

Dietary interventions for rheumatoid arthritis (Review)

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[Intervention Review]

Dietary interventions for rheumatoid arthritis

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ABSTRACT

Background

The question of what potential benefits and harms are associated with certain dietary regimes used in rheumatoid arthritis is an important one for many patients and health care providers.

Objectives

To assess the effectiveness and safety of dietary interventions in the treatment of rheumatoid arthritis.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL)(*The Cochrane Library*, issue 1 2008), MEDLINE, EMBASE, AMED, CINAHL and reference lists of relevant articles (up to January 2008), and contacted authors of included articles.

Selection criteria

Randomised controlled trials (RCTs) or controlled clinical trials (CCTs) where the effectiveness of dietary manipulation was evaluated. Dietary supplement studies (including fish oil supplements) were not included.

Data collection and analysis

Two authors independently selected trials for inclusion, assessed the internal validity of included trials and extracted data. Investigators were contacted to obtain missing information.

Main results

Fourteen RCTs and one CCT, with a total of 837 patients, were included. Due to heterogeneity of interventions and outcomes, baseline imbalance and inadequate data reporting, no overall effects were calculated. A single trial with a moderate risk of bias found that fasting, followed by 13 months on a vegetarian diet, may reduce pain (mean difference (MD) on a 0 to 10 scale -1.89, 95% confidence interval (CI) -3.62 to -0.16), but not physical function or morning stiffness immediately after intervention. Another single trial with a moderate risk of bias found that a 12-week Cretan Mediterranean diet may reduce pain (MD on a 0 to 100 scale -14.00, 95% CI -23.6 to -4.37), but not physical function or morning stiffness immediately after intervention. Two trials compared a 4-week elemental diet with an ordinary diet and reported no significant differences in pain, function or stiffness. Due to inadequate data reporting, the effects of vegan and elimination diets are uncertain. When comparing any dietary manipulation with an ordinary diet we found a significantly

higher total drop-out of 10% (risk difference (RD) 0.10, 95% CI 0.02 to 0.18), higher treatment-related drop-out of 5% (RD 0.05, 95% CI -0.03 to 0.14) and a significantly higher weight loss (weighted mean difference -3.23, 95% CI -4.79 to -1.67 kg) in the diet groups compared to the control groups.

Authors' conclusions

The effects of dietary manipulation, including vegetarian, Mediterranean, elemental and elimination diets, on rheumatoid arthritis are still uncertain due to the included studies being small, single trials with moderate to high risk of bias. Higher drop-out rates and weight loss in the groups with dietary manipulation indicate that potential adverse effects should not be ignored.

PLAIN LANGUAGE SUMMARY

The effect of diets on rheumatoid arthritis

A review of the effect of diets for people with rheumatoid arthritis was conducted by researchers in the Cochrane Collaboration. After searching for all relevant studies, they found 15 studies done by other researchers. Their findings are summarised below.

What is rheumatoid arthritis and what diets have been tried?

Rheumatoid arthritis is a disease in which the body's immune system attacks the lining of the joints. Usually, the joints of the hands and feet are affected first. Joints will become swollen, stiff and painful. There is no cure for RA at present, so treatments aim to relieve pain and stiffness, and improve the ability to move.

To improve symptoms, some people have tried to change what they eat by following a wide variety of special diets. Some people will try to not eat anything for 7 to 10 days to see if it makes a difference. But usually people will try to limit or increase only certain foods. The most common diets tried are vegetarian or vegan, Mediterranean, 'elemental', or elimination diets. Vegan diets do not include meat, fish, eggs and milk products, while some vegetarian diets allow eggs and milk. Mediterranean diets usually include a small amount of meat, more fish, more fruits and vegetables and olive oil. Elemental diets are usually liquid diets that contain nutrients that are broken down to make digestion easier. Elimination diets are used to find foods that might be the cause of symptoms. People usually eliminate foods they think are causing symptoms, and then add in the foods one at a time and see which ones cause symptoms.

What the research says

It is uncertain whether diets improve pain, stiffness and the ability to move better.

Instead, diets may be difficult to stick to, and people may lose weight on these diets even though they did not plan to.

- people who follow special diets may lose 3 kg (6 ½ pounds) more than people who do not follow special diets, even though they did not plan to.

BACKGROUND

Description of the condition

Rheumatoid arthritis is a chronic autoimmune disease that affects between 0.3% and 1.0% of the general population and has a significant impact on patients' physical, emotional and social functioning (Uhlig 2005; Uhlig 2007). Although new drugs have shown promising effects, they are also associated with significant side effects.

Description of the intervention

For decades patients have used different diets to try to improve the symptoms of rheumatoid arthritis and dietary manipulation is still widely used today. Dietary changes may influence the body through several different mechanisms, such as decreasing the inflammatory process, increasing antioxidant levels, changing the lipid profile, and possibly altering the balance of intestinal bacterial flora. The common dietary regimes used by people with rheumatoid arthritis include vegetarian or vegan, Mediterranean, 'elemental' and 'elimination' diets. The vegetarian diet can be either strictly vegan, vegan with or without gluten, or lacto-ovo-vegetarian (including dairy products and eggs).

How the intervention might work

Possible mechanisms of action for dietary manipulation to produce health benefits may include the consequent changes in intestinal flora, and the elimination of possible offending foods. Vegan type diets are also higher in antioxidants and this may be a causal factor in reduced pain and stiffness (Kjeldsen-Kragh 1991). The Mediterranean diet and especially the Cretan diet are high in fruit, vegetables, cereals and legumes, low in red meat, and high in fish and olive oils. These diets could have a protective effect due to their high levels of unsaturated fat and antioxidants (Sköldstam 2003).

The 'elimination' diet is another type of dietary regime whereby patients remove one or more potentially offending food items. These food items are then gradually reintroduced to find out whether any of them aggravate symptoms (Darlington 1986). Elimination therapy is based on the belief that a food antigen plays a role in the pathogenesis of a disease and that its elimination from the diet should result in symptom improvement (Kavanagh 1995).

The 'elemental' diet is believed to be hypoallergenic, and comprises the simplest formulations of amino acids, glucose, medium-chain triglycerides, vitamins and minerals. It is industrially pre-made, is pre-packed in sachets and is used to replace one or more meals a day.

Why it is important to do this review

Previous reviews have reported promising effects of dietary manipulation in the management of rheumatoid arthritis, but emphasise the need for more and better research before any firm conclusions can be drawn (Müller 2001; Rennie 2003). The possible risks or adverse effects of dietary manipulation have not been emphasised in these reviews. Since many people with rheumatoid arthritis may already be compromised nutritionally due to difficulty buying or preparing meals, they may be especially vulnerable to the adverse effects of additional diet restrictions. Therefore, the question of what benefits or harms may be associated with different dietary regimes in rheumatoid arthritis remains an important one for many patients and health care providers.

OBJECTIVES

To assess the effectiveness and safety of dietary interventions in the treatment of rheumatoid arthritis.

The following main comparisons were made.

1. Dietary manipulation versus usual diet.
2. Comparison of different dietary regimes.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were eligible if they were randomised controlled trials or cluster-randomised trials. Controlled clinical trials (CCTs) using inadequate generation of sequence (i.e. case record numbers, alternation, date of admission, date of birth etc.) when allocating patients to different groups were also eligible.

Types of participants

Patients with rheumatoid arthritis, as defined by the American College of Rheumatology (ACR) (Arnett 1988) or other acceptable criteria.

Types of interventions

Studies included at least one treatment group in which a dietary intervention was applied. We included any dietary manipulation, such as elimination diets, diets described as Mediterranean or Cretan, vegetarian, acid-base balance and fasting. Dietary supplement studies were not included (including fish oil supplements). The use of medication, alternative therapies or lifestyle changes was to be comparable in the groups studied. The comparison included other interventions (including other dietary interventions), placebo interventions or usual diet.

Types of outcome measures

Primary outcomes

The primary outcomes considered were pain, functional status, joint stiffness, fatigue and possible adverse effects (such as the number of withdrawals due to adverse events, unwanted weight loss, gastrointestinal symptoms and others).

Secondary outcomes

Secondary outcomes included health-related quality of life, medication use and other outcomes important for patients. We only considered outcomes measured with validated instruments.

Search methods for identification of studies

Electronic searches

We identified relevant studies by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, issue 1 2008), MEDLINE, EMBASE, AMED and CINAHL (up to January 2008), without using any language restrictions.

The search strategy set out in Appendix 1 was used in MEDLINE. We adapted similar search strategies to search the other databases.

Searching other resources

We also scanned the reference lists of included studies and relevant reviews to identify additional relevant trials. We contacted authors of included studies when the reported information was unclear and/or additional information was needed.

Data collection and analysis

Selection of studies

Two authors (SUO and MGB) independently screened the abstracts of all publications obtained from the searches. We retrieved all abstracts that at least one author considered relevant in full text. We resolved uncertainty or disagreement by discussion. When further information was needed, we contacted the authors of studies for clarification. We obtained and assessed all potentially eligible articles, based on the inclusion and exclusion criteria. Trials excluded after reading the full text reports are presented with reasons for exclusion in the table 'Characteristics of excluded studies'.

Assessment of risk of bias in included studies

In order to ensure that variation in effects was not caused by systematic errors in the study design or execution, two authors independently assigned each selected study to quality categories (i.e. assessment of risk of bias). We resolved uncertainty or disagreement by discussion. When further information was needed, we contacted the authors of studies for clarification. We used the following seven criteria.

1) Random generation of allocation

MET: Resulting sequences are unpredictable (explicitly stated use of either computer-generated random numbers, table of random numbers, drawing lots or envelopes, coin tossing, shuffling cards, or throwing dice).

