

## ORIGINAL RESEARCH

# Effects of diet on the outcomes of rheumatic and musculoskeletal diseases (RMDs): systematic review and meta-analyses informing the 2021 EULAR recommendations for lifestyle improvements in people with RMDs

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## ABSTRACT

**Background** A EULAR taskforce was convened to develop recommendations for lifestyle behaviours in rheumatic and musculoskeletal diseases (RMDs). In this paper, the literature on the effect of diet on the progression of RMDs is reviewed.

**Methods** Systematic reviews and meta-analyses were performed of studies related to diet and disease outcomes in seven RMDs: osteoarthritis (OA), rheumatoid arthritis (RA), systemic lupus erythematosus, axial spondyloarthritis, psoriatic arthritis, systemic sclerosis and gout. In the first phase, existing relevant systematic reviews and meta-analyses, published from 2013 to 2018, were identified. In the second phase, the review was expanded to include published original studies on diet in RMDs, with no restriction on publication date. Systematic reviews or original studies were included if they assessed a dietary exposure in one of the above RMDs, and reported results regarding progression of disease (eg, pain, function, joint damage).

**Results** In total, 24 systematic reviews and 150 original articles were included. Many dietary exposures have been studied (n=83), although the majority of studies addressed people with OA and RA. Most dietary exposures were assessed by relatively few studies. Exposures that have been assessed by multiple, well conducted studies (eg, OA: vitamin D, chondroitin, glucosamine; RA: omega-3) were classified as moderate evidence of small effects on disease progression.

**Conclusion** The current literature suggests that there is moderate evidence for a small benefit for certain dietary components. High-level evidence of clinically meaningful effect sizes from individual dietary exposures on outcomes in RMDs is missing.

## Key messages

### What is already known about this subject?

- People's diet can influence health related outcomes, such as cardiovascular outcomes and mental health.
- It is unclear whether dietary factors influence rheumatic and musculoskeletal disease (RMD) specific outcomes.

### What does this study add?

- This study brings together the literature on diet and progression of seven RMDs, concluding that research on diet has largely focused on osteoarthritis and rheumatoid arthritis, and there is little evidence suggesting dietary factors can make large differences to the outcomes of people with RMDs.

### How might this impact on clinical practice or further developments?

- Based on the current literature, health professionals can advise people with RMDs that consuming specific dietary components is unlikely to influence the progression of their RMD, but that it is important to maintain a healthy diet and healthy weight for general health reasons.

Rheumatic and musculoskeletal diseases (RMDs) are a diverse range of conditions that primarily affect people's joints, causing pain, disability and reductions in health-related quality of life (HR-QoL).<sup>1–3</sup> According to the Global Burden of Disease study, RMDs are one

of the leading causes of global disability.<sup>4,5</sup> Some RMDs have effective pharmacological treatments that limit disease progression (eg, rheumatoid arthritis (RA)<sup>6</sup>), whereas others have no effective disease modifying treatment options (eg, osteoarthritis (OA)<sup>7</sup>). However, in all RMDs there is room for additional improvement in outcomes. In the general population, lifestyle modifications have been shown to improve non-RMD related outcomes. For instance, diet (ie, specific food stuffs ingested as part of daily living, and supplements or nutrients ingested to improve health) has a significant impact on the risk of chronic disease<sup>8</sup> and benefits to mental health.<sup>9</sup> However, it is unclear whether lifestyle modifications, such as changes to diet, have a beneficial impact on RMD related outcomes (including disease activity, pain, function, HR-QoL, radiographic damage, fatigue and depression).

In 2018, a EULAR Taskforce was convened to develop recommendations for lifestyle improvements in people with RMDs with regards to RMD progression (including both modifiable (eg, pain, fatigue) and irreversible (eg, joint damage) outcomes).<sup>10</sup> The taskforce decided to focus on six lifestyle factors: diet, exercise, weight, alcohol, smoking and paid work, and seven diseases: RA, OA, axial spondyloarthritis (axSpA), psoriatic arthritis (PsA), systemic lupus erythematosus (SLE), systemic sclerosis (SSc) and gout (henceforth referred to collectively as RMDs). For each of these lifestyle factors, systematic reviews were performed, aiming to collate all relevant literature on each factor in order to formulate evidence based recommendations. This article reports the results of systematic reviews on the effect of diet on progression of RMDs.

## METHODS

### Design

This study was performed in accordance with the EULAR standard operating procedure for EULAR endorsed recommendations<sup>11</sup> and is reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.<sup>12</sup>

### Search strategy

The articles included in this review were identified in two steps. First, a systematic search was conducted aiming to identify published systematic reviews and meta-analyses on any of the included exposures and RMDs (listed below; online supplemental tables 1 and 2) published between 1 January 2013 and 18 September 2018, using the Medline, Embase and Cochrane Library databases. Two reviewers screened the titles and abstracts (JMG, MW) and then a team of four reviewers screened the eligible full texts (JMG, MW, JRC, GC; two reviewers per full text). Only systematic reviews and meta-analyses related to diet are presented in this report.

Then a systematic review of original articles of dietary interventions for people with RMDs was conducted.

Where the research team agreed that sufficient systematic reviews and meta-analyses had been published on a given exposure in a given disease, these exposures were excluded from the systematic review of original articles (OA: vitamin E, bromelain, glucosamine, willow bark extract, chondroitin, *Artemisia annua* extract, green lipped muscle extract, methylsulfonylmethane, avocado/soy bean unsaponifiables, L-carnitine, curcumin, pycnogenol, *Boswellia serrata* extract, *Curcuma longa* extract, passion fruit peel extract, collagen hydrolysate; RA: marine oils, omega-3, probiotics, vitamin D). The search strategy was developed based on a predefined PICO (PICO=participants, intervention/exposure, comparison, outcome (online supplemental table 3 for search strategy)) and implemented in the Medline, Embase and CENTRAL databases on 8 March 2019. Titles and abstracts followed by full texts were screened by two reviewers (JMG, JRC).

### Inclusion and exclusion criteria

For the review to identify relevant published systematic reviews and meta-analyses, the following inclusion criteria were used:

- ▶ Systematic reviews or meta-analyses of randomised controlled trials (RCTs) or observational studies.
- ▶ Including people with an RMD (OA, RA, SLE, axSpA, PsA, SSc, gout).
- ▶ Studying the relationship between diet and outcomes (see online supplemental table 4 for a list of included outcomes).

For the review identifying original studies of dietary exposures in RMDs, the following inclusion criteria were used:

- ▶ Longitudinal study design (randomised trials, non-randomised trials, single-arm intervention studies, longitudinal observational studies).
- ▶ Including adults with an RMD (OA, RA, SLE, axSpA, PsA, SSc, gout).
- ▶ Studying the relationship between dietary exposures and outcomes (see online supplemental table 4 for a list of included outcomes).

Conference abstracts were excluded.

### Risk of bias assessment

The AMSTAR-2 tool was used to assess the risk of bias in published systematic reviews and meta-analyses.<sup>13</sup> Each review was graded as critically low, low, moderate or high quality. The Cochrane Risk of Bias tool was used to assess methodological quality of included RCTs,<sup>14</sup> rating the reporting of four criteria: randomisation procedure, allocation concealment procedure, blinding of participants and blinding of assessors. Each aspect was graded as either low risk of bias, or high/unclear risk of bias. The process was aided by a machine-learning algorithm that identifies passages and estimates a grade for each category. This has been demonstrated to speed up the quality assessment process.<sup>15</sup> A reviewer (JMG) checked each of the algorithm's estimates and the passages that

the algorithm was using to make these estimates, and made any changes to grades where the algorithm did not identify suitable passages. The QUIPS tool was used to assess the quality of observational studies of diet.<sup>16</sup>

### Synthesis of data

Due to the heterogeneity of the studies, the findings from the included studies are presented in the form of a narrative summary, sorted by RMD and then by category of diet exposure (animal products; experimental diets; food components; fruits, vegetables and other plant-based interventions; minerals and supplements; vitamins). For each exposure, results from systematic reviews are presented first where available, followed by results from individual studies published after the reviews. Where no reviews were identified, results from individual studies are presented.

If possible, the results of RCTs were pooled using random effects meta-analysis. Standardised mean differences (SMDs) were calculated if possible for individual studies and combined in meta-analyses as this allows results measured on different instruments to be combined (SMDs in online supplemental tables). An SMD is estimated as the difference between the scores of the intervention and control group at follow-up divided by the pooled SD.<sup>17</sup> The means and SDs were extracted from each RCT, or effect estimates (eg, ORs, relative risk ratios, adjusted where available) from observational studies. SDs were estimated from 95% confidence intervals or standard errors when not reported. Means and SDs were estimated from medians and ranges or IQRs when only these summary statistics were presented using a published formula.<sup>18</sup> Overall, a SMD $\geq 0.2$  was considered a small effect,  $\geq 0.5$  as a medium sized effect, and  $\geq 0.8$  as a large effect.<sup>19</sup> Heterogeneity was quantified using the  $I^2$  statistic. All statistical analyses were performed using Stata version 14 (StataCorp, College Station, TX).

The Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system defines high quality evidence as evidence where further research is very unlikely to change our confidence in the estimate of effect.<sup>20</sup> Therefore, evidence was rated as high quality if supported by meta-analyses of at least five RCTs at low-moderate risk of bias, reporting consistent results without important limitations.<sup>21</sup> GRADE defines moderate quality evidence as evidence where further research is likely to have an important impact on the confidence of the estimate of effect, or may change the estimate.<sup>20</sup> Evidence was rated as moderate if supported by meta-analyses of at least three RCTs or supported by a single RCT with a sample size  $\geq 100$  and at low-moderate risk of bias or multiple large observational studies. GRADE defines low quality evidence as evidence where further research is very likely to have an important influence on our confidence in the estimates, or is likely to change the estimate.<sup>20</sup> Evidence was rated as low if supported by multiple RCTs of small sample size or high risk of bias, or by single observational studies only. GRADE defines very low quality of evidence

as evidence where the estimate of the effect is very uncertain.<sup>20</sup> Evidence was rated as very low if supported by single small RCTs, or non-randomised trials or single arm intervention studies. Evidence could be downgraded in the event of other potential biases (such as study limitations, inconsistency of results, imprecision, publication bias<sup>21</sup> or conflicts of interest).

## RESULTS

### Study selection and study characteristics

The search of systematic reviews and meta-analyses yielded 1507 abstracts, of which 16 were duplicates. Of these, 125 full manuscripts were screened, of which 103 were included (figure 1). Only 24 assessed diet and progression of RMDs, and are included in this review (other references assessed other exposures within the taskforce; eg, exercise, smoking).

The search for original studies identified 4910 abstracts. After removal of 657 duplicates, 4253 titles and abstracts were screened. Of these, 203 full manuscripts were screened, of which 150 are included in this article (figure 2).

