MD is the strongest candidate for a dietary intervention-based therapeutic in RA, as it encompasses many other components that may positively influence gut microbiota in addition to fibre, such as polyphenols and polyunsaturated fatty acids [43]. According to the EULAR response criteria for pharmacological therapy, a change of 1.2 in DAS28 score of an individual patient is considered a significant clinical improvement [44]. The 0.73 difference in mean DAS28 between the high and low adherence to the MD groups represents more than half of this value, and is in the range of minimum significative improvement [44], supporting the potential of MD as an adjunctive RA therapy. Furthermore, the MD is well known for its overall health benefits, as there is robust evidence that greater adherence to the MD reduces the risk of overall mortality and of comorbidities particularly relevant for RA patients, such as cancer and cardiovascular diseases [45, 46].

Few intervention studies with small sample sizes have been conducted regarding the MD effect on RA-related outcomes. In a randomised clinical trial (RCT), patients in the MD group showed a significant decrease in DAS28 of 0.56 and HAQ of 0.15 [47]. A different intervention trial reported that DAS28 remained unchanged in MD and control groups, but HAQ, pain, patient-global assessment, and the reported duration of early morning stiffness were significantly better in the MD group than in controls [48]. A recent study showed beneficial effects of the MD on DAS-28 compared with a low-fat, high-carbohydrate diet, regardless of weight loss [49]. In this trial, after 12 weeks of intervention, the MD reduced DAS-28 by − 1.5 ± 3.01. These findings suggest that dietary patterns may be more relevant than weight loss and are particularly interesting as bodyweight control is central to the treatment of many health conditions [49]. The RCT with the largest sample size (n = 144) and duration of the intervention (24 weeks) reported no statistically significant differences between groups for HAQ Disability Index [50]. However, MD combined with a dynamic exercise program resulted in better results in patients' health-related quality of life compared to each intervention alone in female patients with low disease activity receiving conventional Disease-modifying Antirheumatic Drugs (DMARDs) [50]. These results suggest that current findings on the effects of the MD on RA patients could be amplified if combined with an exercise program and, thus, should be object of further investigation. Furthermore, we found that having a higher BMI was associated with higher HAQ and RAID scores. Obesity has already been reported to decrease the odds of achieving remission and negatively impact disease activity and patient-reported outcomes in RA [51], reinforcing the potential of diet-targeted interventions.

The lack of associations between individual components of diet and clinical parameters of RA in our cohort support the idea that it may be more relevant to interpret diet as a

whole, as in a dietary pattern, instead of its isolated components. This concept has been explored in the literature as 'food synergy', based on the proposition that the interrelations between foods are significant, and highlighting that the evidence for health benefits appears to be stronger when considering a synergistic dietary pattern, compared to individual foods or food components [52]. Dietary pattern analysis goes beyond nutrients and foods and examines the effects of overall diet, which is valuable as people do not eat isolated nutrients, but meals consisting in a variety of different foods that are likely to interact [53]. Furthermore, the effects of single nutrients may be too small to be detected, but their cumulative effects in a dietary pattern may be more evident [53]. Contrary to our findings, it has been reported that RA patients consuming fish more than twice weekly had a significantly lower DAS28-CRP than those who ate fish less than once monthly [54]. This study evaluated a cohort of American patients. For each additional serving of fish per week, DAS28-CRP was significantly reduced by 0.18 [54]. Of note, fishing and fish consumption are also characteristic of the MD [14]. Our contrasting results might be explained by the distinct dietary habits and patterns of fish consumptions among the assessed populations (United States of America, USA, vs. our Portuguese sample) as Portugal has a higher seafood consumption per capita than the USA [55]. In fact, Portugal is reported to have the highest fish consumption per capita in Europe and one of the highest in the world [56]. The consumption of an additionall serving of fish per week might be more relevant in a population with a lower fish consumption, when compared to a population with one of the highest rates of seafood consumptions worldwide.

