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Low protein diets for non-diabetic adults with chronic kidney disease (Review)

Hahn D, Hodson EM, Fouque D

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[Intervention Review]

Low protein diets for non-diabetic adults with chronic kidney disease

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ABSTRACT

Background

Chronic kidney disease (CKD) is defined as reduced function of the kidneys present for 3 months or longer with adverse implications for health and survival. For several decades low protein diets have been proposed for participants with CKD with the aim of slowing the progression to end-stage kidney disease (ESKD) and delaying the onset of renal replacement therapy. However the relative benefits and harms of dietary protein restriction for preventing progression of CKD have not been resolved. This is an update of a systematic review first published in 2000 and updated in 2006 and 2009.

Objectives

To determine the efficacy of low protein diets in preventing the natural progression of CKD towards ESKD and in delaying the need for commencing dialysis treatment in non-diabetic adults.

Search methods

We searched the Cochrane Kidney and Transplant Register of Studies up to 2 March 2018 through contact with the Information Specialist using search terms relevant to this review. Studies in the Register are identified through searches of CENTRAL, MEDLINE, and EMBASE, conference proceedings, the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

We included randomised controlled trials (RCTs) or quasi RCTs in which adults with non-diabetic chronic kidney disease (stages 3 to 5) not on dialysis were randomised to receive a very low protein intake (0.3 to 0.4 g/kg/d) compared with a low protein intake (0.5 to 0.6 g/kg/d) or a low protein intake compared with a normal protein intake (≥ 0.8 g/kg/d) for 12 months or more.

Data collection and analysis

Two authors independently selected studies and extracted data. For dichotomous outcomes (death, all causes), requirement for dialysis, adverse effects) the risk ratios (RR) with 95% confidence intervals (CI) were calculated and summary statistics estimated using the random effects model. Where continuous scales of measurement were used (glomerular filtration rate (GFR), weight), these data were analysed as the mean difference (MD) or standardised mean difference (SMD) if different scales had been used. The certainty of the evidence was assessed using GRADE.

Main results

We identified an additional six studies to include 17 studies with 2996 analysed participants (range 19 to 840). Four larger multicentre studies were subdivided according to interventions so that the review included 21 separate data sets. Mean duration of participant follow-up ranged from 12 to 50 months.

Random sequence generation and allocation concealment were considered at low risk of bias in eleven and nine studies respectively. All studies were considered at high risk for performance bias as they were open-label studies. We assessed detection bias for outcome assessment for GFR and ESKD separately. As GFR measurement was a laboratory outcome all studies were assessed at low risk of detection bias. For ESKD, nine studies were at low risk of detection bias as the need to commence dialysis was determined by personnel independent of the study investigators. Five studies were assessed at high risk of attrition bias with eleven studies at low risk. Ten studies were at high risk for reporting bias as they did not include data which could be included in a meta-analysis. Eight studies reported funding from government bodies while the remainder did not report on funding.

Ten studies compared a low protein diet with a normal protein diet in participants with CKD categories 3a and b (9 studies) or 4 (one study). There was probably little or no difference in the numbers of participants who died (5 studies 1680 participants: RR 0.77, 95% CI 0.51 to 1.18; 13 fewer deaths per 1000; moderate certainty evidence). A low protein diet may make little or no difference in the number of participants who reached ESKD compared with a normal protein diet (6 studies, 1814 participants: RR 1.05, 95% CI 0.73 to 1.53; 7 more per 1000 reached ESKD; low certainty evidence). It remains uncertain whether a low protein diet compared with a normal protein intake impacts on the outcome of final or change in GFR (8 studies, 1680 participants: SMD -0.18, 95% CI -0.75 to 0.38; very low certainty evidence).

Eight studies compared a very low protein diet with a low protein diet and two studies compared a very low protein diet with a normal protein diet. A very low protein intake compared with a low protein intake probably made little or no difference to death (6 studies, 681 participants: RR 1.26, 95% CI 0.62 to 2.54; 10 more deaths per 1000; moderate certainty evidence). However it probably reduces the number who reach ESKD (10 studies, 1010 participants: RR 0.65, 95% CI 0.49 to 0.85; 165 per 1000 fewer reached ESKD; moderate certainty evidence). It remains uncertain whether a very low protein diet compared with a low or normal protein intake influences the final or change in GFR (6 studies, 456 participants: SMD 0.12, 95% CI -0.27 to 0.52; very low certainty evidence).

Final body weight was reported in only three studies. It is uncertain whether the intervention alters final body weight (3 studies, 89 participants: MD -0.40 kg, 95% CI -6.33 to 5.52; very low certainty evidence).Twelve studies reported no evidence of protein energy wasting (malnutrition) in their study participants while three studies reported small numbers of participants in each group with protein energy wasting. Most studies reported that adherence to diet was satisfactory. Quality of life was not formally assessed in any studies.

Authors' conclusions

This review found that very low protein diets probably reduce the number of people with CKD 4 or 5, who progress to ESKD. In contrast low protein diets may make little difference to the number of people who progress to ESKD. Low or very low protein diets probably do not influence death. However there are limited data on adverse effects such as weight differences and protein energy wasting. There are no data on whether quality of life is impacted by difficulties in adhering to protein restriction. Studies evaluating the adverse effects and the impact on quality of life of dietary protein restriction are required before these dietary approaches can be recommended for widespread use.

PLAIN LANGUAGE SUMMARY

Low protein diets for non-diabetic adults with chronic kidney disease

What is the issue?

Various forms of kidney disease can lead to kidney failure with affected people ultimately requiring dialysis treatment. A diet low in protein may be recommended to try to slow the progress of kidney disease to kidney failure. We still do not know whether low protein diets can slow the progress of kidney disease and delay the need to start dialysis.

What did we do?

We searched the Cochrane Kidney and Transplant Specialised Register up to 2 March 2018 for randomised controlled trials (RCT), which enrolled non-diabetic adult patients with chronic kidney disease, not yet requiring dialysis, and which compared different dietary protein intakes, including very low (0.3 to 0.4 g/kg/d), low (0.5 to 0.6 g/kg/d) or normal protein intakes (≥ 0.8 g/kg/d) for 12 months or more.

What did we find?

We examined the evidence from 17 studies (21 data sets) with 2996 people with reduced kidney function. We found that very low protein diets compared with low or normal protein intakes probably reduce the number of people with advanced kidney failure, who progress to dialysis. When low protein diets were compared with normal protein diets, there was little of no difference in the number of people with less severe kidney failure, who progressed to dialysis. Side effects of low protein diets such as weight loss were uncommon but many studies did not report on side effects.

Conclusions

In people with advanced kidney failure, a very low protein intake probably slows the progress to kidney failure. However we need more information on the side effects of low protein diets and on whether quality of life is reduced because of difficulties in keeping to such a diet.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Low protein diet versus normal protein diet for non-diabetic adults with chronic kidney disease (CKD)

Low protein diet versus normal protein diet for non-diabetic adults with CKD

Patient or population: non-diabetic adults with CKD
Setting: all settings
Intervention: low protein diet
Comparison: normal protein diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with normal protein diet	Risk with low protein diet			
Death (all causes)	55 per 1,000	42 per 1,000 (28 to 65)	RR 0.77 (0.51 to 1.18)	1680 (5)	⊕⊕⊕⊖ MODERATE [1]
ESKD	144 per 1,000	151 per 1,000 (105 to 220)	RR 1.05 (0.73 to 1.53)	1814 (6)	⊕⊕⊖⊖ LOW [1 2]
End or change in GFR	The SMD for end or change in GFR was 0.18 lower (0.75 lower to 0.38 higher) with low protein diet compared to normal protein diet		-	1680 (8)	⊕⊖⊖⊖ VERY LOW [1 2 3]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **ESKD:** end-stage kidney disease; **GFR:** glomerular filtration rate; **SMD** - standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The confidence intervals include potential for important benefits and harms
[2] Important and unexplained heterogeneity present
[3] The outcome reported is a surrogate outcome

Summary of findings 2. Very low protein diet versus low or normal protein diet for non-diabetic adults with chronic kidney disease (CKD)

Very low protein diet versus low or normal protein diet for non-diabetic adults with CKD

Patient or population: non-diabetic adults with CKD
Setting: all settings
Intervention: Very low protein diet
Comparison: low or normal protein diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with low or normal protein diet	Risk with very low protein diet			
Death (all causes)	39 per 1,000	49 per 1,000 (24 to 99)	RR 1.26 (0.62 to 2.54)	681 (6)	⊕⊕⊕⊖ MODERATE [1]
ESKD	458 per 1,000	293 per 1,000 (225 to 389)	RR 0.64 (0.49 to 0.85)	1010 (10)	⊕⊕⊕⊖ MODERATE [2]
End or change in GFR	The SMD for end or change in GFR was 0.12 (0.27 lower to 0.52 higher) with very low protein diet compared to low or normal protein diet		-	456 (6)	⊕⊕⊖⊖ LOW [1 2 3 4]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio; **ESKD:** end-stage kidney disease; **GFR:** glomerular filtration rate; **SMD** - standardised mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] The confidence intervals are wide and include potential for important benefits and harms
[2] Serious unexplained heterogeneity
[3] Outcome is a surrogate outcome
[4] Unclear allocation concealment in 4 studies contributing information to analysis

Summary of findings 3. Nutritional measures for non-diabetic adults with chronic kidney disease (CKD)

Nutritional measures for non-diabetic adults with CKD

Patient or population: non-diabetic adults with CKD
Setting: all settings
Intervention: very low of low protein diet
Comparison: normal or low protein diet

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Risk with normal or low protein diet	Risk with very low or low protein diet			
Final body weight: low protein versus normal protein diet	The mean final body weight 3.09 kg lower (5.02 to 1.16 lower) with low protein diet compared to normal protein diet		-	223 (2)	⊕⊖⊖⊖ VERY LOW [1,2]
Final body weight: very low protein diet versus low protein diet	The mean final body weight 1.4 kg higher (3.40 lower to 6.21 higher) with very low protein diet compared to low protein diet		-	291 (4)	⊕⊖⊖⊖ VERY LOW [3,4]
Protein energy wasting (malnutrition)	4 per 1,000	6 per 1,000 (2 to 17)	RR 1.31 (0.42 to 4.13)	2373 (15)	⊕⊕⊖⊖ LOW [2]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1] Increased risk of bias related to incomplete outcome data and selective reporting
[2] Small studies and wide confidence intervals and include potential for important benefits and harms
[3] 3/4 studies are unclear for allocation concealment and random sequence generation
[4] Serious unexplained heterogeneity

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is defined as abnormalities of the structure or function of the kidneys present for 3 months or more with adverse implications for health (KDIGO 2012). It is classified based on the cause, the severity of reduced kidney function as measured by the glomerular filtration rate (GFR) and the severity of albuminuria. KDIGO 2012 defined a GFR of less than 60 mL/min/1.73 m^2 as indicating reduced kidney function (normal GFR in young healthy adults is approximately 125 mL/min/1.73 m^2). CKD is associated with a range of complications leading to adverse health outcomes. Death (all causes) and cardiovascular death increase in individuals with GFR < 60 mL/min/1.73 m^2 (Matshushita 2010). The rate of deterioration in kidney function is variable and depends on the underlying cause of CKD and is associated among other factors with elevated blood pressure, increasing levels of proteinuria and diabetes mellitus. In many people, though not all, with CKD, kidney function deteriorates progressively with people developing symptoms of uraemia. Eventually people require treatment with haemodialysis or peritoneal dialysis with some receiving kidney transplants.

Description of the intervention

The World Health Organisation (WHO) recommends that healthy adults should receive a daily protein intake of 0.8 g/kg/d. Most healthy adults in developed countries consume a diet with a protein intake exceeding 1 g/kg/d. In CKD with reduced GFR, nephrologists and dietitians have prescribed low (0.5 to 0.6 g/kg/d) or very low (0.3 to 0.4 g/kg/d) high biologic-value protein diets aiming to reduce the rate at which GFR deteriorates and to alleviate some of the complications of advanced CKD including metabolic acidosis, bone disease and uraemic symptoms and thus delay the onset of end-stage kidney disease (ESKD), which leads to significant reduction in quality of life. To achieve very low protein intakes, some centres prescribe vegetarian diets (Garneata 2013). Very low protein diets are frequently supplemented with essential amino acids and nitrogen free keto-analogues of amino acids to reduce the risk of malnutrition. If sufficient calories are ingested, keto-analogues can be converted to amino acids via urea recycling. Extensive nutritional counselling is required to ensure that participants understand how to maintain a low or very low protein diet with an adequate calorie intake (30-35 Kcal/kg ideal body weight/day). Compliance with a reduced protein diet is frequently assessed with measurement of the urinary urea nitrogen in 24-hour urine collections and calculation of protein intake using the Maroni formula (6.25 X [urinary urea nitrogen x 0.03 body weight in kg]) (Maroni 1985).

How the intervention might work

Experimental studies in rats have shown that loss of nephrons leads to increased glomerular filtration in the remaining nephrons. The compensatory hyperfiltration results from increased plasma flow rates and increasing hydraulic pressure in the remaining nephrons. Eventually these haemodynamic changes lead to increased glomerular permeability with proteinuria and the development of progressive glomerulosclerosis. Long-term studies in rats have demonstrated that compared with rats with CKD on a high protein diet, rats with CKD on a low protein diet had fewer sclerotic glomeruli and less proteinuria (Hostetter 1986). These experimental data supported the view that protein restriction in people with CKD could protect glomeruli from progressive glomerulosclerosis, slow the deterioration in kidney function and delay the onset of ESKD. In addition, protein restriction reduces uraemic symptoms associated with metabolic acidosis, CKD-metabolic bone disease, hypertension, and fluid overload which could also delay the onset of ESKD even if the rate of kidney function deterioration measured by GFR does not change (Kasiske 1998).

Why it is important to do this review

There remains considerable controversy as to whether protein restriction does slow the rate of deterioration in kidney function in people with non-diabetic CKD with proponents providing data to support or refute the benefit of protein restriction (Johnson 2006; Mandayam 2006). KDIGO 2012 concluded that dietary protein intake < 0.8 g/kg/d did not offer any advantage over 0.8 g/kg/d and suggested that protein restriction to 0.8 g/kg/d be limited to adults with GFR < 30 mL/min/1.73 m^2. KDIGO 2012 also advised that people on any dietary protein restriction required careful monitoring of clinical and biochemical markers to avoid nutritional deficiencies.

Most of the clinical studies (both randomised controlled trials (RCTs) and observational studies) were designed to test the efficacy of reducing protein intake on surrogate kidney function outcomes, such as decline in creatinine clearance (CrCl) or changes in the reciprocal of creatinine over time. Unfortunately, changing protein intake modifies creatinine markers because reducing protein intake decreases creatinine production and changes kidney function (glomerular filtration as well as CrCl) by unidentified mechanisms. Although a few studies used methods to measure GFR using non-creatinine measures such as ^{51}CrEDTA clearance and I-125 Iothalamate clearance, the results from these studies have been conflicting.

Two non-Cochrane systematic reviews (Kasiske 1998; Pedrini 1996) have evaluated the efficacy of reduced protein diets. Pedrini 1996 reported that a low-protein diet significantly reduced the risk of kidney failure or death. In contrast Kasiske 1998 found that dietary protein restriction reduced the rate of decline in estimated GFR by only 0.53 mL/min/y. Because the decision to commence dialysis is not based only on declining GFR but also on the presence of uraemic symptoms and nephrologists vary in their criteria for commencing dialysis, it is quite possible that those on a higher protein intake will have more uraemic symptoms and be considered for dialysis earlier than those on lower protein intakes with an equivalent rate of GFR decline but fewer uraemic symptoms. In this publication we update a Cochrane systematic review first published in 2000 (Fouque 2000b) and updated in 2006 (Fouque 2006) and 2009 (Fouque 2009). The 2009 update (Fouque 2009) reported the composite outcome of death and ESKD (dialysis initiation or renal transplantation) as the primary outcome. Overall fewer events (deaths, ESKD) were observed with very low or low protein intake compared with those occurring with low or normal protein intake suggesting that a reduced protein intake reduces the number of people who die or reach ESKD. We aimed to determine whether the addition of further RCTs would further clarify whether low or very low protein diets benefit adults with non-diabetic CKD by delaying the onset of ESKD and/or slowing the rate of GFR decline without adverse effects on nutritional status.

OBJECTIVES

To determine the efficacy of low protein diets in preventing the natural progression of CKD towards ESKD and in delaying the need for commencing dialysis treatment in non-diabetic adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) in which those in the experimental group received a reduced protein intake for 12 months or more while those in the control group received a higher or normal protein intake. Cross-over studies were to be considered if the starting period of the intervention was randomly allocated and each intervention was in place for at least 12 months.

Types of participants

- Adults suffering from moderate to severe CKD, as estimated by either serum creatinine (SCr), CrCl or GFR measurement but excluding participants on peritoneal dialysis, haemodialysis or following a kidney transplant.
- Because of the difficulty to control for confounding factors, studies of diabetic participants or children with CKD were excluded from the review though studies including small numbers of diabetic participants were included.