UNCLEAR: Vague statement that the study was randomised but not describing the generation of the allocation sequence.

NOT MET: Explicit description of inadequate generation of sequence (i.e. using case record numbers, alternation, date of admission, date of birth) or clear that allocation concealment was not used.

2) Concealment of allocation

MET: Indicates adequate concealment of the allocation (for example, by telephone randomisation or use of consecutively numbered, sealed, opaque envelopes).

UNCLEAR: Indicates uncertainty about whether the allocation was adequately concealed (for example, where the method of concealment is not known).

NOT MET: Indicates that the allocation was definitely not adequately concealed (for example, open random number lists or quasi-randomisation such as alternate days, odd/even date of birth, or hospital number) or explicit statement that the allocation was not random.

3) Outcome assessment

MET: Assessor unaware of the assigned treatment when collecting outcome measures.

UNCLEAR: Blinding of assessor not reported and cannot be verified by contacting investigators.

NOT MET: Assessor aware of the assigned treatment when collecting outcome measures.

4) Co-intervention

MET: Interventions other than diets avoided, controlled or used similarly across comparison groups.

UNCLEAR: Use of interventions other than diets not reported and cannot be verified by contacting the investigators.

NOT MET: Dissimilar use of interventions other than diets across comparison groups, i. e. differences in the care provided to the participants in the comparison groups other than the intervention under investigation.

5) Losses to follow-up

MET: Losses to follow-up less than 20% and equally distributed between comparison groups.

UNCLEAR: Losses to follow-up not reported.

NOT MET: Losses to follow-up greater than 20% in at least one of the groups.

6) Blinding of provider or patient

MET: The patient or the provider or both were blinded to the intervention.

UNCLEAR: Blinding not reported.

NOT MET: The patient and the provider were not blinded to the intervention.

7) Intention-to-treat

MET: Intention-to-treat analysis performed or possible with data provided.

UNCLEAR: Intention-to-treat not reported, and cannot be verified by contacting the investigators.

NOT MET: Intention-to-treat analysis not done and not possible

for review authors to calculate independently.

We grouped studies as those with a low risk of bias or high internal validity (6 to 7 criteria MET), those with a moderate risk of bias (3 to 5 criteria MET), and those with a high risk of bias or low internal validity (less than 3 criteria MET). We also collected and documented other methodological issues such as baseline comparability, sample size etc.

Data synthesis

We made comparisons separately according to type of intervention and control group. Due to heterogeneity in the interventions and outcome measures and inadequate data reporting, we calculated no overall clinical effects. Although most articles of the included trials reported within-group differences between baseline and end of study, only between-group analyses are provided in the present review. Thus, for studies which reported data sufficiently for recalculation of between-group differences, we recalculated and presented results as mean differences (MD) or risk ratios (RR) with 95% confidence intervals (CI). For possible adverse effects (total drop-outs and treatment-related drop-outs) we calculated risk differences (RD) and 95% CI by pooling trials comparing any diet manipulation with ordinary diet.

Grading of evidence

In addition, we used the grading system described and recommended by the Musculoskeletal Group (Tugwell 2004):

Platinum: a published systematic review that has at least two individual randomised controlled trials each satisfying following:

- sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome;
- blinding of patients and assessors for outcomes;
- handling of withdrawals: > 80% follow up (imputations based on methods such as Last Observation Carried Forward (LOCF) are acceptable);
- concealment of treatment allocation.

Gold: at least one randomised clinical trial meeting all of the following criteria for the major outcome(s) as reported:

- sample sizes of at least 50 per group - if these do not find a statistically significant difference, they are adequately powered for a 20% relative difference in the relevant outcome;
- blinding of patients and assessors for outcomes;
- handling of withdrawals > 80% follow up (imputations based on methods such as LOCF are acceptable);
- concealment of treatment allocation.

Silver: randomised trials that do not meet the above criteria. Silver ranking would also include evidence from at least one study of non-randomised cohorts that did and did not receive the therapy, or evidence from at least one high quality case-control study. A

randomised trial with a 'head-to-head' comparison of agents would be considered silver-level ranking, unless a reference was provided for comparison of one of the agents to placebo, and showing at least a 20% relative difference.

Bronze: the bronze ranking is given to evidence if at least one high quality case series without controls (including simple before/after studies in which patients act as their own control) or if the conclusion is derived from expert opinion based on clinical experience, without reference to any of the foregoing (for example, argument from physiology, bench research or first principles).

Clinical relevance tables

Clinical relevance tables are compiled under additional tables to improve the readability of the review. For dichotomous outcomes, we calculated the numbers needed to treat. Continuous outcome tables are also presented under additional tables. Absolute benefit is calculated as the improvement in the intervention group minus the improvement in the control group, in the original units. We calculated the relative difference in the change from baseline as the absolute benefit divided by the baseline mean of the control group.

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The electronic searches identified 1029 studies, of which 967 were clearly not relevant, and 62 were retrieved in full text. Forty-seven of these were excluded, thus 15 trials were included in this review.

Included studies

Fourteen RCTs, with a total of 707 participants and one CCT (McKellar 2007) with 130 participants, published between 1979 and 2007, were included in this review. One was undertaken in the USA, eight in the Nordic countries, four in the UK, one in Italy and one in the Netherlands.

Comparisons

Two of the studies (Kjeldsen-Kragh 1991; Sköldstam 1979) compared 7 to 10 days of fasting followed by a vegetarian diet with an ordinary diet. Two studies (Holst-Jensen 1998; Kavanagh 1995) compared an elemental diet with an ordinary diet, two studies compared an elemental diet with a well-mixed soup (Haugen 1994) or oral prednisolone 15 mg/day (Podas 2007), while another study (van de Laar 1992) compared two different elemental diets. Another two studies (Hafström 2001; Nenonen 1998) compared vegan diets with an ordinary diet. Two studies (McKellar 2007;

Sköldstam 2003) compared a Mediterranean diet with an ordinary diet or healthy eating, and one study (Darlington 1986) compared an elimination diet with ordinary food. Finally, three studies (Hansen 1996; Panush 1983; Sarzi-Puttini 2000) compared different special diet regimens ('Dong-diet', 'Graastener-diet' and 'hypoallergenic-diet') with 'usual' or 'well-balanced' diets.

Participants

Four studies included patients with rheumatoid arthritis diagnosed according to the 1987 ACR criteria (Hafström 2001; Holst-Jensen 1998; Sköldstam 2003; van de Laar 1992), while seven other studies included patients with rheumatoid arthritis diagnosed according to the ARA criteria (Hansen 1996; Kavanagh 1995; Nenonen 1998; Podas 2007; Sarzi-Puttini 2000; Sköldstam 1979). Three studies included patients with 'definite' rheumatoid arthritis diagnosed according to other criteria (Darlington 1986; Kjeldsen-Kragh 1991; McKellar 2007; Panush 1983). In eleven of the studies, between 70% and 100% of the participants were women. In one study (Panush 1983) 34.6% of the participants were women, while one study did not provide information about the sex distribution (Hafström 2001). The participants' mean age varied between 49.5 years (Holst-Jensen 1998) and 58.5 years (Sköldstam 2003). One study did not provide information regarding the participants' age (Darlington 1986).

Outcomes

In most studies outcomes were measured by the end of the interventions, ranging from 4 weeks (Kavanagh 1995) to 13 months (Kjeldsen-Kragh 1991), while in three studies outcomes were also measured at one to six months follow-up (Holst-Jensen 1998; Nenonen 1998; van de Laar 1992). Generally, many outcome measures were used. The median number of outcome measures was six (ranging from 1 to 10). One study (Sköldstam 2003) explicitly defined four outcomes as primary outcome measures and two others (Hafström 2001; Podas 2007) defined one outcome measure (ACR-20 response criteria, i.e. a 20% improvement in tender and swollen joint counts plus a 20% improvement in three of the following five core measures: patient and physical global assessments, pain, functional status and an acute phase reactant). Pain and duration of morning stiffness was the most frequently used outcome measure (10 studies), number of tender and/or swollen joints in nine and physical functioning by Health Assessment Questionnaire (HAQ) in eight studies (outlined in detail in the 'Characteristics of included studies' table).

Ten trials reported on weight loss. One study (van de Laar 1992) did not report the reasons for drop-outs or any other adverse effects.

Risk of bias in included studies

Three of the authors (MGB or KBH and GS) independently assessed 15 studies using seven criteria for validity, resulting in 105 separate assessments. There was initially agreement in 77 (73%)

of the assessments, and disagreement between the authors in 28 (27%). The disagreements were easily resolved by discussion.

Twelve studies met three, four or five criteria of internal validity, and were assessed to have a moderate risk of bias. Three studies were assessed to have a high risk of bias. Kavanagh 1995 and Sköldstam 1979 met two criteria of internal validity and one study was a CCT (McKellar 2007). Four of the studies were described as 'double-blind' (Haugen 1994; Panush 1983; Sarzi-Puttini 2000; van de Laar 1992), i.e. both providers and patients were blinded, while in one study only patients were blinded (Darlington 1986). The studies by Kjeldsen-Kragh 1991, Panush 1983 and Sköldstam 2003 were initially assessed as 'unclear' for 'random generation of allocation' and 'concealment of allocation', but were later graded as 'met' following correspondence with the authors. The study by Sköldstam 2003 was initially assessed as 'unclear' for 'outcome assessment', but was later graded as 'not met' following correspondence with the contact author.

Effects of interventions

Most articles of the included trials reported within-group differences between baseline and end of study. Since the purpose of a RCT is to compare outcomes between groups, we only present between-group analyses in the present review.