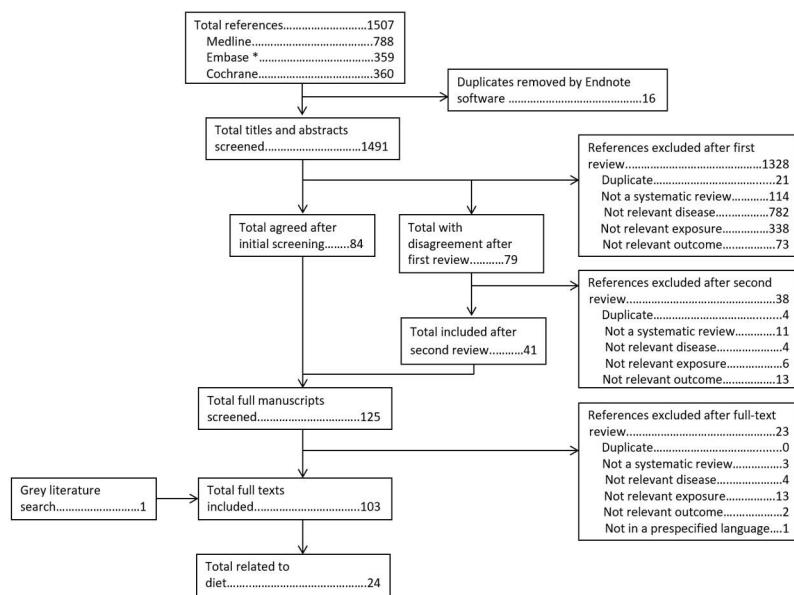
### Osteoarthritis

#### Animal products

In total, two systematic reviews,<sup>22 23</sup> 10 RCTs,<sup>24–33</sup> one single-arm intervention<sup>34</sup> and one prospective cohort study<sup>35</sup> assessed animal products in OA. One meta-analysis<sup>22</sup> reported moderate effects of undenatured type II collagen on pain and function (pain: SMD  $-0.67$ , 95% CI  $-1.01$  to  $-0.33$ ; function: SMD  $-0.55$ , 95% CI  $-0.94$  to  $-0.17$ ). Milk consumption was studied by one prospective cohort study, which reported a reduction in joint space narrowing as milk consumption increased.<sup>35</sup> One small RCT reported moderate effects on pain, function and stiffness following egg-shell membrane consumption.<sup>30</sup> An RCT studying *Channa striatus* extract (common name: striped snakehead fish) reported moderate sized effects for pain, function and stiffness.<sup>24</sup> One meta-analysis<sup>23</sup> and four RCTs studying fish oil supplements were included. The meta-analysis reported small, non-significant effects of fish oil on pain (SMD  $-0.16$ , 95% CI  $-0.57$  to  $0.24$ ) and function (SMD  $0.11$ , 95% CI  $-0.13$  to  $0.35$ ) in OA.<sup>23</sup> One meta-analysis of one RCT<sup>22</sup> reported a small effect of green-lipped mussel extract on pain that was not significant (SMD  $-0.37$ , 95% CI  $-0.81$  to  $0.08$ ). Promerim was assessed by one single-arm intervention study.<sup>34</sup> Pain improved after receiving promerim and exercise (online supplemental tables 5–13).

#### Experimental diets

One meta-analysis,<sup>36</sup> three RCTs<sup>37–39</sup> and one single arm intervention study<sup>40</sup> assessed experimental diets for OA. One meta-analysis compared dietary restriction plus exercise versus exercise controls, reporting small benefits in favour of pain (SMD  $-0.24$ , 95% CI  $-0.50$  to  $0.02$ ) and function (SMD  $-0.34$ , 95% CI  $-0.59$  to  $-0.08$ ).<sup>36</sup> One RCT reported no difference in pain or function between



**Figure 1** Flowchart of search strategy to identify published systematic reviews and meta-analyses. \*Embase search excluded journals included in Medline.

low and very low calorie diets.<sup>39</sup> A single arm intervention study reported reductions in pain, functional limitations and stiffness when following a low calorie diet,<sup>40</sup> and a small scale RCT reported improvements on several subscales of the SF36 from a whole-food, plant based diet in OA.<sup>38</sup> Another small scale RCT reported no benefit of the Mediterranean diet for physical function in people with OA<sup>37</sup> (online supplemental tables 14–18).

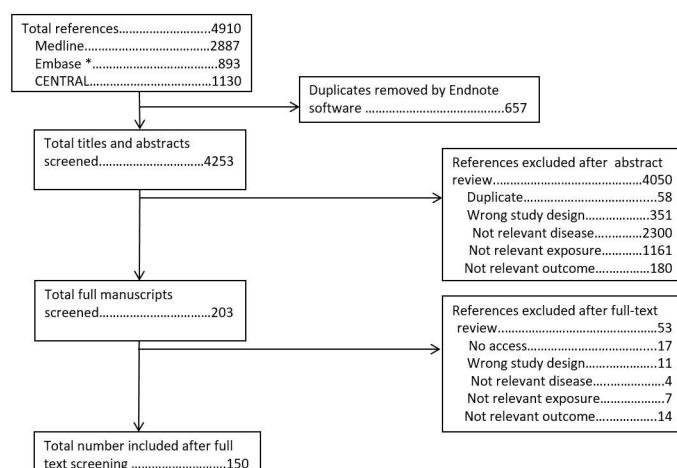
#### Food components

Two prospective cohort studies using data from the Osteoarthritis Initiative assessed the association between specific food components and OA progression.<sup>41 42</sup> One large prospective study reported that higher fibre intake was associated with lower odds of being in high pain trajectories.<sup>41</sup> The other reported that higher fat intake

was associated with faster joint space narrowing progression<sup>42</sup> (online supplemental tables 19 and 20).

#### Fruits, vegetables and other plant based interventions

In total, three meta-analyses,<sup>22 43 44</sup> two systematic reviews,<sup>7 45</sup> 20 RCTs<sup>46–65</sup> and one single arm intervention study<sup>66</sup> assessing fruit and vegetables were identified. *Artemisia annua* extract was included in one meta-analysis,<sup>22</sup> reporting no significant benefit on pain (SMD -0.37, 95% CI -1.03 to 0.29) and function (SMD -0.15, 95% CI -0.81 to 0.50). Avocado and soybean unsaponifiables (ASU) were assessed by two meta-analyses<sup>22 44</sup> and two systematic reviews.<sup>7 45</sup> One meta-analysis reported moderate sized effects of ASUs on pain (SMD -0.57, 95% CI -0.95 to -0.19) and function (SMD -0.48, 95% CI -0.69 to -0.28),<sup>22</sup> whereas the other reported small



**Figure 2** PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for review of individual studies of diet. \*Embase search excluded journals included in Medline.

effects (pain: 8% reduction, 95% CI 1% to 16%; function: 7% reduction, 95% CI 2% to 12%).<sup>44</sup> One systematic review<sup>45</sup> reported that only one out of four RCTs reported a significant effect on pain; the other<sup>7</sup> identified a meta-analysis<sup>67</sup> reporting a small effect on pain. Two meta-analyses<sup>22 44</sup> assessed *Boswellia serrata* extract, both reporting significant effects on pain and function, one reporting large effects (pain: SMD -1.61, 95% CI -2.10 to -1.13; function: SMD -1.15, 95% CI -1.63 to -0.68), the other moderate effects (pain, 100 point scale: -17, 95% CI -26 to -8; function, 100 point scale: -8, 95% CI -14 to -2). Bromelain was included in one meta-analysis, which reported no significant effect on pain (SMD -0.05, 95% CI -0.75 to 0.64) and a small, non-significant effect on function (SMD -0.34, 95% CI -1.04 to 0.36).<sup>22</sup> One meta-analysis<sup>22</sup> including one RCT<sup>68</sup> assessing *Curcuma longa* reported large effects on pain (SMD -1.63, 95% CI -2.22 to -1.03) and function (SMD -1.27, 95% CI -1.83 to -0.70). The same meta-analysis<sup>22</sup> included two RCTs assessing curcumin, again reporting large effects on pain (SMD -1.19, 95% CI -1.93 to -0.45) and function (SMD -1.13, 95% CI -1.80 to -0.46). Two RCTs assessed fruit powders of *Elaeagnus angustifolia* (Russian olive), reporting small to moderate sized effects on pain and function.<sup>50 63</sup> Passion fruit was included in one meta-analysis,<sup>22</sup> which identified one RCT<sup>69</sup> reporting large effects on pain (SMD -1.65, 95% CI -2.44 to -0.86) and function (SMD -1.55, 95% CI -2.33 to -0.77). *Rosa canina* mix was studied by three RCTs. Two<sup>58 60</sup> reported moderate to large effects of *Rosa canina* mix on pain and function. The third was a crossover study<sup>59</sup> and reported the effects only when the placebo was taken first, indicating crossover effects. All three studies were funded by companies producing the intervention. Two papers reported on the same RCT assessing sesame powder, reporting a medium sized significant effect on pain.<sup>49 51</sup> One meta-analysis<sup>22</sup> and three RCTs<sup>63-65</sup> assessed various tree bark extracts. The meta-analysis reported large effects of pine tree extract on pain (SMD -1.21, 95% CI -1.53 to -0.89) and function (SMD -1.84, 95% CI -2.32 to -1.35). One RCT reported a large effect of *Phellodendron* on pain in normal weight people with OA, but not overweight people.<sup>64</sup> One meta-analysis<sup>43</sup> reported a moderate sized effect of turmeric on pain (pooled mean difference -15.36, 95% CI -26.94 to -3.77). One RCT reported no effect on C-reactive protein (CRP) and 6 min walk test of *Scutellaria baicalensis* and *Acacia catechu*.<sup>61</sup> RCTs tested aquamin,<sup>55</sup> argan oil,<sup>56</sup> cherry juice,<sup>53 54</sup> garlic capsules,<sup>46</sup> ginger,<sup>52</sup> green tea extract,<sup>57</sup> pomegranate,<sup>47 48</sup> seaweed extract,<sup>62</sup> and *Elaeagnus angustifoli* and *Boswellia Thurifera*,<sup>63</sup> reporting no consistent effects on pain and function (online supplemental tables 21–43).

### Minerals and supplements

Two meta-analyses,<sup>22 70</sup> three systematic reviews,<sup>7 45 71</sup> four RCTs<sup>72-75</sup> and one single arm study<sup>76</sup> assessed various minerals and supplements for OA. Two meta-analyses<sup>22</sup> studied chondroitin for OA, one including nine studies<sup>22</sup>

and the other 12,<sup>70</sup> and reported a small effect of chondroitin on pain (SMD -0.34, 95% CI -0.49 to -0.19<sup>22</sup>; SMD -0.51, 95% CI -0.74 to -0.28)<sup>70</sup> and an inconsistent effect on function (SMD -0.36, 95% CI -0.58 to -0.13<sup>22</sup>; SMD 0.11, 95% CI -0.47 to 0.68).<sup>70</sup> However, two systematic reviews concluded that chondroitin was not associated with reductions in pain.<sup>45 71</sup> A third cited a range of meta-analyses reporting a wide range of effect sizes.<sup>7</sup> One meta-analysis and two systematic reviews included glucosamine for OA. The meta-analysis<sup>22</sup> reported small effect sizes for pain (SMD -0.28, 95% CI -0.52 to -0.04) and function (SMD -0.45, 95% CI -0.73 to -0.17). The systematic reviews<sup>7 45</sup> identified a Cochrane review<sup>77</sup> that reported a moderate sized benefit for pain as well as a large scale RCT<sup>78</sup> that reported a null effect. One meta-analysis included three RCTs assessing methylsulfonylmethane supplementation, reporting a small effect on pain (SMD -0.47, 95% CI -0.80 to -0.14) and a large effect on function (SMD -1.10, 95% CI -1.81 to -0.38).<sup>22</sup> RCTs reported large effects on CRP and erythrocyte sedimentation rate from calcium fructobate,<sup>74</sup> and medium-large effects on pain and function from creatine,<sup>73 75</sup> L-carnitine<sup>22</sup> and *Lactobacillus casei shirota*.<sup>72</sup> One single arm intervention tested a multi-mineral containing 72 natural minerals, reporting improvements in pain and function following the intervention<sup>76</sup> (online supplemental tables 44–53).