Types of interventions

- Studies comparing a normal protein intake (≥ 0.8 g/kg/d) with a low protein intake (0.5 to 0.6 g/kg/d) or very low protein intake (0.3 to 0.4 g/kg/d) for 12 months or more
- Studies comparing a low protein intake (0.5 to 0.6 g/kg/d) with a very low protein intake (0.3 to 0.4 g/kg/d) for 12 months or more
- Studies in which participants received supplements of essential amino acids, keto-analogues or both were included provided that the total nitrogen intake differed between treatment groups.

Types of outcome measures

Primary outcomes

- Death (all causes)
- ESKD as defined by the need to commence dialysis during follow up or to receive a kidney transplant during follow-up.

Secondary outcomes

- End of study or change in GFR
- End of study body weight
- End of study body mass index (BMI)
- Development of protein energy wasting (malnutrition) as defined by the study authors
- Quality of life.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register up to 2 March 2018 through contact with the Information Specialist using search terms relevant to this review. The Cochrane Kidney and Transplant Specialised Register contains studies identified from several sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL)
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of kidney-related journals and the proceedings of major kidney conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected kidney and transplant journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of Cochrane Kidney and Transplant. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the Specialised Register section of information about Cochrane Kidney and Transplant.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of review articles, relevant studies and clinical practice guidelines.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous studies.

Data collection and analysis

Selection of studies

The initial review and updates to 2009 was undertaken by four authors using the search strategy described. The titles and abstracts were screened by two authors, based on the defined inclusion criteria. They discarded studies that were not relevant (i.e. studies of lipid lowering agents) although studies and reviews that could have included relevant data or information on studies was retained initially. Disagreements were resolved by discussion.

This update was undertaken by three authors (DH, EH, DF). Potentially relevant studies were initially determined by two authors from titles and abstracts. Full text articles of potentially eligible articles were reviewed for eligibility by two authors to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction and assessment of risk of bias were performed independently by two authors using standardised data extraction forms. Studies in languages other than English were translated before data extraction. Where more than one report of a study was identified, data were extracted from the most complete report but the remaining reports were checked for additional information. Where there were discrepancies between reports, data from the

primary source were used. Any further information required from the original authors was requested by written correspondence and any relevant information obtained in this manner was included in the review. Any disagreements were resolved in consultation with the third author.

Assessment of risk of bias in included studies

The following items were assessed independently by two authors using the risk of bias assessment tool (Higgins 2011) (Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

For dichotomous outcomes (death (all causes), requirement for dialysis, adverse effects) the risk ratios (RR) with 95% confidence intervals (CI) for individual studies were calculated and summary statistics estimated using the random effects model. Where continuous scales of measurement were used to assess the effects of treatment (GFR, weight, BMI), these data were analysed as the mean difference (MD) or standardised mean difference (SMD) if different scales had been used. Either final levels or change in levels were included in meta-analyses of continuous scales of measurement. When both measures were provided in a study, final levels were included. Where standard deviations (SD) for changes in levels or final levels were missing and not available from triallists, these were imputed (Higgins 2011).

Unit of analysis issues

Data from cross-over studies were to be included in the meta-analyses if separate data for the first part of the study were available. No cross-over studies were identified.

Dealing with missing data

We aimed to analyse available data in meta-analyses using intention-to-treat (ITT) data. However, where ITT data were not provided, or additional information could not be obtained from authors, available published data were used in the analyses.

Assessment of heterogeneity

We first assessed the heterogeneity by visual inspection of the forest plot. Heterogeneity was then analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). A guide to the interpretation of I^2 values was as follows.

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity.

The importance of the observed value of I^2 depends on the magnitude and direction of treatment effects and the strength of evidence for heterogeneity (e.g. P-value from the Chi^2 test, or a confidence interval for I^2) (Higgins 2011).

Assessment of reporting biases

The search strategy used aimed to reduce publication bias related to failure to publish negative results. Where there were multiple publications from the same study, the primary publications and additional reports were reviewed to identify all outcomes to reduce the risk of selective outcome reporting bias.

Data synthesis

Data were combined using random-effects model for dichotomous and continuous data.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to assess differences in results possibly related to population groups, different ways of measuring decline in GFR and to risk of bias assessment but there were too few studies in each analysis to allow meaningful subgroup analyses.

Sensitivity analysis

Where a single study differed considerably from the other studies in the meta-analysis, this study was temporarily excluded to determine whether its removal altered the results of the meta-analysis.

'Summary of findings' tables

We presented the main results of the review in 'Summary of findings' tables. These tables present key information concerning the quality of the evidence, the magnitude of the effects of the interventions examined, and the sum of the available data for the main outcomes (Schünemann 2011a). The 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach (GRADE 2008). The GRADE approach defines the quality of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The quality of a body of evidence involves consideration of within-trial risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We presented the following outcomes in the 'Summary of findings' tables.

- Death in low protein versus normal protein diet groups
- ESKD in low protein versus normal protein diet groups
- End or change in GFR low protein versus normal protein diet
- Death in very low protein versus higher protein diet groups
- ESKD in very low versus low protein diet groups
- End or change in GFR in very low protein diet versus higher protein diet
- Adverse effects - weight loss in very low protein diet versus higher protein diets

RESULTS

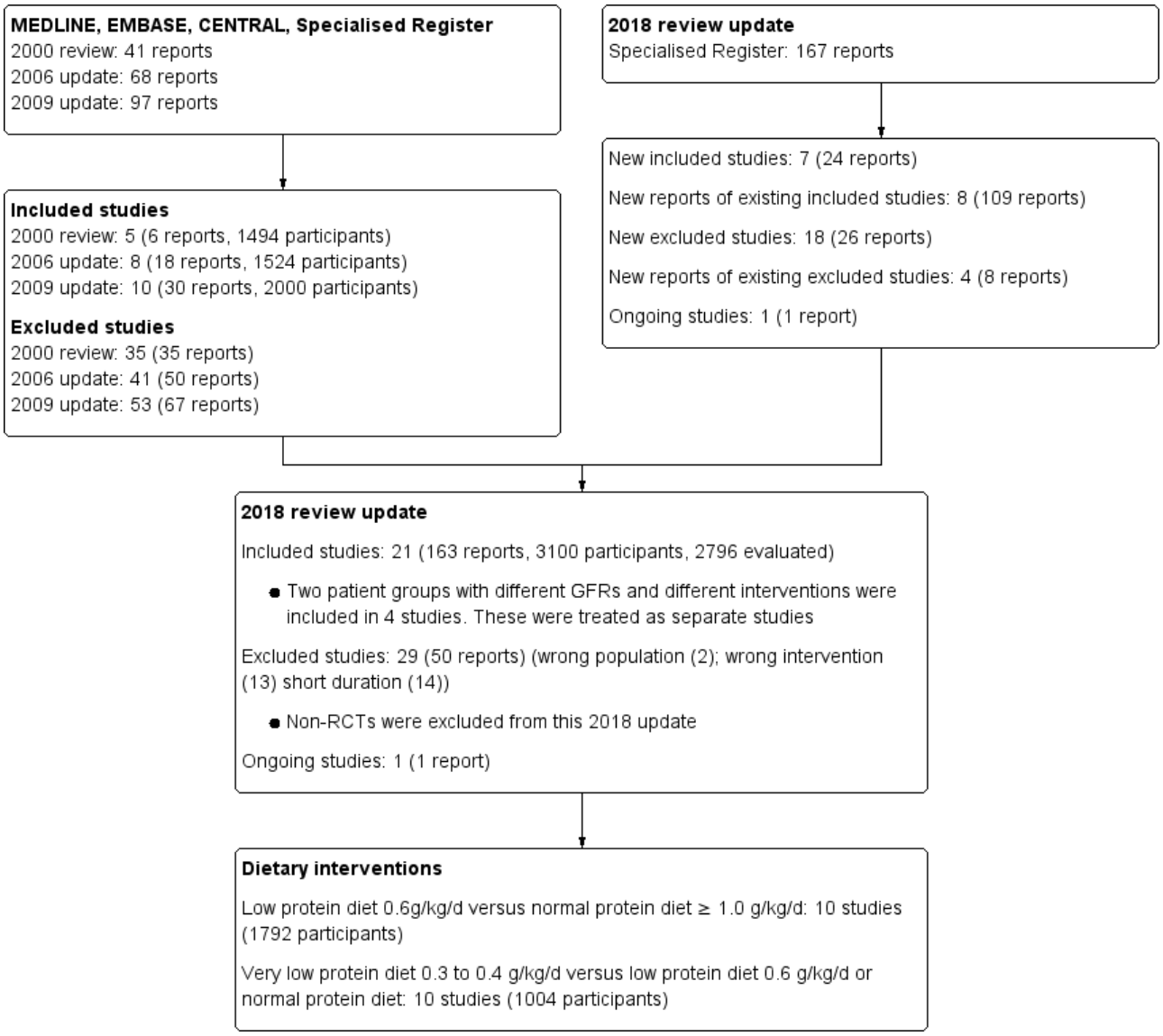
Description of studies

Results of the search

The first version of this review included five studies (six reports; 1494 participants) (Fouque 2000b). Subsequent updates of the review published in 2006 and 2009 included eight studies (18 reports; 1524 participants) (Fouque 2006) and 10 studies (30 reports; 2000 participants) (Fouque 2009) respectively.

For this latest update of our search (to 2 March 2018) we identified seven new studies with 24 reports (Anonymous Study 1 1990; Anonymous Study 2 1990; Bergstrom 1986; Garneata 2013; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; Meloni 2004; Milovanov 2009; Teplan 1998) and 109 additional reports of eight previously included studies. We excluded 34 reports. Therefore 17 studies (21 data sets; 163 reports; 3100 randomised participants, 2996 analysed particpants) were included in the update of this review (Figure 1).

Figure 1. Study flow diagram



One ongoing study was identified and will be assessed in a future update (NCT01418508).

Included studies

Two previously included studies (MDRD Study 1 1989; MDRD Study 2 1989; Rosman Study 1 1984; Rosman Study 2 1984) and two newly identified studies (Anonymous Study 1 1990; Anonymous Study 2 1990; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989) were divided into two studies each because they included two groups of participants with different mean GFRs, who received different protein intakes (low protein intake versus normal protein intake or very low protein intake versus low protein intake). Teplan 1998 (published only as an abstract) was a three-arm study comparing very low (0.4 g/kd/d), low (0.6 g/kg/d) and a restricted diet (0.8 to 1.0 g/kg/d); data could not be extracted and was not

included in any of the meta-analyses. Therefore in this systematic review we considered there to be 21 separate studies.

Nine studies (Anonymous Study 1 1990; Bergstrom 1986; Locatelli 1989; MDRD Feasibility Study A 1989; MDRD Study 1 1989; Meloni 2004; Milovanov 2009; Rosman Study 1 1984; Williams 1991), in which most participants had CKD category 3a or 3b (KDIGO 2012), compared a prescribed low protein diet (0.5 to 0.6 g/kg/d) with a normal protein diet (≥ 1 g/kg/d). A tenth study (Cianciaruso 2008a), which included participants with CKD category 4 and randomised participants to a low protein diet (0.55 g/kg/d) or to the WHO recommended normal protein intake (0.8 g/kg/d), was included in the meta-analyses with studies comparing low with normal protein intake. Protein intake was estimated from urinary urea nitrogen measurements (Maroni 1985). The mean calculated protein intake was 0.68 g/kg/d (range 0.49 to 0.85 g/kg/d) for the low protein intervention and 1.0 g/kg/d (range 0.61 to 1.54 g/kg/d) for the normal or free protein diet group. No data on calculated protein intake were available for Rosman Study 1 1984 since data on urea excretion were only provided graphically.

Eight studies (Anonymous Study 2 1990; Di Iorio 2003; Garneata 2013; Chauveau 1986; Malvy 1999; MDRD Feasibility Study B 1989; MDRD Study 2 1989; Mircescu 2007), in which participants had CKD stage 4/5 compared prescribed very low protein diets (0.3 to 0.4 g/kg/d with keto-analogues) with low protein diets (0.58 to 0.65 g/kg/d). The mean calculated protein intake for the participants who received a very low protein diet was 0.4 g/kg/d (range 0.29 to 0.5 g/kg/d) and it was 0.64 g/kg/d (range 0.56 to 0.79 g/kg/d) for participants receiving the low protein diet. No data on calculated protein intake were available for Chauveau 1986 since data on urea excretion were not provided. Ihle 1989 and Rosman Study 2 1984, in which participants had CKD category 4 and which compared very low protein diets (0.4 g/kg/d) with normal protein diets, were included with the eight studies comparing very low with low protein intakes. Actual protein intake could not be calculated for these two studies.

Seven studies were multicentre studies (Anonymous Study 1 1990; Anonymous Study 2 1990; Locatelli 1989; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; MDRD Study 1 1989; MDRD Study 2 1989), two studies involved two sites (Malvy 1999; Williams 1991) and the remainder were single centre studies. Participant numbers ranged from 19 to 840 with an age range of 15 to 75 years.

Glomerulopathies accounted for CKD in between 23% (Williams 1991) and 60% (Meloni 2004) of participants; the types of kidney disease included were not reported in Bergstrom 1986, while Milovanov 2009 included only participants with lupus nephritis or other vasculitides. Six diabetic nephropathy participants (three in each group) were included in Di Iorio 2003. Anonymous Study 1 1990 and Anonymous Study 2 1990 reported that fewer than 10% of diabetic participants were included among the 554 participants assessed for inclusion in the study though it was unclear whether any diabetic participants were included in the 336 randomised participants. No diabetic participants were included in the remaining studies.

We chose to include Anonymous Study 1 1990 and Anonymous Study 2 1990 although there were known to be some participants from one centre, who were included in these studies and in Locatelli 1989. We were unable to obtain an exact number of participants included in both studies. However it appeared that only about 30 participants were included in both studies, which would be only 8.9% of 336 randomised participants in Anonymous Study 1 1990 and Anonymous Study 2 1990 and 6.6% of 456 randomised participants in Locatelli 1989 (personal communication from Professor Norbert Gretz).

Mean duration of follow up ranged from 12 to 50 months.

See Characteristics of included studies

Excluded studies

In the 2009 update, there were 53 excluded studies (67 reports). In the 2016 update we identified a total of 71 excluded studies (101 reports). Based on the Cochrane recommendations for dealing with excluded studies, we limited the excluded studies to randomised controlled trials (RCT) and removed all non-randomised studies from excluded studies. Therefore in this update we have excluded 29 studies. Of these 13 studies investigated ineligible interventions for this review, two studies included an ineligible population such as dialysis participants or participants with diabetes mellitus and in 14 studies the duration of follow-up was less than one year.

See Characteristics of excluded studies.