In our cohort, mean DII (0.00 ± 0.17) was not significantly different from the mean DII of the Portuguese population (-0.10 ± 1.46, $p = 0.578$) and no associations were found between DII and RA disease outcomes. Similarly to our results, in the trial by Matsumoto et al. [57], DII score was not associated with RA disease activity. However, authors found that the diet of RA patients had a higher DII compared to controls and, in a longitudinal analysis, an anti-inflammatory change in the DII score was associated with maintaining a low disease activity for 6 years. Of interest, no association was found between change in disease activity at the EULAR response level, leading authors to speculate whether the impact of DII may be especially relevant in contributing to maintaining disease activity in patients whose base disease activity is relatively well maintained [57]. The fact that the DII score appeared to be associated with the maintenance of low disease activity is particularly valuable as further treatment adjustments are generally not implemented in low disease activity RA patients. Our study design does not allow for the evaluation of how DII may affect the maintenance of disease activity. Additionally, when comparing mean DII from our cohort and the general population, which were not significantly different, it is important to point out that the DII of our sample was calculated with 28 food parameters and for the Portuguese population only 24 were used due to missing information on omega-3, omega-6, selenium and caffeine intake. This different calculation may contribute to explain the inconsistencies in our findings.

On the other hand, Tandorsost et al. reported that patients with the highest DII had significantly higher DAS28, TJC, and serum inflammatory markers such as hs-CRP and Tumour Necrosis Factor- alpha [58]. Although DAS28 considers both TJC and SJC, the authors only report significant differences for TJC. In our sample, neither TJC or SJC were significantly different between groups of adherence to the MD or associated with DII. When taking into account more clinical parameters, by calculating disease activity scores, associations were still not found for DII. In a different perspective, other authors found DII to be positively associated with risk of developing RA [21, 59]. As for intervention trials, an anti-inflammatory diet induced no significant clinically-relevant reductions in DAS28 in a crossover RCT, with a diet containing food items with suggested anti-inflammatory properties compared with a control diet nutritionally similar to the diet of the general population of the country where the study took place (Sweden) [60]. Overall, although with inconsistent results, evidence suggests that a diet a higher inflammatory potential measured by DII may possibly act as a risk factor for RA and its severity, and more studies are needed.

Our study has several limitations. First, this study was single-centred and had a relatively small sample. The observational design does not allow extrapolations regarding the causal link between dietary intake and the different RA clinical outcomes. Despite using validated tools for the assessment of dietary intake, this data is particularly vulnerable to errors as it is self-reported. Patients were given adequate time and support to fully answer the questions proposed to them and certified dietitians were responsible for the dietary data collection, being trained to adequately address questions on this subject, but ultimately data remains self-reported and subject to bias and limitations. This may contribute to justify divergent results in the literature, as well as in our results, such as inconsistencies in the findings between the MD and DII with regard to RA disease outcomes. The tool used to assess adherence to the MD consisted of a total of fourteen straightforward questions, while DII was calculated based on a validated Portuguese FFQ with 86 questions, which demanded a wider attention spam from patients. Nevertheless, our findings are in line with the increasing number of recent studies suggesting that diet, specifically the MD pattern, may have a relevant role in the future of RA management Finally, RA patients commonly ask for advice on dietary intake. In our cohort, a quarter of patients restricted certain foods

due to the belief of a possible RA-related benefit. As long-term dietary restrictions, when carried out without the supervision of a dietitian, may lead to nutritional deficiencies, a multidisciplinary approach in RA is mandatory. It is also appropriate to point out that our patient population resides in a Mediterranean country and, therefore, possibly could have the opportunity to follow a MD, if adequately advised. As this was an observational study, dietary counselling was not performed and, to adequality address the relationship between diet and RA, intervention studies are warranted,

Conclusion

Higher adherence to the MD was significantly associated with lower disease activity, lower impact of disease and lower functional disability in RA patients. These associations remained significant after adjusting for several confounders. Although these findings warrant confirmation by interventional research, our results suggest that the MD is a promising intervention to complement current pharmacological treatment strategies in RA.

Acknowledgements The authors wish to express their gratitude to all professionals of the Rheumatology Department of Centro Hospitalar Universitário Lisboa Norte, particularly Drs. Cristina Ponte, Joaquim Pereira, Maria João Saavedra and Rita Barros, for supporting the study.

Author contributions SC: investigation, visualization, roles/writing—original draft. MF: investigation, visualization, roles/writing—original draft. JV: data curation, writing—review & editing. EC: formal analysis, writing—review & editing. JM-M: resources, writing—review & editing. AMD-M: resources. ED: resources, writing—review & editing. JEF: conceptualisation, methodology, resources, supervision, validation, project administration, writing—review & editing. CSG: conceptualisation, methodology, resources, supervision, validation, project administration, writing—review & editing.

Funding No funding was received for conducting this study.