### Vitamins

In total, three meta-analyses,<sup>22 79 80</sup> three systematic reviews,<sup>71 81 82</sup> eight RCTs<sup>83-90</sup> and three prospective cohort studies<sup>91-93</sup> were identified studying vitamin supplementation for OA. RCTs testing multi-vitamins,<sup>88</sup> vitamin B3<sup>89</sup> and vitamin B12<sup>90</sup> reported small non-significant effects on pain. One prospective cohort study reported that self-reported vitamin C supplementation was not associated with lower risk of radiographic progression.<sup>91</sup> One RCT compared vitamin E+versus placebo and reported a small effect on pain after 8 weeks.<sup>87</sup> Three meta-analyses,<sup>22 79 80</sup> three systematic reviews,<sup>71 81 82</sup> four RCTs<sup>83-86</sup> and one prospective cohort study<sup>93</sup> were identified that studied the effect of vitamin D. The meta-analyses reported small effects on pain and function as a result of vitamin D (pain: SMD -0.19, 95% CI -0.31 to -0.06<sup>22</sup>; SMD -0.32, 95% CI -0.63 to -0.02,<sup>79</sup> mean difference in The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) -1.65, 95% CI -2.16 to -1.14<sup>80</sup>; function: SMD -0.36, 95% CI -0.61 to -0.11,<sup>22</sup> mean difference WOMAC -1.87, 95% CI -2.58 to -1.17).<sup>80</sup> The systematic reviews reported no effect on pain, but a small effect on function. Three out of six observational studies included in a systematic review reported an inverse relationship between vitamin D and radiographic progression.<sup>82</sup> The latest RCT not included in the meta-analyses reported no difference in pain between high and low doses of vitamin D after participants underwent total knee replacement.<sup>83</sup> One meta-analysis<sup>22</sup> and one systematic review<sup>71</sup> studied vitamin E.

**Table 1** Osteoarthritis results summary

Quality/effect size	None	Small	Medium	Large
Very low	Artemisia annua (function), bromelain (pain), ginger (pain), green tea extract (pain, function), Mediterranean diet (function), <i>Scutellaria baicalensis</i> and <i>Acacia catechu</i> (6MWT, CRP), <i>Uncaria guianensis</i> extract (pain), WFPB diet (pain), vitamin B12 (pain)	Aquamin (pain), <i>Artemisia annua</i> (pain), bromelain (function), vitamin B3 (pain), vitamin C+E (pain)	Aquamin (function), creatine (pain, function), egg-shell membrane (pain, function, stiffness), multi-mineral (pain, function), promerim (pain), seaweed extract (pain, function), sesame powder (pain), turmeric (pain)	Calcium fructobate (CRP, ESR), L-carnitine (pain, function), passion fruit extract (pain, function), <i>Phellodendron amurense</i> extract (pain)
Low	Cherry juice (pain, function), <i>Elaeagnus angustifoli</i> extract + <i>Boswellia thurifera</i> (pain, function), garlic (pain, function), pomegranate (pain, function), vitamin C (radiographic progression), vitamin E (pain, function)	Argan oil (pain), <i>Channa striatus</i> (pain), <i>Elaeagnus angustifoli</i> extract (pain, function), fruit powder (pain, function), green lipped mussel extract (pain), low calorie diet (pain, function), methylsulfonylmethane (pain), multi-vitamins (pain), vitamin D (radiographic progression)	Argan oil (function), <i>Boswellia Serrata</i> (pain, function), <i>Channa striatus</i> (function), collagen (pain, function), fibre (pain), fat (JSW), <i>Lactobacillus casei shirota</i> (stiffness), milk (JSW)	<i>Curcuma longa</i> (pain, function), curcumin (pain, function), <i>Lactobacillus casei shirota</i> (pain, function), methylsulfonylmethane (function), pine tree extract (pain, function), <i>Rosa canina</i> mix (pain, function)
Moderate	Fish oil (pain, function)	ASU (pain, function), chondroitin (pain, function), glucosamine (pain, function), vitamin D (pain, function)	–	–
High	–	–	–	–

ASU, avocado and soybean unsaponifiable; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; JSW, joint space width; 6MWT, 6 min walk test; WFPB, whole food plant based.

Both reported no effect of vitamin E on pain (SMD 0.01, 95% CI -0.44 to 0.45) and the meta-analysis reported no effect of vitamin E on function (SMD -0.10, 95% CI -0.55 to 0.35) (online supplemental tables 54–62).

## Summary

There were only relatively few studies for most dietary exposures in OA, meaning that the evidence for these exposures was graded as low or very low (table 1). For diets that had moderate evidence (fish oil, chondroitin, glucosamine, vitamin D, ASU), the effect sizes for outcomes were generally small and therefore not clinically relevant.

## Rheumatoid arthritis

### Animal products

In total, three meta-analyses,<sup>23 94 95</sup> one systematic review,<sup>96</sup> 12 RCTs<sup>97–107</sup> and one non-randomised trial<sup>108</sup> assessed products derived from animals for RA. One RCT compared collagen extracted from pigskins with placebo, reporting no significant effect on pain, function

and disease activity.<sup>99</sup> Three meta-analyses,<sup>23 94 95</sup> one systematic review,<sup>96</sup> eight RCTs<sup>97 98 100–105</sup> and one non-randomised trial<sup>108</sup> studied the effect of fish oils and omega-3 on RA progression. The meta-analyses reported small effects of fish oils on pain (SMD -0.32, 95% CI -0.59 to -0.05<sup>94</sup>; SMD -0.21, 95% CI -0.42 to -0.00),<sup>23</sup> with the same results from the meta-analysis of identified RCTs (SMD -0.27, 95% CI -0.54 to 0.00) (online supplemental figure 3). One meta-analysis reported a small, significant effect on function (SMD -0.26, 95% CI -0.46 to -0.06),<sup>94</sup> whereas another reported no effect (SMD 0.05, 95% CI -0.11 to 0.21).<sup>23</sup> One RCT reported an improvement in disease activity,<sup>97</sup> whereas another reported no effect.<sup>98</sup> Two RCTs studied the effect of mussel extracts, reporting small non-significant effects on pain and function (online supplemental tables 63–67).

### Experimental diets

One meta-analysis,<sup>95</sup> 12 RCTs,<sup>109–120</sup> five non-randomised trials,<sup>121–125</sup> one single arm study<sup>126</sup> and one extension to

an RCT comparing responders with non-responders<sup>127</sup> studied experimental diets in RA. Multiple RCTs and non-randomised trials studied liquid elemental diets,<sup>109 113 115 116</sup> hypoallergenic diets,<sup>112 117 125</sup> ketogenic diets<sup>124</sup> and vegetarian or vegan diets,<sup>111 114 118-120 123 126 127</sup> reporting no effect on the majority of outcomes assessed, including pain, function, joint counts, acute phase reactants, and morning stiffness. One meta-analysis,<sup>95</sup> one RCT<sup>110</sup> and two non-randomised trials<sup>121 122</sup> studied the Mediterranean diet for RA. The meta-analysis reported no significant effect of the Mediterranean diet on fatigue (SMD 0.37, 95% CI -0.18 to 0.93).<sup>95</sup> The RCT<sup>110</sup> reported a large effect of the diet on pain and a small effect on disease activity (online supplemental tables 68-74).

### Fruits, vegetables and other plant based interventions

One meta-analysis,<sup>95</sup> eight RCTs,<sup>128-135</sup> one non-randomised trial<sup>136</sup> and three single arm studies<sup>137-139</sup> assessed plant based interventions for RA. RCTs tested microalgae oil,<sup>128</sup> herbal medicine,<sup>135</sup> pomegranate extract,<sup>129</sup> quercetin<sup>130 132 134</sup> and rose hip powder,<sup>133</sup> reporting no consistent effects on outcomes, including pain, function, disease activity, joint counts and QoL. *Andrographis paniculata* was included in one meta-analysis, which reported no effect on fatigue.<sup>95</sup> One RCT<sup>131</sup> investigated a combination of ginger, curcumin and black pepper for RA and reported large effects on the Disease Activity Score 28 (DAS28) and its components. One single arm intervention study assessed gum arabic powder, concluding that DAS28 and its components fell after administration.<sup>137</sup> However, there was no control group. One non-randomised trial of *Nigella sativa* oil reported moderate benefits in terms of pain, disease activity, tender and swollen joints and morning stiffness<sup>136</sup> (online supplemental tables 75-85).

### Minerals and supplements

Two meta-analyses,<sup>140 141</sup> 14 RCTs<sup>134 142-153</sup> and one single arm study<sup>154</sup> assessed minerals and supplements for RA. Two meta-analyses<sup>140 141</sup> assessed studies on probiotics in RA, both reporting either small non-significant effects or no effects on function (SMD -0.30, 95% CI -0.89 to 0.29<sup>140</sup>; MD -0.11, 95% CI -0.23 to 0.01),<sup>141</sup> swollen joint count (SMD -0.30, 95% CI -0.62 to 0.02<sup>140</sup>; MD 0.17, 95% CI -0.39 to 0.73)<sup>141</sup> and CRP (SMD -0.32, 95% CI -0.65 to 0.00; MD -1.40, 95% CI -4.06, 1.26)<sup>141</sup> and an inconsistent effect on disease activity (SMD -0.58, 95% CI -0.97 to -0.19<sup>140</sup>; MD 0.02, 95% CI -0.58 to 0.63).<sup>141</sup> RCTs tested alpha lipoic acid,<sup>134 145</sup> co-enzyme Q10,<sup>144</sup> creatine,<sup>143</sup> glucosamine,<sup>148</sup> linoleic acid,<sup>147</sup> manganese<sup>152</sup> and zinc,<sup>150 151</sup> reporting no effects on outcomes including pain, function and acute phase reactants. One RCT studied ambrotose complex for RA, reporting a small effect on pain but no effect on any other outcomes.<sup>146</sup> An RCT compared grape juice enriched with potassium with standard grape juice, reporting large effects in terms of pain, disease activity, tender and swollen joint counts and acute phase reactants.<sup>153</sup> An RCT assessing a combination

of supplements (beta-hydroxy-beta-methylbutyrate, glutamine and arginine) reported moderate effects on disease activity, function and fatigue<sup>149</sup> (online supplemental tables 86-98).

### Vitamins

One meta-analysis,<sup>155</sup> six RCTs,<sup>147 156-160</sup> one non-randomised trial<sup>161</sup> and two single arm studies<sup>162 163</sup> assessed vitamin supplementation in RA. One meta-analysis reported no significant effect of vitamin D supplementation on pain (MD 2.79, 95% CI -1.87 to 7.44) and disease activity (MD -0.31, 95% CI -0.86 to 0.25). Two RCTs reported inconsistent effects on pain, function and disease activity.<sup>156 158</sup> Two RCTs studied vitamin B6, with one<sup>157</sup> reporting no significant effect on disease activity, swollen/tender joint count and acute phase reactants, and the other<sup>159</sup> reporting no effect on CRP. One RCT<sup>160</sup> assessing vitamin E reported a large effect on pain, but no effect on swollen/tender joint counts and morning stiffness. Another RCT<sup>147</sup> reported no effect of vitamin E on acute phase reactants (online supplemental tables 99-104).

### Summary

The evidence for most dietary exposures in RA was graded as low or very low (table 2), primarily due to small numbers of studies with small sample sizes. The dietary exposures with moderate quality evidence (probiotics, vitamin D, fish oil/omega-3) showed either no effect or effect sizes that are probably not clinically significant.

### Systemic lupus erythematosus

#### Animal products

One systematic review,<sup>164</sup> six RCTs<sup>165-170</sup> and one non-randomised trial<sup>171</sup> assessed fish oil/omega-3 for SLE. Two out of three studies included in the systematic review<sup>164</sup> reported reductions in disease activity following omega-3 intervention. The largest RCT reported no difference in disease activity between omega-3 and placebo.<sup>167</sup> Another RCT reported reductions in disease activity in the fish group from baseline and no reduction in the placebo group, but did not compare the two groups.<sup>168</sup> One other RCT<sup>166</sup> reported large effects on pain and function following omega-3 intervention, but no effect on fatigue. Two RCTs reported no effect of omega-3 on CRP<sup>165 168</sup> (online supplemental tables 105-107).