Risk of bias in included studies

Figure 2; Figure 3

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

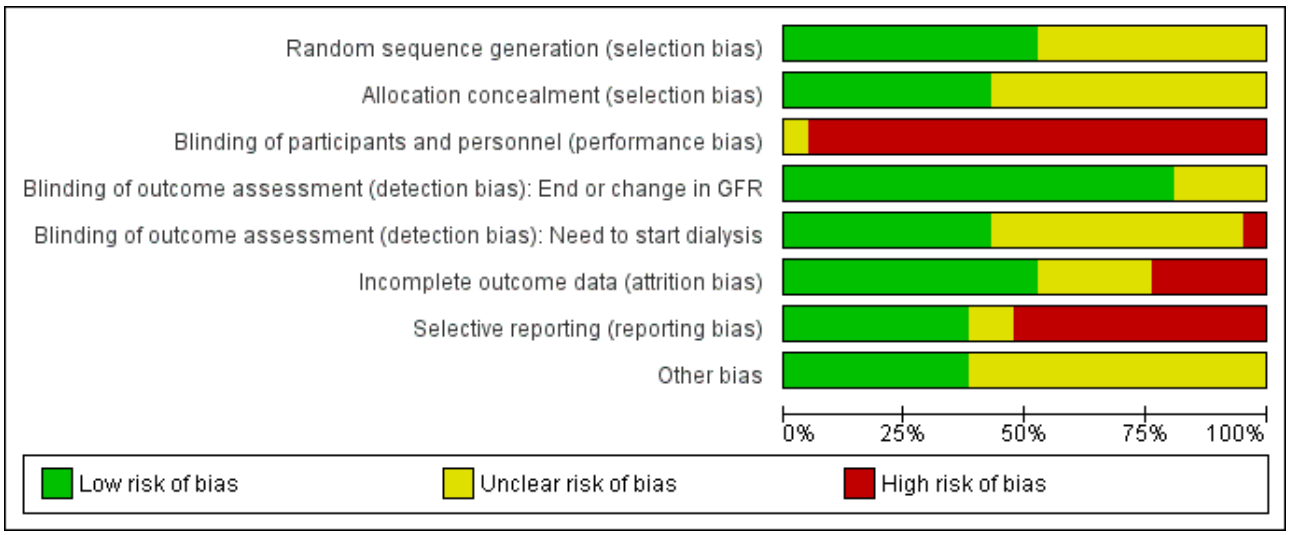


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

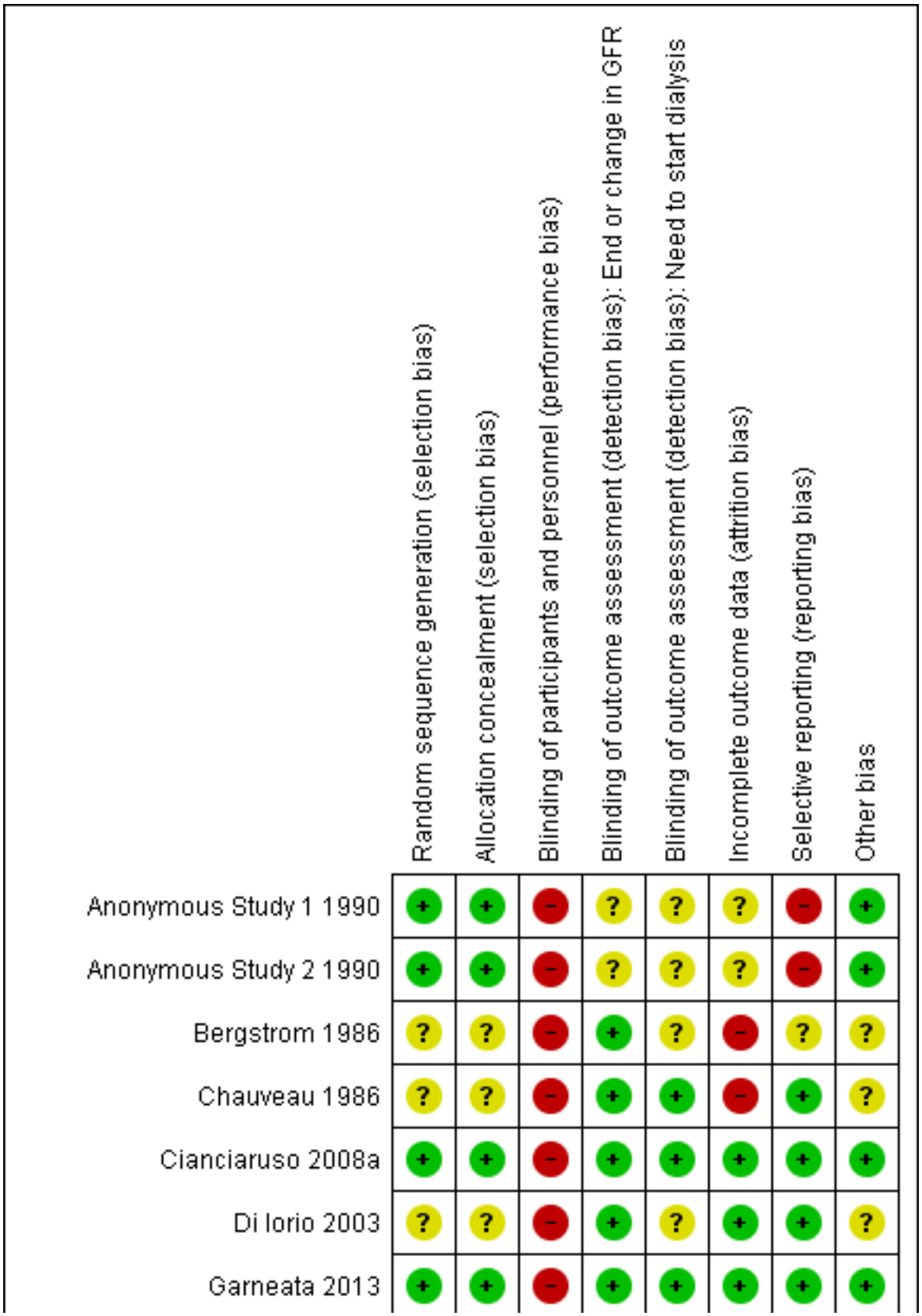
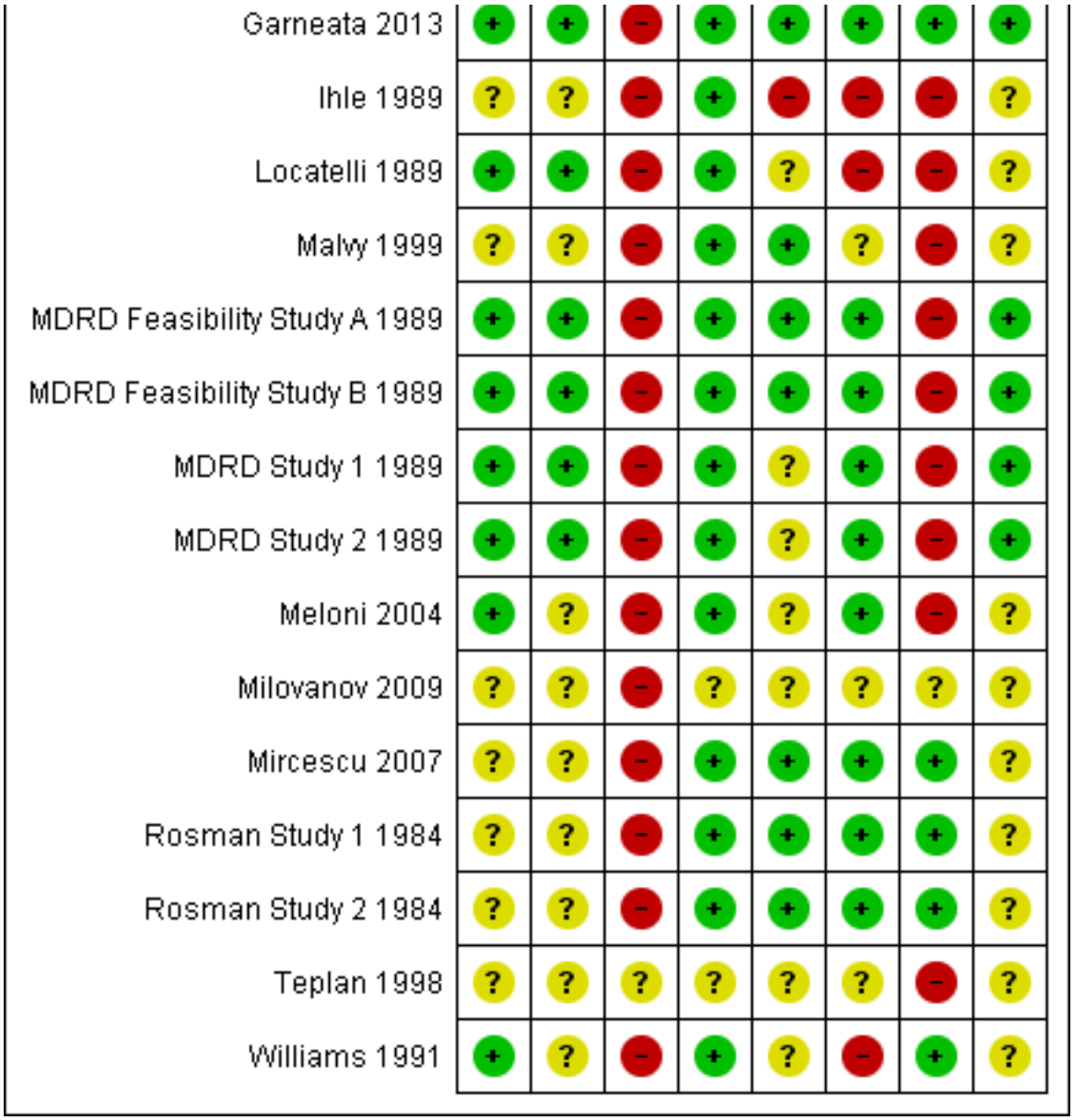


Figure 3. (Continued)



Allocation

Random sequence generation was considered at low risk of bias in 11 studies (Anonymous Study 1 1990; Anonymous Study 2 1990; Cianciaruso 2008a; Garneata 2013; Locatelli 1989; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; MDRD Study 1 1989; MDRD Study 2 1989; Meloni 2004; Williams 1991) and unclear in the remaining studies.

Allocation concealment was considered to be at low risk of bias in nine studies (Anonymous Study 1 1990; Anonymous Study 2 1990; Cianciaruso 2008a; Garneata 2013; Locatelli 1989; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; MDRD Study 1 1989; MDRD Study 2 1989) and assessed as unclear in the remaining studies with insufficient information available to permit judgement.

Blinding

All 20 studies were open-label studies and so were considered at high risk for performance bias.

Detection bias (outcome assessment) was recorded separately for GFR and for the need to commence dialysis. All studies which reported this outcome were assessed to be at low risk for detection bias for GFR measurement as the outcomes were laboratory-based and unlikely to be influenced by lack of blinding. Nine studies were assessed as at low risk of bias for need to commence dialysis as they provided information to indicate that the onset of ESKD with the start of dialysis treatment was assessed independently of the study investigators (Chauveau 1986; Cianciaruso 2008a; Garneata 2013; Malvy 1999; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; Mircescu 2007; Rosman Study 1 1984; Rosman Study 2 1984). One study was at high risk (Ihle 1989) and the remaining

studies did not provide any information on how the onset of ESKD was assessed.

Incomplete outcome data

Five studies were considered at high risk of attrition bias as more than 10% of participants were lost to follow up or excluded from the analysis (Bergstrom 1986; Chauveau 1986; Ihle 1989; Locatelli 1989; Williams 1991). Eleven studies (Cianciaruso 2008a; Di Iorio 2003; Garneata 2013; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; MDRD Study 1 1989; MDRD Study 2 1989; Meloni 2004; Mircescu 2007; Rosman Study 1 1984; Rosman Study 2 1984) were assessed as at low risk of detection bias and in the remaining four studies, it was unclear how many participants were lost to follow-up.

Selective reporting

Studies were considered to be at high risk of bias if data were provided in a format, which could not be entered into the meta-analyses or if the study did not provide data on death, requirement for dialysis or the nutritional status of the participants. We assessed 11 studies at high risk of selective reporting (Anonymous Study 1 1990; Anonymous Study 2 1990; Ihle 1989; Locatelli 1989; Malvy 1999; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; MDRD Study 1 1989; MDRD Study 2 1989; Meloni 2004; Teplan 1998). Eight studies were assessed as low risk of selective reporting (Cianciaruso 2008a; Chauveau 1986; Di Iorio 2003; Garneata 2013; Mircescu 2007; Rosman Study 1 1984; Rosman Study 2 1984; Williams 1991) and two studies were judged as unclear.

Other potential sources of bias

We assessed eight studies (Anonymous Study 1 1990; Anonymous Study 2 1990; Cianciaruso 2008a; Garneata 2013; MDRD Feasibility Study A 1989; MDRD Feasibility Study B 1989; MDRD Study 1 1989; MDRD Study 2 1989) to be at low risk of potential bias as they were funded by educational or philanthropic organisations and the remaining fourteen studies were considered as unclear as there was insufficient information to permit judgement regarding funding sources.

Effects of interventions

See: **Summary of findings for the main comparison** Low protein diet versus normal protein diet for non-diabetic adults with chronic kidney disease (CKD); **Summary of findings 2** Very low protein diet versus low or normal protein diet for non-diabetic adults with chronic kidney disease (CKD); **Summary of findings 3** Nutritional measures for non-diabetic adults with chronic kidney disease (CKD)

Low protein diets versus normal or free protein diet

Eleven studies compared low protein diets (0.55 to 0.6 g/kg/d) with a normal or free protein diet (0.8 to 1 g/kg/d). Nine studies enrolled participants with category 3a and 3b CKD while one study (Cianciaruso 2008a) enrolled participants with CKD category 4 and 5.

Death (all causes)

Five of 10 studies reported data on death (all causes), which could be included in a meta-analysis. The certainty of the evidence was considered as moderate (Summary of findings for the main comparison) because of imprecision. Thus a low protein intake probably leads to little or no difference in death between participants, who received a lower protein diet, and those receiving a normal or free protein diet (Analysis 1.1 (5 studies, 1680 participants): RR 0.77, 95% CI 0.51 to 1.18; I^2 = 0%). There were 13 fewer deaths per 1000 in the low protein group (27 fewer to 10 more deaths). Five studies did not report this outcome.

End-stage kidney disease

Six of 10 studies reported data on this outcome, which could be included in a meta-analysis. The certainty of the evidence was considered as low (Summary of findings for the main comparison) because of imprecision and moderate heterogeneity. A low protein diet may make little or no difference in the number of participants who reached ESKD compared with a normal protein diet (Analysis 1.2 (6 studies, 1814 participants): RR 1.05, 95% CI 0.73 to 1.53; I^2 = 62%). There were 7 participants more per 1000 reaching ESKD in the low protein group (39 fewer to 76 more) compared with the normal protein group. Removal of Cianciaruso 2008a, which included participants with CKD category 4, did not influence the heterogeneity. Exclusion of Anonymous Study 1 1990 reduced this heterogeneity (I^2 = 26%). Anonymous Study 1 1990 did not report information which allowed us to determine whether there was detection bias or selective reporting in this study so it is possible that increased risk of bias in these domains in this study contributed to the heterogeneity. Four studies (Bergstrom 1986, MDRD Feasibility Study A 1989; Meloni 2004; Milovanov 2009) did not report on this outcome.

End or change in GFR

Eight of 10 studies reported data on this outcome, which could be included in a meta-analysis. Studies used different methods to express the final GFR or the change in GFR. Because of imprecision, use of a surrogate outcome and substantial heterogeneity (Summary of findings table 1), the certainty of the evidence was considered to be very low. It therefore remains uncertain whether a low protein diet influences the final or change in GFR compared with a normal protein diet (Analysis 1.3; 8 studies, 1680 participants): SMD -0.18, 95% CI -0.75 to 0.38; I^2 = 96%). Heterogeneity was reduced by exclusion of the studies by Locatelli 1989 and Meloni 2004 but it was not clear why these studies should provide data that differed from other studies. Anonymous Study 1 1990 did not report this outcome while Rosman Study 1 1984 only reported the data as medians, which could not be included in the meta-analysis.

Very low protein diet versus low protein diet

Eight studies compared a very low protein diet (0.3 to 0.4 g/kg/d) with a low protein diet (0.58 to 0.65 g/kg/d) while two studies compared a very low protein diet with a normal protein diet. All studies enrolled participants with CKD category 4.

Death (all causes)

Six of 10 studies reported data for this outcome, which could be included in a meta-analysis. Because of imprecision in the results, the certainty of the evidence was considered to be moderate (Summary of findings 2). Thus a very low protein intake probably leads to little or no difference in death between participants, who received a lower protein diet, and those receiving a normal or free protein diet (Analysis 2.1 (6 studies, 681 participants): RR 1.26, 95% CI 0.62 to 2.54; I^2 = 0%). There were 10 more deaths per 1000 in the very low protein group (15 fewer to 60 more) compared with

the normal or low protein group. Anonymous Study 2 1990; Di Iorio 2003; Ihle 1989; MDRD Feasibility Study B 1989 did not report data for this outcome.

End-stage kidney disease

All ten studies reported data on this outcome, which could be included in a meta-analysis. Because of moderate heterogeneity, the certainty of the evidence was considered to be moderate (Summary of findings 2). Thus a very low protein diet probably reduces the number of participants, who reach ESKD, compared with a low or normal protein intake (Analysis 2.2 (10 studies, 1010 participants): RR 0.64, 95% CI 0.49 to 0.85; I^2 = 56%). There were 165 fewer participants per 1000, who reached ESKD with a very low protein diet compared with a low or normal protein diet (69 to 233 fewer). Exclusion of MDRD Feasibility Study B 1989 reduced heterogeneity slightly though it remains unclear why this study's results differed from those of the other studies. Exclusion of Ihle 1989 and Rosman Study 2 1984, which compared a very low protein intake with a normal protein intake, did not influence the degree of heterogeneity.

End or change in GFR

Six of 10 studies reported data on this outcome, which could be included in a meta-analysis. Because of substantial heterogeneity, use of a surrogate outcome and a high risk of bias in some included studies, the certainty of the evidence was considered to be very low (Summary of findings 2). It therefore remains uncertain whether a low protein diet influences the final or change in GFR compared with a normal protein diet (Analysis 2.3 (6 studies, 456 participants): SMD 0.12, 95% CI -0.27 to 0.52; I^2 = 68%). Heterogeneity was reduced with the exclusion of MDRD Study 2 1989 and MDRD Feasibility Study B 1989. Both of these studies were at low risk of bias for selection bias unlike the other studies included in the analysis but the reason for the heterogeneity remains unclear. Garneata 2013 reported the data on GFR as medians with 95% confidence intervals and these data could not be included in the meta-analysis. The study found a significantly higher GFR in the very low protein group compared with the low protein group after 15 months (P < 0.01). Three studies did not report the outcome (Anonymous Study 2 1990; Malvy 1999; Rosman Study 2 1984).

Other outcomes

Most studies did not discuss adverse events. However all the studies reported that body weight, BMI and mid arm circumferences were measured though most studies did not provide numerical data that could be included in meta-analyses.

Most studies reported on dietary adherence and measured this at one to three monthly intervals using urine nitrogen excretion to calculate protein intake and/or by dietary recall or interviews, facilitated by dietitians. The differences between prescribed protein intakes and actual protein intakes are shown in Table 1 and Table 2. While most studies reported that adherence to diet was satisfactory, studies of participants with CKD 3a and 3b tended to have larger differences between actual protein intakes and prescribed protein intakes (Table 1). Anonymous Study 1 1990 and Anonymous Study 2 1990 reported large SD for actual protein intakes because of the wide variation among participants in adherence to diet. Two studies (Chauveau 1986; Locatelli 1989) specifically reported difficulty in maintaining dietary adherence with the low protein diet. Garneata 2013 excluded people who were not able to agree to adhere to protein restriction. No study formally assessed quality of life.