Data availability All data supporting the findings of this study is available within the paper. Further inquiries can be directed to the corresponding author.

Declarations

Conflict of interest The authors declare that they have no conflict of interest to disclose.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards, with the approval of the Lisbon Academic Medical Center Ethical Committee (Ref. Nº 262/19). All participants gave their informed consent prior to their inclusion in the study.

Consent for publication All co-authors have read and approved the submission of this manuscript for publication.

References

1. Smolen JS, Aletaha D, McInnes IB (2016) Rheumatoid arthritis. Lancet 388(10055):2023–2038. https://doi.org/10.1016/S0140-6736(16)30173-8
2. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. N Engl J Med 365(23):2205–2219. https://doi.org/10.1056/NEJMra1004965
3. McInnes IB, Schett G (2017) Pathogenetic insights from the treatment of rheumatoid arthritis. Lancet 389(10086):2328–2337. https://doi.org/10.1016/S0140-6736(17)31472-1
4. Smolen JS, Landewé RBM, Bijlsma JWJ, Burmester GR, Dougados M, Kerschbaumer A et al (2020) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 79(6):S685–S699. https://doi.org/10.1136/annrheumdis-2019-216655
5. van Riel PLCM, Renskers L (2016) The disease activity score (DAS) and the disease activity score using 28 joint counts (DAS28) in the management of rheumatoid arthritis. Clin Exp Rheumatol 34(4):40–44
6. England BR, Tiong BK, Bergman MJ, Curtis JR, Kazi S, Mikuls TR et al (2019) 2019 Update of the american college of rheumatology recommended rheumatoid arthritis disease activity measures. Arthritis Care Res 71(12):1540–1555. https://doi.org/10.1002/acr.24042
7. Scherer HU, Häupl T, Burmester GR (2020) The etiology of rheumatoid arthritis. J Autoimmun 110:102400. https://doi.org/10.1016/j.jaut.2019.102400
8. Gioia C, Lucchino B, Tarsitano MG, Iannuccelli C, Di Franco M (2020) Dietary habits and nutrition in rheumatoid arthritis: Can diet influence disease development and clinical manifestations? Nutrients 12(5):1456. https://doi.org/10.3390/nu12051456
9. Philippou E, Nikiphorou E (2018) Are we really what we eat? Nutrition and its role in the onset of rheumatoid arthritis. Autoimmun Rev 17(11):1074–1077. https://doi.org/10.1016/j.autrev.2018.05.009
10. Romão VC, Fonseca JE (2021) Etiology and risk factors for rheumatoid arthritis: a state-of-the-art review. Front Med 8:689698. https://doi.org/10.3389/fmed.2021.689698
11. Tedeschi SK, Frits M, Cui J, Zhang ZZ, Mahmoud T, Iannaccone C et al (2017) Diet and rheumatoid arthritis symptoms: survey results from a rheumatoid arthritis registry. Arthritis Care Res 69(12):1920–1925. https://doi.org/10.1002/acr.23225
12. Küçükdeveci AA (2019) Nonpharmacological treatment in established rheumatoid arthritis. Best Pract Res Clin Rheumatol 33(5):101482. https://doi.org/10.1016/j.berh.2019.101482
13. Bonaccio M, Iacoviello L, Donati MB, de Gaetano G (2021) The tenth anniversary as a UNESCO world cultural heritage: an unmissable opportunity to get back to the cultural roots of the Mediterranean diet. Eur J Clin Nutr 76(2):179–183. https://doi.org/10.1038/s41430-021-00924-3
14. UNESCO. The Mediterranean Diet. Available online: https://www.unesco.org/archives/multimedia/document-1680-eng-2. Accessed 15 Feb 2022
15. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A (2008) Adherence to Mediterranean diet and health status: meta-analysis. BMJ 337:a1344. https://doi.org/10.1136/bmj.a1344
16. Forsyth C, Kouvari M, D'Cunha NM, Georgousopoulou EN, Panagiotakos DB, Mellor DD et al (2018) The effects of the Mediterranean diet on rheumatoid arthritis prevention and treatment: a systematic review of human prospective studies. Rheumatol Int 38(5):737–747. https://doi.org/10.1007/s00296-017-3912-1
17. Philippou PE, Petersson SD, Rodomar C, Nikiphorou E (2021) Rheumatoid arthritis and dietary interventions: systematic review