#### Experimental diets

Three systematic reviews<sup>164 172 173</sup> identified one RCT<sup>174</sup> comparing a low glycaemic diet with a low calorie diet, concluding no effect on disease activity or fatigue. An RCT<sup>175</sup> reported a large effect of a cholesterol lowering educational programme on QoL compared with no advice (online supplemental tables 108-110).

#### Food components

Three observational cohort studies<sup>176-178</sup> assessed the association between food components and outcomes in SLE. Two cohort studies<sup>176 177</sup> assessed the association

**Table 2** Rheumatoid arthritis results summary

Quality/ effect size	None	Small	Medium	Large
Very low	Collagen (pain, function, disease activity), creatine (function, disease activity), elemental diets (pain, function, TJC, SJC, MS), glucosamine (CRP, ESR), herbal medicine (function, TJC, SJC), hypoallergenic diets (pain, TJC, SJC, MS), ketogenic diets (TJC, CRP, ESR), Linoleic acid (CRP, ESR), manganese (disease activity), Mediterranean diet (disease activity), microalgae oil (SJC), pomegranate (pain, function, TJC, SJC), vitamin B6 (SJC), vitamin E (TJC, SJC, MS, CRP, ESR)	Gum arabic (disease activity), herbal medicine (pain), Mediterranean diet (fatigue, function), microalgae oil (function, disease activity, TJC), mussel extracts (pain, function), quercetin (disease activity, TJC, SJC), vitamin B6 (disease activity, TJC, CRP, ESR)	<i>Nigella sativa</i> oil (pain, disease activity, TJC, SJC, morning stiffness)	Ginger+curcumin + black pepper (disease activity), Mediterranean diet (pain), potassium (pain, disease activity, TJC, SJC, CRP, ESR), vitamin E (pain)
Low	Alpha-lipoic acid (pain, CRP), ambrotose complex (function), <i>Andrographis Paniculata</i> (fatigue), rose hip powder (function, QoL), vegetarian/vegan diet (pain, function),	Alpha-lipoic acid (function), ambrotose complex (pain), antioxidant combinations (disease activity), co-enzyme Q10 (CRP), rose hip powder (pain, disease activity), zinc (pain, function)	Beta-hydroxy-beta-methylbutyrate+glutamine + arginine (disease activity, function, fatigue), quercetin (pain, function)	Antioxidant combinations (pain, function)
Moderate	Fish oil/omega-3 (function, disease activity), probiotics (function, SJC, CRP, disease activity), vitamin D (pain, disease activity)	Fish oil/omega-3 (pain)	–	–
High	–	–	–	–

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MS, morning stiffness; QoL, quality of life; SJC, swollen joint count; TJC, tender joint count.

between consumption of various food elements and risk of active disease and atherosclerotic vascular events. High consumption of vitamin B6, fibre and vitamin C was associated with lower risk of developing active disease. None of the food components investigated were associated with reduced risk of atherosclerotic vascular events. Another cohort study<sup>178</sup> investigated poor nutrition in SLE, reporting that lower calorie intake was associated with more organ damage and lower percentage of protein was associated with worse mental health (online supplemental tables 111–113).

#### Fruits, vegetables and other plant based interventions

Two RCTs<sup>179 180</sup> studied plant based interventions for SLE. One RCT<sup>180</sup> reported no effect of curcumin on disease activity, and the other RCT<sup>179</sup> reported no effect of green tea extract on disease activity, but significant benefit in terms of fatigue (median (IQR) at 3 months, green tea: 81 (63.1–95.5); placebo: 56.2 (28.1–84.3), p=0.006) (online supplemental tables 114–116).

#### Minerals and supplements

One RCT<sup>169</sup> and one non-randomised trial<sup>181</sup> studied mineral supplementation for SLE. The non-randomised trial<sup>181</sup> assessed calcium+vitamin D supplementation compared with no treatment or steroid treatment. The supplements had a large effect compared with no treatment on disease activity and a moderate effect on erythrocyte sedimentation rate, but no effect compared with steroids. Another RCT<sup>169</sup> assessed copper supplementation, reporting no effect on disease activity (online supplemental tables 117–119).

#### Vitamins

One meta-analysis,<sup>155</sup> one systematic review<sup>173</sup> and two RCTs<sup>182 183</sup> studied vitamins in SLE. All studies assessed vitamin D, with all studies reporting no significant effect of vitamin D on disease activity,<sup>155 182</sup> fatigue<sup>173</sup> and anti-dsDNA level<sup>155 183</sup> (online supplemental tables 120–122).

**Table 3** Systemic lupus erythematosus results summary

Quality/effect size	None	Small	Medium	Large
Very low	Copper (disease activity), curcumin (disease activity), fish oil/omega-3 (CRP), green tea extract (disease activity), low glycaemic (disease activity, fatigue)	Fish oil/omega-3 (ESR)	Calcium+vitamin D (ESR), green tea extract (fatigue)	Calcium+vitamin D (disease activity), cholesterol lowering education (QoL), fish oil/omega-3 (pain, function)
Low	Vitamin D (disease activity, fatigue, anti-dsDNA)	Fish oil/omega-3 (disease activity), fibre (disease activity), poor nutrition (organ damage), vitamin B6 (disease activity), vitamin C (disease activity)	–	–
Moderate	–	–	–	–
High	–	–	–	–

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; QoL, quality of life.

## Summary

The evidence for fish oil/omega-3 for SLE was rated as moderate but showed no effect on outcomes (table 3). The evidence for all other studies was rated as low or very low.

## Axial spondyloarthritis

### Food components

One systematic review<sup>184</sup> of 16 studies assessed various food components in axSpA. There was no association between the consumption of alpha-linoleic acid, carbohydrates, linoleic acid, long-chain omega-3 fatty acids, fibre, polyunsaturated fatty acids, protein or saturated fatty acids and disease activity or acute phase reactant levels. There was no association between fat consumption and acute phase reactant level. (online supplemental tables 123 and 124).

### Minerals and supplements

One RCT<sup>185</sup> assessed probiotic supplementation versus placebo, reporting no significant effect on pain, function, disease activity, tender/swollen joints and spinal mobility (online supplemental tables 125 and 126).

## Summary

The evidence for dietary exposures in axSpA was rated as very low (table 4).

## Psoriatic arthritis

### Animal products

Three RCTs<sup>186–188</sup> assessed marine animal oil/omega-3 for PsA. The studies reported no significant effect on pain,<sup>186 187</sup> function,<sup>186 187</sup> disease activity,<sup>186</sup> tender joints,<sup>186–188</sup> swollen joints<sup>186 187</sup> enthesitis,<sup>186</sup> psoriasis severity,<sup>186</sup> patient global<sup>187</sup> and acute phase reactants<sup>187 188</sup> (online supplemental tables 127 and 128).

## Minerals and supplements

One RCT<sup>189</sup> studied supplementation of selenium, co-enzyme Q10 and vitamin E for psoriasis with joint involvement and radiographic erosion, reporting a large effect on disease severity but no effect on psoriasis severity (online supplemental tables 129 and 130).

## Summary

The evidence for marine animal oil/omega-3 for PsA was rated as moderate and showed no effect on outcomes (table 4). Other dietary exposures were rated as low evidence.

## Systemic sclerosis

### Experimental diets

Two single arm studies<sup>190 191</sup> assessed medical nutrition therapy for SSc. One single arm study<sup>190</sup> assessed a diet and lifestyle plan, reporting improvements in patient global assessment but not in QoL. Another single arm study<sup>191</sup> provided supplements for vitamin and mineral deficiencies and encouraged healthy eating. There were no significant changes on any of the SF36 dimensions (online supplemental tables 131 and 132).

### Vitamins

Three RCTs<sup>192–194</sup> studied vitamin supplementation in SSc. Two RCTs tested vitamins C and E (one also included selenium and beta-carotene) for SSc, one reporting better Rodnan Skin score at 1 month,<sup>192</sup> the other reporting no difference in frequency of Raynaud's attacks.<sup>193</sup> The final RCT<sup>194</sup> assessed vitamin D supplementation, reporting a large effect on Rodnan skin score at 9 months (online supplemental tables 133–135).

## Summary

The evidence for dietary exposures in SSc was rated as low or very low (table 5).

**Table 4** Axial spondyloarthritis and psoriatic arthritis results summary

Quality/effect size	None	Small	Medium	Large
Very low	<b>axSpA</b> Alpha-linoleic acid (disease activity, ESR, CRP), carbohydrates (disease activity, ESR, CRP), fat (disease activity, ESR, CRP), fibre (disease activity), linoleic acid (disease activity, ESR, CRP), long-chain omega-3 fatty acids (disease activity, CRP), polyunsaturated fatty acids (disease activity, CRP), probiotics (pain, function, SJC, spinal mobility), protein (disease activity, ESR, CRP), saturated fatty acids (disease activity, ESR, CRP)	<b>axSpA</b> Long-chain omega-3 fatty acids (ESR), polyunsaturated fatty acids (ESR), probiotics (disease activity, TJC)		<b>PsA</b> Selenium+coenzyme Q10+vitamin E (disease activity)
	<b>PsA</b> Selenium+coenzyme Q10+vitamin E (psoriasis severity)			
Low	<b>PsA</b> Marine animal oil/omega-3 (CRP)	<b>PsA</b> Marine animal oil/omega-3 (ESR)	<b>PsA</b> Marine animal oil/omega-3 (function, SJC)	-
Moderate	<b>PsA</b> Marine animal oil/omega-3 (pain, disease activity, TJC, enthesitis, patient global, psoriasis severity)	-	-	-
High	-	-	-	-

axSpA, axial spondyloarthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PsA, psoriatic arthritis; SJC, swollen joint count; TJC, tender joint count.

## Gout

### Animal products

Two systematic reviews<sup>195 196</sup> identified one RCT<sup>197</sup> which assessed enriched milk powder for gout. Pain scores were significantly lower in the intervention group, but this was judged not to be clinically significant. There was no difference between the groups in terms of function, uric

acid level and gout flares (online supplemental tables 136 and 137).

### Fruits, vegetables and other plant based interventions

One RCT<sup>198</sup> studied Chinese herbal medicine and concluded it had no significant hypouricemic effect (online supplemental tables 138 and 139).

**Table 5** Systemic sclerosis and gout results summary

Quality/effect size	None	Small	Medium	Large
Very low	<b>SSc</b> Nutrition therapy (QoL, pain, mental health, physical health, fatigue), vitamin C+E (Raynaud's attacks)	<b>SSc</b> Nutrition therapy (patient global)	-	<b>SSc</b> Vitamin C+E (Rodnan skin score), vitamin D (Rodnan skin score)
	<b>Gout</b> Vitamin C (uric acid)	<b>Gout</b> Herbal medicine (uric acid)		
Low	<b>Gout</b> Enriched milk powder (function, uric acid, gout flare)	<b>Gout</b> Enriched milk powder (pain)	-	-
Moderate	-	-	-	-
High	-	-	-	-

QoL, quality of life; SSc, systemic sclerosis.

## Vitamins

One RCT<sup>199</sup> and one single arm study<sup>200</sup> assessed vitamin C supplementation for gout. The control arm was treated with allopurinol in the RCT, and demonstrated greater reductions in uric acid. The single arm study reported no changes in uric acid (online supplemental tables 140 and 141).

## Summary

The evidence for dietary exposures in gout was rated as low or very low (table 5).