Body weight

Seven studies in total reported data on end of study body weight. The data were subgrouped according to protein intakes. Because of small numbers, imprecision and a high risk of bias, the certainty of the evidence was considered to be very low (Summary of findings 3).

In two studies which compared low protein diets with normal protein diets, the certainty of the evidence was considered very low because of increased risk of bias and imprecision, and therefore it is uncertain whether a low protein diet reduces the final body weight (Analysis 3.1.1 (2 studies, 223 participants): MD -3.09 kg, 95% CI -5.02 to -1.16; I^2 = 0%). Cianciaruso 2008a reported final body weights as a percentage of the baseline; actual weights could not be calculated as baseline weights were provided separately for men and women. At 12 months, the final body weights were 99.8% or more of baseline weights.

In four studies which compared very low protein diets with low protein diets, the certainty of the evidence was considered very low because of increased risk of bias and imprecision, and therefore it is uncertain whether a low protein diet reduces the final body weight (Analysis 3.1.2 (4 studies, 291 participants): MD 1.4 kg, 95% CI 3.40 to 6.21; I^2 = 56%).

Thus it is uncertain whether the intervention alters final body weight. The data for MDRD Study 1 1989; MDRD Study 2 1989 are shown in Table 3 as data were reported separately for men and women so could not be added to the meta-analysis. Three studies reported that body weight dropped during the first few months of commencing a low protein diet but that subsequently weight stabilised (Ihle 1989; Malvy 1999; Meloni 2004).

Protein energy wasting (malnutrition)

Fifteen studies made reference to protein energy wasting. Of these 12 studies reported no evidence of malnutrition while three studies reported small numbers of participants with protein energy wasting in both groups (Analysis 3.2 (15 studies, 2373 participants): RR 1.31, 95% CI 0.42 to 4.13; I^2 = 0%; low certainty evidence).

Body mass index

Four studies reported on this outcome. Two studies (Anonymous Study 1 1990; Meloni 2004) comparing a low protein with a normal protein diet, found no difference in BMI between groups. Two studies (Anonymous Study 2 1990; Garneata 2013) comparing very low protein with a low protein diet, also demonstrated no difference between diet groups. Studies were not combined in a meta-analysis as three studies (Anonymous Study 1 1990; Anonymous Study 2 1990; Garneata 2013) provided the data as medians and ranges.

DISCUSSION

Summary of main results

For this update we identified six additional studies to provide a total of 17 studies (21 data sets) with 3100 participants (2996 analysed participants) so we were able to report separately on the outcomes of death (all causes), numbers with ESKD, and final or change in GFR. We could also report data separately for studies

which compared low with normal protein intakes and those which compared very low with low protein intakes. We sub-divided four studies which compared different protein intakes in participants with different stages of CKD so that 20 studies were included in this review.

Ten studies, mainly evaluating participants with CKD categories 3a and 3b, compared a low prescribed protein diet (0.55 to 0.6 g/kg/d) with a normal protein diet (0.8 to ≥ 1.0 g/kg/d). The difference in calculated protein intake was 0.32 g/kg/d between the intervention groups. A low protein diet compared with a normal protein diet probably makes little or no difference in the numbers of participants who died (moderate certainty evidence) and may make little or no difference in the number of participants who progressed to ESKD (low certainty evidence). It remains uncertain whether a low protein diet compared with a normal protein intake impacts on the final or change in GFR (very low certainty evidence) (Summary of findings for the main comparison).

Ten studies, which evaluated participants with CKD 4 or 5, compared a prescribed very low protein diet (0.3 to 0.4 g/kg/d) with a low protein diet (0.58 to 0.65 g/kg/d) (eight studies) or with a normal protein diet (two studies). The difference in calculated protein intake was 0.25 g/kg/d between the intervention groups. A very low protein intake compared with a low protein intake probably makes little or no difference to death but it probably reduces the number of participants, who reach ESKD (moderate certainty evidence). It remains uncertain whether a very low protein diet compared with a low or normal protein intake influences the final or change in GFR (very low certainty evidence) (Summary of findings 2).

Fifteen studies reported on the numbers of participants with protein energy wasting (malnutrition); 12 studies had no participants with protein energy wasting while three studies reported small numbers in both treatment groups. Only eight studies provided numerical data for body weight although most studies reported that weight was measured. Only three of the 15 studies reported any evidence of protein energy wasting. No study formally assessed quality of life in the participants. Most studies reported that adherence to diet was satisfactory though studies of participants with CKD 3a and 3b tended to have smaller differences between actual protein intakes, as measured by urinary nitrogen excretion, and prescribed protein intakes.

Overall completeness and applicability of evidence

For this review we identified 16 studies (reported as 20 studies) which evaluated the efficacy and safety of low protein diets in non-diabetic CKD. Several studies, particularly the older and smaller studies, were of low methodological quality. The primary outcomes of this review (death and ESKD) were not reported in 10 and 4 studies respectively. Numerical data on weight difference and protein energy wasting were provided in few studies though all the studies reported that participants' body weight, BMI and mid arm circumference were measured. Adherence was reported in all the studies and was measured at one to three monthly intervals utilising urine nitrogen excretion for calculated protein intake or dietary recall. While most studies reported satisfactory adherence, difficulty in maintaining adherence was reported in two studies. No studies reported any assessment of quality of life although one study commented that quality of life would be improved if participants were not restricted in their dietary protein intake. Quality of life is significantly reduced in patients who require dialysis. Quality of life should be assessed with dietary interventions, aimed at delaying the onset of ESKD, to confirm that any impact of diet on quality of life is minimal compared with the impact of dialysis treatment.

Although Anonymous Study 1 1990, Anonymous Study 2 1990 and Bergstrom 1986 were reported as full text journal articles, these articles only provided preliminary results and our updated search and contact with authors did not identify a publication of the full results for the studies. Most studies were small with only five studies enrolling more than 100 participants in each treatment group. Although we identified six studies not previously included in this review, only Garneata 2013 was a large, well reported and high quality study. Only two new studies (Garneata 2013; Milovanov 2009) and the full text publication of Cianciaruso 2008a were published since the 2009 update. The other four new studies identified for this update had been published before 2009.

Quality of the evidence

For all the studies included in the review, full length journal articles were available. However included studies were commonly reported incompletely and were of poor methodological quality and this may reflect pre-2001 CONSORT (Consolidated Standards of Reporting Trials) practices in the older studies (www.consort-statement.org). Random sequence generation and allocation concealment were considered at low risk of bias in 11 and nine studies respectively. All studies were considered at high risk for performance bias as they were open-label studies. We assessed bias for outcome assessment (detection bias) for GFR and ESKD separately. As the outcome measurement for GFR measurement was a laboratory outcome all studies were assessed at low risk of detection bias. We felt it important to include a separate assessment of bias for outcome assessment of ESKD as this outcome is more likely to be at risk of detection bias. Eight of 16 studies, reporting data on this outcome, were at unclear or high risk for detection bias; the other eight studies were at low risk of bias since the need to commence dialysis was determined by personnel independent of the trial investigators. Where outcome assessment for the need to commence dialysis is not blinded, the time of dialysis commencement may be influenced by the physicians' knowledge of the treatment groups (Kasiske 1998). Five studies were assessed at high risk of attrition bias with eleven studies at low risk. Eleven studies were at high risk for reporting bias as they did not include data which could be included in a meta-analysis.

The overall certainty of the evidence using GRADE (GRADE 2011a; GRADE 2011b) was assessed as moderate, low or very low for different outcomes (Summary of findings for the main comparison; Summary of findings 2). The certainty of the evidence for death was assessed as moderate for studies comparing low with normal protein diets and for studies comparing very low with low or normal protein diets. The certainty of the evidence for ESKD was low for studies comparing low with normal protein diets and moderate for studies comparing very low with low or normal protein intake. The certainty of the evidence for end or change in GFR and body weight was assessed as very low.

Potential biases in the review process

A comprehensive search of the Cochrane Kidney and Transplant's Specialised Register was performed for this review thus reducing

the possibility that potential eligible studies were omitted from the review. Eligible studies published after the last search date or published in conference proceedings not routinely searched could have been missed. The review was completed independently by at least two authors who participated in all steps of the review, which limited the risk of errors in determining study eligibility, in data extraction, in risk of bias assessment and in data synthesis.

Agreements and disagreements with other studies or reviews

The 2009 update of this review found that reduced protein intake in CKD participants reduced the number of participants, who died or reached ESKD (Fouque 2009). The benefit was primarily seen in the subgroup of studies comparing very low protein diets with low or normal protein diets. In this update with additional studies, we were able to report separately on death and ESKD. We confirmed that the reduction in the number of participants reaching ESKD was limited to studies comparing very low protein diet with low or normal protein diets (moderate certainty evidence).

Two other systematic reviews have evaluated the efficacy of low protein diets in participants with CKD. Five RCTs, including 1413 participants with non-diabetic CKD, were reviewed by Pedrini 1996. Dietary protein restriction compared with a normal protein intake reduced the risk of the combined outcome of death and ESKD (RR 0.67, 95% CI 0.50 to 0.89). All five RCTs are included in our updated review and include two large studies (Locatelli 1989; MDRD Study 1 1989; MDRD Study 2 1989). This study evaluated the number of participants reaching ESKD but did not evaluate change in GFR.

Kasiske 1998 evaluated 13 RCTs (1919 participants) including four studies of patients with diabetic CKD. As in this systematic review, the Modification of Diet in Renal Disease study (MDRD Study 1 1989; MDRD Study 2 1989) was treated as two studies. The difference in dietary protein intake between the intervention and control groups was 0.33 ± 0.26 g/kg/d. In the pooled results, the authors found that dietary protein restriction reduced the rate of decline in estimated GFR by only 0.53 mL/min/y (95% CI 0.08 to 0.98). They concluded that though there was a decline in GFR with protein restriction, the magnitude of this effect was relatively weak. This review evaluated changes in GFR but not the number of participants, who died or reached ESKD. The authors pointed out that their results were in keeping with the major findings of the MDRD study, which showed little benefit of protein restriction on the number of participants reaching ESKD or on GFR in participants with GFR below 30 mL/min/1.73 m^2 (MDRD Study 2 1989).

The use of low protein diets in participants with CKD varies between countries and within countries. Few nephrologists in the USA or Canada prescribe dietary therapy for participants with CKD (Kalantar- Zadeh 2016) following the negative results of the MDRD study (MDRD Study 1 1989; MDRD Study 2 1989) while low protein diets are more commonly prescribed in Europe (Bellizzi 2016). International (KDIGO 2012) and national guidelines (Wright 2011) now recommend protein intakes of 0.75 to 0.8 g/kg/d for adults with GFR ≤ 30 mL/min/ 1.73 m^2. These recommendations are in line with the recommended daily intake (RDI) for the general population. The average protein intake in adults in developed countries is approximately twice the RDI so guidelines suggest that participants with excess protein intakes reduce their intake to RDI levels since a high protein intake may accelerate the decline of kidney function in CKD (KDIGO 2012; Johnson 2013).

AUTHORS' CONCLUSIONS

Implications for practice

Available data from RCTs outlined in this systematic review found that very low protein diets (0.3 to 0.4 g/kg/d with supplements of essential amino acids and keto-analogues) compared with low or normal protein intakes probably reduce the number of participants with CKD 4 or 5, who progress to ESKD (moderate certainty evidence). Compared with normal protein diets (0.8 to ≥ 1.0 g/kg/d), low protein diets (0.5 to 0.6 g/kg/d) in participants with CKD 3 may make little or no difference to the number progressing to ESKD (low certainty evidence). However there were very limited data available on adverse effects - in particular weight differences and protein energy malnutrition - and on participants' quality of life, which could be affected by difficulties in maintaining dietary adherence. In this systematic review, we found a very small difference in GFR between very low and low protein intakes although the ESKD was lower in the participants receiving a very low protein intake compared with a low protein intake. This suggests that the benefit of protein restriction in participants with advanced CKD is not due to a direct effect on kidney function but via its role in maintaining nutrition and health in participants with CKD, particularly in correcting metabolic acidosis and reducing adverse effects associated with phosphate and sodium retention (Mitch 2016;Kalantar-Zadeh 2017).

Implications for research

Additional studies in CKD participants are required to evaluate the effects of nutritional interventions, including reduced protein intake, on slowing the progression to ESKD. These include strategies to control metabolic acidosis, to reduce phosphate retention leading to lower parathyroid hormone levels and less metabolic bone disease and to reduce sodium intake, which would enhance the efficacy of angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists or other antiproteinuric medications in slowing the progression to ESKD (Mitch 2016; Bellizzi 2016). Further information on the role of the different rates of CKD progression prior to the intervention and of adherence to reduced protein diets on CKD outcome are required to understand the contribution of dietary restrictions to slowing the progression to ESKD. Whether a reduced protein intake, achieved with satisfactory adherence to the diet and without interfering with quality of life, could achieve these outcomes needs to be further evaluated (Piccoli 2016).

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Anonymous Study 2 1990 *{published data only}*

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Anonymous Study 1 1990

Methods	• Study design: parallel RCT (554 assessed for eligibility; 336 randomised); stratified before randomisation into two groups * GFR 20 to 60 mL/min/1.73 m^2; run-in for 12 months to demonstrate declining GFR • Study duration: date of first recruitment not stated. Last follow up September 1991 • Study follow-up period: about 50 months
Participants	• Countries: Italy, Germany, Sweden • Setting: multicentre (outpatient departments) (number of sites not reported) • Patients with GFR 20 to 60 mL/min/1.73 m^2; run-in for 12 months • Number: low protein diet group (70); normal protein diet group (64) • Mean age: 50 years • Sex (M:F ratio): 1.4:1 • Exclusion criteria: stable GFR during run-in period
Interventions	Low protein diet group • Prescribed protein intake: 0.6 g/kg/d • Median calculated protein intake: 0.49 g/kg/d during 1 year Normal protein diet group • Prescribed protein intake: free diet • Median calculated protein intake: 0.61 g/kg/d during 1 year Co-interventions

Anonymous Study 1 1990 *(Continued)*

	• All groups received 35 Kcal/kg
Outcomes	• ESKD measured by number commencing dialysis
Notes	• Funded by grant from Bundesministerium für Forschung und Technologie • Primary endpoint of reports was dietary compliance • No report of final study results identified • Fewer than 50 of 554 assessed for eligibility had diabetic kidney disease • Information on sequence generation and allocation concealment kindly provided by Professor Norbert Gretz

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation scheme for each centre
Allocation concealment (selection bias)	Low risk	Sealed and numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Unclear risk	No information provided. Outcome not reported in this study
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	Unclear how endpoint of onset of ESKD and the need for dialysis was determined
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear whether data on all participants were reported
Selective reporting (reporting bias)	High risk	No report of death or GFR; medians of BMI only available
Other bias	Low risk	Grant from Bundesministerium für Forschung und Technologie, FRG (No. 0704743)

Anonymous Study 2 1990

Methods	• Study design: parallel RCT (554 assessed for eligibility; 336 randomised); stratified before randomisation into two groups * GFR < 20 mL/min/1.73 m^2; run-in for three months to demonstrate declining GFR • Study duration: date of first recruitment not stated. Last follow up September 1991 • Study follow-up period: about 50 months
Participants	• Countries: Italy, Germany, Sweden

Anonymous Study 2 1990 *(Continued)*

- Setting: multicentre (number of sites not reported)
- Patients with GFR < 20 to 60 mL/min/1.73 m^2; run-in for 3 months
- Number: very low protein diet group (99); low protein diet group (103)
- Mean age: 50 years
- Sex (M:F ratio): 1.4:1
- Exclusion criteria: stable GFR during run-in period

Interventions	Very low protein diet group • Prescribed protein intake: 0.3 g/kg/d protein + amino acid/keto acid supplement • Median calculated protein intake: 0.35 g/kg/d during 1 year Low protein diet group • Prescribed protein intake: 0.6 g/kg/d protein • Median calculated protein intake: 0.56 g/kg/d during 1 year Co-interventions • All groups received 35 Kcal/kg/d
Outcomes	• ESKD measured by number commencing dialysis
Notes	• Funded by grant from Bundesministerium für Forschung und Technologie • Primary endpoint of reports was dietary compliance • No report of final study results identified • Fewer than 50 of 554 assessed for eligibility had diabetic kidney disease • Information on sequence generation and allocation concealment kindly provided by Professor Norbert Gretz

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation scheme for each centre
Allocation concealment (selection bias)	Low risk	Sealed and numbered envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Unclear risk	No information provided. Outcome not reported in this study
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	Unclear how end point of the onset of ESKD and the need for dialysis was determined
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear whether data on all participants were reported

Anonymous Study 2 1990 *(Continued)*

Selective reporting (reporting bias)	High risk	No report of death or GFR; medians of BMI only available
Other bias	Low risk	Grant from Bundesministerium für Forschung und Technologie, FRG (No. 0704743)