Main comparison (I) - Dietary manipulations versus usual diet

I.1 Seven to ten days with fasting followed by vegetarian diet compared with ordinary diet

Two trials with a total of 79 patients were included in this comparison. Kjeldsen-Kragh 1991 (moderate risk of bias) compared 7 to 10 days of fasting followed by 3.5 months of a vegan diet and nine months with a lacto-vegetarian diet with usual diet. Sköldstam 1979 (high risk of bias) compared 7 to 10 days of fasting followed by nine weeks on a lacto-vegetarian diet with usual diet.

Pain

In the study of Kjeldsen-Kragh 1991, the mean difference (MD) in favour of the intervention group at three weeks follow-up was -1.06 (95% confidence interval (CI) -2.32 to 0.20; $P = 0.10$) and -1.89 (95% CI -3.62 to -0.16; $P = 0.03$) at 13 months follow-up. Sköldstam 1979 found a mean difference in favour of the intervention group in change from baseline to nine weeks follow-up at -0.9 (95% CI -2.98 to 1.18; $P = 0.40$). In both studies pain was assessed on a 0 to 10 visual analogue scale (VAS).

Physical function

The mean difference in Health Assessment Questionnaire (HAQ) score (0 to 3) in favour of the intervention group was -0.07 (95% CI -0.46 to 0.32; $P = 0.72$) at three weeks follow-up, and -0.07 (95% CI -0.48 to 0.34; $P = 0.74$) at 13 months follow-up in the study of Kjeldsen-Kragh 1991. Sköldstam 1979 did not report on physical function.

Stiffness

In the study of [Kjeldsen-Kragh 1991](#) the mean difference in morning stiffness (hours) in favour of the intervention group was -0.85 (95% CI -1.71 to 0.01; P = 0.05) at three weeks follow-up and -1.08 (95% CI -2.23 to 0.07; P = 0.07) at 13 months follow-up. [Sköldstam 1979](#) found a mean difference (on a 0 to 10 scale) in favour of the intervention group in change from baseline to nine weeks follow-up at -0.70 (95% CI -3.09 to 1.69; P = 0.57).

Body weight

In the study of [Kjeldsen-Kragh 1991](#) there was an imbalance between the groups at baseline (intervention group mean body weight 70.0 kg versus control group mean 66.9 kg). After 13 months, the intervention group had lost 4.6 kg, while the control group remained stable. Thus, although the intervention group had a significantly higher weight loss than the control group, there was no significant difference between the groups after 13 months (MD 1.5 kg, 95% CI -8.80 to 5.80; P = 0.69). In the study of [Sköldstam 1979](#) there was also a small difference between the groups at baseline (intervention group mean body weight 71.0 kg versus control group mean 68.5 kg). After nine weeks the intervention group had lost more weight than the control group; mean difference in change from baseline to nine weeks follow-up was -3.20 (95% CI -4.83 to -1.57; P < 0.001).

Possible adverse effects

[Kjeldsen-Kragh 1991](#) reported that the total number of drop-outs was 10 (37%) in the intervention group and nine (35%) in the control group, while the number of treatment-related drop-outs was five (18.5%) patients in the intervention group and seven (27%) in the control group. [Sköldstam 1979](#) reported that one (6%) patient withdrew in the diet group due to side effects and another experienced temporary side effects. See also [Table 1](#).

Table 1. Clinical relevance table - 7 to 10 days fasting and 13 months vegetarian diet versus usual diet

Outcome (scale)	No. of patients (no. of studies)	Control Baseline mean	Wt Absolute change (95%CI)	Relative change(%) (95%CI)	Statistical Sig-nificance	Level of evidence
Pain VAS (0 to 10, 0 is best)	34 (1)	4.73	19% lower (-16, -36)	43 % lower (-36, -82)	Yes	Silver
Morning stiffness (hours)	34 (1)	2.13 hours	-1.08 hours less [-2.23, 0.07]	50 % less (-3, 100)	Yes	Silver
HAQ score (0 to 3, 0 is best)	34 (1)	0.92	2% (-11, 16)	8% lower (-37, 52)	No	Silver

Table 1. Clinical relevance table - 7 to 10 days fasting and 13 months vegetarian diet versus usual diet (Continued)

Body weight	34 (1)	66.9 kg	1.5 kg fewer (-8.8 to 5.8)	2 lower (-13, 9)	No	Silver
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1.2 Vegan diet compared with ordinary diet

Two trials ([Hafström 2001](#) (moderate risk of bias); [Nenonen 1998](#) (moderate risk of bias)) with a total of 109 patients, compared 12 months with a vegan diet free of gluten ([Hafström 2001](#)) and three months with an uncooked vegan diet ([Nenonen 1998](#)) with an ordinary diet.

Pain

[Hafström 2001](#) did not report on pain separately, while [Nenonen 1998](#) reported that the VAS for pain at rest and on movement did not behave statistically differently in the intervention and control groups (data not reported).

Physical function

[Hafström 2001](#) did not report on function separately, while [Nenonen 1998](#) reported that the HAQ score did not behave statistically differently in the intervention and control groups (data not reported).

Stiffness

[Hafström 2001](#) did not report on stiffness separately, while [Nenonen 1998](#) reported that morning stiffness did not behave statistically differently in the intervention and control groups (data not reported).

Body weight

[Hafström 2001](#) did not report on body weight, while [Nenonen 1998](#) reported that “the intervention group lost weight, 9%, during the intervention, while the controls gained 1% of weight”. The difference between the groups was significant ($P = 0.0001$).

Thus, none of the studies provided data on pain, physical function, stiffness or body weight separately for meta-analysis. [Hafström 2001](#), however, measured improvement in signs and symptoms with the ACR 20 response criteria (i.e. a 20% improvement in tender and swollen joint counts plus a 20% improvement in three of the five following remaining core measures: patient and physical global assessments, pain, functional status, and an acute phase reactant) and found that the response rate was higher in the vegan group than in non-vegan group after three months (RR 5.89, 95% CI 0.78 to 44.47), after six months (RR 4.79, 95% CI 1.17 to 19.55) and after 12 months (end of intervention) (RR 8.91, 95% CI 1.24 to 64.30).

Possible adverse effects

In the study by [Hafström 2001](#) three (7.9%) patients in the intervention group and two (7.2%) in the control group dropped out. Furthermore, they reported that 22 (57.9%) of the patients in the vegan group and 25 (89.3%) in the non-vegan group completed at least nine months of their diet, but reasons for non-compliance are not reported. [Nenonen 1998](#) reported that half of the patients experienced adverse effects (nausea, diarrhoea) during the diet and stopped the experiment prematurely; three during the first days and eight after two months. See also [Table 2](#)

Table 2. Clinical relevance table - 12 months vegan (gluten free) diet versus usual diet

Outcome (scale)	No. of patients (no. of studies)	Control base-line	Absolute change	Relative change*	%	NNT(B) or NNT(H)	Statistical significance	Level of evidence
20% improvement in signs and symptoms (ACR 20)	61 (1)	4%	34% (13, 48)	800% (6300)	(0,	4 (2, 105)	Yes	Silver

1.3 Four weeks with elemental diet compared with ordinary diet

Two trials ([Holst-Jensen1998](#) (moderate risk of bias); [Kavanagh 1995](#) (high risk of bias)) with a total of 77 patients, compared four weeks with an elemental diet with an ordinary diet.

Pain

In the study of [Holst-Jensen1998](#) pain was measured on a 0 to 10 Numerical Rating Scale. At four weeks follow-up the median total pain score (defined as the sum of the following three pain scores: pain now, the worst pain during last week, the average pain level during the last week) was 12.0 in the intervention group and 16.0 in the control group (no significant difference). Neither at three nor six months follow-up were there any significant differences between the groups. [Kavanagh 1995](#) did not measure pain.

Physical function

No significant difference in HAQ score was found in the study of [Holst-Jensen1998](#) at four weeks follow-up (median score in the intervention group 0.88 compared to 1.32 in the control group), or at three and six months follow-up. In the study of [Kavanagh 1995](#) the mean functional score (type of scale not reported) was 9.7 and 10.5 in the intervention group and control group, respectively (no significant difference).

Stiffness

[Holst-Jensen1998](#) found no significant difference in the duration of morning stiffness at four weeks (median duration in the intervention group was 30 minutes compared to 75 minutes in the control group), or at three and six months follow up. [Kavanagh 1995](#) did not measure stiffness.

Body weight

At four weeks follow up [Kavanagh 1995](#) reported that the intervention group had lost more weight than the control group; mean difference -3.9 kg (95% CI -11.12 to 3.32; P = 0.29). [Holst-Jensen 1998](#) reported that body mass index was the variable with the most pronounced change and that there was significant between-group differences after four weeks.

Possible adverse effects

[Holst-Jensen1998](#) reported that two (13%) patients dropped out in the intervention group because of side effects, compared to none in the control group. Furthermore, they reported that "side effects were reported frequently and early in the course by ten of the thirteen (77%) patients that completed the intervention". In the trial of [Kavanagh 1995](#) none of the patients in the intervention group dropped out during the four-week period of elemental diet compared to two (8.7%) in the control group. In total 11 (45.8%) patients in the intervention group and 18 (78.3%) patients in the control group dropped out of the study, but the reasons for the drop-outs are not described. See also [Table 3](#).

Table 3. Clinical relevance table - 4 weeks elemental diet versus usual diet

Outcome (scale)	No. of patients (no. of studies)	Control Baseline mean	Wt Absolute Change (95%CI)	Relative Change(%)	Statistical Sig-nificance	Level of evidence
Functional score (no scale reported)	45 (1)	9.32	can not be calculated	9% less (-46, 30)	No	Silver
Body weight (kg)	45 (1)	67 kg	4 kg less (-11, 3]	6% lower (-17, 5)	No	Silver

Pain

1.4 Mediterranean diet compared with ordinary diet/healthy eating

We included one RCT ([Sköldstam 2003](#) (moderate risk of bias)) with a total of 56 patients and one CCT ([McKellar 2007](#) (high risk of bias)) with a total of 130 patients. [Sköldstam 2003](#) compared a 12-week Cretan Mediterranean diet with an ordinary diet, while [McKellar 2007](#) compared a six-week hands-on cooking course, backed up with written information, with written information only.

After 12 weeks [Sköldstam 2003](#) found a significant difference (P = 0.004) in pain VAS (0 to 100 mm) in favour of the intervention group; mean difference -14.00 (95% CI -23.63 to -4.37). [McKellar 2007](#) reported significant differences in favour of the intervention group in VAS pain scores (0 to 100) at three and six months follow up (P = 0.011 and 0.049, respectively). In the intervention group the median score was 50, both at baseline, three months and six months follow up. In the control group the median scores were 55 at baseline, 62 at three months and 63 at six months follow up.

Physical function

After 12 weeks Sköldstam 2003 reported a non-significant difference ($P = 0.16$) in HAQ score (0 to 3) in favour of the intervention group (MD -0.20, 95% CI -0.48 to 0.08). However, a significant difference ($P = 0.012$) in change from baseline to follow up in favour of the intervention group was reported. McKellar 2007 reported a significant difference in favour of the intervention group in HAQ score (0 to 3) at three months follow up ($P = 0.03$). In the intervention group the median score was 1.75 at baseline and 1.625 at three and six months follow up. In the control group the median score was 1.75 at baseline and 1.87 at three and six months follow up.

Stiffness

Sköldstam 2003 reported a non-significant difference ($P = 0.11$) in morning stiffness in favour of the intervention group; mean difference 26 minutes (95% CI -58.08 to 6.08). However, there were imbalances between the groups at baseline (intervention group mean 49 minutes versus control group mean 64). McKellar 2007 reported a significant difference in favour of the intervention group in early morning stiffness at six months follow-up ($P = 0.041$). In the intervention group the median morning stiffness was 30 minutes at baseline and three months and 15 minutes at six months follow-up. In the control group the median morning stiffness was

60 minutes at baseline and 30 minutes at three and six months follow-up. Thus, there was considerable imbalance between the groups at baseline.

Body weight

In the study of Sköldstam 2003 there was imbalance between the groups at baseline (intervention group mean 78.9 kg versus control group mean 73.0 kg). After 12 weeks the average body weight was still higher in the intervention group (mean 75.9 kg) than in the control group (mean 72.6 kg). However, the change from baseline was significantly higher in the intervention group than the control group ($P < 0.001$). McKellar 2007 reported that the intervention group lost weight (median 0.9 kg over the six-month period), whereas the control group showed a weight gain (median 3 kg). This difference was not statistically significant.

Possible adverse effects

Five patients were excluded from Sköldstam 2003. Two in the control group because of inactive disease at the baseline assessment and three in the intervention group because of lack of motivation, relapse of a rheumatoid pleuritis and dyspepsia. Thus, two (6.9%) of the 29 patients allocated to the diet group withdrew because of the treatment compared to none in the control group. McKellar 2007 did not report of any exclusions. See also Table 4.

Table 4. Clinical relevance table - 12 weeks Mediterranean diet versus usual diet

Outcome (scale)	No. of patients (no. of studies)	Control Baseline mean	Wt Absolute Change (95%CI)	Relative Change(%)	Statistical Sig-nificance	Level of evidence
Pain VAS (0 to 100, 0 is best)	51 (1)	31	14% lower (-24, -4)	45% lower (-77, -13)	Yes	Silver
Morning stiffness (minutes)	51 (1)	64	26 minutes less [-58, 6]	40% lower (-91, 9)	No	Silver
HAQ score (0 to 3, 0 is best)	51 (1)	0.8	7% lower (-16, 3)	25% lower (-60, 10)	No	Silver
Body weight (kg)	51 (1)	73 kg	3 kg more (-4, 11]	5% more (-5, 14)	No	Silver

them was significant”.

1.5 Elimination diet compared with ordinary diet

One trial (Darlington 1986 (moderate risk of bias)) with a total of 53 patients, compared six weeks of elimination diet with ordinary diet. Due to inadequate data reporting, no between-group analyses were possible. The authors concluded as follows: “When the dietary and placebo groups were compared the dietary group did better for all thirteen variables for which differences between

Possible adverse effects

In total eight patients defaulted too early for analysis, but group allocation and reasons for the drop-outs are not described. Other possible adverse effects were not reported.

1.6 Special diet regimens compared with 'usual' or 'well-

balanced' diets

Three trials ([Hansen 1996](#) (moderate risk of bias); [Panush 1983](#) (moderate risk of bias); [Sarzi-Puttini 2000](#) (moderate risk of bias)), with a total of 192 patients, were included in this comparison.

[Panush 1983](#) (moderate risk of bias) compared 10 weeks of a diet free of additives, preservatives, fruit, red meat, herbs and dairy products ('Dong diet') with a placebo diet. Pain and body weight were not reported, whereas there were no significant differences in walking speed (function) and morning stiffness (data not reported).

[Hansen 1996](#) (moderate risk of bias) compared six months with a diet adjusted for energy intake, fish-meal and antioxidants ('Graastener diet') with ordinary diet. After six months there were no significant differences in change in VAS pain (MD -0.40, 95% CI -0.89 to 0.09; P = 0.11), HAQ score (MD -0.01, 95% CI -0.23 to 0.21; P = 0.93) or duration of morning stiffness (MD -3.00 minutes, 95% CI -23.47 to 17.47; P = 0.77) between the groups. Body weight was not reported.

[Sarzi-Puttini 2000](#) (moderate risk of bias) compared 20 weeks of a hypoallergenic diet high in unsaturated fat and low in saturated fats with a well balanced diet. After six months on the diet there were no significant differences in VAS (0 to 100) pain (MD -2.80, 95% CI -13.33 to 7.73; P = 0.60), duration of morning stiffness (MD -5.20 minutes, 95% CI -27.59 to 17.19; P = 0.65) or body weight (MD 1.40, 95% CI -6.94 to 9.74; P = 0.74) between the groups. Physical function was not reported. See also [Table 5](#).

Table 5. Clinical relevance table - 20 weeks hypoallergenic diet versus well-balanced diet

Outcome (scale)	No. of patients (no. of studies)	Control Baseline mean	Wt solute (95%CI)	Ab-Change	Rela-tive Change(%) (95%CI)	Statistical Sig-nificance	Level evidence	of
Pain VAS (0 to 100, 0 is best)	42 (1)	44	3% (-13, 8)		6 (-30, 17)	No	Silver	
Morning stiff-ness (minutes)	42 (1)	51 minutes	5 minutes less [-28, 17]		10% less (-33, 54)	No	Silver	
Body weight (kg)	42 (1)	70 kg	1 kg more (-7, 10)		2% more (-10, 14)	No	Silver	

Possible adverse effects

[Panush 1983](#) reported that in total seven patients (21%) withdrew due to lack of interest or inability to comply, but group allocation and specific reasons for the drop-outs are not described. In the trial of [Hansen 1996](#) 28 patients (25.7%) dropped out of the study, 18 (33.3%) of them were allocated to the diet group and 10 (18.2%) to the control group. Eighteen of the drop-outs were related to the

treatment, but the group allocation was not reported. [Sarzi-Puttini 2000](#) reported that four patients (16%) in the control group and three patients (12%) in the intervention group dropped out, of which two (8%) in both groups were treatment-related.

Possible adverse effects when comparing any diet manipulation with ordinary diet

By pooling six of the ten studies comparing any diet manipulation

with an ordinary diet we found a significantly higher total drop-out rate in the diet group (risk difference (RD) 0.10, 95% CI 0.02 to 0.18 and relative risk (RR) 1.51, 95% CI 1.08 to 2.12). Five of the studies provided data on treatment-related drop-outs and the pooled risk difference was higher in the diet group, although not statistically significant (RD 0.05, 95% CI -0.03 to 0.14 and RR 1.56, 95% CI -0.72 to 3.37). Finally, eight of ten studies reported a significantly higher weight loss in the diet group compared with the ordinary diet group. Two studies (Hafström 2001; Hansen 1996) did not report on weight loss. Five studies provided data on body weight. However, in four of them the intervention group was heavier than the control group at baseline (Kjeldsen-Kragh 1991; Sarzi-Puttini 2000, Sköldstam 1979; Sköldstam 2003). Thus, by comparing changes from baseline to after intervention we found that the mean weight loss was 3.23 kg (95% CI 4.79 to 1.67) higher in the diet groups than in the control groups.

Main comparison (2) - comparison of different dietary manipulations

2.1 Four weeks with allergen-free diet versus allergen-restricted diet

One trial van de Laar 1992 (moderate risk of bias) with a total of 94 patients compared an allergen-free diet with an allergen-restricted diet containing only lactoproteins yellow dyes. After four weeks, no difference between the groups was found in morning stiffness, whereas the allergen-restricted group lost more weight (MD 1.10 kg, 95% CI 0.31 to 1.89; $P = 0.006$) than the allergen-free group. Pain and physical function were not reported.

Possible adverse effects

In total 16 patients (17%) dropped out during the diet period, reported to be equally distributed between the two groups. However, the reasons for drop-outs or any other adverse effects were not reported.

2.2 Three weeks with elemental diet versus a well-mixed blended soup

One trial Haugen 1994 (moderate risk of bias) with 17 patients was included. After three weeks on diet the authors reported no significant differences in pain, morning stiffness or body weight (data not provided). Physical function was not measured.

Possible adverse effects

Six of the patients (60%) in the elemental diet group reported diarrhoea compared to none in the control group.

2.3 Two weeks with elemental diet versus oral prednisolone 15 mg/day

One trial Podas 2007 (moderate risk of bias) with 30 patients was included. After two weeks no significant differences in pain, physical function, stiffness or body weight were reported between the groups. Median VAS pain values were 4.9 in the elemental group and 2.6 in the prednisolone group and median HAQ scores were 1.8 in the elemental group and 1.4 in the prednisolone group. Median duration of morning stiffness was 105 minutes in the elemental group and nine minutes in the prednisolone group, while median body weight was 64.2 kg in the elemental group and 73.9 kg in the prednisolone group.

Possible adverse effects

Three patients in the elemental diet group withdrew from the study; two found the elemental diet unpalatable and one had a deterioration of symptoms. In addition one patient receiving the elemental diet complained of constipation. No steroid treated patient withdrew during the study period.

DISCUSSION

Summary of main results

In this review we found 11 randomised controlled trials and one controlled clinical trial, with a total of 696 patients, which compared dietary manipulation with an ordinary diet. In addition, we identified three RCTs, with a total of 141 patients, which compared different types of dietary manipulation. Results from single trials with moderate risk of bias indicate that both fasting followed by a vegetarian diet and a Cretan Mediterranean diet may improve pain when compared to an ordinary diet. However, no effects were found for physical function, stiffness or other important outcomes. Two trials with a moderate risk of bias indicate no effect of elemental diet. The effects of vegan and elimination diets are uncertain. Higher drop-out rates and weight loss in the groups with manipulated diets indicate that potential adverse effects should not be ignored.

Overall completeness and applicability of evidence

Although some studies reported an improvement in some rheumatic symptoms, possible mechanisms of action are still unknown. Common denominators for most dietary interventions are an increase in fruits and vegetables and fibre, a reduction in saturated fat, calorie restriction and factors such as altered antioxidant levels, weight loss and allergies/intolerances, and have been proposed as possible mechanisms. It is therefore possible that simply changing from an unhealthy to a healthier diet during the study period could explain some of the positive changes in rheumatic

symptoms. Also, when a dietary intervention is compared to ordinary eating, one cannot exclude the possibility that the beneficial effects in subjective outcomes can be attributed to a placebo effect. Dietary manipulation is not for everybody, especially those at nutritional risk. The palatability and rigid regimens of some of these diets might reduce dietary intake. A more serious consequence of diet manipulation is the elimination of one or more food groups, which may lead to a potential risk of deficiency in several nutrients. For example, a strict vegan diet, without special diet planning, may cause deficiency in several vitamins and minerals, and protein. Not only does a strict dietary regime affect nutrition, but it is also difficult to maintain a social life when a special diet must be adjusted for. The safety of these diets is questionable and they are not recommended without consulting a clinical dietician. On the other hand, diets such as the Mediterranean regime include foods that most of us will aim to eat on a daily basis, such as moderate amounts of lean meat, unsaturated fats instead of saturated fats, plenty of fruits and vegetables, and fish daily. The diet is also nutritionally adequate and covers all the food groups. It is also recommended for people with heart disease and osteoporosis, and we know that people with rheumatoid arthritis are more prone to develop both (Solomon 2006; van Staa 2006).

Despite the fact that rheumatoid arthritis patients may be especially vulnerable to the adverse effects of diet restrictions, the possible risks are not particularly emphasised in the included trials. By comparing any manipulated diet with ordinary diet we found a 10% higher total drop-out rate and 5% higher treatment-related drop-outs in the diet groups (although this was not statistically significant). Seven of the ten studies included in this comparison also reported a significantly higher weight loss in the diet group and the pooled estimate from five of these studies showed a 3.2 kg higher weight loss. There is empirical evidence indicating that low body mass, loss of fat-free body mass and abnormal vitamin B6 status are associated with the severity of symptoms in rheumatoid arthritis (Arshad 2007; Chiang 2003; Munro 1997) and that some of these effects do not seem to be reversible, even with adequate treatment (Metsios 2007). There is even data indicating that a low body mass index is associated with a significantly increased risk of cardiovascular death (Kremers 2004). Thus, the potential harmful effects of weight loss and a low body mass index in rheumatoid arthritis patients should definitely not be ignored.

Potential biases in the review process

There are several limitations of the present review. The results are based on relatively small and most often single trials, which we assessed to have moderate or high risk of bias. Most of the trials employed many different outcome measures, increasing the probability of detecting significant differences in some of them by chance. On the other hand, because we have only focused on pain, physical function, stiffness and side effects (i.e. the predefined primary outcomes) there might be effects on important outcomes that are not reported in the present review. Small trials may also be under-

powered and thus increase the chance of not detecting clinically relevant differences. For example, in the study of Kjeldsen-Kragh 1991 the difference in morning stiffness was approximately one hour ($P = 0.07$) and in the study of Sköldstam 2003 the difference in morning stiffness was 26 minutes ($P = 0.11$). These results may indicate that clinically relevant differences were not statistically significant because of lack of statistical power. However, in the study of Sköldstam 2003 there were imbalances between the groups at baseline (intervention group mean 49 minutes versus control group mean 64), which illustrates the pitfalls associated with the analysis and interpretation of results from small trials. Also, the finding that in four of five studies that provided adequate data on body weight there were baseline differences in the same direction, underlines this problem. Two other studies also compared an ordinary diet with fasting followed by a vegetarian diet (Sköldstam 1979) and a Mediterranean diet (McKellar 2007), respectively. Since the validity of these trials was low, the results were given low weight. The studies of Kjeldsen-Kragh 1991 and Sköldstam 1979 also presented results for the fasting period separately. We have chosen not to emphasise these results because we considered fasting only as one element of the 'fasting-vegetarian' intervention and because fasting alone is not helpful unless there are lasting effects after patients start eating again.

Although all articles were randomised controlled trials or controlled clinical trials, many of them presented within-group analyses (baseline to end of study within groups) as the primary analysis. Since the purpose of a randomised controlled trial is to compare outcomes between groups, we only present between-group analyses in this review. Many studies therefore reported significant differences (within groups) which are not in concordance with the results presented in this review. Finally, the use of different outcome measures together with inadequate data reporting made quantitative data pooling, and thus a precise estimate of effects, impossible.

Since there is no 'gold standard' for assessing the internal validity of a trial, our approach can be discussed. For example, we considered blinding of providers and patients as recommended by the Cochrane Musculoskeletal Group, even where it was unlikely to be applicable when a strict diet regimen is compared to usual diet. However, even if blinding is not feasible, its absence may still be associated with bias. The beneficial effects of dietary manipulation, when compared to usual diet, may therefore in part be attributed to the placebo effect. Also, some empirical evidence suggests that review authors blinded to the names of authors, institutions and journals produce lower and more consistent scores than those who use open assessments (Jadad 1996), while other evidence does not show any effect of blinding on the results (Verhagen 1998). Because the number of trials in this review was relatively small, and we were familiar with most of the studies, we did not consider blinding.

AUTHORS' CONCLUSIONS

Implications for practice

The effects of dietary manipulation, including vegetarian, Mediterranean, elemental and elimination diets, are still uncertain due to the included studies in this review being small single trials with moderate to high risk of bias. There is some evidence that fasting followed by a vegetarian diet and a Cretan Mediterranean diet improve pain, but not stiffness and physical function, when compared to an ordinary diet. There is also some evidence that an elemental diet is not more effective than an ordinary diet. Few studies provided any long-term results or information on whether the experimental diet was used after the intervention period. Of concern is the finding that dietary manipulation may be associated with higher drop-out rates, which may suggest difficulty following the diet. Dietary manipulation may also be associated with weight loss, which can put patients at nutritional risk.

Implications for research

Given the fact that dietary manipulation is still widely used, there is a need for more and better research on dietary interventions for rheumatoid arthritis. New trials should be sufficiently powered, use a limited number of predefined outcome measures and provide long-term follow-up measurements. Possible adverse effects should be emphasised.

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van Staa TP, Geusens P, Bijlsma JW, Leufkens HG, Cooper C. Clinical assessment of the long-term risk of fracture in patients with rheumatoid arthritis. *Arthritis and Rheumatism* 2006;**54**:3104–12.

Verhagen 1998

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Darlington 1986

Methods	<p>RCT Random generation of allocation: UNCLEAR Concealment of allocation: UNCLEAR Co-interventions: UNCLEAR Losses to follow-up: MET Intention-to-treat: UNCLEAR Outcome assessment: MET Blinding of provider or patient: MET (patients blinded)</p>	
Participants	<p>Country: UK Number: 45 Age: Sex: 89% women Inclusion criteria: rheumatoid arthritis patients</p>	
Interventions	<p>Both groups started with 2 weeks washout period Intervention group (diet intervention): during the first week, the patients ate only foods which they tolerated. Other foods were then reintroduced one at a time. At first further foods unlikely to cause intolerance were reintroduced, then foods which often cause intolerance, and finally normal diet. Control group: 6 weeks with ordinary food before then also proceeding to the diet group</p>	
Outcomes	<p>a) Day and night pain (4-point scale) b) Average pain (VAS) c) Duration of morning stiffness (minutes) d) Grip strength e) Number of painful joints</p>	
Notes	Silver	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hafström 2001

Methods	<p>RCT</p> <p>Random generation of allocation: UNCLEAR</p> <p>Concealment of allocation: UNCLEAR</p> <p>Co-interventions: MET</p> <p>Losses to follow-up: MET</p> <p>Intention-to-treat: MET</p> <p>Outcome assessment: UNCLEAR</p> <p>Blinding of provider or patient: NOT MET</p>	
Participants	<p>Country: Sweden</p> <p>Number: 66</p> <p>Mean age 50 years</p> <p>Sex:</p> <p>Inclusion criteria:</p> <p>a) Rheumatoid arthritis according to the 1987 ACR criteria</p> <p>b) Disease duration at least 2 years</p> <p>c) Age between 20 and 69 years</p> <p>d) Not tried dietary manipulation earlier</p> <p>e) No history of food sensitivity or food allergy</p> <p>f) Active disease</p> <p>g) Stable doses of NSAIDs, daily dose of oral corticosteroids < 7.5 mg and DMARDs</p>	
Interventions	<p>For both groups the diet was introduced during an initial week of instruction in the theory and practical preparation of the diet in question by a dietician</p> <p>Intervention group: the patients ate a vegan diet free from gluten, which contained vegetables, root vegetables, nuts and fruits. Of cereals the diet contained buckwheat, millet, corn, rice and sunflower seeds. Sesame milk was a source of calcium.</p> <p>Control group: well-balanced diet (non-vegan diet) - 12 weeks with ordinary food</p> <p>Each patient was allowed to get advice and help in maintaining their respective diets from physicians, dieticians and nurses. Compliance was assessed by dietary intake records.</p>	
Outcomes	<p>Main outcome:</p> <p>ACR-20 response criteria</p> <p>Secondary outcome:</p> <p>Radiographic progression</p>	
Notes	Silver	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hansen 1996

Methods	RCT Random generation of allocation: UNCLEAR Concealment of allocation: UNCLEAR Co-interventions: MET Losses to follow-up: NOT MET Intention-to-treat: MET Outcome assessment: MET Blinding of provider or patient: NOT MET	
Participants	Country: Denmark Number: 109 Mean age: 57 years Sex: 74.6% women Inclusion criteria: a) Rheumatoid arthritis according to the 1988 ARA criteria, including a positive RF b) Active disease was defined by at least 2 of the following 3 criteria: 1) 4 swollen joints 2) Morning stiffness of 60 minutes or greater 3) ESR 28 mm/hour Exclusion criteria: Underweight patients and those with severe concomitant disorders	
Interventions	Intervention group: experimental diet - 6 months on the Graastener diet. The diet is composed of an energy intake adjusted to obtain near standard BMI, fat content 20% to 30% of total energy intake, 1.5 g protein per kg body weight, 800 g fresh fish per week. If necessary capsules of omega-3 fish oils were given. Nuts and beans were given to increase intake of antioxidants. Control group: the patients in the control group ate ordinary food for 6 months	
Outcomes	a) Tender/swollen joints (28-joint count) b) Pain intensity (VAS) c) Health Assessment Questionnaire (HAQ) d) Patients global assessment e) Physicians global assessment f) Acute phase reactant g) X-ray h) Duration of morning stiffness i) Concomitant medication	
Notes	Silver	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Haugen 1994

Methods	<p>RCT</p> <p>Random generation of allocation: UNCLEAR</p> <p>Concealment of allocation: UNCLEAR</p> <p>Co-interventions: MET</p> <p>Losses to follow-up: MET</p> <p>Intention-to-treat: UNCLEAR</p> <p>Outcome assessment: MET</p> <p>Blinding of provider or patient: MET</p>	
Participants	<p>Country: Norway</p> <p>Number: 20</p> <p>Age: mean 50 years</p> <p>Sex: 16 women; 4 men</p> <p>Inclusion criteria:</p> <p>a) Rheumatoid arthritis according to the ARA criteria</p> <p>Active disease was defined by at least 4 of the following 5 criteria:</p> <ol style="list-style-type: none"> 1) 6 tender and/or painful joints; 2) 3 swollen joints; 3) morning stiffness of 45 minutes or greater; 4) ESR 28 mm/hour; <p>b) stable doses of drug treatment.</p>	
Interventions	<p>Intervention group: experimental diet comprised an elemental diet, E028, for 3 weeks and 1 week with regular diet. The elemental diet was naturally and artificially flavoured with orange, blackcurrant, pineapple and tomato flavourings from which the patients could choose freely.</p> <p>Control group: the control group was served a well-mixed and blended soup for 3 weeks. They were served 2 different soups: one was made of meat, cod, shrimps, milk, fresh cream, cream of wheat, corn flour and maltodextrine. The second was made of milk and soy oil, and was flavoured with either orange juice, pineapple juice or blackcurrant squash.</p> <p>Both soups were prepared in the hospital kitchen and the patients were given a week's supply of frozen soup in portions of 360 kcal every week at the time of the clinical examination.</p>	
Outcomes	<p>Main outcome:</p> <ol style="list-style-type: none"> a) Joint count; Ritchie's articular index b) Grip strength c) Duration of morning stiffness d) Pain (VAS) e) ESR, CRP, Hb, albumin and erythrocyte count f) Global assessment (5-point scale) 	
Notes	Silver	
<i>Risk of bias</i>		
Item	Authors' judgement	Description

Haugen 1994 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Holst-Jensen 1998

Methods	<p>RCT</p> <p>Random generation of allocation: UNCLEAR</p> <p>Concealment of allocation: UNCLEAR</p> <p>Co-interventions: MET</p> <p>Losses to follow-up: MET</p> <p>Intention-to-treat: MET</p> <p>Outcome assessment: UNCLEAR</p> <p>Blinding of provider or patient: NOT MET</p>
Participants	<p>Country: Denmark</p> <p>Number: 30</p> <p>Median age 49.5 years</p> <p>Sex: 80% women</p> <p>Inclusion criteria:</p> <p>a) Rheumatoid arthritis according to the 1987 ACR criteria</p> <p>b) Disease duration at least 6 months.</p> <p>c) Age between 18 and 75 years</p> <p>Active disease was defined by at least 3 of the following 4 criteria:</p> <p>1) 6 tender and/or painful joints;</p> <p>2) 3 swollen joints;</p> <p>3) morning stiffness of 45 minutes or greater;</p> <p>4) ESR 28 mm/hour;</p> <p>d) stable doses of NSAIDs, daily dose of oral corticosteroids < 7.5 mg.</p>
Interventions	<p>Intervention group: the experimental group received a liquid elemental diet for 4 weeks. Water and soda water were allowed. The cartons contained hydrolysed soy protein, 15% of total energy, lipids 30% and carbohydrate 55% of total energy. The daily dosage of diet was calculated from recommended energy intake to sick adults of 30 kcal/kg body weight/day. The participants were allowed to call the nurse if any problem about the diet arose.</p> <p>Control group: the control group ate their regular food and were requested not to change food habits during the study</p>
Outcomes	<p>a) Duration of morning stiffness</p> <p>b) Health Assessment Questionnaire (HAQ)</p> <p>c) Number of swollen joints</p> <p>d) Pain intensity</p> <p>e) Joint tenderness</p> <p>f) General assessment of health</p> <p>g) ESR</p>
Notes	Silver

Holst-Jensen 1998 (Continued)

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Kavanagh 1995

Methods	RCT Random generation of allocation: UNCLEAR Concealment of allocation: UNCLEAR Co-interventions: MET Losses to follow-up: MET 0 to 4 weeks follow-up; NOT MET 8 to 24 weeks follow-up Intention-to-treat: UNCLEAR Outcome assessment: MET Blinding of provider or patient: NOT MET
Participants	Country: England Number: 47 Mean age: 45.6 years Sex: 78.7% women Inclusion criteria: ARA criteria Exclusion criteria: use of corticosteroids and disease-modifying anti-rheumatic drugs
Interventions	Intervention group: 4 weeks with elemental 028 (E028) and foods like chicken, fish, rice, carrots, runner beans and bananas. This period was followed by reintroduction of food. First foods unlikely to cause intolerance were introduced, followed by foods which more often cause intolerance. Foods were introduced one at a time at intervals no shorter than 2 days. If a foodstuff was suspected to cause worsening of joint pain or stiffness, it was eliminated from the diet. Control group: the patients in this group ingested 2 sachets of E028 daily in addition to their normal diet. They were encouraged to use the solution as a substitute.
Outcomes	a) Duration of morning stiffness b) Grip strength c) Functional score d) Ritchie articular index e) Thermographic joint score f) ESR and CRP
Notes	Silver

Risk of bias

Item	Authors' judgement	Description
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Kavanagh 1995 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Kjeldsen-Kragh 1991

Methods	RCT Random generation of allocation: MET Concealment of allocation: MET Co-interventions: MET Losses to follow-up: NOT MET Intention-to-treat: MET Outcome assessment: MET Blinding of provider or patient: NOT MET
Participants	Country: Norway Number: 53 Mean age 54.5 years Sex: 85% women Inclusion criteria: rheumatoid arthritis patients with 3 of the 4 following: a) 6 tender and/or painful joints; b) 3 swollen joints; c) morning stiffness of 45 minutes or greater; d) ESR 28 mm/hour.
Interventions	Intervention group: fasting for 7 to 10 days. The dietary intake during the fast consisted of herbal teas, garlic, vegetable broth, decoction of potatoes and parsley and juice extracts from carrots, beets and celery. Fruit juices were not allowed. After the fast the patients reintroduced a food item every second day. The patients were asked to have a diet free from gluten, meat, fish, eggs, dairy products, refined sugar or citrus fruits during the first 3.5 months. Salt, strong spices, preservatives, alcohol, tea and coffee were not allowed. After the first 3.5 months the patients were allowed to reintroduce milk, dairy products and gluten. Control group: the patients stayed for 4 weeks at a convalescent home and were recommended to eat ordinary food throughout the study
Outcomes	a) Global assessment (5-point scale) b) Ritchie index c) Number of tender and swollen joints d) Pain (VAS) e) Health Assessment Questionnaire (HAQ) f) Duration of morning stiffness
Notes	Silver

Risk of bias

Item	Authors' judgement	Description
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Kjeldsen-Kragh 1991 (Continued)

Allocation concealment?	Yes	Graded as 'met' after correspondence with the author
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McKellar 2007

Methods	CCT Random generation of allocation: NOT MET Concealment of allocation: NOT MET Co-interventions: MET Losses to follow-up: MET Intention-to-treat: MET Outcome assessment: UNCLEAR Blinding of provider or patient: NOT MET
Participants	Country: Scotland, UK Number: 130 Mean age: 54 years Sex: 100% women Inclusion criteria: rheumatoid arthritis patients
Interventions	Intervention group: a 6-week cookery course (with emphasis on a Mediterranean-type diet) delivered by nutritionists. The patients attended a weekly 2-hour cookery class and received a folder with written information on a Mediterranean-type diet, healthy eating and recipes. Control group: control patients received readily available written information on healthy eating only.
Outcomes	a) Tender and swollen joints count b) Patient global and pain score (VAS) c) Duration of early morning stiffness (EMS) d) DAS28 e) HAQ score f) Erythrocyte sedimentation rate (ESR) g) C reactive protein h) Interleukin 6 (IL6)
Notes	Silver

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	No	C - Inadequate

Nenonen 1998

Methods	<p>RCT Random generation of allocation: UNCLEAR Concealment of allocation: UNCLEAR Co-interventions: MET Losses to follow-up: MET Intention-to-treat: MET Outcome assessment: MET Blinding of provider or patient: NOT MET</p>	
Participants	<p>Country: Finland Number: 43 Mean age: 53 years Sex: 86% wome Inclusion criteria: rheumatoid arthritis patients diagnosed with the ARA criteria: a) Chronic and active RA (Steinbrocker's functional class II-III) b) > 5 tender and/or painful joints c) > 3 swollen joints d) CRP > 10 ml/l e) ESR > 20 mm/hour</p>	
Interventions	<p>Intervention group: 3 months with living food, an uncooked vegan diet rich in lactobacilli. The patients received all components of their diet from a specialised kitchen in packed forms. The diet does not contain any animal products, raffinated substances or added salt. The items were soaked, sprouted, fermented, blended or dehydrated. Compliance was followed by daily interviews, dietary records and by analysing their daily urinary sodium excretion. Control group: the patients in this group ate an ordinary diet in their homes.</p>	
Outcomes	<p>a) Composite index after Paulus b) DAS c) Subjective assessments of rheumatic pain, swelling of joints, morning stiffness, ability to move and general impression on modified VAS scales</p>	
Notes	<p>Silver</p>	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Panush 1983

Methods	RCT Random generation of allocation: MET Concealment of allocation: MET Co-interventions: MET Losses to follow-up: NOT MET Intention-to-treat: MET Outcome assessment: MET Blinding of provider or patient: MET	
Participants	Country: USA Number: 33 Mean age: 55 years Sex: 34.6 % women Inclusion criteria: rheumatoid arthritis patients with at least 3 of the following: a) 6 tender and/or painful joints; b) 3 swollen joints; c) morning stiffness of 45 minutes or greater; d) ESR 28 mm/hour.	
Interventions	Intervention group: experimental diet - during a 10-week intervention period the patients were served a diet free from: dairy products, sardines, turkey, red meat, tomatoes, fruits, alcohol, hot spices, herbs, garlic, vinegar and additives. Fish was permitted. Of other food categories they were only allowed to eat egg whites, vegetable oil, soybean margarine, oatmeal, cream of wheat or grits, sugar, maple and corn syrup, coffee, non-herb tea and soda water. Control group: placebo diet - during a 10-week intervention period this group was served a diet free from: sour cream, ice milk, cheddar cheese, turkey, cabbage, brussel sprouts, cauliflower, bananas, strawberries, corn flakes, colas and vanilla.	
Outcomes	a) Duration of morning stiffness b) Number of tender joints c) Number of swollen joints d) Grip strength e) Walk time 15 metres f) Patient assessment (5-point scale) g) Examiner assessment (5-point scale) The authors note that 183 variables were analysed.	
Notes	Silver	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	MET

Podas 2007

Methods	<p>RCT Random generation of allocation: UNCLEAR Concealment of allocation: UNCLEAR Co-interventions: MET Losses to follow-up: MET Intention-to-treat: MET Outcome assessment: MET Blinding of provider or patient: NOT MET</p>	
Participants	<p>Country: UK Number: 30 Mean age: 50 years Sex: 73% women Inclusion criteria: patients with newly diagnosed or established active rheumatoid arthritis (using the revised ARA criteria). Active rheumatoid arthritis was defined by any combination of 3 or more of the following criteria: 3 or more swollen joints, 6 or more tender joints, morning stiffness of longer than 45 minutes and an erythrocyte sedimentation rate (ESR) of more than 28 mm in the first hour.</p>	
Interventions	<p>Intervention group: liquid elemental diet E028 (86 kcal and 2.5 g protein/100 ml) of orange and pineapple flavour as their only source of nutrition for 2 weeks and free access to bottled water. Control group: oral prednisolone (15 mg) was given daily for 2 weeks while the patients ate a normal diet.</p>	
Outcomes	<p>ACR-20 response criteria were defined as primary end point Secondary outcomes included: a) duration of morning stiffness (EMS); b) pain on a 10 cm VAS scale; c) the Ritchie articular index (RAI) which grades joint tenderness (0 to 3) over 63 joints; d) 16 swollen joint score (63 joints); e) HAQ; f) global patient and physician assessment scores on a 5-grade scale (much worse, worse, same, better, much better); g) ESR, C-reactive protein (CRP).</p>	
Notes	<p>Silver</p>	
<p><i>Risk of bias</i></p>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sarzi-Puttini 2000

Methods	<p>RCT</p> <p>Random generation of allocation: UNCLEAR</p> <p>Concealment of allocation: UNCLEAR</p> <p>Co-interventions: MET</p> <p>Losses to follow-up: MET</p> <p>Intention-to-treat: UNCLEAR</p> <p>Outcome assessment: MET</p> <p>Blinding of provider or patient: MET</p>	
Participants	<p>Country: Italy</p> <p>Number: 50</p> <p>Mean age: 50 years</p> <p>Sex: 78% women</p> <p>Inclusion criteria:</p> <p>a) Rheumatoid arthritis according to the 1987 ACR criteria</p> <p>b) Functional class I to III (Steinbroker)</p> <p>c) Age between 25 and 70 years</p> <p>d) Stable dosage and anti-rheumatic therapy for at least 12 weeks prior the study entry</p> <p>Active disease was defined by at least 4 of the following 5 criteria:</p> <p>1) 5 tender and/or painful joints;</p> <p>2) 3 swollen joints;</p> <p>3) morning stiffness of 45 minutes or greater;</p> <p>4) ESR 30 mm/hour;</p> <p>5) VAS \geq 4.</p> <p>Patients were allowed to continue pre-study therapy</p>	
Interventions	<p>Intervention group: experimental diet contained hypoallergenic foods such as rice, cornmeal, cornbread, hydrolysed milk, fresh pineapple and cooked apple. Allergenic foods such as wheat meal, eggs, milk, strawberries, acid fruit, tomato, chocolate, crustaceans, and dried fruit were deprived. All canned or transformed foods together with spices and aromatic plants were excluded.</p> <p>Control group: the control group ate a diet which included common allergenic foods but restricted the intake of nourishment containing a lot of saturated fatty acids</p>	
Outcomes	<p>a) Morning stiffness</p> <p>b) Health Assessment Questionnaire (HAQ)</p> <p>c) Number of tender and swollen joints</p> <p>d) Pain (VAS)</p> <p>e) Ritchies index</p> <p>f) Investigators' and patients' global assessment of disease (VAS)</p>	
Notes	<p>Silver</p>	
<i>Risk of bias</i>		
Item	Authors' judgement	Description

Sarzi-Puttini 2000 (Continued)

Allocation concealment?	Unclear	B - Unclear
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Sköldstam 1979

Methods	<p>RCT Random generation of allocation: UNCLEAR Concealment of allocation: UNCLEAR Co-interventions: UNCLEAR Losses to follow-up: MET Intention-to-treat: MET Outcome assessment: UNCLEAR Blinding of provider or patient: NOT MET</p>	
Participants	<p>Country: Sweden Number: 26 Mean age: 53 years Sex: 73% women Inclusion criteria: a) Rheumatoid arthritis according to the ARA criteria b) Low-moderate inflammatory activity c) Daily use of NSAIDs</p>	
Interventions	<p>Intervention group: fasting and vegetarian diet - patients underwent a period of 7 to 10 days of fasting. After fasting a plain lacto-vegetarian diet was instituted. The patients were instructed for 1 week and were recommended to continue the diet for 9 weeks. No animal or fish protein was allowed. Yoghurt was allowed freely, but fresh milk and cream were discouraged. Alcohol, tobacco, coffee and tea were not allowed. The patients were recommended to be restrictive with salt, sugar and white flour. Grain products were allowed in small quantities. All subjects were counselled weekly by a dietician. Control group: 9 weeks with ordinary diet</p>	
Outcomes	<p>a) Pain rating scale (4-point scale) b) Stiffness rating scale (4-point scale) c) Body weight d) Daily dose of NSAIDs</p>	
Notes	<p>Silver</p>	
Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sköldstam 2003

Methods	RCT Random generation of allocation: MET Concealment of allocation: MET Co-interventions: MET Losses to follow-up: MET Intention-to-treat: MET Outcome assessment: NOT MET Blinding of provider or patient: NOT MET
Participants	Country: Sweden Number: 56 Mean age: 58.5 years Sex: 82% women Inclusion criteria: a) Rheumatoid arthritis according to the 1987 ACR criteria b) Disease duration at least 2 years. c) Stable disease activity Exclusion criteria: DMARDs dose unchanged > 3 months, corticosteroids > 4 weeks, NSAIDS > 10 days. Daily dose of oral corticosteroids < 12.5 mg Baseline DAS28 > 2.0 No other conditions Not vegetarians or patients already living on a Mediterranean-like diet
Interventions	Intervention group: a Cretan Mediterranean Diet (MD) according to de Lorgeril was tested. During the 3-week Outpatient-based Rehabilitation Programme (ORP) they were served a MD from the hospital canteen. Six lessons of MD food and cooking were provided by a dietician. For the rest of the study (9 weeks at home) written instructions and recipes were given. Some food items (oils, margarine, frozen vegetables and tea) were supplied free. The dietician was available for telephone consultations. No recommendations were given about alcohol consumption. Control group: during the 3-week ORP they were served ordinary hospital food. For the rest of the study (9 weeks) they were advised to not experiment with the diet
Outcomes	Main outcomes: a) DAS 28 b) Health Assessment Questionnaire (HAQ) c) SF-36 d) Daily dose of NSAIDS
Notes	Silver
<i>Risk of bias</i>	
Item	Authors' judgement Description

Sköldstam 2003 (Continued)

Allocation concealment?	Yes	graded as 'met' after correspondence with the author
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van de Laar 1992

Methods	<p>RCT</p> <p>Random generation of allocation: UNCLEAR</p> <p>Concealment of allocation: UNCLEAR</p> <p>Co-interventions: MET</p> <p>Losses to follow-up: NOT MET</p> <p>Intention-to-treat: MET</p> <p>Outcome assessment: MET</p> <p>Blinding of provider or patient: MET</p>
Participants	<p>Country: The Netherlands</p> <p>Number: 94</p> <p>Mean age: 58 years</p> <p>Sex: 70% women</p> <p>Inclusion criteria:</p> <p>a) Rheumatoid arthritis according to the 1987 ACR criteria, including a positive RF</p> <p>b) Disease onset after 16 years of age</p> <p>Active disease was defined by at least 3 of the following 4 criteria:</p> <p>1) 5 tender and/or painful joints;</p> <p>2) 2 swollen joints;</p> <p>3) morning stiffness of 45 minutes or greater;</p> <p>4) ESR 28 mm/hour;</p> <p>d) stable doses of NSAIDs, daily dose of oral corticosteroids < 10 mg/day.</p> <p>Exclusion criteria:</p> <p>Patients in functional class 4 according to Steinbrocker</p>
Interventions	<p>Intervention group: experimental diet - 4 weeks with the patient's normal diet, 4 weeks with an elemental diet which is potentially free from allergenic. It contained 16 g free aminoacids, 13.6 g fat and 55 g lactose per 90 g. The patients were allowed to consume 3 apples, tea, allergen-free chewing gum and sugar per day. For the remaining 4 weeks the patients returned to their usual diets.</p> <p>Control group: the patients in the control group received milk allergens in the second 4-week period. It contained 20 g lactoprotein, 16 g fat and 48 g lactose per 90 g</p>
Outcomes	<p>Main outcomes:</p> <p>a) Duration of morning stiffness</p> <p>b) Number of tender joints</p> <p>c) Number of swollen joints</p> <p>d) Pain according to Ritchie index</p> <p>e) Global assessment and fatigue (VAS)</p> <p>f) Body weight</p> <p>g) Grip strength</p> <p>h) 30 feet walking time</p>

van de Laar 1992 (Continued)

Notes	Silver	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

ACR = American College of Rheumatology
 BMI = Body mass index
 CCT = Controlled clinical trial
 CRP = C-reactive protein
 DAS = Disease activity state
 ESR = Erythrocyte sedimentation rate
 HAQ = Health assessment questionnaire
 RCT = Randomised controlled trial
 RF = Rheumatoid factor
 SF-36 = Medical outcomes study short form survey, 36 items
 VAS = Visual analogue scale

Characteristics of excluded studies [ordered by study ID]

Adam 2003	Not relevant intervention and outcome
Gorden 2002	Not a RCT
Hafström 1988	Not relevant outcomes
Haugen 1990	Not a RCT
Iwashige 2004	Not a RCT
Karatay 2006	Not a RCT
Kjeldsen-Kragh 1999	Not a RCT
McDougall 2002	Not a RCT
Rauma 1993	Not a RCT
Silverio 2003	Not a RCT

(Continued)

Skiöldstam 1986	Not a RCT
Sundquist 1982	Not a RCT
Van De Laar 1992	Not a RCT

RCT = randomised controlled trial

DATA AND ANALYSES

Comparison 1. 7 to 10 days fasting followed by vegetarian diet vs ordinary diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 10) 3 weeks follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-2.32, 0.20]
2 Physical function (HAQ, 0 to 3) 3 weeks follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.46, 0.32]
3 Morning stiffness (hrs) 3 weeks follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.85 [-1.71, 0.01]
4 Body weight (kg) 3 weeks follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-3.40 [-10.59, 3.79]
5 Pain change (0 to 10) 9 weeks follow-up	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.90 [-2.98, 1.18]
6 Stiffness change (0 to 10) 9 weeks follow-up	1	25	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-3.09, 1.69]
7 Body weight (kg) change 9 weeks follow-up	1	25	Mean Difference (IV, Fixed, 95% CI)	-3.03 [-4.83, -1.57]
8 Pain (0 to 10) 13 months follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.89 [-3.62, -0.16]
9 Physical function (HAQ, 0 to 3) 13 months follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.48, 0.34]
10 Morning stiffness (hrs) 13 months follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.09 [-2.23, 0.07]
11 Body weight (kg) 13 months follow-up	1	34	Mean Difference (IV, Fixed, 95% CI)	-1.06 [-8.80, 5.80]

Comparison 2. Vegan diet vs ordinary diet.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Response rate ACR20 criteria 12 months follow-up	1	61	Risk Ratio (M-H, Fixed, 95% CI)	8.91 [1.24, 64.30]

Comparison 3. Elemental diet vs ordinary diet.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Function 4 weeks follow-up	1	45	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-4.37, 2.77]
2 Body weight (kg) 4 weeks follow-up	1	45	Mean Difference (IV, Fixed, 95% CI)	-3.90 [-11.12, 3.32]

Comparison 4. Mediterranean diet vs ordinary diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain (0 to 100) 12 weeks follow-up	1	51	Mean Difference (IV, Fixed, 95% CI)	-14.01 [-23.63, -4.37]
2 Function (HAQ, 0 to 3) 12 weeks follow-up	1	51	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.48, 0.08]
3 Morning stiffness (min) 12 weeks follow-up	1	51	Mean Difference (IV, Fixed, 95% CI)	-26.01 [-58.08, 6.08]
4 Body weight (kg) 12 weeks follow-up	1	51	Mean Difference (IV, Fixed, 95% CI)	3.30 [-3.97, 10.57]

Comparison 5. Graastener diet vs normal diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in VAS pain 6 months follow-up	1	81	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.89, 0.09]
2 Change in function (HAQ, 0 to 3) 6 months follow-up	1	81	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.23, 0.21]
3 Change in morning stiffness (min) 6 months follow-up	1	81	Mean Difference (IV, Fixed, 95% CI)	-3.01 [-23.47, 17.47]

Comparison 6. Hypoallergenic diet vs a well-balanced diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain VAS (0 to 100) 6 months follow-up	1	43	Mean Difference (IV, Fixed, 95% CI)	-2.80 [-13.33, 7.73]
2 Morning stiffness (min) 6 months follow-up	1	43	Mean Difference (IV, Fixed, 95% CI)	-5.20 [-27.59, 17.19]
3 Body weight (kg) 6 months follow-up	1	43	Mean Difference (IV, Fixed, 95% CI)	1.40 [-6.94, 9.74]

Comparison 7. Possible adverse effects - any diet manipulation vs ordinary diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total drop-outs	6	374	Risk Difference (M-H, Fixed, 95% CI)	0.10 [0.02, 0.18]
2 Treatment-related drop-outs	5	208	Risk Difference (M-H, Fixed, 95% CI)	0.05 [-0.03, 0.14]
3 Body weight (kg)	5	200	Mean Difference (IV, Fixed, 95% CI)	-3.23 [-4.79, -1.67]

Comparison 8. Allergen-free diet vs allergen-restricted diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in morning stiffness (min) 4 weeks follow-up	1	78	Mean Difference (IV, Fixed, 95% CI)	3.90 [-12.80, 20.60]
2 Change in body weight (kg) 4 weeks follow-up	1	78	Mean Difference (IV, Fixed, 95% CI)	1.02 [0.31, 1.89]

WHAT'S NEW

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CONTRIBUTIONS OF AUTHORS

KBH planned and initiated the review, searched for RCTs, assessed the trials, extracted data, contacted authors of RCTs, drafted and redrafted the final review. MGB planned and initiated the review, searched for RCTs, assessed trials and contacted authors of RCTs. LF searched for RCTs and assessed trials. GS planned and initiated the review, assessed the trials and contributed to the statistical analyses. SUO planned and initiated the review, assessed the trials and extracted data. KBH is the guarantor for the review.

DECLARATIONS OF INTEREST

None known.

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