of clinical trials. Nutr Rev 79(4):410–428. https://doi.org/10.1093/nutrit/nuaa033
18. Shivappa N, Godos J, Hébert JR, Wirth MD, Piuri G, Speciani AF et al (2018) Dietary inflammatory index and cardiovascular risk and mortality—a meta-analysis. Nutrients 10(2):200. https://doi.org/10.3390/nu10020200
19. Namazi N, Larijani B, Azadbakht L (2018) Association between the dietary inflammatory index and the incidence of cancer: a systematic review and meta-analysis of prospective studies. Public Health 164:148–156. https://doi.org/10.1016/j.puhe.2018.04.015
20. Garcia-Arellano A, Martínez-González MA, Ramallal R, Salas-Salvadó J, Hébert JR, Corella D et al (2019) Dietary inflammatory index and all-cause mortality in large cohorts: The SUN and PREDIMED studies. Clin Nut 38(3):1221–1231. https://doi.org/10.1016/j.clnu.2018.05.003
21. Jandari S, Mosalmanzadeh N, Shadmand Foumani Moghadam MR, Soleimani D, Shivappa N, Hébert JR et al (2021) Dietary inflammatory index and healthy eating index-2015 are associated with rheumatoid arthritis. Public Health Nutr 24(18):6007–6014. https://doi.org/10.1017/S1368980021001105
22. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO et al (2010) 2010 Rheumatoid arthritis classification criteria: an American college of rheumatology/European league against rheumatism collaborative initiative. Arthritis Rheum 62(9):2569–2581. https://doi.org/10.1002/art.27584
23. Lopes C (2000) Reprodutibilidade e Validação de um questionário semi-quantitativo de frequência alimentar. Alimentação e enfarte agudo do miocárdio: um estudo caso-controlo de base populacional. Tese de Doutoramento. Universidade do Porto. p.79–115
24. Lopes C, Aro A, Azevedo A, Ramos E, Barros H (2007) Intake and adipose tissue composition of fatty acids and risk of myocardial infarction in a male Portuguese community sample. J Am Diet Assoc 107(2):276–286. https://doi.org/10.1016/j.jada.2006.11.008
25. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E et al (2010) Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr 103(12):1808–1816. https://doi.org/10.1017/S0007114509993837
26. Martínez-González MA, García-Arellano A, Toledo E, Salas-Salvadó J, Buil-Cosiales P, Corella D et al (2012) A 14-item mediterranean diet assessment tool and obesity indexes among high-risk subjects: The PREDIMED trial. PLoS ONE 7(8):e43134. https://doi.org/10.1371/journal.pone.0043134
27. Afonso L, Moreira T, Oliveira A (2014) Índices de adesão ao padrão alimentar mediterrânico – a base metodológica para estudar a sua relação com a saúde. Factores de Risco
28. Shivappa N, Steck SE, Hurley TG, Hussey JR, Hébert JR (2014) Designing and developing a literature-derived, population-based dietary inflammatory index. Public Health Nutr 17(8):1689–1696. https://doi.org/10.1017/S1368980013002115
29. Lopes C, Torres D, Oliveira A, Severo M, Guiomar S, Alarcão V et al (2018) National Food, Nutrition and Physical Activity Survey of the Portuguese general population IAN-AF 2015–2016: Summary of Results.
30. Gossec L, Dougados M, Rincheval N, Balanescu A, Boumpas DT, Canadelo S et al (2009) Elaboration of the preliminary rheumatoid arthritis impact of disease (RAID) score: A EULAR initiative. Ann Rheum Dis 68(11):1680–1685. https://doi.org/10.1136/ard.2008.100271
31. Bruce B, Fries JF (2005) The health assessment questionnaire (HAQ). Clin Exp Rheumatol 23:S14–S18
32. Ingegnoli F, Schioppo T, Scotti I, Ubiali T, De Lucia O, Murgo A et al (2020) Adherence to Mediterranean diet and patient perception of rheumatoid arthritis. Complement Ther Med 52:102519. https://doi.org/10.1016/j.ctim.2020.102519
33. Diamanti AP, Panebianco C, Salerno G, Di Rosa R, Salemi S, Sorgi ML et al (2020) Impact of mediterranean diet on disease activity and gut microbiota composition of rheumatoid arthritis patients. Microorganisms 8(12):1989. https://doi.org/10.3390/microorganisms8121989
34. Makki K, Deehan EC, Walter J, Bäckhed F (2018) The impact of dietary fiber on gut microbiota in host health and disease. Cell Host Microbe 23(6):705–715. https://doi.org/10.1016/j.chom.2018.05.012
35. Dourado E, Ferro M, Guerreiro CS, Fonseca JE (2020) Diet as a modulator of intestinal microbiota in rheumatoid arthritis. Nutrients 12(11):3504. https://doi.org/10.3390/nu12113504
36. Liu L, Xie S (2023) Dietary fiber intake associated with risk of rheumatoid arthritis among US adults: NHANES 2010–2020. Medicine 102(12):e33357. https://doi.org/10.1097/MD.0000000000033357
37. Häger J, Bang H, Hagen M, Frech M, Träger P, Sokolova MV et al (2019) The role of dietary fiber in rheumatoid arthritis patients: a feasibility study. Nutrients 11(10):2392. https://doi.org/10.3390/nu11102392
38. Zhang X, Zhang D, Jia H, Feng Q, Wang D, Liang D et al (2015) The oral and gut microbiomes are perturbed in rheumatoid arthritis and partly normalized after treatment. Nat Med 21(8):895–905. https://doi.org/10.1038/nm.3914
39. Holers VM, Demoruelle MK, Kuhn KA, Buckner JH, Robinson WH, Okamoto Y et al (2018) Rheumatoid arthritis and the mucosal origins hypothesis: protection turns to destruction. Nat Rev Rheumatol 14(9):542–557. https://doi.org/10.1038/s41584-018-0070-0
40. Berthelot JM, Bandiaky ON, Le GB, Amador G, Chaux AG, Soueidan A et al (2022) Another look at the contribution of oral microbiota to the pathogenesis of rheumatoid arthritis: a narrative review. Microorganisms 10(1):59. https://doi.org/10.3390/microorganisms10010059
41. Ferro FM, Charneca S, Dourado E, Sousa Guerreiro C, Fonseca JE (2021) Probiotic supplementation for rheumatoid arthritis: a promising adjuvant therapy in the gut microbiome era. Front Pharmacol 12:711788. https://doi.org/10.3389/fphar.2021.711788
42. Guerreiro CS, Calado Â, Sousa J, Fonseca JE (2018) Diet, microbiota, and gut permeability-the unknown triad in rheumatoid arthritis. Front Med. https://doi.org/10.3389/fmed.2018.00349
43. Merra G, Noce A, Marrone G, Cintoni M, Tarsitano MG, Capacci A et al (2021) Influence of mediterranean diet on human gut microbiota. Nutrients 13(1):7. https://doi.org/10.3390/nu13010007
44. Fransen J, van Riel PLCM (2009) The disease activity score and the EULAR response criteria. Rheum Dis Clin North Am 35(4):745–757. https://doi.org/10.1016/j.rdc.2009.10.001
45. Dinu M, Pagliai G, Casini A, Sofi F (2018) Mediterranean diet and multiple health outcomes: an umbrella review of meta-analyses of observational studies and randomised trials. Eur J Clin Nutr 72(1):30–43. https://doi.org/10.1038/ejcn.2017.58
46. England BR, Thiele GM, Anderson DR, Mikuls TR (2018) Increased cardiovascular risk in rheumatoid arthritis: Mechanisms and implications. BMJ 361:k1036. https://doi.org/10.1136/bmj.k1036
47. Sköldstam L, Hagfors L, Johansson G (2003) An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. Ann Rheum Dis 62(3):208–214. https://doi.org/10.1136/ard.62.3.208
48. McKellar G, Morrison E, McEntegart A, Hampson R, Tierney A, Mackle G et al (2007) A pilot study of a Mediterranean-type diet intervention in female patients with rheumatoid arthritis living in areas of social deprivation in Glasgow. Ann Rheum Dis 66(9):1239–1243. https://doi.org/10.1136/ard.2006.065151

49. Sadeghi A, Tabatabaiee M, Mousavi MA, Mousavi SN, Abdollahi Sabet S, Jalili N (2022) Dietary pattern or weight loss: which one is more important to reduce disease activity score in patients with rheumatoid arthritis? A randomised feeding trial. Int J Clin Pract. https://doi.org/10.1155/2022/6004916
50. García-Morales JM, Lozada-Mellado M, Hinojosa-Azaola A, Llorente L, Ogata-Medel M, Pineda-Juárez JA et al (2020) Effect of a dynamic exercise program in combination with mediterranean diet on quality of life in women with rheumatoid arthritis. J Clin Rheumatol 26(7S Suppl 2):S116–S122. https://doi.org/10.1097/RHU.0000000000001064
51. Liu Y, Hazlewood GS, Kaplan GG, Eksteen B, Barnabe C (2017) Impact of obesity on remission and disease activity in rheumatoid arthritis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 62(2):157–165. https://doi.org/10.1002/acr.22932
52. Jacobs DR, Gross MD, Tapsell LC (2009) Food synergy: an operational concept for understanding nutrition. Am J Clin Nutr 89(5):1543S-1548S. https://doi.org/10.3945/ajcn.2009.26736B
53. Hu FB (2002) Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol 13(1):3–9. https://doi.org/10.1097/00041433-200202000-00002
54. Tedeschi SK, Bathon JM, Giles JT, Lin T-C, Yoshida K, Solomon DH (2018) The relationship between fish consumption and disease activity in rheumatoid arthritis. Arthritis Care Res (Hoboken) 70(3):327–332. https://doi.org/10.1002/acr.23295
55. FAO (2022) The State of World Fisheries and Aquaculture 2022. Towards Blue Transformation. Rome, FAO. Doi: https://doi.org/10.4060/cc0461en
56. Bjørndal T, Lappo A, Ramos J (2015) An economic analysis of the Portuguese fisheries sector 1960–2011. Mar Policy 51:21–30. https://doi.org/10.1016/j.marpol.2014.06.004
57. Matsumoto Y, Shivappa N, Sugioka Y, Tada M, Okano T, Mamoto K et al (2021) Change in dietary inflammatory index score is associated with control of long-term rheumatoid arthritis disease activity in a Japanese cohort: the TOMORROW study. Arthritis Res Ther 23(1):105. https://doi.org/10.1186/s13075-021-02478-y
58. Tandorost A, Kheirouri S, Moludi J, Seyedmardani S (2021) Association of Dietary Inflammatory Index (DII) with disease activity and inflammatory cytokines in the patients with rheumatoid arthritis. Int J Clin Pract 75(11):e14792. https://doi.org/10.1111/ijcp.14792
59. Xiang S, Wang Y, Qian S, Li J, Jin Y, Ding X et al (2022) The association between dietary inflammation index and the risk of rheumatoid arthritis in Americans. Clin Rheumatol 41(9):2647–2658. https://doi.org/10.1007/s10067-022-06217-9
60. Vadell AKE, Bärebring L, Hulander E, Gjertsson I, Lindqvist HM, Winkvist A (2020) Anti-inflammatory diet in rheumatoid arthritis (ADIRA) - a randomised, controlled crossover trial indicating effects on disease activity. Am J Clin Nutr 111(6):1203–1213. https://doi.org/10.1093/ajcn/nqaa019

Authors and Affiliations

Sofia Charneca[1] · Margarida Ferro[1] · João Vasques[1] · Elisabete Carolino[2] · Joana Martins-Martinho[3,4] · Ana Margarida Duarte-Monteiro[3,4] · Eduardo Dourado[3,4] · João Eurico Fonseca[3,4] · Catarina Sousa Guerreiro[1,5]

✉ Eduardo Dourado
eduardo.dourado@edu.ulisboa.pt

Sofia Charneca
sofiacharneca98@gmail.com

Margarida Ferro
margarida.ferro97@gmail.com

João Vasques
joaof_vasques@hotmail.com

Elisabete Carolino
etcarolino@estesl.ipl.pt

Joana Martins-Martinho
joanamartinsmartinho@gmail.com

Ana Margarida Duarte-Monteiro
amdm@campus.ul.pt

João Eurico Fonseca
jecfonseca@gmail.com

Catarina Sousa Guerreiro
cfguerreiro@medicina.ulisboa.pt

[1] Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisbon, Portugal

[2] H&TRC- Health & Technology Research Center, ESTeSL-Escola Superior de Tecnologia da Saúde, Instituto Politécnico de Lisboa, Lisbon, Portugal

[3] Serviço de Reumatologia, Centro Hospitalar Universitário Lisboa Norte, Centro Académico de Medicina de Lisboa, Lisbon, Portugal

[4] Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Avenida Professor Egas Moniz, 1649-028 Lisbon, Portugal

[5] Instituto de Saúde Ambiental, Faculdade de Medicina, Universidade de Lisboa, Centro Académico de Medicina de Lisboa, Lisbon, Portugal