Bergstrom 1986

Methods	• Study design: parallel RCT • Study duration: June 1983 to September 1988 • Study follow-up period: More than 200 days
Participants	• Country: Sweden • Setting: single centre renal outpatient department • Patients aged 20 to 70 years with CrCl < 70 mL/min/1.73 m^2 and linear progression of CKD; patients were randomised if they demonstrated significant progression of CKD over 12 or 24 months • Number (randomised/analysed): low protein diet group (11/7); normal protein intake group (12/9) • Mean age ± SD (years): not reported • Sex (M/F): not reported • Exclusion criteria: treatment with immunosuppressive drugs, corticosteroids or NSAIDs
Interventions	Low protein diet group • Prescribed protein intake: 0.55 g/kg/d + essential amino acids 0.1 g/kg/d • Calculated protein intake: 0.65 ± 0.18 g/kg/d at end of study Normal protein diet group • Prescribed protein intake: unrestricted protein diet • Calculated protein intake: 0.86 ± 0.15 g/kg/d at end of study Co-interventions • Interventions to maintain blood pressure < 160/90, bicarbonate ≥ 20 mmol/L and serum phosphate ≤ 1.7 mmol/L
Outcomes	• GFR at end of study (Cr-51 EDTA measurement and CrCl)
Notes	• 57 participants assessed for eligibility; 23 randomised. 34 excluded (10 had stable kidney function, 8 progressed to ESKD, 3 withdrew before randomisation, 13 still in 12 to 24 month control period to determine progress of CKD) • Funding source: not reported • Contact with study authors for additional information: no • Other: last identified report was an interim report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement

Bergstrom 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measurement of GFR and laboratory measure unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	No information provided. Need to start dialysis was not recorded as a study outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	30% (7/23) excluded from analysis or lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Only outcome reported was GFR and unclear what other outcomes planned
Other bias	Unclear risk	Insufficient information to permit judgement

Chauveau 1986

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up period: 12 months
Participants	• Country: France • Setting: Single centre • Patients with good general medical condition; motivated to take low protein diet; CrCl 5 to 15 mL/min/1.73 m^2; SCr > 500 µmol/L in females and > 600 µmol/L in males; declining kidney function over 3 months • Number: very low protein diet group (10); low protein diet group (9) • Mean age ± SD (years): very low protein diet group (66.3 ± 6); low protein diet group (55.6 ± 10.5) • Sex M/F: very low protein diet group (5/5); low protein diet group (2/7) • Exclusion criteria: kidney disease due to diabetes; systemic disease; nephrotic syndrome; proteinuria > 3 g/d; unstable obstructive uropathy; unable to attend monthly follow-up; GI tract disorders; Not motivated to take low protein diet
Interventions	Very low protein diet group • Prescribed protein intake: 0.4 g protein/kg/d + oral supplement with keto acids (1 tab Ketosteril /6 kg BW/d) • Calculated protein intake: 0.5 g/kg/d Low protein diet group • Prescribed protein intake: 0.6 g protein/kg/d • Calculated protein intake: 0.7 g/kg/d Both groups had calorie intake of 35 to 40 Kcal/kg/d Co-interventions

Chauveau 1986 *(Continued)*

	• Bicarbonate supplements, iron and water soluble vitamins • Vitamin D and phosphate binders • Treatment for hypertension
Outcomes	• 1/serum creatinine against time • CrCl • Compliance with diet • Commencement of dialysis • Death (all causes)
Notes	• Withdrawal from therapy if poor adherence or intolerance to keto acids or to the low protein diet, uraemic symptoms, or evidence of under-nutrition, serum urea > 50 mmol/L and/or SCr > 1200 µmol/L • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Primary outcome (1/Cr or CrCl) was laboratory based and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	Decision to commence dialysis made by dialysis staff independently of study investigators
Incomplete outcome data (attrition bias) All outcomes	High risk	26% (5/19) excluded from analysis of 1/Cr but information on dialysis available for all
Selective reporting (reporting bias)	Low risk	Reported on dialysis, death, body weight, GFR measure reported
Other bias	Unclear risk	Insufficient information to permit judgement

Cianciaruso 2008a

Methods	• Study design: parallel RCT • Study duration: January 1999 to December 2006 • Study follow-up period: Mean 13 ± 4 months (6 to 18 months)
Participants	• Country: Italy

Cianciaruso 2008a *(Continued)*

- Setting: single centre University Hospital CKD clinic
- Patients aged ≥ 18 years with eGFR ≤ 30 mL/min/1.73 m^2; stable kidney function for at least 3 months
- Number (randomised/evaluated for primary outcome (serum urea nitrogen concentration)): low protein diet group (212/200); normal protein diet group (211/192)
- Mean age ± SD (years): low protein diet group (62 ± 18); normal protein diet group (62 ± 18)
- Sex (M/F): low protein diet group (112/88); normal protein diet group (110/82)
- Exclusion criteria: unstable kidney function; malignant disease; treatment with immunosuppressive drugs; UPE > 5 g/24 h; pregnancy

Interventions	Low protein diet group • Prescribed protein intake: 0.55 g/kg/d • Calculated protein intake at 12 months: 0.63 ± 0.13 g/kg/d Normal protein diet group • Prescribed protein intake: 0.8 g/kg/d • Calculated protein intake at 12 months: 0.88 ± 0.06 g/kg/d Cointerventions • Calorie intake 30 Kcal/kg/d • Overweight participants were prescribed 25 kcal/kg/d • Daily multivitamin and mineral tablet • Dietary sodium intake restricted to 2.5 g/d • Calcium supplements to guarantee calcium intake of 1000 to 1500 mg/d • Iron supplementation (200 mg/d oral element iron) as required to maintain transferrin saturation ≥ 20%
Outcomes	• ESKD (commencement of dialysis) • Death (all causes) • Monthly decrease in eGFR (eGFR calculated from MDRD equation) • Body weight • Protein-calorie malnutrition (body weight loss > 5% in one month or 7.5% in 3 months or BMI < 20 kg/m^2 + albumin < 3.2 g/dL + normal CRP)
Notes	• Funding source: Italian Ministry of University & Scientific Research (PRIN-2001; Grant 061427) • Contact with study authors for additional information: no • Other: patient survival/ESKD at 12 month and average follow up of 32 months also provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomised list, which was concealed from investigators
Allocation concealment (selection bias)	Low risk	Numbered opaque sealed envelopes opened in sequence by administration staff personnel not involved in patient care
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management

Cianciaruso 2008a *(Continued)*

Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measure & calculation (eGFR measured by MDRD formula) unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	Single centre study with same criteria for commencing dialysis (eGFR = 6 mL/min/1.73 m^2, hyperkalaemia, fluid overload, malnutrition)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients accounted for; 9/423 (2%) lost to follow-up at mean 13 months; 15/423 (3.5%) lost to follow-up by 4 years
Selective reporting (reporting bias)	Low risk	All expected outcomes (death, commencement of dialysis, GFR, protein-calorie malnutrition) reported
Other bias	Low risk	Investigator driven. Partially funded by grant from Italian Ministry of University & Scientific Research (PRIN-2001; Grant 061427)

Di Iorio 2003

Methods	• Study design: parallel RCT • Study duration: not reported • Study follow-up period: 24 months
Participants	• Country: Italy • Setting: single centre; renal outpatient clinic • Patients with CrCl ≤ 25 mL/min/1.73 m^2 (CKD stage 4) receiving low protein diet (0.6 g/kg/d) for 6 to 12 months and ESA for 6 to 12 months • Number: very low protein diet group (10); low protein diet group (10) • Mean age ± SD (years): very low protein diet group (57 ± 17); low protein diet group (52 ± 15) • Sex (M/F): very low protein diet group (6/4); low protein diet group (6/4) • Exclusion criteria: bleeding or diseases potentially affecting ESA response (i.e. neoplastic diseases, infectious diseases, severe malnutrition)
Interventions	Very low protein diet group • Prescribed protein intake: 0.3 g protein/kg/d + keto-analogues and essential amino acids (Alfa Kappa 1 tablet/5 kg body weight) • Calculated protein intake: 0.5 ± 0.01 g/kg/d at 12 months Low protein diet group • Prescribed protein intake: 0.6 g protein/kg/d • Calculated protein intake 0.79 ± 0.02 g/kg/d at 12 months Co-interventions • Sodium restriction • Iron supplementation (maintain transferrin saturation > 20% and serum ferritin 100 to 500 mg/dL) • Antihypertensive therapy (maintain blood pressure < 140/90 mmHg) • 2 to 3 g/d of sodium bicarbonate, folic acid and vitamin B12 supplements • Phosphate binders (maintain serum phosphate levels < 5.5 mg/dL)

Di Iorio 2003 *(Continued)*

Outcomes	• ESKD: end point was GFR ≤ 7 mL/min/1.73 m^2 or development of uraemic complications requiring haemodialysis • GFR measured by CrCl • Body weight at 12 months
Notes	• Three patients in each group had diabetic kidney disease • 3 month run-in period before randomisation to verify stability of Hb coefficient • All participants required to restrict dietary sodium intake • Primary outcome was % reduction in ESA dose • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Outcome was based on laboratory outcome and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	No information provided on criteria used to commence dialysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	All included participants accounted for
Selective reporting (reporting bias)	Low risk	Reported on expected outcomes (death, dialysis, GFR, body weight)
Other bias	Unclear risk	Insufficient information to permit judgement

Garneata 2013

Methods	• Study design: parallel RCT • Study duration: March 2006 to April 2009 • Study follow-up period: 15 months
Participants	• Country: Romania • Setting: Single centre; renal outpatient clinic

Garneata 2013 *(Continued)*

- Stable GFR for 3 months before enrolment while receiving low protein diet (0.6 g/kg/d); CKD stage 4 (GFR < 30 mL/min/1.73 m^2); agreed to keep to the diet and to the monitoring schedule; compliance confirmed if protein & energy intake ± 10% & visit adherence ± 7 days after 1st visit
- Number: very low protein diet group (104); low protein diet group (103)
- Median age (years): very low protein diet group (55.2); low protein diet group (53.6)
- Sex M/F: very low protein diet group (65/39); low protein diet group (61/42)
- Exclusion criteria: poorly controlled hypertension; diabetes; heart failure; malabsorption; liver disease; chronic inflammation; uraemic symptoms; anorexia

Interventions	Very low protein diet group • Prescribed protein intake: 0.3 g vegetable protein/kg/d + Ketosterol 1 tablet/5 kg body weight • Calculated protein intake: median 0.29 g/kg/d (0.29 to 0.31) during 1 year Low protein diet group • Prescribed protein intake 0.6 g protein/kg/d • Calculated protein intake: median 0.58 g/kg/d (0.57 to 0.59) during 1 year Both groups received 30 kcal/d Co-interventions • Water soluble vitamins, nutritional counselling, antihypertensive and lipid lowering agents, iron supplements and EPO, vitamin D and calcium supplements, phosphate binders
Outcomes	• Need to start dialysis • Death (all causes) • SGA, BMI
Notes	• Information on sequence generation and allocation concealment requested from authors and received • Funding source: none received

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using computer generated numbers
Allocation concealment (selection bias)	Low risk	Allocation utilising opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	End point of eGFR (calculated from serum creatinine by MDRD formula) is a laboratory measure and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	End point of the onset of ESKD determined by committee without knowledge of treatment groups

Garneata 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	3.3% lost to follow up/discontinued diet but all participants included in analyses
Selective reporting (reporting bias)	Low risk	Expected outcomes (ESKD, death (all causes), GFR, BMI) reported
Other bias	Low risk	No funding support received

Ihle 1989

Methods	• Study design: parallel RCT • Duration of study: not reported • Study follow-up period: 18 months
Participants	• Country: Australia • Setting: single centre, outpatient department • Patients with stable SCr 350 to 1000 µmol/L for 3 months before enrolment; CKD stage: 4-5 • Number (randomised/analysed): very low protein diet group (34/31); normal protein diet group (38/33) • Mean age ± SD (years): very low protein diet group (37.2. ± 5.7); normal protein diet group (36.8 ± 4.8) • Sex (M/F): very low protein diet group (22/9); normal protein diet group (21/12) • Exclusion criteria: potentially reversible kidney dysfunction; systemic disease (diabetes, connective tissue disorders); medications that could alter course of disease (immunosuppressive agents, ACEi)
Interventions	Very low protein diet group • Prescribed protein intake: 0.4 g protein/kg/d Normal protein diet group • Prescribed protein intake: > 0.75 g/kg/d Both groups received 35 to 40 kcal/kg/d Co-interventions • Not reported
Outcomes	• ESKD: SCr > 1300 µmol/L or uraemic symptoms requiring dialysis • Decline in GFR over time (measured by Cr-51 EDTA clearance) • Body weight
Notes	• Three participants withdrew voluntarily; 5 excluded for not complying with medication or dietary regimen • Data from 64 evaluated participants included • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement

Ihle 1989 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Primary outcome was laboratory measurement of GFR by EDTA clearance and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	High risk	Decision to commence dialysis depending on uraemic symptoms and/or SCr > 1300 µmol/L
Incomplete outcome data (attrition bias) All outcomes	High risk	8/72 (11%) excluded from analyses (3 withdrew; 5 excluded for non-compliance with diet)
Selective reporting (reporting bias)	High risk	Report on number reaching ESKD & GFR. Body weight only reported graphically. Deaths not reported but there appear to be no deaths
Other bias	Unclear risk	Insufficient information to permit judgement

Locatelli 1989

Methods	• Study design: parallel RCT • Study duration of study: April 1984 to May 1985 • Study follow-up period: 2 years
Participants	• Country: Italy • Setting: multicentre (21 sites) • Patients with CKD aged 18 to 65 years; GFR < 60 mL/min/1.73 m^2 • Number (randomised/completed): low protein diet group (226/165); normal protein diet group (230/146) • Mean age, range (years): all participants (48.5; range 18 to 65) • Sex M/F: all participants (247/209) • Exclusion criteria: variation in SCr > 100% in 3 month preliminary observation period; nephrotic syndrome (proteinuria > 3g/24 h, serum albumin < 25 g/L); acute obstruction of urinary tract; acute infectious disease; systemic illness (malignancy/ autoimmune disease); disease necessitating drugs that might affect underlying kidney disease; previous surgery of the GI tract; body weight < 45 kg and > 90 kg
Interventions	Low protein diet group • Prescribed protein intake: 0.6 g protein/kg/d • Calculated protein intake: 0.72 g/kg/d Normal protein diet group • Prescribed protein intake: 1.0 g protein/kg/d • Calculated protein intake: 0.9 g/kg/d Co-interventions

Locatelli 1989 *(Continued)*

	• Antihypertensive medications, phosphate binders, vitamins, bicarbonate • No patient received vitamin D or ACEi
Outcomes	• Number requiring dialysis or doubling of baseline SCr • Fall in GFR measured by CrCl • Body weight
Notes	• True difference in protein intake < 0.4 g protein/kg/d, estimated to be 0.18 g/kg/d based on urinary urea nitrogen analysis and 0.3 g/kg/d based on diet records • Events recorded at 24 months from the start of study • Information on numbers requiring dialysis provided by Professor Locatelli • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomisation- blocks of 4, 1/1 ratio performed at study headquarters "
Allocation concealment (selection bias)	Low risk	Central randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measurement and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	31.7% lost by final follow up
Selective reporting (reporting bias)	High risk	Not all reviews pre-specified outcomes mentioned. No weights, no adverse events
Other bias	Unclear risk	Insufficient information to permit judgement

Malvy 1999

Methods	• Study design: parallel RCT • Study duration: January 1983 to May 1987 • Study follow-up period: 3 to 35 months
Participants	• Country: France • Setting: multicentre (two sites)

Malvy 1999 *(Continued)*

	• Patients with CKD with GFR < 19 mL/min/1.73 m^2 (calculated by Cockcroft formula) • Number: very low protein diet group (25); low protein diet group (25) • Mean age ± SD (years): very low protein diet group (53.8 ± 11); low protein diet group (56.0 ± 14) • Sex (M/F): very low protein diet group (14/11); low protein diet group (15/10) • Exclusion criteria: DM; cancer; systemic disease; obstructive uropathy; RPGN; lethal disease
Interventions	Very low protein diet group • Protein intake: 0.3 g protein/kg/d • Oral keto acid supplement (Ketosteril 1 tab/6 kg/d): 0.17 g/kg/d • Calculated protein intake: 0.58 g/kg/d Low protein diet group • Protein intake: 0.6 g protein/kg/d • Calculated protein intake: 0.79 g/kg/d Co-interventions • Vitamin supplements, antihypertensive medications
Outcomes	• ESKD: CrCl < 5 mL/min/1.73 m^2 or uraemic intolerance diagnosed by two nephrologists and requiring dialysis • Weight, lean body mass, fat body mass • Death (all causes)
Notes	• Information on numbers reaching ESKD provided by Dr Bagros • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Primary outcome of CrCl based on laboratory outcome so unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	GFR < 5 mL/min/1.73 m^2 estimated from (CrCl + urea clearance)/2 or uraemic symptoms requiring dialysis as determined by 2 nephrologists
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear whether all participants included in outcome measurement