## Studies of more than one RMD

One single arm study<sup>201</sup> of a powdered meal replacement included people with OA and people with RA, reporting a slight improvement in the 50 foot walk test. A non-randomised trial<sup>202</sup> assessing linoleic acid included people with RA and people with axSpA and reported no effect on tender or swollen joint count, morning stiffness, grip strength and ESR (online supplemental tables 142 and 143).

## DISCUSSION

Many studies have been published assessing diet in OA and RA, with relatively fewer studies in the other RMDs. However, the majority of exposures in all RMDs have only been assessed by a handful of studies, which were often underpowered and at moderate to high risk of bias. Typically, these studies reported low effect sizes for outcomes, although some reported large effects. This could be due to publication bias<sup>203</sup> or influence of commercial sponsors. When many studies have been performed (eg, chondroitin for OA<sup>70</sup>) or RCTs with large sample sizes have been conducted (eg, vitamin D for OA)<sup>84 85</sup> the effect sizes on outcomes are small and not clinically meaningful. Therefore, based on the current evidence, there is no single dietary intervention which has substantial benefits on the outcomes of people with OA and RA.<sup>204</sup> While there have been far fewer research studies published for the other included RMDs, again there is no consistent evidence that any dietary exposure significantly improves outcomes in these conditions. Despite this, people with RMDs should still aim for a healthy, balanced diet given the literature demonstrating the benefits in terms of non-RMD outcomes and lack of harms.<sup>8 9</sup> Furthermore, the impact of a healthy diet on weight and body composition (ie, calorie balance) is likely important for determining outcomes. This was the focus of a separate review as part of this project.<sup>205</sup>

Alongside the influence of publication bias on these results, many studies were rated as having moderate or high risk of bias (see online supplementary material). Studies often failed to report on the randomisation or allocation concealment process as well as steps taken to ensure participants and assessors were blinded to group allocation. These factors could also influence the results, potentially inflating reported effect sizes. Furthermore, there was limited reporting of adverse events.

This review has a number of strengths. Its broad scope allows us to gain a global understanding of the effect of diet in RMDs. The review was conducted with rigour, with multiple assessors screening the titles, abstracts and full texts. Furthermore, appropriate quality assessment tools were utilised to assess the quality of all included studies. However, given the scope of the research question it is possible that some studies were missed in the review. This was limited as much as possible by designing and testing an extensive search strategy as well as including other published systematic reviews and meta-analyses, increasing the likelihood of including as many relevant studies as possible. Furthermore, some exposures were deemed to be sufficiently covered in previous reviews and were not included in the search of original articles. However, this may mean some articles were not included (eg, due to when they were published). Lastly, while the research team included a range of experts in rheumatology research and evidence synthesis, no specific nutritionists or dietitians were included in the authorship team.

Future research on diet in RMDs should aim for higher methodological and reporting standards. Some studies did not report data in sufficient detail for extraction and thus inclusion in this review. For example, an RCT by Kjeldsen-Kragh and colleagues from 1991 tested a vegetarian diet and fasting and reported a significant improvement in many patient reported outcomes (eg, pain, disability), but only presented data in the form of line-graphs meaning no precise data could be extracted.<sup>206</sup> Furthermore, studies should be sufficiently powered with long-term follow-up. Standardised definitions for different diet exposures should be formulated to allow comparison across studies, and standard outcomes assessed. Finally, research into the additive or synergistic effect of different dietary components should be researched, given the complex and interrelated nature of people's diets.

In conclusion, this broad systematic review of 174 published articles shows there is large heterogeneity in the literature on the effects of diet on RMD outcomes, both within and across RMDs. There are many published research studies on RA and OA, investigating a range of dietary exposures. For the other included RMDs, the current evidence base is limited. From the current evidence, there appears to be no single dietary factor which leads to meaningful improvements in RMD outcomes.

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#### REFERENCES

- Smolen JS, Aletaha D, Barton A, et al. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;4:18001.
- Martel-Pelletier J, Barr AJ, Cucutini FM, et al. Osteoarthritis. *Nat Rev Dis Primers* 2016;2:16072.
- Kaul A, Gordon C, Crow MK, et al. Systemic lupus erythematosus. *Nat Rev Dis Primers* 2016;2:16039.
- March L, Smith EUR, Hoy DG, et al. Burden of disability due to musculoskeletal (MSK) disorders. *Best Pract Res Clin Rheumatol* 2014;28:353–66.
- GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet* 2020;396:1204–22.
- Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews. *Cochrane Database Syst Rev* 2009;4:CD007848.
- McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363–88.
- Schulze MB, Martínez-González MA, Fung TT, et al. Food based dietary patterns and chronic disease prevention. *BMJ* 2018;361:k2396.
- Stranges S, Samaraweera PC, Taggart F, et al. Major health-related behaviours and mental well-being in the general population: the health survey for England. *BMJ Open* 2014;4:e005878.
- Gwinnutt JM, Wieczorek M, Balanescu A, et al. 2021 EULAR recommendations regarding lifestyle behaviours and work participation to prevent progression of rheumatic and musculoskeletal diseases. *Ann Rheum Dis* 2022. doi:10.1136/annrheumdis-2021-222020. [Epub ahead of print: 08 Mar 2022].
- van der Heijde D, Aletaha D, Carmona L, et al. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
- Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
- Soboczenski F, Trikalinos TA, Kuiper J, et al. Machine learning to help researchers evaluate biases in clinical trials: a prospective, randomized user study. *BMC Med Inform Decis Mak* 2019;19:96.
- Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013;158:280–6.
- Cochrane. Cochrane Handbook: 9.2.3.2 the standardized mean difference. Available: [https://handbook-5-1.cochrane.org/chapter\\_9/2\\_3\\_2\\_the\\_standardized\\_mean\\_difference.htm](https://handbook-5-1.cochrane.org/chapter_9/2_3_2_the_standardized_mean_difference.htm) [Accessed 20 Jan 2021].
- Wan X, Wang W, Liu J, et al. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
- Cohen J. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, NJ: Erlbaum, 1988.
- Guyatt GH, Oxman AD, Vist GE, et al. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
- Guyatt GH, Oxman AD, Kunz R, et al. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;336:995–8.

22 Liu X, Machado GC, Eyles JP, et al. Dietary supplements for treating osteoarthritis: a systematic review and meta-analysis. *Br J Sports Med* 2018;52:167–75.

23 Senftleber NK, Nielsen SM, Andersen JR, et al. Marine oil supplements for arthritis pain: a systematic review and meta-analysis of randomized trials. *Nutrients* 2017;9:42.

24 Azidah AK, Arifah AK, Roslida AH, et al. A randomized, double-blind study comparing multiple doses of Channa striatus supplementation for knee osteoarthritis. *Orient Pharm Exp Med* 2017;17:345–54.

25 Hill CL, March LM, Aitken D, et al. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. *Ann Rheum Dis* 2016;75:23–9.

26 Chen JS, Hill CL, Lester S, et al. Supplementation with omega-3 fish oil has no effect on bone mineral density in adults with knee osteoarthritis: a 2-year randomized controlled trial. *Osteoporos Int* 2016;27:1897–905.

27 Kumar S, Sugihara F, Suzuki K, et al. A double-blind, placebo-controlled, randomised, clinical study on the effectiveness of collagen peptide on osteoarthritis. *J Sci Food Agric* 2015;95:702–7.

28 Schauss AG, Stenehjem J, Park J, et al. Effect of the novel low molecular weight hydrolyzed chicken sternal cartilage extract, BioCell collagen, on improving osteoarthritis-related symptoms: a randomized, double-blind, placebo-controlled trial. *J Agric Food Chem* 2012;60:4096–101.

29 Nagaoka I, Nabeshima K, Murakami S, et al. Evaluation of the effects of a supplementary diet containing chicken comb extract on symptoms and cartilage metabolism in patients with knee osteoarthritis. *Exp Ther Med* 2010;1:817–27.

30 Ruff KJ, Winkler A, Jackson RW, et al. Eggshell membrane in the treatment of pain and stiffness from osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo-controlled clinical study. *Clin Rheumatol* 2009;28:907–14.

31 Kalman DS, Heimer M, Valdeon A, et al. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. *Nutr J* 2008;7:3.

32 Hesslink R, Armstrong D, Nagendran MV, et al. Cetylated fatty acids improve knee function in patients with osteoarthritis. *J Rheumatol* 2002;29:1708–12.

33 Stammers T, Sibbald B, Freeling P. Efficacy of cod liver oil as an adjunct to non-steroidal anti-inflammatory drug treatment in the management of osteoarthritis in general practice. *Ann Rheum Dis* 1992;51:128–9.

34 Kilinc BE, Oc Y, Albakan G, et al. An observational 1-Month trial on the efficacy and safety of Promerim for improving knee joint. *Clin Med Insights Arthritis Musculoskelet Disord* 2018;11:117954411875 7496:117954411875749.

35 Lu B, Driban JB, Duryea J, et al. Milk consumption and progression of medial tibiofemoral knee osteoarthritis: data from the osteoarthritis initiative. *Arthritis Care Res* 2014;66:802–9.

36 Alrushud AS, Rushton AB, Kanavaki AM, et al. Effect of physical activity and dietary restriction interventions on weight loss and the musculoskeletal function of overweight and obese older adults with knee osteoarthritis: a systematic review and mixed method data synthesis. *BMJ Open* 2017;7:e014537.

37 Dyer J, Davison G, Marcora SM, et al. Effect of a Mediterranean type diet on inflammatory and cartilage degradation biomarkers in patients with osteoarthritis. *J Nutr Health Aging* 2017;21:562–6.

38 Clinton CM, O'Brien S, Law J, et al. Whole-foods, plant-based diet alleviates the symptoms of osteoarthritis. *Arthritis* 2015;2015:1–9.

39 Riecke BF, Christensen R, Christensen P, et al. Comparing two low-energy diets for the treatment of knee osteoarthritis symptoms in obese patients: a pragmatic randomized clinical trial. *Osteoarthritis Cartilage* 2010;18:746–54.

40 López-Gómez JJ, Izaola-Jáuregui O, Torres-Torres B, et al. Influence of a meal-replacement diet on quality of life in women with obesity and knee osteoarthritis before orthopedic surgery. *Nutr Hosp* 2018;35:71–7.

41 Dai Z, Lu N, Niu J, et al. Dietary fiber intake in relation to knee pain trajectory. *Arthritis Care Res* 2017;69:1331–9.

42 Lu B, Driban JB, Xu C, et al. Dietary fat intake and radiographic progression of knee osteoarthritis: data from the osteoarthritis initiative. *Arthritis Care Res* 2017;69:368–75.

43 Daily JW, Yang M, Park S. Efficacy of Turmeric extracts and curcumin for alleviating the symptoms of joint arthritis: a systematic review and meta-analysis of randomized clinical trials. *J Med Food* 2016;19:717–29.

44 Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthritis. *Cochrane Database Syst Rev* 2014;5:CD002947.

45 Percope de Andrade MA, Campos TVdeO, Abreu-E-Silva GMde. Supplementary methods in the nonsurgical treatment of osteoarthritis. *Arthroscopy* 2015;31:785–92.

46 Salimzadeh A, Alipoor E, Dehghani S, et al. The effect of 12-week garlic supplementation on symptom relief in overweight or obese women with knee osteoarthritis. *Int J Clin Pract* 2018;72:e13208.

47 Rafrat M, Hemmati S, Jafarabadi M. Pomegranate ( *Punica granatum L.*) peel hydroalcoholic extract supplementation reduces pain and improves clinical symptoms of knee osteoarthritis: a randomized double-blind placebo controlled study. *Iran Red Crescent Med J* 2017;19.

48 Ghoochan N, Karandish M, Mowlia K, et al. The effect of pomegranate juice on clinical signs, matrix metalloproteinases and antioxidant status in patients with knee osteoarthritis. *J Sci Food Agric* 2016;96:4377–81.

49 Khadem Haghigian M, Alipoor B, Malek Mahdavi A, et al. Effects of sesame seed supplementation on inflammatory factors and oxidative stress biomarkers in patients with knee osteoarthritis. *Acta Med Iran* 2015;53:207–13.

50 Ebrahimi AA, Nikniaz Z, Ostadrahimi A, et al. The effect of *Elaeagnus angustifolia L.* whole fruit and medulla powder on women with osteoarthritis of the knee: a randomized controlled clinical trial. *Eur J Integr Med* 2014;6:672–9.

51 Eftekhar Sadat B, Khadem Haghigian M, Alipoor B, et al. Effects of sesame seed supplementation on clinical signs and symptoms in patients with knee osteoarthritis. *Int J Rheum Dis* 2013;16:578–82.

52 Paramdeep G. Efficacy and tolerability of ginger (*Zingiber officinale*) in patients of osteoarthritis of knee. *Indian J Physiol Pharmacol* 2013;57:177–83.

53 Schumacher HR, Pullman-Moor S, Gupta SR, et al. Randomized double-blind crossover study of the efficacy of a tart cherry juice blend in treatment of osteoarthritis (oa) of the knee. *Osteoarthritis Cartilage* 2013;21:1035–41.

54 Kuehl KS, Elliot DL, Sleigh AE, et al. Efficacy of Tart cherry juice to reduce inflammation biomarkers among women with inflammatory osteoarthritis (oa). *Journal of Food Studies* 2012;1:14–25.

55 Frestedt JL, Kuskowski MA, Zenk JL. A natural seaweed derived mineral supplement (Aquaminn F) for knee osteoarthritis: a randomised, placebo controlled pilot study. *Nutr J* 2009;8:7.

56 Essouiri J, Harzy T, Benchaicha N, et al. Effectiveness of argan oil consumption on knee osteoarthritis symptoms: a randomized controlled clinical trial. *Curr Rheumatol Rev* 2017;13:231–5.

57 Hashempur MH, Sadrneshin S, Mosavat SH, et al. Green tea (*Camellia sinensis*) for patients with knee osteoarthritis: a randomized open-label active-controlled clinical trial. *Clin Nutr* 2018;37:85–90.

58 Moré M, Gruenwald J, Pohl U, et al. A Rosa canina - *Urtica dioica* - *Harpagophytum procumbens/zezheri* Combination Significantly Reduces Gonarthrosis Symptoms in a Randomized, Placebo-Controlled Double-Blind Study. *Planta Med* 2017;83:1384–91.

59 Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital (stand. powder of a subspecies of *Rosa canina* fruits), reduces pain and improves general wellbeing in patients with osteoarthritis--a double-blind, placebo-controlled, randomised trial. *Phytomedicine* 2004;11:383–91.

60 Warholm O, Skaar S, Hedman E, et al. The effects of a standardized herbal remedy made from a subtype of *Rosa canina* in patients with osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. *Curr Ther Res Clin Exp* 2003;64:21–31.

61 Arjmandi BH, Ormsbee LT, Elam ML, et al. A combination of *Scutellaria baicalensis* and *Acacia catechu* extracts for short-term symptomatic relief of joint discomfort associated with osteoarthritis of the knee. *J Med Food* 2014;17:707–13.

62 Myers SP, O'Connor J, Fitton JH, et al. A combined phase I and II open label study on the effects of a seaweed extract nutrient complex on osteoarthritis. *Biologics* 2010;4:33–44.

63 Karimifar M, Soltani R, Hajhashemi V, et al. Evaluation of the effect of *Elaeagnus angustifolia* alone and combined with *Boswellia thurifera* compared with ibuprofen in patients with knee osteoarthritis: a randomized double-blind controlled clinical trial. *Clin Rheumatol* 2017;36:1849–53.

64 Oben J, Enonchong E, Kothari S, et al. Phellodendron and citrus extracts benefit joint health in osteoarthritis patients: a pilot, double-blind, placebo-controlled study. *Nutr J* 2009;8:38.

65 Piscoya J, Rodriguez Z, Bustamante SA, et al. Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species *Uncaria guianensis*. *Inflamm Res* 2001;50:442–8.

66 Hunt S, Stebbings S, McNamara D. An open-label six-month extension study to investigate the safety and efficacy of an extract of *Artemisia annua* for managing pain, stiffness and functional

limitation associated with osteoarthritis of the hip and knee. *N Z Med J* 2016;129:97–102.

67 Christensen R, Bartels EM, Astrup A, et al. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (oa) patients: a meta-analysis of randomized controlled trials. *Osteoarthritis Cartilage* 2008;16:399–408.

68 Madhu K, Chanda K, Saji MJ. Safety and efficacy of Curcuma longa extract in the treatment of painful knee osteoarthritis: a randomized placebo-controlled trial. *Inflammopharmacology* 2013;21:129–36.

69 Farid R, Rezaieyazdi Z, Mirfeizi Z, et al. Oral intake of purple passion fruit peel extract reduces pain and stiffness and improves physical function in adult patients with knee osteoarthritis. *Nutr Res* 2010;30:601–6.

70 Singh JA, Noorbaloochi S, MacDonald R, et al. Chondroitin for osteoarthritis. *Cochrane Database Syst Rev* 2015;1:CD005614.

71 Gallagher B, Tjoumakaris FP, Harwood MI, et al. Chondroprotection and the prevention of osteoarthritis progression of the knee: a systematic review of treatment agents. *Am J Sports Med* 2015;43:734–44.

72 Lei M, Guo C, Wang D, et al. The effect of probiotic Lactobacillus casei Shirota on knee osteoarthritis: a randomised double-blind, placebo-controlled clinical trial. *Benef Microbes* 2017;8:697–703.

73 Neves M, Gualano B, Roschel H, et al. Beneficial effect of creatine supplementation in knee osteoarthritis. *Med Sci Sports Exerc* 2011;43:1538–43.

74 Scorei R, Mitrut P, Petrisor I, et al. A double-blind, placebo-controlled pilot study to evaluate the effect of calcium fructoborate on systemic inflammation and dyslipidemia markers for middle-aged people with primary osteoarthritis. *Biol Trace Elem Res* 2011;144:253–63.

75 Roy BD, de Beer J, Harvey D, et al. Creatine monohydrate supplementation does not improve functional recovery after total knee arthroplasty. *Arch Phys Med Rehabil* 2005;86:1293–8.

76 Bansal H, Bansal A, Agrawal D, et al. Chondroprotection using naturally occurring mineral supplementation formula in degenerative osteoarthritis of the knees. *J Stem Cells* 2014;9:65–76.

77 Towheed TE, Maxwell L, Anastassiades TP, et al. Glucosamine therapy for treating osteoarthritis. *Cochrane Database Syst Rev* 2005;2:CD002946.

78 Clegg DO, Reda DJ, Harris CL, et al. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;354:795–808.

79 Diao N, Yang B, Yu F. Effect of vitamin D supplementation on knee osteoarthritis: a systematic review and meta-analysis of randomized clinical trials. *Clin Biochem* 2017;50:1312–6.

80 Gao X-R, Chen Y-S, Deng W. The effect of vitamin D supplementation on knee osteoarthritis: a meta-analysis of randomized controlled trials. *Int J Surg* 2017;46:14–20.

81 Hussain S, Singh A, Akhtar M, et al. Vitamin D supplementation for the management of knee osteoarthritis: a systematic review of randomized controlled trials. *Rheumatol Int* 2017;37:1489–98.

82 Bastick AN, Belo JN, Runhaar J, et al. What are the prognostic factors for radiographic progression of knee osteoarthritis? A meta-analysis. *Clin Orthop Relat Res* 2015;473:2969–89.

83 Bischoff-Ferrari HA, Orav EJ, Egli A, et al. Recovery after unilateral knee replacement due to severe osteoarthritis and progression in the contralateral knee: a randomised clinical trial comparing daily 2000 IU versus 800 IU vitamin D. *RMD Open* 2018;4:e000678.

84 Arden NK, Cro S, Sheard S, et al. The effect of vitamin D supplementation on knee osteoarthritis, the video study: a randomised controlled trial. *Osteoarthritis Cartilage* 2016;24:1858–66.

85 Jin X, Jones G, Cicuttini F, et al. Effect of vitamin D supplementation on tibial cartilage volume and knee pain among patients with symptomatic knee osteoarthritis: a randomized clinical trial. *JAMA* 2016;315:1005–13.

86 McAlindon T, LaValley M, Schneider E, et al. Effect of vitamin D supplementation on progression of knee pain and cartilage volume loss in patients with symptomatic osteoarthritis: a randomized controlled trial. *JAMA* 2013;309:155–62.

87 Medhi B, Manpreet S, Deonis X. Comparative clinical trial of paracetamol alone and vitamin C and E as an add on therapy in patients suffering from primary knee osteoarthritis. *JK Science* 2012;14:38–42.

88 Colker CM, Swain M, Lynch L, et al. Effects of a milk-based bioactive micronutrient beverage on pain symptoms and activity of adults with osteoarthritis: a double-blind, placebo-controlled clinical evaluation. *Nutrition* 2002;18:388–92.

89 Jonas WB, Rapoza CP, Blair WF. The effect of niacinamide on osteoarthritis: a pilot study. *Inflamm Res* 1996;45:330–4.

90 Flynn MA, Irvin W, Krause G. The effect of folate and cobalamin on osteoarthritic hands. *J Am Coll Nutr* 1994;13:351–6.

91 Perego J, Wilder FV. The effects of vitamin C supplementation on incident and progressive knee osteoarthritis: a longitudinal study. *Public Health Nutr* 2011;14:709–15.

92 Wilder FV, Leaverton PE, Rogers MW, et al. Vitamin supplements and radiographic knee osteoarthritis: the Clearwater osteoarthritis study. *J Musculoskelet Res* 2009;12:85–93.

93 McAlindon TE, Felson DT, Zhang Y, et al. Relation of dietary intake and serum levels of vitamin D to progression of osteoarthritis of the knee among participants in the Framingham study. *Ann Intern Med* 1996;125:353–9.

94 Gioxari A, Kaliora AC, Marantidou F, et al. Intake of  $\omega$ -3 polyunsaturated fatty acids in patients with rheumatoid arthritis: a systematic review and meta-analysis. *Nutrition* 2018;45:114–24.

95 Cramp F, Hewlett S, Almeida C, et al. Non-Pharmacological interventions for fatigue in rheumatoid arthritis. *Cochrane Database Syst Rev* 2013;8:CD008322.

96 Abdulrazaq M, Innes JK, Calder PC. Effect of  $\omega$ -3 polyunsaturated fatty acids on arthritic pain: A systematic review. *Nutrition* 2017;39:457–66.

97 Rajaei E, Mowla K, Ghorbani A, et al. The effect of omega-3 fatty acids in patients with active rheumatoid arthritis receiving DMARDs therapy: double-blind randomized controlled trial. *Glob J Health Sci* 2015;8:18–25.

98 Reed GW, Leung K, Rossetti RG, et al. Treatment of rheumatoid arthritis with marine and botanical oils: an 18-month, randomized, and double-blind trial. *Evid Based Complement Alternat Med* 2014;2014:857456.

99 Arborelius M, Konttinen YT, Nordström DC, et al. Gly-X-Y repeat sequences in the treatment of active rheumatoid arthritis. *Rheumatol Int* 1999;18:129–35.

100 Sköldstam L, Börjesson O, Kjällman A, et al. Effect of six months of fish oil supplementation in stable rheumatoid arthritis. A double-blind, controlled study. *Scand J Rheumatol* 1992;21:178–85.

101 Tulleken JE, Limburg PC, Muskiet FA, et al. Vitamin E status during dietary fish oil supplementation in rheumatoid arthritis. *Arthritis Rheum* 1990;33:1416–9.

102 van der Tempel H, Tulleken JE, Limburg PC, et al. Effects of fish oil supplementation in rheumatoid arthritis. *Ann Rheum Dis* 1990;49:76–80.

103 Cleland LG, French JK, Betts WH, et al. Clinical and biochemical effects of dietary fish oil supplements in rheumatoid arthritis. *J Rheumatol* 1988;15:1471–5.

104 Magaro M, Altomonte L, Zoli A, et al. Influence of diet with different lipid composition on neutrophil chemiluminescence and disease activity in patients with rheumatoid arthritis. *Ann Rheum Dis* 1988;47:793–6.

105 Kremer JM, Jubiz W, Michalek A, et al. Fish-Oil fatty acid supplementation in active rheumatoid arthritis. A double-blinded, controlled, crossover study. *Ann Intern Med* 1987;106:497–503.

106 Lindqvist HM, Gjertsson I, Eneljung T, et al. Influence of Blue Mussel (*Mytilus edulis*) Intake on Disease Activity in Female Patients with Rheumatoid Arthritis: The MIRA Randomized Cross-Over Dietary Intervention. *Nutrients* 2018;10:481.

107 Fu Y, Li G, Zhang X, et al. Lipid extract from hard-shelled mussel (*Mytilus coruscus*) improves clinical conditions of patients with rheumatoid arthritis: a randomized controlled trial. *Nutrients* 2015;7:625–45.

108 Cleland LG, Caughey GE, James MJ. Reduction of cardiovascular risk factors with longterm fish oil treatment in early rheumatoid arthritis. *J Rheumatol* 2006;33:1973–9.

109 Podas T, Nightingale JMD, Oldham R, et al. Is rheumatoid arthritis a disease that starts in the intestine? A pilot study comparing an elemental diet with oral prednisolone. *Postgrad Med J* 2007;83:128–31.

110 Sköldstam L, Hagfors L, Johansson G. An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis. *Ann Rheum Dis* 2003;62:208–14.

111 Hafström I, Ringertz B, Spångberg A, et al. A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens. *Rheumatology* 2001;40:1175–9.

112 Sarzi-Puttini P, Comi D, Boccazzini L, et al. Diet therapy for rheumatoid arthritis. A controlled double-blind study of two different dietary regimens. *Scand J Rheumatol* 2000;29:302–7.

113 Holst-Jensen SE, Pfeiffer-Jensen M, Monsrud M, et al. Treatment of rheumatoid arthritis with a peptide diet: a randomized, controlled trial. *Scand J Rheumatol* 1998;27:329–36.

114 Nenonen MT, Helve TA, Rauma AL, et al. Uncooked, lactobacilli-rich, vegan food and rheumatoid arthritis. *Br J Rheumatol* 1998;37:274–81.

115 Kavanagh R, Workman E, Nash P, et al. The effects of elemental diet and subsequent food reintroduction on rheumatoid arthritis. *Br J Rheumatol* 1995;34:270–3.

116 Haugen MA, Kjeldsen-Kragh J, Førre O. A pilot study of the effect of an elemental diet in the management of rheumatoid arthritis. *Clin Exp Rheumatol* 1994;12:275–9.

117 van de Laar MA, van der Korst JK. Food intolerance in rheumatoid arthritis. I. A double blind, controlled trial of the clinical effects of elimination of milk allergens and azo dyes. *Ann Rheum Dis* 1992;51:298–302.

118 Panush RS, Carter RL, Katz P, et al. Diet therapy for rheumatoid arthritis. *Arthritis Rheum* 1983;26:462–71.

119 Sundqvist T, Lindström F, Magnusson KE, et al. Influence of fasting on intestinal permeability and disease activity in patients with rheumatoid arthritis. *Scand J Rheumatol* 1982;11:33–8.

120 Sköldstam L, Larsson L, Lindström FD. Effect of fasting and lactovegetarian diet on rheumatoid arthritis. *Scand J Rheumatol* 1979;8:249–55.

121 Abendroth A, Michalsen A, Lüdtke R, et al. Changes of intestinal microflora in patients with rheumatoid arthritis during fasting or a Mediterranean diet. *Fortschr Komplementmed* 2010;17:307–13.

122 McKellar G, Morrison E, McEntegart A, et al. 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* 2007;66:1239–43.

123 Adam O, Beringer C, Kless T, et al. Anti-Inflammatory effects of a low arachidonic acid diet and fish oil in patients with rheumatoid arthritis. *Rheumatol Int* 2003;23:27–36.

124 Fraser DA, Thoen J, Djoseland O, et al. Serum levels of interleukin-6 and dehydroepiandrosterone sulphate in response to either fasting or a ketogenic diet in rheumatoid arthritis patients. *Clin Exp Rheumatol* 2000;18:357–62.

125 Denissov LN, Sharafetdinov K, Samsonov MA. On the medicinal efficacy of dietetic therapy in patients with rheumatoid arthritis. *Int J Clin Pharmacol Res* 1992;12:19–25.

126 McDougall J, Bruce B, Spiller G, et al. Effects of a very low-fat, vegan diet in subjects with rheumatoid arthritis. *J Altern Complement Med* 2002;8:71–5.

127 Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, et al. Vegetarian diet for patients with rheumatoid arthritis--status: two years after introduction of the diet. *Clin Rheumatol* 1994;13:475–82.

128 Dawczynski C, Dittrich M, Neumann T, et al. Docosahexaenoic acid in the treatment of rheumatoid arthritis: A double-blind, placebo-controlled, randomized cross-over study with microalgae vs. sunflower oil. *Clin Nutr* 2018;37:494–504.

129 Ghavipour M, Sotoudeh G, Tavakoli E, et al. Pomegranate extract alleviates disease activity and some blood biomarkers of inflammation and oxidative stress in rheumatoid arthritis patients. *Eur J Clin Nutr* 2017;71:92–6.

130 Javadi F, Ahmadzadeh A, Eghtesadi S, et al. The effect of quercetin on inflammatory factors and clinical symptoms in women with rheumatoid arthritis: a double-blind, randomized controlled trial. *J Am Coll Nutr* 2017;36:9–15.

131 Hemmati A, Rajaei E, Houshmand G. Study the effects of anti-inflammatory curcumex capsules containing three plants (ginger, curcumin and black pepper) in patients with active rheumatoid arthritis. *The IIOAB Journal* 2016;7:389–92.

132 Javadi F, Eghtesadi S, Ahmadzadeh A, et al. The effect of quercetin on plasma oxidative status, C-reactive protein and blood pressure in women with rheumatoid arthritis. *Int J Prev Med* 2014;5:293–301.

133 Willich SN, Rossnagel K, Roll S, et al. Rose hip herbal remedy in patients with rheumatoid arthritis - a randomised controlled trial. *Phytomedicine* 2010;17:87–93.

134 Bae S-C, Jung W-J, Lee E-J, et al. Effects of antioxidant supplements intervention on the level of plasma inflammatory molecules and disease severity of rheumatoid arthritis patients. *J Am Coll Nutr* 2009;28:56–62.

135 Li EK, Tam L-S, Wong CK, et al. Safety and efficacy of Ganoderma lucidum (lingzhi) and San Miao San supplementation in patients with rheumatoid arthritis: a double-blind, randomized, placebo-controlled pilot trial. *Arthritis Rheum* 2007;57:1143–50.

136 Gheita TA, Kenawy SA. Effectiveness of Nigella sativa oil in the management of rheumatoid arthritis patients: a placebo controlled study. *Phytother Res* 2012;26:1246–8.

137 Kamal E, Kaddam LA, Dahawi M, et al. Gum arabic fibers decreased inflammatory markers and disease severity score among rheumatoid arthritis patients, phase II trial. *Int J Rheumatol* 2018;2018:4197537.

138 Kumar G, Srivastava A, Sharma SK, et al. Efficacy & safety evaluation of Ayurvedic treatment (Ashwagandha powder & Siddh Makardhwaj) in rheumatoid arthritis patients: a pilot prospective study. *Indian J Med Res* 2015;141:100–6.

139 Matsuno H, Nakamura H, Katayama K, et al. Effects of an oral administration of glucosamine-chondroitin-querceitin glucoside on the synovial fluid properties in patients with osteoarthritis and rheumatoid arthritis. *Biosci Biotechnol Biochem* 2009;73:288–92.

140 Aqaeeinezhad Rudbane SM, Rahmadel S, Abdollahzadeh SM, et al. The efficacy of probiotic supplementation in rheumatoid arthritis: a meta-analysis of randomized, controlled trials. *Inflammopharmacology* 2018;26:67–76.

141 Mohammed AT, Khattab M, Ahmed AM, et al. The therapeutic effect of probiotics on rheumatoid arthritis: a systematic review and meta-analysis of randomized control trials. *Clin Rheumatol* 2017;36:2697–707.

142 Zamani B, Farshbaf S, Golkar HR, et al. Synbiotic supplementation and the effects on clinical and metabolic responses in patients with rheumatoid arthritis: a randomised, double-blind, placebo-controlled trial. *Br J Nutr* 2017;117:1095–102.

143 Wilkinson TJ, Lemmey AB, Jones JG, et al. Can creatine supplementation improve body composition and objective physical function in rheumatoid arthritis patients? A randomized controlled trial. *Arthritis Care Res* 2016;68:729–37.

144 Abdollahzad H, Alipour B, Aghdashli MA, et al. Coenzyme Q10 supplementation in patients with rheumatoid arthritis: are there any effects on cardiovascular risk factors? *Eur J Integr Med* 2015;7:534–9.

145 Mirtaheri E, Gargari BP, Kolahi S, et al. Effects of alpha-lipoic acid supplementation on inflammatory biomarkers and matrix metalloproteinase-3 in rheumatoid arthritis patients. *J Am Coll Nutr* 2015;34:310–7.

146 Alavi A, Goodfellow L, Fraser O, et al. A double-blind, randomized, placebo-controlled study to explore the efficacy of a dietary plant-derived polysaccharide supplement in patients with rheumatoid arthritis. *Rheumatology* 2011;50:1111–9.

147 Aryaeian N, Shahram F, Djalali M, et al. Effect of conjugated linoleic acid, vitamin E and their combination on lipid profiles and blood pressure of Iranian adults with active rheumatoid arthritis. *Vasc Health Risk Manag* 2008;4:1423–32.

148 Nakamura H, Masuko K, Yudoh K, et al. Effects of glucosamine administration on patients with rheumatoid arthritis. *Rheumatol Int* 2007;27:213–8.

149 Marcora S, Lemmey A, Maddison P. Dietary treatment of rheumatoid cachexia with beta-hydroxy-beta-methylbutyrate, glutamine and arginine: a randomised controlled trial. *Clin Nutr* 2005;24:442–54.

150 Mattingly PC, Mowat AG. Zinc sulphate in rheumatoid arthritis. *Ann Rheum Dis* 1982;41:456–7.

151 Simkin PA. Oral zinc sulphate in rheumatoid arthritis. *Lancet* 1976;2:539–42.

152 Bepler CR, Rogers FB. A double blind study using manganese against placebo in rheumatoid arthritis. *Am J Med Sci* 1957;234:459–61.

153 Rastmanesh R, Abargouei AS, Shadman Z, et al. A pilot study of potassium supplementation in the treatment of hypokalemic patients with rheumatoid arthritis: a randomized, double-blinded, placebo-controlled trial. *J Pain* 2008;9:722–31.

154 Rasker JJ, Kardaun SH. Lack of beneficial effect of zinc sulphate in rheumatoid arthritis. *Scand J Rheumatol* 1982;11:168–70.

155 Franco AS, Freitas TQ, Bernardo WM, et al. Vitamin D supplementation and disease activity in patients with immune-mediated rheumatic diseases: a systematic review and meta-analysis. *Medicine* 2017;96:e7024.

156 Batooei M, Tahamoli-Roudsari A, Basiri Z, et al. Evaluating the effect of oral N-acetylcysteine as an adjuvant treatment on clinical outcomes of patients with rheumatoid arthritis: a randomized, double blind clinical trial. *Rev Recent Clin Trials* 2018;13:132–8.

157 Huang S-C, Wei JC-C, Wu DJ, et al. Vitamin B(6) supplementation improves pro-inflammatory responses in patients with rheumatoid arthritis. *Eur J Clin Nutr* 2010;64:1007–13.

158 Nourmohamm I, Athari-Nik S, Vafa MR, et al. Effects of antioxidant supplementations on oxidative stress in rheumatoid arthritis patients. *J Biol Sci* 2009;10:63–6.

159 Chiang E-PI, Selhub J, Bagley PJ, et al. Pyridoxine supplementation corrects vitamin B6 deficiency but does not improve inflammation in patients with rheumatoid arthritis. *Arthritis Res Ther* 2005;7:R1404–11.

160 Edmonds SE, Winyard PG, Guo R, et al. Putative analgesic activity of repeated oral doses of vitamin E in the treatment of rheumatoid

arthritis. Results of a prospective placebo controlled double blind trial. *Ann Rheum Dis* 1997;56:649–55.

161 Helmy M, Shohayeb M, Helmy MH, et al. Antioxidants as adjuvant therapy in rheumatoid disease. A preliminary study. *Arzneimittelforschung* 2001;51:293–8.

162 Jalili M, Kolahi S, Aref-Hosseini S-R, et al. Beneficial role of antioxidants on clinical outcomes and erythrocyte antioxidant parameters in rheumatoid arthritis patients. *Int J Prev Med* 2014;5:835–40.

163 van Vugt RM, Rijken PJ, Rietveld AG, et al. Antioxidant intervention in rheumatoid arthritis: results of an open pilot study. *Clin Rheumatol* 2008;27:771–5.

164 Rodríguez-Huerta MD, Trujillo-Martín MM, Rúa-Figueroa Íñigo, et al. Healthy lifestyle habits for patients with systemic lupus erythematosus: a systemic review. *Semin Arthritis Rheum* 2016;45:463–70.

165 Curado Borges M, de Miranda Moura Dos Santos F, Weiss Telles R, et al. Omega-3 fatty acids, inflammatory status and biochemical markers of patients with systemic lupus erythematosus: a pilot study. *Rev Bras Reumatol Engl Ed* 2017;57:526–34.

166 Arriens C, Hynan LS, Lerman RH, et al. Placebo-Controlled randomized clinical trial of fish oil's impact on fatigue, quality of life, and disease activity in systemic lupus erythematosus. *Nutr J* 2015;14:82.

167 Bello KJ, Fang H, Fazeli P, et al. Omega-3 in SLE: a double-blind, placebo-controlled randomized clinical trial of endothelial dysfunction and disease activity in systemic lupus erythematosus. *Rheumatol Int* 2013;33:2789–96.

168 Wright SA, O'Prey FM, McHenry MT, et al. A randomised interventional trial of omega-3-polyunsaturated fatty acids on endothelial function and disease activity in systemic lupus erythematosus. *Ann Rheum Dis* 2008;67:841–8.

169 Duffy EM, Meenagh GK, McMillan SA, et al. The clinical effect of dietary supplementation with omega-3 fish oils and/or copper in systemic lupus erythematosus. *J Rheumatol* 2004;31:1551–6.

170 Westberg G, Tarkowski A. Effect of MaxEPA in patients with SLE. A double-blind, crossover study. *Scand J Rheumatol* 1990;19:137–43.

171 Lozovoy MAB, Simão ANC, Morimoto HK, et al. Fish oil n-3 fatty acids increase adiponectin and decrease leptin levels in patients with systemic lupus erythematosus. *Mar Drugs* 2015;13:1071–83.

172 del Pino-Sedeño T, Trujillo-Martín MM, Ruiz-Irastorza G, et al. Effectiveness of nonpharmacologic interventions for decreasing fatigue in adults with systemic lupus erythematosus: a systematic review. *Arthritis Care Res* 2016;68:141–8.

173 Yuen HK, Cunningham MA. Optimal management of fatigue in patients with systemic lupus erythematosus: a systematic review. *Ther Clin Risk Manag* 2014;10:775–86.

174 Davies RJ, Lomer MCE, Yeo SI, et al. Weight loss and improvements in fatigue in systemic lupus erythematosus: a controlled trial of a low glycaemic index diet versus a calorie restricted diet in patients treated with corticosteroids. *Lupus* 2012;21:649–55.

175 Shah M, Kavanagh A, Coyle Y, et al. Effect of a culturally sensitive cholesterol lowering diet program on lipid and lipoproteins, body weight, nutrient intakes, and quality of life in patients with systemic lupus erythematosus. *J Rheumatol* 2002;29:2122–8.

176 Minami Y, Hirabayashi Y, Nagata C, et al. Intakes of vitamin B6 and dietary fiber and clinical course of systemic lupus erythematosus: a prospective study of Japanese female patients. *J Epidemiol* 2011;21:246–54.

177 Minami Y, Sasaki T, Arai Y, et al. Diet and systemic lupus erythematosus: a 4 year prospective study of Japanese patients. *J Rheumatol* 2003;30:747–54.

178 Karlson EW, Daltroy LH, Lew RA, et al. The relationship of socioeconomic status, race, and modifiable risk factors to outcomes in patients with systemic lupus erythematosus. *Arthritis Rheum* 1997;40:47–56.

179 Shamekh Z, Amani R, Habibagahi Z, et al. A randomized, double-blind, placebo-controlled clinical trial examining the effects of green tea extract on systemic lupus erythematosus disease activity and quality of life. *Phytother Res* 2017;31:1063–71.

180 Singgih Wahono C, Diah Setyorini C, Kalim H, et al. Effect of *Curcuma xanthorrhiza* Supplementation on Systemic Lupus Erythematosus Patients with Hypovitamin D Which Were Given Vitamin D<sub>3</sub> towards Disease Activity (SLEDAI), IL-6, and TGF-β1 Serum. *Int J Rheumatol* 2017;2017:7687053.

181 Al-Kushi AG, Azzeb FS, Header EA, et al. Effect of vitamin D and calcium supplementation in patients with systemic lupus erythematosus. *Saudi J Med Med Sci* 2018;6:137–42.

182 Karimzadeh H, Shirzadi M, Karimifar M. The effect of vitamin D supplementation in disease activity of systemic lupus erythematosus patients with vitamin D deficiency: a randomized clinical trial. *J Res Med Sci* 2017;22:4.

183 Andreoli L, Dall'Ara F, Piantoni S, et al. A 24-month prospective study on the efficacy and safety of two different monthly regimens of vitamin D supplementation in pre-menopausal women with systemic lupus erythematosus. *Lupus* 2015;24:499–506.

184 Macfarlane TV, Abbood HM, Pathan E, et al. Relationship between diet and ankylosing spondylitis: a systematic review. *Eur J Rheumatol* 2018;5:45–52.

185 Jenks K, Stebbings S, Burton J, et al. Probiotic therapy for the treatment of spondyloarthritis: a randomized controlled trial. *J Rheumatol* 2010;37:2118–25.

186 Kristensen S, Schmidt EB, Schlemmer A, et al. Beneficial effect of n-3 polyunsaturated fatty acids on inflammation and analgesic use in psoriatic arthritis: a randomized, double blind, placebo-controlled trial. *Scand J Rheumatol* 2018;47:27–36.

187 Madland TM, Björkjaer T, Brunborg LA, et al. Subjective improvement in patients with psoriatic arthritis after short-term oral treatment with seal oil. A pilot study with double blind comparison to soy oil. *J Rheumatol* 2006;33:307–10.

188 Veale DJ, Torley HI, Richards IM, et al. A double-blind placebo controlled trial of Efamol marine on skin and joint symptoms of psoriatic arthritis. *Br J Rheumatol* 1994;33:954–8.

189 Kharaeva Z, Gostova E, De Luca C, et al. Clinical and biochemical effects of coenzyme Q(10), vitamin E, and selenium supplementation to psoriasis patients. *Nutrition* 2009;25:295–302.

190 Doerfler B, Allen TS, Southwood C, et al. Medical nutrition therapy for patients with advanced systemic sclerosis (Mnt pass): a pilot intervention study. *JPEN J Parenter Enteral Nutr* 2017;41:678–84.

191 Ortiz-Santamaría V, Puig C, Soldevilla C, et al. Nutritional support in patients with systemic sclerosis. *Peumatol Clin* 2014;10:283–7.

192 Ostojic P, Damjanov N. Effects of micronutrient antioxidants (alpha-tocopherol and ascorbic acid) on skin thickening and lung function in patients with early diffuse systemic sclerosis. *Rheumatol Int* 2011;31:1051–4.

193 Herrick AL, Hollis S, Schofield D, et al. A double-blind placebo-controlled trial of antioxidant therapy in limited cutaneous systemic sclerosis. *Clin Exp Rheumatol* 2000;18:349–56.

194 Hulshof MM, Bouwes Bavinck JN, Bergman W, et al. Double-Blind, placebo-controlled study of oral calcitriol for the treatment of localized and systemic scleroderma. *J Am Acad Dermatol* 2000;43:1017–23.

195 Andrés M, Sivera F, Falzon L, et al. Dietary supplements for chronic gout. *Cochrane Database Syst Rev* 2014;10:CD010156.

196 Moi JHY, Sriranganathan MK, Edwards CJ, et al. Lifestyle interventions for chronic gout. *Cochrane Database Syst Rev* 2013;5:CD010039.

197 Dalbeth N, Ames R, Gamble GD, et al. Effects of skim milk powder enriched with glycomacropeptide and G600 milk fat extract on frequency of gout flares: a proof-of-concept randomised controlled trial. *Ann Rheum Dis* 2012;71:929–34.

198 Yu XN, Wu HY, Deng YP, et al. "Yellow-dragon Wonder-fruit Formula" for hyperuricemia in gout patients with dampness-heat pouring downward pattern: a pilot randomized controlled trial. *Trials* 2018;19:551.

199 Stamp LK, O'Donnell JL, Frampton C, et al. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. *Arthritis Rheum* 2013;65:1636–42.

200 Azzeb FS, Al-Hebshi AH, Al-Essimii HD, et al. Vitamin C supplementation and serum uric acid: a reaction to hyperuricemia and gout disease. *PharmaNutrition* 2017;5:47–51.

201 Bradley M, Golden E. Powdered meal replacement - can they benefit overweight patients with concomitant conditions exacerbated by obesity? *Current Therapeutic Research* 1990;47:429–36.

202 Jäntti J, Isomäki H, Laitinen O, et al. Linoleic acid treatment in inflammatory arthritis. *Int J Clin Pharmacol Ther Toxicol* 1985;23:89–91.

203 Sutton AJ, Duval SJ, Tweedie RL, et al. Empirical assessment of effect of publication bias on meta-analyses. *BMJ* 2000;320:1574–7.

204 Thomas S, Browne H, Mobasher A, et al. What is the evidence for a role for diet and nutrition in osteoarthritis? *Rheumatology* 2018;57:iv61–74.

205 Gwinnutt JM, Wieczorek M, Cavalli G, et al. Effects of physical exercise and body weight on disease-specific outcomes of people with rheumatic and musculoskeletal diseases (RMDs): systematic reviews and meta-analyses informing the 2021 EULAR

recommendations for lifestyle improvements in people with RMDs.  
*RMD Open* 2022;8:e002168.

206 Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet* 1991;338:899–902.