Malvy 1999 *(Continued)*

Selective reporting (reporting bias)	High risk	Numbers reaching GFR endpoint only available graphically
Other bias	Unclear risk	Insufficient information to permit judgement

MDRD Feasibility Study A 1989

Methods	• Study design: parallel RCT • Study duration: September 1985 to September 1988 • Study follow-up period: 14 months (mean); range 2 to 22 months
Participants	• Country: USA • Setting: multicentre (9 sites) • CKD with GFR 25 to 80 mL/min/1.73 m^2 with age 18 to 75 years and showing progressive decline in GFR; dietary protein intake ≥ 0.9 g/kg/d • Number: low protein diet group (10); normal protein diet group (11) • Mean age ± SD: 44.8 ± 12.3 years • Sex M/F: 15/6 • Exclusion criteria: doubtful compliance; pregnancy; body weight < 80% or > 160% of standard body weight; proteinuria > 10 g/d; renal artery stenosis; urinary tract obstruction; DM requiring insulin; kidney transplant; chronic medical conditions; immunosuppressive agents, NSAIDs
Interventions	Low protein diet • Prescribed protein diet: 0.575 g protein/kg/d • Calculated protein intake: 0.85 ± 0.03 g/kg/d Normal protein diet • Prescribed protein diet: 1.2 g protein /kg/d • Calculated protein intake: 1.04 ± 0.04 g/kg/d Co-interventions • Antihypertensive medications, phosphate binders
Outcomes	• Slope of GFR decline over time (rate of change of GFR) by renal clearance of I-125 Iothalamate • Death (all causes) • Number reaching ESKD • Malnutrition
Notes	• Third group (9), which received very low protein diet, not included in analyses • Data on deaths not separated between patient groups • Funding source: National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random permutated blocks to ensure equal balance of participants assigned to each treatment combination"

MDRD Feasibility Study A 1989 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Centrally administered at data co-ordination centre through telephone contact"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measurement (iothalamate clearance) and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	Onset of ESKD endpoint reviewed by Clinical Committee without knowledge of dietary assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; 4 patients lost to follow-up
Selective reporting (reporting bias)	High risk	No report of numbers in each group death (combined data only). No information on final weights provided
Other bias	Low risk	National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

MDRD Feasibility Study B 1989

Methods	• Study design: parallel RCT • Study duration: September 1985 to September 1988 • Study follow-up period: 14 months (mean); range 2 to 22 months
Participants	• Country: USA • Setting: multicentre (9 sites) • CKD with GFR 7.5 to 24 mL/min/1.73 m^2; aged 18 to 75 years and showing progressive decline in GFR over 3 months to 3 years; dietary protein intake ≥ 0.9 gm/kg/d • Number: very low protein diet group (22); low protein diet group (23) • Mean age ± SD: 50.4 ± 12.5 years (includes 21 participants treated with a very low protein diet + amino-acids & not included in analyses) • Sex M/F: 25/20 (includes 21 participants treated with a very low protein diet + amino-acids and not included in analyses) • Exclusion criteria: doubtful compliance; pregnancy; body weight < 80% or > 160% of standard body weight; proteinuria > 10 g/d; renal artery stenosis; urinary tract obstruction; DM requiring insulin; kidney transplant; chronic medical conditions; immunosuppressive agents; NSAIDs
Interventions	Very low protein diet • Prescribed protein intake: 0.28 g protein/kg/d + keto acid/amino acid mixture (total nitrogen content 28.6 mg/kg/d) • Calculated protein intake: 0.5 ± 0.03g/kg/d Low protein diet • Prescribed protein intake: 0.575 g protein /kg/d (range 0.46 to 0.69 g/kg/d)

MDRD Feasibility Study B 1989 *(Continued)*

	• Calculated protein intake: 0.72 ± 0.03 g/kg/d Co-interventions • Antihypertensive medications, phosphate binders, iron supplements
Outcomes	• Slope of GFR decline over time by renal clearance of I^{125} Iothalamate • Death (all causes) • Number reaching ESKD • Malnutrition
Notes	• Third group of participants (21) receiving very low protein + amino acids excluded from analyses • Data on deaths not separated between groups • Funding source: National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random permutated blocks to ensure equal balance of participants assigned to each treatment combination"
Allocation concealment (selection bias)	Low risk	"Centrally administered at data co-ordination centre through telephone contact"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measurement (iothalamate clearance) and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	Onset of ESKD endpoint reviewed by Clinical Committee without knowledge of dietary assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for; 1 patient lost to follow-up
Selective reporting (reporting bias)	High risk	No report of numbers in each group on death (combined data only). No information on final weights provided
Other bias	Low risk	National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

MDRD Study 1 1989

Methods	• Study design: parallel RCT • Study duration: 1 January 1989 to 31 December 31 1992

MDRD Study 1 1989 *(Continued)*

	• Study follow-up period: 2.2 years (mean)
Participants	• Country: USA • Setting: multicentre (15 sites) • CKD with CrCl 30 to 70 mL/min/1.73 m^2; aged 18 to 70 years; mean arterial BP < 125 mmHg; dietary protein intake > 0.9 g/kg/d • Number: low protein diet group (291); normal protein diet group (294) • Mean age: 52 years • Sex (M:F): ratio 0.6 for all included participants (MDRD study 1 and 2) • Exclusion criteria: pregnancy; body weight < 80% or > 160% of standard body weight; DM requiring insulin; kidney transplant; chronic medical conditions
Interventions	Low protein diet • 0.58 g protein/kg/d • Calculated protein intake: 0.7 g/kg/d (taken from Fig 1) Normal protein diet • 1.3 g protein/kg/d • Calculated protein intake: 1.1 g/kg/d (taken from Fig 1) Co-interventions • Antihypertensive medications, phosphate binders
Outcomes	• Slope of GFR decline over time by renal clearance of I-125 Iothalamate • Death (all causes) • Number reaching ESKD
Notes	• Data on dialysis numbers were obtained from the authors • 15 deaths overall in study but unclear which groups these occurred in • Funding source: National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random permutated blocks to ensure equal balance of participants assigned to each treatment combination" Patients stratified before randomisation according to blood pressure & rate of progression of kidney disease during 3 month baseline period
Allocation concealment (selection bias)	Low risk	"Centrally administered at data co-ordination centre through telephone contact"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measurement (iothalamate clearance) and unlikely to be influenced by lack of blinding

MDRD Study 1 1989 *(Continued)*

Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	No information on criteria for starting dialysis provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 lost to follow-up from low protein diet group and 3 lost to follow-up from normal protein diet group
Selective reporting (reporting bias)	High risk	No report of numbers in each group reaching ESKD or death (combined data only); did report weight & GFR measure
Other bias	Low risk	National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

MDRD Study 2 1989

Methods	• Study design: parallel RCT • Duration of study duration: 1 January 1989 to 31 December 1992 • Study follow-up period: 2.2 years (mean)
Participants	• Country: USA • Setting: Renal outpatient clinics; 15 centres • Relevant health status: GFR < 30 mL/min/1.73 m^2; aged 18 to 70 years; mean arterial BP < 125 mmHg; dietary protein > 0.9 g/kg/d • Number: very low protein diet group (126); low protein diet group (129) • Mean age: 52 years • Sex M/F ratio: 0.6 • Exclusion criteria: pregnancy; body weight < 80% or > 160% of standard body weight; DM requiring insulin; kidney transplant; chronic medical conditions
Interventions	Very low protein diet group • 0.28 g protein/kg/d with oral keto acid and essential amino acid supplement (nitrogen content 28.8 mg/kg/d) • Calculated protein intake: 0.4 g/kg/d (taken from Fig 1) Low protein diet group • 0.58 g protein/kg/d • Calculated protein intake: 0.7 g/kg/d (taken from Fig 1) Co-interventions • Antihypertensive medications including ACEi and calcium channel blockers, phosphate binders
Outcomes	• Slope of GFR decline over time by renal clearance of I-125 Iothalamate • Death (all causes) • Number reaching ESKD
Notes	• Funding source: National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA
Risk of bias	

MDRD Study 2 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random permutated blocks to ensure equal balance of participants assigned to each treatment combination" Patients stratified before randomisation according to blood pressure & rate of progression of kidney disease during 3 month baseline period"
Allocation concealment (selection bias)	Low risk	"Centrally administered at data co-ordination centre through telephone contact"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Laboratory measurement (iothalamate clearance) and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	No information on criteria for starting dialysis provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss to follow-up 1.2% (3/255) in study 2
Selective reporting (reporting bias)	High risk	No report of numbers in each group reaching ESKD or death (combined data only). Did report weight & GFR measure
Other bias	Low risk	National Institute of Diabetes, Digestive and Kidney Disease and Health Care Finance Administration, NIH, USA

Meloni 2004

Methods	• Study type: parallel RCT • Duration of study duration: 1 January 2001 to 31 December 2001 • Study follow-up period: 1 year
Participants	• Country: Italy • Setting: single centre • Patients with CKD; GFR < 60 mL/min/1.73 m^2 • Number: low protein diet group (44); normal protein diet group (45) • Mean age ± SD (years): low protein diet group (60.2 ± 13.5); normal protein diet group (64.2 ± 13.4) • Sex M/F: 46/43 • Exclusion criteria: systemic disease chronic infection; cancer; receiving corticosteroids/immunosuppressive agents
Interventions	Low protein diet group • Prescribed protein intake: 0.6 g protein/kg/d • Calculated protein intake at 1 year: 0.67± 0.21 g/kg/d

Meloni 2004 *(Continued)*

	Normal protein diet group • Prescribed protein diet: free protein diet • Calculated protein intake at 1 year: 1.54 ± 0.39g/kg/d Co-interventions • Treatment for hypertension, hyperlipidaemia, anaemia
Outcomes	• GFR at 12 months measured by Cr-51 EDTA clearance • Body weight • BMI
Notes	• Average GFR 46.8 ± 5.8 mL/min/1.73 m^2 of all included participants • Study separately randomised 80 participants with DM into low and normal protein groups • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Simple randomisation using dedicated software generating casual numbers to assign participants to treatment groups and remaining participants were placed in control group"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Primary outcome of GFR was measured by EDTA clearance and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	No information provided as "need to start dialysis" was not a reported outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appear to have completed follow up
Selective reporting (reporting bias)	High risk	Did not report on deaths or ESKD
Other bias	Unclear risk	Insufficient information to permit judgement

Milovanov 2009

Methods	• Study design: parallel RCT • Study duration: not reported

Milovanov 2009 *(Continued)*

	• Study follow-up period: 3 to 35 months
Participants	• Country: Russia • Setting: single centre • Patients with CKD 3-4; lupus nephritis; systemic vasculitis • Number: low protein diet group + keto/amino acids (18); normal protein diet (10) • Mean age ± SD (years): not reported • Sex M/F: not reported • Exclusion criteria: not reported
Interventions	Low protein diet group • Prescribed protein intake: 0.7g/kg/d (animal protein 0.4g/kg/d, vegetable protein 0.2g/kg/d and essential amino acids 0.1 g/kg/d) • Actual protein intake: not reported Normal diet group • Prescribed protein intake: free protein diet 1.1 to 1.3 g/kg/d • Actual protein intake: not reported Co-interventions • Not reported
Outcomes	• Final GFR: method of measurement not reported
Notes	• Dr Larisa Prikhodina assisted with translation and data extraction • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Unclear risk	Method of GFR measurement unclear
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement

Milovanov 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient information to permit judgement

Mircescu 2007

Methods	• Study design: open-label, parallel RCT • Study duration: 15 January 2004 to 15 February 2005 • Study follow-up period: 60 weeks with a 12-week baseline phase
Participants	• Country: Romania • Setting: single centre • Relevant health status: adults with eGFR 30 mL/min/1.73 m^2 by MDRD formula; Stable kidney function for at least 12 weeks before enrolment (reduction in eGFR ≤ 4 mL/min/y); well controlled arterial pressure; proteinuria < 1 g/g urinary creatinine; good nutritional status (SGA A/B; serum albumin > 35 g/L); anticipated good compliance with the prescribed diet • Number: very low protein diet (27); low protein diet (26) • Mean age ± SD (years): very low protein diet (55 ± 12.7); low protein diet (53.6 ± 11.0) • Sex M/F: Very low protein diet (17/10); low protein diet (15/11) • Other relevant information: not reported • Exclusion criteria: poorly controlled arterial pressure (> 145/85 mmHg); comorbid conditions (DM, heart failure, active hepatic disease, digestive diseases with malabsorption, inflammation/anti-inflammatory therapy); uraemic complications (pericarditis, polyneuropathy); feeding inability (anorexia, nausea)

Interventions	Very low protein diet
	• Prescribed protein diet: 0.3 g/kg/d vegetable protein + keto-analogues/essential amino acids (Ketosteril 1 capsule/5 kg of ideal body weight/d)
	• Calculated protein intake at 48 weeks: 0.32 ± 0.07g/kg/d
	Low protein diet
	• Prescribed protein intake: 0.6 g/kg/d (including high biological value proteins)
	• Calculated protein intake 48 weeks: 0.59 ± 0.08 g/kg/d
	Total recommended energy intake: 30 kcal/kg/d
	Co-interventions
	• All received calcium and water soluble vitamin supplementation as required
	• Serum ferritin
	  * < 200 ng/mL: 100 mg IV iron sucrose weekly
	  * 200 to 400 ng/mL: 100 mg IV iron sucrose every other week
	  * 400 to 500 ng/mL: 100 mg IV iron sucrose monthly
	  * > 500 ng/mL: iron administration stopped

Outcomes	• Death (all causes) • ESKD and commencement of dialysis • Change in GFR by MDRD formula • Adverse events
Notes	• Dietary compliance was assessed weekly for the first month, every 4 weeks for the next 8 weeks and every 12 weeks thereafter

Mircescu 2007 *(Continued)*

- Funding source: "C-reactive protein, and parathyroid hormone, as well as logistics for the transportation of blood samples to the central laboratory, were supported by F. Hoffmann-LaRoche. No other financial support was received by any of the authors"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	eGFR calculated from SCr using MDRD formula. Based on laboratory measure and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	"RRT initiation was decided by the Ethical Committee of the Hospital considering the clinical and biochemical status of the patient (...). Members of the Committee were unaware of which arm the patient had been assigned to"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for
Selective reporting (reporting bias)	Low risk	All reviews prespecified outcomes mentioned
Other bias	Unclear risk	Insufficient information to permit judgement

Rosman Study 1 1984

Methods	• Study design: parallel RCT • Study duration: January 1982 to January 1984 • Follow up: 153/248 followed up for at least 36 months
Participants	• Country: Netherlands • Setting: single centre • Patients with CKD with CrCl 30 to 60 mL/min/1.73 m^2; aged 15 to 73 years • Number: low protein diet group (74); normal protein diet group (77) • Mean age (range): 48 years (15 to 73) • Sex M/F ratio: 0.54 • Exclusion criteria: immunological diseases or cancer; patients on NSAIDs
Interventions	Low protein diet group (group B) • Prescribed protein diet: 0.6 g protein/kg/d

Rosman Study 1 1984 *(Continued)*

	• Calculated protein intake: not available (graphical only) Normal protein diet groups (Groups A1, A2) • Prescribed protein diet: free diet • Calculated protein intake: not available (graphical only) Co-interventions • Antihypertensive medications; sodium restriction; vitamin supplement; phosphate binders
Outcomes	• GFR decline measured by slope of reciprocal SCr (1/SCr) over time • Number with ESKD • Number of deaths • Weight
Notes	• Updated report (1989) from previous paper (Lancet 1984; ii:1291-1296) • Eight participants received a kidney transplant in the low protein diet group and four in the control group and were counted as kidney death events • Urea excretion given graphically only • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	End point of CrCl is a laboratory outcome and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	Need to start dialysis determined by CrCl < 4 mL/min/1.73 m^2 Also included in analysis of ESKD were participants who received pre-emptive transplants
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% (10/248) excluded from analysis (lost to follow-up 9, withdrawn 1)
Selective reporting (reporting bias)	Low risk	Reported ESKD, GFR, death and weight but weight and GFR data not able to be included in meta-analyses
Other bias	Unclear risk	Insufficient information to permit judgement

Rosman Study 2 1984

Methods	• Study design: parallel RCT • Study duration: January 1982 to January 1984 • Study follow-up period: 153 of 248 followed up for at least 36 months
Participants	• Country: Netherlands • Setting: single centre • CKD with CrCl 10 to 30 mL/min/1.73 m^2 • Number: very low protein diet (56); normal protein diet group (41) • Mean age (range): 48 years (15 to 73) • Sex M/F ratio: 0.54 • Exclusion criteria: immunological diseases or cancer; patients on NSAIDs
Interventions	Very low protein diet group (Group C) • Prescribed protein intake: 0.4 g protein/kg/d • Calculated protein intake: not reported (graphical only) Normal protein diet group (Group A2) • Prescribed protein intake: free diet • Calculated protein intake: not reported (graphical only) Co-interventions • Antihypertensive medications; sodium restriction; vitamin supplement; phosphate binders
Outcomes	• GFR measured by slope of reciprocal SCr (1/SCr) over time • Number with ESKD • Number of deaths • Weight
Notes	• Updated report (1989) from previous paper (Lancet 1984; ii:1291-1296) • Eight participants received a renal transplant in the low protein diet group and four in the control group and were counted as renal death event • Data from total of 248 participants included in review • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	End point of CrCl is a laboratory outcome and unlikely to be influenced by lack of blinding

Rosman Study 2 1984 *(Continued)*

Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Low risk	Need to start dialysis determined by CrCl < 4 mL/min/1.73 m2 Also included in analysis of ESKD were participants who received pre-emptive transplants
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% (10/248) excluded from analysis (lost to follow up 9, withdrawn 1)
Selective reporting (reporting bias)	Low risk	Reported ESKD, GFR, death and weight but weight and GFR data not able to be included in meta-analyses
Other bias	Unclear risk	Insufficient information to permit judgement

Teplan 1998

Methods	• Study design: parallel RCT • Duration of study: not reported • Study follow-up period: 3 years
Participants	• Country: Czech Republic • Setting: outpatient • Patients with CKD • Number: very low protein diet (35); low protein diet (38); restricted protein diet (32) • Age range: 26 to 78 years • Sex (M/F): 50/55 • Exclusion criteria: diabetic kidney disease; failure to co-operate; compliance ≤ 50%; severe associated disease (cancer, severe forms of atherosclerosis, chronic infection, immunosuppression)
Interventions	Very low protein diet • Prescribed protein diet: 0.4 g/kg/d + keto amino acids Low protein diet • Prescribed protein diet: 0.6 g/kg/d Restricted protein diet • Prescribed protein diet: 0.8 to 1.0 g/kg/d Co-interventions • Hypertension treated with low dose ACEi and CCB
Outcomes	• Metabolic status • Kidney function (SCr, urea, proteinuria)
Notes	• Abstract-only publication; no full text publication identified • Funding source: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement

Teplan 1998 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Study was described as randomised, method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Unclear risk	Insufficient information to permit judgement
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	Insufficient information to permit judgement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to permit judgement
Selective reporting (reporting bias)	High risk	No extractable data; no full-text publication identified
Other bias	Unclear risk	Insufficient information to permit judgement

Williams 1991

Methods	• Study design: parallel RCT • Duration of study: not reported • Study follow-up period: 1 to 58 months (17.7 months in low protein diet group; 21.4 months in normal protein diet group)
Participants	• Country: UK • Setting: multicentre (2 sites) • CKD with Cr > 150 µmol/L in males and > 130 µmol/L in females; evidence of kidney functional deterioration on > 3 serial measurements of SCr/CrCl over 6 months pre randomisation; adults < 70 years; SCr < 900 µmol/L and phosphate < 2 mmol/L with stable biochemistry • Number: low protein diet group (33); normal protein diet group (32) • Mean age ± SEM (years): low protein diet group (43 ± 2.3); normal protein diet group (44.5 ± 2.2) • Sex M/F: low protein diet group (20/13); normal protein diet group (21/11) • Exclusion criteria SCr > 900 µmol/L and/or phosphate > 2 mmol/L; uraemic symptoms; receiving active therapy for underlying kidney disease, malignancy; psychologically unstable or non-compliant; obese on reducing diet; dietary protein < 0.8 g/kg/d; withdrawn if developed clinical signs of malnutrition
Interventions	Low protein diet group • Prescribed protein diet: 0.6 g protein/kg/d • Calculated protein intake: 0.69 ± 0.02 g/kg/d Normal protein diet group

Williams 1991 *(Continued)*

- Prescribed protein intake: > 0.8 g protein/kg/d
- Calculated protein diet: 1.14 ± 0.05 g/kg/d

Daily energy intake: 30 kcal/kg/d

Co-interventions

- Antihypertensive medications; sodium restriction; vitamin supplements

Outcomes	• Number requiring dialysis • Number of deaths • Change in 24 hr CrCl • Slope of reciprocal SCr (1/SCr) over time • Weight
Notes	• A third group of participants (low phosphorus intake, n = 30) was not kept for analysis • Events recorded at 18 months from the start of study • Funding source: supported by the Mersey Region Association for Kidney Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pack of numbered cards and random number tables
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded and lack of blinding may influence patient management
Blinding of outcome assessment (detection bias): End or change in GFR End of change in GFR	Low risk	Primary outcome (change in CrCl) was a laboratory measure and unlikely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias): Need to start dialysis Need to start dialysis	Unclear risk	No information provided on criteria for starting dialysis
Incomplete outcome data (attrition bias) All outcomes	High risk	15% (10/65) excluded from calculation of primary outcome of change in CrCl
Selective reporting (reporting bias)	Low risk	Reported on number requiring dialysis, deaths, change in creatinine and weight
Other bias	Unclear risk	Insufficient information to permit judgement

ACEi - angiotensin-converting enzyme inhibitors; BMI - body mass index; BP - blood pressure; CCB - calcium channel blockers; CKD - chronic kidney disease; CrCl - creatinine clearance; CRP - C-reactive protein; DM - diabetes mellitus; ESA - erythrocyte stimulating agent; ESKD - end-stage kidney disease; EPO - erythropoietin; GI - gastrointestinal; (e)GFR - (estimated) glomerular filtration rate; Hb - haemoglobin; MAP - mean arterial pressure; M/F - male/female; MDRD - Modification of Diet in Renal Disease; NSAID - nonsteroidal anti-inflammatory drugs;

RPGN - rapidly progressive glomerulonephritis; SCr - serum creatinine; SD - standard deviation; SGA - Subjective Global Assessment; UPE - urinary protein excretion

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bernard 1996	Wrong intervention: RCT comparing keto acid supplements with no supplements in participants on the same protein intake; patients only treated for three months
Bernhard 2001	Wrong intervention: RCT, randomised to keto acid supplements with participants maintaining the same protein diet
Choi 2012a	Wrong intervention: RCT comparing keto acid supplementation with no supplements in participants on the same low protein diets
Coresh 1994	Wrong intervention: RCT, participants randomised to keto acid supplements
Di Iorio 2009a	Wrong duration of follow-up: cross-over study comparing very low protein diet supplemented with keto acids with low protein diet; follow-up for only 6 months in each part of study
Di Iorio 2012a	Wrong duration of follow-up: cross-over study comparing very low protein diet supplemented with keto acids with low protein diet; each intervention for one week only
DODE Study 2000	Wrong intervention: RCT, participants randomised to diet or dialysis
El Nahas 1987	Wrong intervention: RCT comparing different distribution through day of protein intake; protein intake in both groups the same
ERIKA Study 2007	Wrong population. included 35% diabetic patients
Garibotti 2018	Wrong duration: 24 weeks duration only
Garini 1992	Wrong intervention: RCT comparing very low protein intake (0.4 g/kg/d) + keto acids/essential amino acids (0.2 g/kg/d) with low protein intake (0.6 g/kg/d) but nitrogen intake did not differ between groups
Hecking 1980	Wrong duration: six weeks duration only
Herselman 1995	Wrong duration: RCT comparing very low protein diet with low protein diet; follow-up only for 9 months
Ideura 2003	Wrong duration: RCT comparing different protein intakes but duration of follow up is uncertain
IRCCA Study 1990	Wrong intervention: RCT, randomised to keto acid supplements
Kopple 1982	Wrong duration: RCT comparing low with very low protein diet but follow up averaged only 12 weeks
Laville 1994	Wrong duration: RCT comparing low protein with normal protein diet but follow-up for only 6 months
Lim 2000	Wrong duration: six months duration only
Maksic 2004	Wrong duration: RCT, six months duration

Study	Reason for exclusion
Prakash 2004	Wrong duration: less than 12 months duration; compared low protein with very low protein diet supplemented with keto-analogues
Ren 2002	Wrong intervention: RCT comparing same low protein diet (0.5 to 0.6 g/kg/d) in both groups with keto acids added in one group
Rosenberg 1987	Wrong duration: cross-over study with participants only studied for 11 days in each phase
Sanchez 2010	Wrong intervention and duration: RCT comparing low protein diet with diet in which some foods were replaced by low protein foods; follow-up only 6 months
Teplan 2003	Wrong intervention: RCT comparing additional keto acids with no addition in participants on a low protein diet and EPO
Teplan 2006	Wrong intervention: RCT comparing low protein diet (0.6 g/kg/d) + keto-analogues with low protein diet + placebo in obese participants with CKD
Ursea 2002	Wrong duration: RCT comparing 0.3 g/kg of protein (with keto-analogues) versus 0.6 g/kg but follow up only to 6 months
Vujic 1987	Wrong intervention: RCT but no separation in reported nitrogen intake as low protein diet supplemented by amino acids equivalent to 0.2 g/kg/d of protein
Zhang 2015	Wrong duration: RCT comparing low protein with normal protein diet but outcome data only available to 6 months
Zhang 2016b	Wrong population: patients with steroid resistant nephrotic syndrome and minor reduction in GFR

CKD - chronic kidney disease; EPO - erythropoietin; GFR - glomerular filtration rate; RCT - randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT01418508

Trial name or title	Effects of Low Protein Diet Supplemented Keto-/Amino Acid in Preventing the Progression of Chronic Kidney Disease (CKD) (ELPD Study)
Methods	• Parallel RCT
Participants	Inclusion criteria • Patients aged 18 to 75 years with CKD stage 3b and 4 (15 mL/min/1.73 m^2 < GFR < 45 mL/min/1.73 m^2, estimated by EPI formula) receiving conservative treatment for CKD Exclusion criteria • DM • Incapable of following study requirements to control diet • GFR < 15 mL/min/1.73 m^2 • Hypercalcaemia or hyperkalaemia (> normal upper limit) • Other serious disease (heart, lung, brain) within the last 3 months • Cardiac failure stage IV NYHA
Interventions	• Low protein diet plus alpha-keto acid 0.6 g protein/kg/d • Very low protein diet plus alpha-keto acid 0.3 g protein/kg/d

NCT01418508 *(Continued)*

Outcomes	• Changes in GFR (1 year) • Compliance to diet • Quality of life (1 year) • Cardiovascular death • Nutritional status defined by anthropo-plicometry, biochemistry, body bioimpedance analysis, subjective global nutritional assessment
Starting date	August 2011
Contact information	Xuemei Li, M.D.& Ph.D. 8610-65295058 0605.mei@gmail.com, Limeng Chen, M.D.& Ph.D. 8610-65295351 climeng2000@yahoo.com.c
Notes	Investigators contacted but no reply received

CKD - chronic kidney disease; DM - diabetes mellitus; GFR - glomerular filtration rate; NYHA - New York Heart Association; RCT - randomised controlled trial

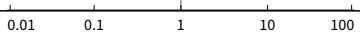
DATA AND ANALYSES

Comparison 1. Low protein diet versus normal protein diet

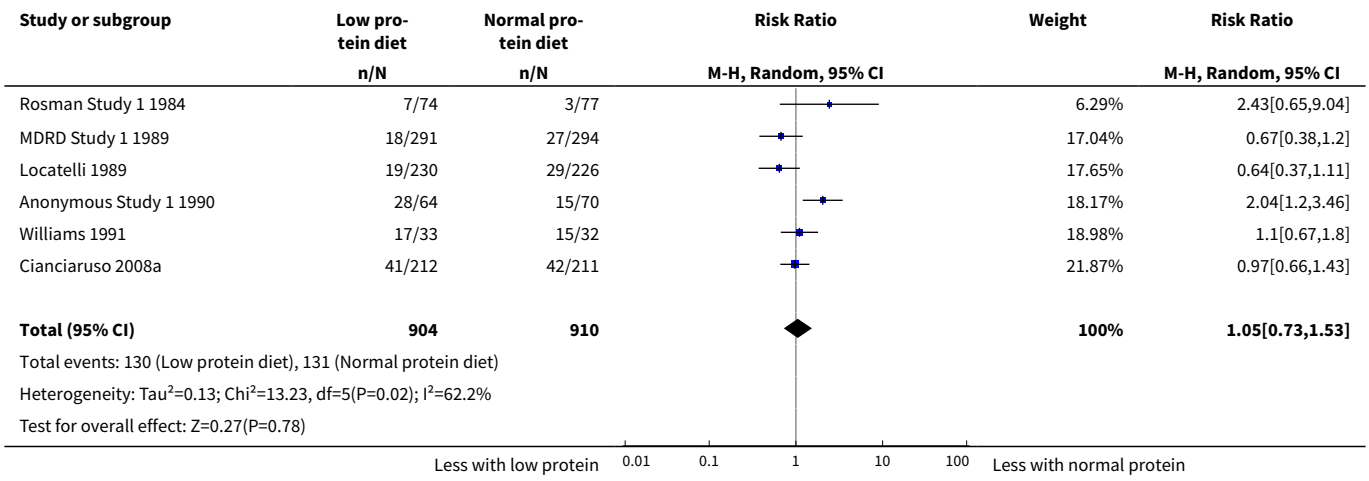
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	5	1680	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.51, 1.18]
2 ESKD	6	1814	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.73, 1.53]
3 End or change in GFR	8	1680	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.75, 0.38]

Analysis 1.1. Comparison 1 Low protein diet versus normal protein diet, Outcome 1 Death (all causes).

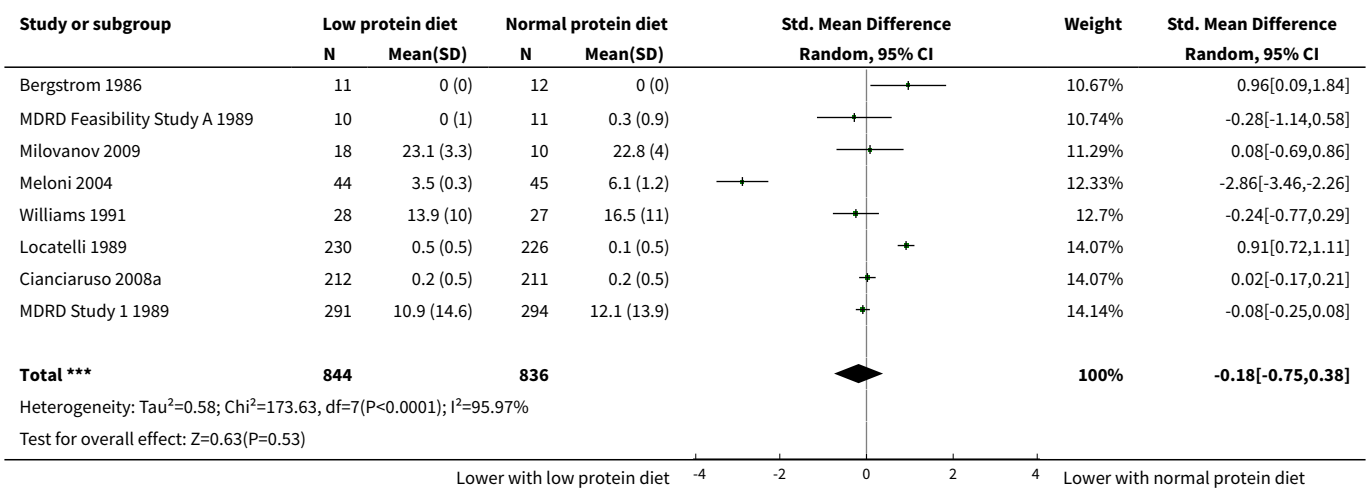
Study or subgroup	Low protein diet n/N	Normal protein diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Williams 1991	1/33	1/32		2.41%	0.97[0.06,14.85]
Locatelli 1989	2/230	3/226		5.67%	0.66[0.11,3.88]
Rosman Study 1 1984	4/74	7/77		12.77%	0.59[0.18,1.95]
MDRD Study 1 1989	5/291	10/294		15.96%	0.51[0.17,1.46]
Cianciaruso 2008a	23/212	25/211		63.19%	0.92[0.54,1.56]
Total (95% CI)	**840**	**840**		**100%**	**0.77[0.51,1.18]**
Total events: 35 (Low protein diet), 46 (Normal protein diet)					
Heterogeneity: Tau^2=0; Chi^2=1.26, df=4(P=0.87); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					



Analysis 1.2. Comparison 1 Low protein diet versus normal protein diet, Outcome 2 ESKD.



Analysis 1.3. Comparison 1 Low protein diet versus normal protein diet, Outcome 3 End or change in GFR.



Comparison 2. Very low protein diet versus low or normal protein diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (all causes)	6	681	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.62, 2.54]
2 ESKD	10	1010	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.49, 0.85]
3 End or change in GFR	6	456	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.27, 0.52]

Analysis 2.1. Comparison 2 Very low protein diet versus low or normal protein diet, Outcome 1 Death (all causes).

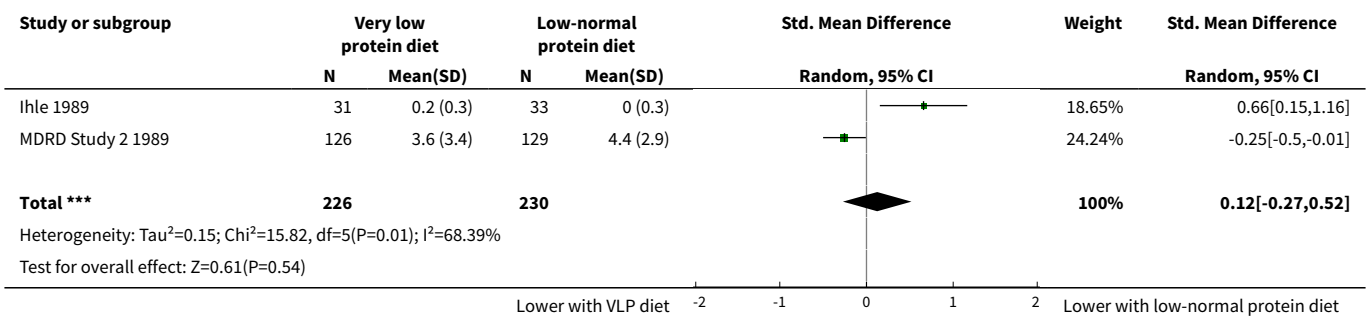
Study or subgroup	Very low protein diet n/N	Low-normal protein diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Garneata 2013	0/104	0/103			Not estimable
Chauveau 1986	1/10	0/9		5.21%	2.73[0.12,59.57]
Mircescu 2007	0/27	2/26		5.54%	0.19[0.01,3.84]
Malvy 1999	2/25	2/25		14.02%	1[0.15,6.55]
Rosman Study 2 1984	4/56	3/41		23.84%	0.98[0.23,4.13]
MDRD Study 2 1989	10/126	6/129		51.39%	1.71[0.64,4.56]
Total (95% CI)	**348**	**333**		**100%**	**1.26[0.62,2.54]**
Total events: 17 (Very low protein diet), 13 (Low-normal protein diet)					
Heterogeneity: Tau^2=0; Chi^2=2.31, df=4(P=0.68); I^2=0%					
Test for overall effect: Z=0.64(P=0.52)					

Analysis 2.2. Comparison 2 Very low protein diet versus low or normal protein diet, Outcome 2 ESKD.

Study or subgroup	Very low protein diet n/N	Low-normal protein diet n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Mircescu 2007	1/27	7/26		1.76%	0.14[0.02,1.04]
Ihle 1989	2/31	9/33		3.2%	0.24[0.06,1.01]
Di Iorio 2003	2/10	7/10		3.84%	0.29[0.08,1.05]
MDRD Feasibility Study B 1989	6/22	4/23		4.9%	1.57[0.51,4.82]
Chauveau 1986	5/8	7/9		10.53%	0.8[0.42,1.52]
Garneata 2013	11/104	31/103		10.69%	0.35[0.19,0.66]
Rosman Study 2 1984	15/56	21/41		12.84%	0.52[0.31,0.88]
Malvy 1999	11/25	17/25		13.03%	0.65[0.39,1.09]
MDRD Study 2 1989	44/126	50/129		17.96%	0.9[0.65,1.24]
Anonymous Study 2 1990	61/99	77/103		21.25%	0.82[0.68,1]
Total (95% CI)	**508**	**502**		**100%**	**0.64[0.49,0.85]**
Total events: 158 (Very low protein diet), 230 (Low-normal protein diet)					
Heterogeneity: Tau^2=0.09; Chi^2=20.27, df=9(P=0.02); I^2=55.6%					
Test for overall effect: Z=3.1(P=0)					

Analysis 2.3. Comparison 2 Very low protein diet versus low or normal protein diet, Outcome 3 End or change in GFR.

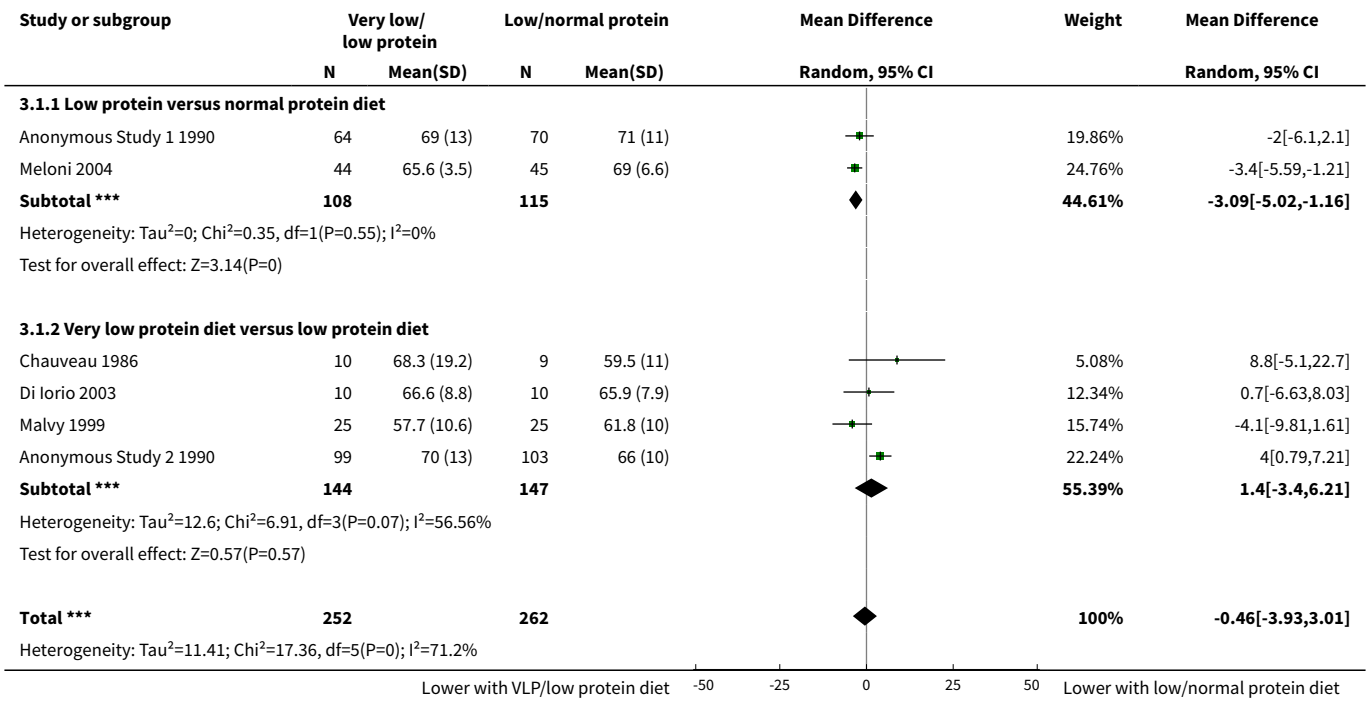
Study or subgroup	Very low protein diet N	Very low protein diet Mean(SD)	Low-normal protein diet N	Low-normal protein diet Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Chauveau 1986	10	8.2 (1.5)	9	7.8 (2.2)		11.17%	0.21[-0.7,1.11]
Di Iorio 2003	10	15.7 (6.4)	10	14.2 (5.1)		11.5%	0.25[-0.63,1.13]
MDRD Feasibility Study B 1989	22	0.3 (0.3)	23	0.4 (0.3)		16.73%	-0.43[-1.02,0.17]
Mircescu 2007	27	0.3 (0.1)	26	0.2 (0.1)		17.71%	0.46[-0.08,1.01]



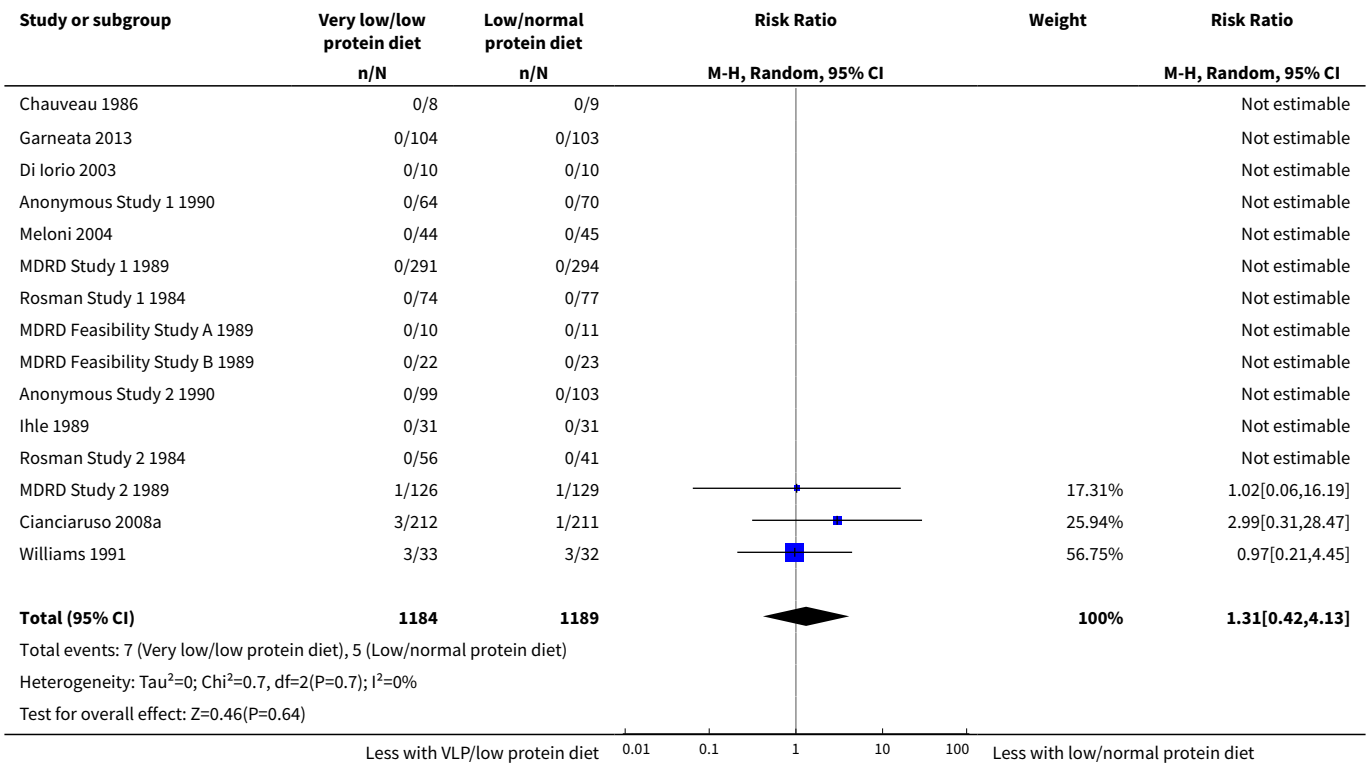
Comparison 3. Nutritional measures

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Final body weight	6	514	Mean Difference (IV, Random, 95% CI)	-0.46 [-3.93, 3.01]
1.1 Low protein versus normal protein diet	2	223	Mean Difference (IV, Random, 95% CI)	-3.09 [-5.02, -1.16]
1.2 Very low protein diet versus low protein diet	4	291	Mean Difference (IV, Random, 95% CI)	1.40 [-3.40, 6.21]
2 Protein energy wasting	15	2373	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.42, 4.13]

Analysis 3.1. Comparison 3 Nutritional measures, Outcome 1 Final body weight.



Analysis 3.2. Comparison 3 Nutritional measures, Outcome 2 Protein energy wasting.



ADDITIONAL TABLES

Table 1. Prescribed versus calculated differences in protein intake in studies comparing low with normal or free protein diets

Study	Difference in prescribed protein intake	Difference in actual protein intake	Difference between prescribed and actual protein intake
Anonymous Study 1 1990	0.4 g/kg/d	0.12 g/kg/d	0.28 g/kg/d
Bergstrom 1986	0.45 g/kg/d	0.21 g/kg/d	0.24 g/kg/d
Cianciaruso 2008a	0.25 g/kg/d	0.17 g/kg/d	0.08 g/kg/d
Chauveau 1986	0.2 g/kg/d	0.2 g/kg/d	0 g/kg/d
Locatelli 1989	0.4 g/kg/d	0.18 g/kg/d	0.22 g/kg/d

Table 1. Prescribed versus calculated differences in protein intake in studies comparing low with normal or free protein diets *(Continued)*

MDRD Feasibility Study A 1989	0.625 g/kg/d	0.19 g/kg/d	0.435 g/kg/d
MDRD Study 1 1989	0.72 g/kg/d	0.4 g/kg/d	0.32 g/kg/d
Meloni 2004	0.4 g/kg/d	0.87 g/kg/d	0.47 g/kg/d
Williams 1991	0.4 g/kg/d	0.45 g/kg/d	0.05 g/kg/d

Table 2. Prescribed versus calculated differences in protein intake in studies comparing very low with low protein diets

Study	Difference in prescribed protein intake	Difference in actual protein intake
Anonymous Study 2 1990	0.3 g/kg/d	0.21 g/kg/d
Di Iorio 2003	0.3 g/kg/d	0.29 g/kg/d
Garneata 2013	0.3 g/kg/d	0.29 g/kg/d
Malvy 1999	0.3 g/kg/d	0.21 g/kg/d
MDRD Feasibility Study B 1989	0.295 g/kg/d	0.22 g/kg/d
MDRD Study 2 1989	0.3 g/kg/d	0.3 g/kg/d
Mircescu 2007	0.3 g/kg/d	0.27 g/kg/d

Table 3. Final body weight in participants in MDRD studies 1 and 2 *(Continued)*

	MDRD Study 1				MDRD Study 2			
	Usual protein diet		Low protein diet		Low protein diet		Very low protein diet	
	Final body weight (kg)	N	Final body weight (kg)	N	Final body weight (kg)	N	Final body weight (kg)	N
Men	88.5 ± 14.6	179-183	83.2 ± 12.8	165-170	79.6 ± 11.5	74-77	79.3 ± 10.9	69-71
Women	72.2 ± 14.9	98-105	69.3 ± 13.7	107-115	65.9 ± 11.9	49-51	65.0 ± 14.3	49-52

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Diet Therapy, this term only 2. MeSH descriptor Diet, Protein-Restricted, this term only 3. (protein*):ti,ab,kw and (diet*):ti,ab,kw in Trials 4. (protein NEAR/2 restrict*):ti,ab,kw in Trials 5. (protein NEAR/2 reduc*):ti,ab,kw in Trials 6. "low protein diet*":ti,ab,kw in Trials 7. (#1 OR #2 OR #3 OR #4 OR #5 OR #6) 8. MeSH descriptor Renal Insufficiency, this term only 9. MeSH descriptor Renal Insufficiency, Chronic explode all trees 10.MeSH descriptor Kidney Diseases, this term only 11.(chronic NEXT kidney):ti,ab,kw or (chronic NEXT renal):ti,ab,kw in Trials 12.(CKF or CKD or CRF or CRD):ti,ab,kw in Trials 13.(predialysis or pre-dialysis):ti,ab,kw in Trials 14.(#8 OR #9 OR #10 OR #11 OR #12 OR #13) 15.(#7 AND #14)
MEDLINE (OVID SP)	1. Diet Therapy/ 2. Diet, Protein Restricted/ 3. (protein$ and diet$).tw. 4. protein restrict$.tw. 5. protein reduc$.tw. 6. low protein diet$.tw. 7. or/1-6 8. Renal Insufficiency/ 9. exp Renal Insufficiency, Chronic/ 10.Kidney Diseases/ 11.(chronic kidney or chronic renal).tw. 12.(CKF or CKD or CRF or CRD).tw. 13.(predialysis or pre-dialysis).tw. 14.exp Uremia/ 15.uremi.tw. 16.or/8-15 17.and/7,16
EMBASE (OVID SP)	1. protein restriction/ 2. diet restriction/ 3. (protein$ and diet$).tw. 4. low protein diet$.tw. 5. protein restric$.tw. 6. protein reduc$.tw. 7. or/1-6 8. kidney failure/ 9. chronic kidney disease/ 10.(predialysis or pre-dialysis).tw. 11.(chronic adj kidney) or (chronic adj renal).tw.

(Continued)

12.(CKF or CKD or CRF or CRD).tw.
13.(renal insufficiency or kidney insufficiency).tw.
14.or/8-13

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement.
Incomplete outcome data	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across

(Continued)

Attrition bias due to amount, nature or handling of incomplete outcome data.	groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

WHAT'S NEW

Date	Event	Description
7 September 2018	New citation required and conclusions have changed	New studies added; SOF tables included
7 September 2018	New search has been performed	Six new studies added. Conclusions changed.
7 February 2012	Amended	Search strategies & search methods updated

HISTORY

Protocol first published: Issue 4, 2000
Review first published: Issue 4, 2000

Date	Event	Description
12 May 2009	New citation required but conclusions have not changed	Author list updated
31 March 2009	Amended	Two new studies added, no change to conclusions
13 October 2008	Amended	Converted to new review format.
30 November 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DH and EH selected additional studies for inclusion in the 2018 update, undertook data analysis and risk of bias assessment and wrote the review update.

DF reviewed the data and contributed to writing the review.

DECLARATIONS OF INTEREST

Professor Denis Fouque has received lecture fees for nutrition in renal disease.

SOURCES OF SUPPORT

Internal sources

- Hospices Civils de Lyon, France.
- University Claude Bernard Lyon 1, France.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Diet, Protein-Restricted [adverse effects] [mortality]; Cause of Death; Chronic Disease; Disease Progression; Kidney Diseases [*diet therapy]; Kidney Failure, Chronic [*prevention & control]; Protein-Energy Malnutrition [etiology]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans