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Nutrition and dietary intake and their association with mortality and hospitalization in adults with chronic kidney disease treated with hemodialysis

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I finally want to dedicate this work to my beloved family, my husband Francesco and my daughter Eva, my Dad, my Mom and my brother Francesco, and thank my friends, Valentina and Annalisa.

Summary

The aim of this body of work was to evaluate the association between exposure to different nutrients and dietary patterns and the risk of mortality (all-cause and cause-specific) and hospital admissions (any, and cause-specific) in adults with chronic kidney disease (CKD) and specifically those with or end stage kidney disease (ESKD) receiving hemodialysis for renal replacement therapy.

Adults receiving hemodialysis still experience high mortality rates. Several interventions that address the typical cardiovascular risk factors which are almost universally present in people with ESKD have been introduced. These interventions unfortunately do not significantly improve health outcomes in such populations. They are effective on a series of surrogate biomarkers, but survival remains poor in these populations. The search continues to be on for novel and testable determinants of health in hemodialysis in order to identify additional interventions. Nutrition and dietary patterns are potential factors influencing health in other health settings but poorly explored in the setting of ESKD. Such research area warrants investigation in multinational studies in men and women treated with hemodialysis, given the potential impact at population level.

My PhD, in the area of clinical epidemiology research in ESKD, focused on understanding the impact of diet and nutrient intake, on CKD and ESKD through a comprehensive and systematic series of literature reviews and the design and conduct of the first large scale multinational primary cohort study to explore the association between nutrition (dietary intake) and clinical adverse events in the setting of hemodialysis (the Dietary Intake in Hemodialysis, DIET-HD study).

The results of my work are presented in the following chapters, which represent the results of studies published with my strong contribution:

Chapter 1. Meta-analysis of cohort studies evaluating the association between dietary patterns and mortality or end-stage kidney disease among adults with chronic kidney disease. Published, Clin J Am Soc Nephrol. 2016 Dec 8.

Chapter 2. Rationale and protocol of the DIET-HD study, a prospective, multinational, cohort study evaluation the prevalence of nutrition patterns and the association of dietary intake/patterns and the risk of mortality and hospitalisation in adults receiving hemodialysis. Published, BMJOpen. 2015 Mar 20;5(3): e006897.

Chapter 3: A prospective cohort study (arising from DIET-HD) of the association between the dietary intake of n-3 and cardiovascular and all-cause mortality in adults treated with hemodialysis. Published, Clin Nutr. 2017 Dec 6.

Chapter 4-5: Analysis of the benefits and harms of large categories of interventions related to nutritional aspects in CKD/hemodialysis (two network meta-analyses of randomized controlled trials comparing and ranking the efficacy of phosphate binding agents in CKD and the relative efficacy and safety of glucose-lowering drugs including insulin in people with type 2 diabetes, a major risk factor for CKD and ESKD). Published, Am J Kidney Dis. 2016 Nov;68(5):691-702; JAMA. 2016 Jul 19;316(3):313-24.

Chapter 6: Analysis of the benefits and harms of dietary intervention in people with CKD (specific nutritional interventions for CKD/ESKD) in the form of a Cochrane systematic review of randomized controlled trials. Published, Cochrane Database Syst Rev. 2017 Apr 23;4:CD011998.

Chapter 7: Analysis of patients perspectives on dietary and fluid restrictions in CKD (thematic synthesis of patient views from qualitative studies). Published, Am J Kidney Dis. 2015 Apr;65(4):559-73.

This large series of studies has been designed and conducted with coordination of my supervisors (and will continue to generate substantial research output in my post-doctoral work) with the intention of acquiring competence in several areas of clinical research methodology including systematic reviews of both randomized and prognostic studies, the design and conduct of a primary cohort study, and qualitative research methods.

Publications arising from the thesis and produced during the years of my PhD in collaboration with other members of the extended research team

As indicated in the introduction, all chapters presented in this thesis have been published in peer reviewed medical journals. Over these years, besides the specific studies which form the core of this PhD, my research has been focused on strategies to prevent adverse vascular outcomes in CKD/ESKD, and will continue in this direction. I have also gained some relevant expertise in specific methods of research which have been useful to help other members of the extended team with their studies. Below I report the full list of publications during these years, and in brackets the relevant chapters of this thesis:

1: Saglimbene VM, Wong G, Ruospo M, Palmer SC, Campbell K, Larsen VG, Natale P, Teixeira-Pinto A, Carrero JJ, Stenvinkel P, Gargano L, Murgo AM, Johnson DW, Tonelli M, Gelfman R, Celia E, Ecder T, Bernat AG, Del Castillo D, Timofte D, Török M, Bednarek-Skublewska A, Duława J, Stroumza P, Hoischen S, Hansis M, Fabricius E, Wollheim C, Hegbrant J, Craig JC, Strippoli GFM. Dietary n-3 polyunsaturated fatty acid intake and all-cause and cardiovascular mortality in adults on hemodialysis: The DIET-HD multinational cohort study. Clin Nutr. 2017 Dec 6. pii: S0261-5614(17)31418-8. doi: 10.1016/j.clnu.2017.11.020. [Epub ahead of print] PubMed PMID: 29248251. (Chapter 3)

2: van Zwieten A, Wong G, Ruospo M, Palmer SC, Barulli MR, Iurillo A, Saglimbene V, Natale P, Gargano L, Murgo M, Loy CT, Tortelli R, Craig JC, Johnson DW, Tonelli M, Hegbrant J, Wollheim C, Logroscino G, Strippoli GFM; COGNITIVE-HD study investigators. Prevalence and patterns of cognitive impairment in adult hemodialysis patients: the COGNITIVE-HD study. Nephrol Dial Transplant. 2017 Nov 22. doi: 10.1093/ndt/gfx314. [Epub ahead of print] PubMed PMID: 29186522.

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6: Ruospo M, Saglimbene VM, Palmer SC, De Cosmo S, Pacilli A, Lamacchia O, Cignarelli M, Fioretto P, Vecchio M, Craig JC, Strippoli GF. Glucose targets for preventing diabetic kidney disease and its progression. Cochrane Database Syst Rev. 2017 Jun 8;6:CD010137. doi: 10.1002/14651858.CD010137.pub2. Review. PubMed PMID: 28594069.

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haemodialysis: a multinational cohort study. Nephrol Dial Transplant. 2017 Feb 1;32(2):377-384. doi: 10.1093/ndt/gfw016. PubMed PMID: 28186569.

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Mortality in People With End-Stage Kidney Disease Treated With Hemodialysis: A Multinational Cohort Study. Am J Kidney Dis. 2015 Oct;66(4):666-76. doi: 10.1053/j.ajkd.2015.04.051. Epub 2015 Jun 25. PubMed PMID: 26120038.

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Introduction

The main body of my work focused on investigating the potential role of new non established risk factors for chronic kidney disease (CKD) and adverse vascular outcomes in CKD/end stage kidney disease (ESKD). As several strategies to address recognized risk factors for CKD and adverse vascular events in CKD have not been proven to determine significant benefits, I wanted to evaluate the potential prognostic value of novel risk factors for CKD/adverse vascular events in ESKD, specifically nutritional aspects. These have been the subject of previous research in cardiovascular disease and the intake of certain nutrient categories proved to be protective for the risk of chronic degenerative diseases in general and adverse vascular outcomes (examples include the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, etc.).

Long-term hemodialysis treatment for ESKD is associated with an annual mortality of between 15% and 35%, depending on geographies; in Italy it is between 12-15% with some variability between regions. Existing interventions, including management of dyslipidemia, anemia, dialysis adequacy among others, have unfortunately not shown to dramatically affect the risk of such adverse outcomes in hemodialysis. Contention exists around some interventions (phosphate binding agents, glucose control, antihypertensive agents), which have been a subject of study in my thesis. Nonetheless, overall, there is considerable evidence that treatment of established cardiovascular risk factors is not effective in reducing adverse vascular outcomes in hemodialysis, as one would, on opposite, expect.

Nutritional intake and dietary patterns are potential determinants of health outcomes in hemodialysis patients. Malnutrition (commonly referred to as protein-energy wasting) frequently occurs in patients treated with long-term hemodialysis. The accumulation of uremic metabolites, metabolic acidosis, dietary restrictions, inflammation and additional frequent comorbidities, including cardiac dysfunction, can suppress appetite, decrease protein and energy intake, and increase catabolic processes in this population. Malnutrition affects 20 to 70% of dialysis patients in general and particularly hemodialysis and increases with duration of dialysis treatment; approximately 5 to 10% of people treated with hemodialysis experience severe malnutrition.

Premature death in people with end-stage kidney disease is strongly associated with lower body mass, lower serum cholesterol and other markers of impaired nutrition. Several studies have shown a consistent association between low serum albumin, low height-adjusted body weight and malnutrition (assessed by subjective global assessment) and total and cardiovascular-specific

mortality in the hemodialysis population. In addition, protein-energy wasting (incorporating both malnutrition and other metabolic derangements in patients with end-stage kidney disease, such as inflammation) is a strong risk factor for premature death. Other dietary and nutrition factors have potential clinical effects in the setting of end-stage kidney disease. The Mediterranean diet specifically characterized by high intake of olive oil, fruit, nuts, vegetables and cereals, more moderate fish and poultry intake and lower consumption of dairy foods, red and processed meats and sweets, prevents cardiovascular events in the general population, but this is unproven in the setting of ESKD/hemodialysis. In general, data evaluating the association between dietary composition and clinical outcomes in people treated with hemodialysis are limited and largely derive from small, single-center, retrospective studies. Finally, the perspective of patients on hemodialysis, who are recipients of a series of restrictions in their dietary activities, are perceived by clinicians and the patients themselves but have not been the subject of formal study.

Therefore, in the work of my thesis, I have contributed to design and conduct a primary study, the largest worldwide multinational, prospective cohort study to evaluate nutrition and dietary patterns and their association with major health outcomes in adults treated with hemodialysis in a multinational setting. The intention of this study was to identify the prevalence of dietary patterns, and the association of specific nutrient intakes and the risk of adverse vascular outcomes in ESKD/hemodialysis. Subsequent to the full analysis of this study, will be the design of primary intervention studies based around nutritional strategies in this population.

As one of the researchers involve in the inception, design and conduct of this study, I have not only contributed to the original research idea, but have been involved in the preparation of case report forms of the food frequency questionnaires to be received by all patients in the 11 countries in Europe and South America involved in the study, I was responsible for recruitment, data collection and data entry as well as data analysis and manuscript drafting.

The study idea generated from the previous conduct of a series of comprehensive systematic literature reviews including meta-analysis both for existing cohort studies and existing randomized trials of interventions (the latter based upon methodology of the Cochrane Collaboration).

I finally have conducted a qualitative research study in the area of nutrition and CKD/ESKD to understand patients perspectives, a matter of specific important in the current era of research.

In performing all this work, I have gained skills in the area of searching and synthesizing evidence. I have developed highly sensitive search strategies for multiple databases (MEDLINE, EMBASE, The Cochrane Central Registry), screened thousands of scientific papers and extracted data from the selected publications to identify, evaluate and synthetize a large body of evidence on:

- association between dietary patterns and mortality or end-stage kidney disease among adults with chronic kidney disease (meta-analysis of cohort studies)
- comparing and ranking phosphate binding strategies for CKD (network meta-analysis of randomized controlled trials (RCTs))
- evaluating the relative efficacy and safety of glucose-lowering drugs including insulin in people with type 2 diabetes (network meta-analysis of RCTs)
- assessing the benefits and harms of dietary interventions among people with chronic kidney disease (meta-analysis of RCTs)
- evaluating/eliciting patients perspective on dietary and fluid restrictions in CKD (qualitative meta-analysis)

So, the overall project is based on clinical epidemiology methods and includes multiple sub-projects:

1. Systematic reviews/meta-analyses
    - Systematic review/meta-analysis of cohort studies evaluating association between nutritional exposures and the outcomes of interest
    - Systematic review/meta-analysis of randomized trials evaluating the effects of specific/nonspecific nutritional interventions on the outcomes of interest
    - Systematic review/meta-analysis and thematic synthesis of qualitative studies to describe patients' perspectives on dietary management in chronic kidney disease
2. A large scale 'ad hoc designed' prospective cohort study assessing the association between nutritional exposures and the outcomes of interest (first study of its kind ever designed and conducted in this specific population setting).

Aim of the thesis

Adults with chronic kidney disease treated with hemodialysis experience high mortality rates. Effective interventions addressing established cardiovascular risk factors to improve health outcomes for long-term hemodialysis patients remain unproven and novel and testable determinants of health in hemodialysis are needed. Nutrition and dietary patterns are potential factors influencing health in other settings that warrant exploration in multinational studies in men and women treated with hemodialysis.

In the current PhD project entitled “Nutrition and dietary intake and their association with mortality and hospitalization in adults with chronic kidney disease treated with hemodialysis” I aimed to evaluate the association between the exposure to different nutrition and dietary patterns and the risk of mortality (all-cause and cause-specific) and hospital admissions (any, and cause-specific) for adults with end stage kidney disease (ESKD) treated with hemodialysis.

CHAPTER I: HEALTHY DIETARY PATTERNS AND RISK OF MORTALITY AND ESRD IN CKD: A META-ANALYSIS OF COHORT STUDIES

Jaimon T Kelly, Suetonia C. Palmer, Shu Ning Wai, Marinella Ruospo, Juan-Jesus Carrero, Katrina L. Campbell, Giovanni FM Strippoli.

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Abstract

Background and objectives

Patients with chronic kidney disease are advised to follow dietary recommendations that restrict individual nutrients. Emerging evidence indicates overall eating patterns may better predict clinical outcomes, however evidence for dietary patterns in kidney disease has not been previously synthesized.

Design, setting, participants and measurements

This systematic review aimed to evaluate the association between dietary patterns and mortality or end-stage kidney disease among adults with chronic kidney disease. Medline, Embase, and reference lists were systematically searched to 24 November 2015 by two independent review authors. Eligible studies were longitudinal cohort studies reporting the association of dietary patterns with mortality, cardiovascular events, or end-stage kidney disease.

Results

A total of seven studies involving 15,285 participants were included. Healthy dietary patterns were generally higher in fruit and vegetables, fish, legumes, cereals, whole grains, and fiber and lower in red meat, salt, and refined sugars. In six studies, healthy dietary patterns were consistently associated with lower mortality (adjusted relative risk 0.73, 95% confidence interval 0.63 to 0.83; risk difference 46 fewer (29 to 63 fewer) events per 1000 people over five years). There was no evidence of an association between healthy dietary patterns and risk of end-stage kidney disease (1.04, 0.68 to 1.40).

Conclusions

Thus, healthy dietary patterns are associated with lower mortality in people with kidney disease. Interventions to support adherence to increased fruit and vegetable, fish, legume, whole grains, and fiber intake and reduced red meat, sodium, and refined sugars could be effective tools to lower mortality in people with kidney disease.

Introduction

Chronic kidney disease affects about 10% to 13% of adults[1] and represents a public health challenge due to the substantially increased risks of death and cardiovascular disease among affected people.[2] [3] Patients who have chronic kidney disease are advised to follow dietary recommendations that restrict individual nutrients such as phosphorus, salt, potassium, and protein to prevent short- and long-term clinical complications.[4] Historically, dietary advice has been based on individual nutrients or food groups instead of whole eating patterns, although considered complex, challenging to adhere to, and an intense burden for some patients.[5] In addition, there is limited evidence that restricting or supplementing specific nutrients or single food groups effectively prevents clinical complications including kidney failure or death.[6-9] Fluid and dietary restrictions remain frequently identified as priority areas of research by patients with kidney disease and healthcare providers.[10]

Recent evidence has linked dietary patterns rich in fruit and vegetables, fish, legumes, cereals, and nuts with reduced cardiovascular events and death in healthy adults and those at high risk of cardiovascular disease.[11-14] In parallel, there is an emerging trend toward the study of whole dietary patterns rather than single nutrient or food group restrictions among people with kidney disease.[15-17] However, existing cohort studies of dietary patterns in people with kidney disease have small sample sizes, while existing randomized trials are insufficiently powered to establish the role of whole dietary patterns on mortality and kidney failure limiting the impact of single studies to inform clinical practice and policy.[18] [19] Existing dietary guidelines lack robust evidence for effects on patient-centered outcomes.[20]

The aim of this study was to conduct a meta-analysis of the evidentiary basis for the association of dietary patterns with mortality and cardiovascular endpoints to establish the potential role of dietary patterns among people with chronic kidney disease.

Methods

Our primary aim was to assess the association of healthy dietary patterns on the risk of mortality and end-stage kidney disease in adults with chronic kidney disease. This systematic review followed a pre-specified review protocol, prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO)[21] and reported using the preferred reporting items for systematic reviews and meta-analysis (PRISMA).[22]

Data sources and Searches

We searched Medline, Embase, and reference lists of retrieved studies for prospective cohort studies available online reporting the association between dietary patterns and clinical outcomes among adults who have chronic kidney disease on November 30, 2015. We did not have any language or date restriction for the search. The search terms are shown in Supplemental Table 1.

Study Selection

Dietary patterns were defined as overall habitual food intake ascertained by healthy eating guidelines or *a priori* diet quality score; dietary pattern analysis; and/or consumption of whole food groups such as fruit and vegetables. We excluded single nutrient or food-group based modifications from this review including isolated protein or sodium restriction. We required follow up for at least 24 weeks to ensure sufficient follow-up of dietary patterns on patient-level outcomes, and explicit reporting of outcomes either as raw data or adjusted effect estimates with 95% confidence intervals. We used definitions of chronic kidney disease according to international clinical practice guidelines.[4].

Data Extraction and Quality Assessment

Two authors (JK, SW) independently reviewed all retrieved records for eligibility using reference management software. The two authors extracted data and adjudicated risk of bias, with differences resolved by discussion. We contacted authors for information missing or unclear from included studies. The risk of bias was assessed using the Newcastle-Ottawa tool.[23] We then used the grading of recommendations assessment, development, and evaluation (GRADE) methodology to rate the quality of the evidence for mortality as high, moderate, low or very low.[24] Observational studies begin as low quality evidence, but can be rated upward to moderate or high quality evidence if they collectively demonstrate a large magnitude of effect, or a dose-response

gradient. Outcomes were death, health-related quality of life, end-stage kidney disease, major cardiovascular events, blood pressure, serum cholesterol, and major adverse events.

Data Synthesis and Analysis

We carried out analyses according to a pre-defined protocol to compare healthy eating patterns (generally higher intake of fruit, vegetables, cereals, legumes, whole grains and fiber, and fish, and lower intake of red meat, salt, and refined sugar) versus dietary intake less representative of these eating patterns. We then summarized adjusted risks (hazard ratio, odds ratio or relative risk) provided in studies using random-effects inverse variance meta-analysis. A fixed-effect model was also used to ensure robustness of the model chosen and susceptibility to outliers. Estimated numbers of events incurred or avoided with dietary change was calculated as a risk difference based on a five year risk of mortality reported in a systematic review of cohort studies.[25] We used the I^2 statistic to assess heterogeneity – the proportion of total variation observed in the association of dietary intake and outcome among studies beyond that expected by chance, with an I^2 value less than 25% considered as low heterogeneity and more than 75% as high heterogeneity. We assessed for small study effects in analyses for mortality by visual evaluation of the funnel plot for symmetry.

Sensitivity analyses were done excluding studies in which the same cohort of participants may have been represented more than once and excluding studies involving adults with end-stage kidney disease. We planned subgroup analyses based on gender, duration of follow up, study quality, and geographical region. Analyses were performed using Stata 13, with 95% confidence intervals excluding a risk ratio of 1.0 used to denote statistical significance.

Results

Study Selection and Baseline Characteristics

The systematic search yielded seven cohort studies (Figure 1), involving 15 285 patients with chronic kidney disease (Table 1).[17 26-31] The participants were followed for between 4 and 13 years on average, totaling approximately 91 000 patient years of follow up. All but one study involved people with chronic kidney disease defined as an estimated glomerular filtration rate below 60-70 ml/min per 1.73 m^2 body surface area or albuminuria.[17 26-30] One study enrolled adults treated with dialysis.[31] Studies involved people living in the United States,[17 26 27 29 30] Sweden,[28] and Japan.[31] Healthy dietary patterns were reported as generally consistent with a higher intake of fruits and vegetables, legumes, cereals, whole grains and fiber, and fish, and lower intake of red meat, and products containing sodium and refined sugars (Table 2). All studies were published between 2013 and 2015. There were 3983 deaths and 1027 end-stage kidney disease events recorded during follow up.

Risk of Bias and Evidence Quality

Risks of bias in the included studies is shown in Supplemental Figure 1. Overall, studies were considered at low risk of bias for characteristics considered important to the reliability of cohort studies. When GRADE (directness, precision, consistency, and study limitations) recommendations were considered, the evidence quality for all-cause mortality was considered low based on the non-randomized study design, without incurring further downgrades in evidence quality for indirectness, imprecise results, heterogeneity, or study reporting limitation.

Outcomes

All-cause mortality

When compared with other dietary patterns, a dietary pattern richer in vegetables, fruit, fish, cereals, whole grains and fiber, legumes, and nuts and seeds and lower in red meat, sodium and refined sugars was associated with a lower risk of death. In six studies among 13 930 participants followed for between 4 and 13 years the relative risk of all-cause mortality was 0.73 (95% confidence interval 0.63 to 0.83) (figure 2). There was no heterogeneity between studies (I^2 =0%) and no evidence of small study effects (Supplemental Figure 2). Based on an estimated five year mortality of 17% in people with chronic kidney disease,[25] the risk difference with a healthy dietary

pattern compared to other dietary patterns was 46 fewer deaths per 1000 people (29 to 63 fewer) over 5 years.

End-stage kidney disease

There was no evidence of an association between a healthy dietary pattern and risk of end-stage kidney disease in three studies (n=10 071 people) with follow up ranging between 4 and 6.4 years. The risk of end-stage kidney disease among people with chronic kidney disease was 1.04 (0.68 to 1.40) with no evidence of statistical heterogeneity between studies (Figure 3).

Major cardiovascular events, health-related quality of life, adverse events, blood pressure

There were insufficient numbers of studies to conduct meta-analysis for risks of major cardiovascular events. In one study involving 3006 people, a healthy diet score was not associated with risk of atherosclerotic events (1.01, 0.47 to 2.18).[17] In a single study among 1355 dialysis patients, an "unbalanced dietary pattern" with high sodium intake and higher vegetable and lower fish and meat intake, was associated with a higher risk of a composite of hospitalization due to cardiovascular disease or death due to any cause.[31]

There was no reporting of health-related quality of life, or cardiovascular-related death, adverse events, or hyperkaliemia as individual endpoints. There was no information about the effects of healthy dietary patterns on blood pressure or serum cholesterol levels during follow up.

Sensitivity analyses

Results were similar when single studies were removed to exclude the possibility that participants had been included in analyses more than once (Supplemental Table 2). There was no evidence that results in meta-analyses for mortality were different based on country of origin, age, duration of follow up time, or quality of studies (Supplemental Table 3).

Discussion

This meta-analysis comprising approximately 90 000 person years of follow up and including 3983 mortality events showed that dietary patterns rich in vegetables and fruits, legumes, whole grains, and fiber together with lower consumption of red meat, sodium, and refined sugars were consistently associated with reduced mortality in people with chronic kidney disease. There was insufficient information in existing cohort studies to determine the impact of healthy dietary patterns on risks of end-stage kidney disease, and major cardiovascular complications, or health-related quality of life. To our knowledge this is the first cumulative assessment of whole dietary patterns and their impact on mortality and clinical complications in people with chronic kidney disease.

The association of healthy dietary patterns with reduced mortality in people with chronic kidney disease is in contrast with the lack of association between restrictions of individual dietary components for food groups including serum phosphorus,[7 32 33] sodium[6] and protein[34] intake and mortality, although individual studies addressing these questions have had small sample sizes and low power to discern the relative impact of nutritional modifications. The findings of the current meta-analysis are consistent with accruing large-scale evidence of consistent mortality benefits with adherence to a plant-based dietary pattern among people without existing chronic disease[35] although in a large randomized controlled trial of Mediterranean diet, a primarily plant-based diet including extra virgin olive oil or nuts, there was no statistical evidence of reduced mortality alone in people at high risk of cardiovascular events, although a Mediterranean dietary pattern reduced the risk of a composite of non-fatal and fatal cardiovascular events.[11] To date, randomized trials testing the effects of dietary patterns rich in fruits and vegetables or a Mediterranean diet in adults with kidney disease are preliminary and have not examined mortality as an endpoint.[18 36 37] As in our study, there is limited evidence for the impact of eating patterns on risks of end-stage kidney disease in the literature, although cohort studies suggest dietary patterns rich in fruit and vegetables may retard progression to chronic kidney disease and decrease albuminuria and blood pressure.[38-42]

Recent research in chronic kidney disease has seen a shift from the decades-long focus on assessing and modifying single nutrient components of diet among people with chronic kidney disease reflecting in practice guidelines,[4] to an increasing analysis of whole dietary patterns. As a result, this study shows accumulating evidence over the last five years of analyses that consider all

food groups thought to be important for health. While existing single-nutrient approaches have had limited impact on health in people with kidney disease, this study of the building evidence for healthy dietary patterns on mortality risk suggests that this shift to wider dietary approaches across several food groups is appropriate and aligns with existing patient priorities.[10] Given the prevalence of chronic kidney disease in the community, data supporting specific dietary patterns potentially has an important public health impact, and warrants the prioritization of additional resources to support a randomized trial of dietary intake in this population. Highly-efficient trial design, embedded within registries or electronic health records might increase the feasibility and reduce the costs of an adequately powered dietary trial in the wider population with kidney disease. This is particularly relevant given the progressive shift toward more Western dietary patterns[43] and the relative lack of treatments proven to reduce the burden of premature death and kidney failure among people with kidney disease. A recent additional cohort study showing a dose-dependent association between red meat intake and risk of end-stage kidney disease and reduced risks when other sources of protein are substituted further adds weight to the need to understand the impact of whole food dietary patterns on clinical outcomes in the setting of kidney disease.[44]

While this study was prospectively planned and conducted independently by two authors, providing highly consistent findings among studies, and precise risk estimates for the mortality endpoint, some limitations of this study can be identified. First, the healthy dietary patterns we identified were not standardized, and represent a heterogeneous range of dietary intake. For example, some dietary patterns included milk products as healthy food groups[27] whereas others defined milk and milk product intake as less desirable.[26 28 30] However, the key elements of greater fruit and vegetable intake were present in all studies. Second, these studies were based on dietary self-recalls via differing methods (food frequency questionnaires versus food records), although the results among all studies were consistent, and not apparently influenced by this factor. Third, included patients had a range of kidney function, although all had an estimated glomerular filtration rate below 60-70 ml/min per 1.73 m^2 or albuminuria. Fourth, all the studies included in meta-analysis for mortality were conducted in United States or Sweden, and thus the results may not be generalizable to other global regions including lower resourced regions. Fifth, we did not find any association of dietary change with end-stage kidney disease. End-stage kidney disease is a rarer complication of chronic kidney disease due to the competing risk of death; accumulated studies evaluating the impact of diet on this outcome had relatively few recorded events as would

be expected, even when linked to dialysis census databases. Sixth, it was not possible to assess for evidence of publication bias. Finally, this study is based on non-randomized data leading to the potential for the findings to be partly explained by residual confounding and leading to low quality evidence. The results are hypothesis-generating and represent an important indication for a future randomized trial and public policy, particularly as dietary and lifestyle interventions are highly ranked research priorities by patients and clinicians.

In summary, this meta-analysis shows that adherence to dietary patterns rich in fruit and vegetables, fish, legumes, cereals, whole grains and fiber, and lower in red meat, and products containing sodium and refined sugars is associated with reduced mortality in people with chronic kidney disease. This finding represents a shift in evidence from management of single nutrient or food groups in the care of kidney disease and aligns with the experiences of patients who describe nutritional advice as frequently complex and difficult to follow. This evidence might prompt the prioritization of randomized trials of dietary patterns among people with kidney disease and re-evaluation of dietary advice as a public health tool to lower mortality in people with kidney disease.

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Table 1: Characteristics of included studies

First author	Dietary pattern	Country	Study name	No. of participants	Years of follow-up (person-years) *	Definition of kidney disease	Age at entry (mean or median)	Estimated GFR, mean ± SD (ml/min/1.73 m^2)	Endpoints (no. of events)
Chen et al, 2016[26]	Plant versus animal protein	United States	Third National Health and Nutrition Examination Survey (NHANES III)	1065 men and women	6.2 years (6603)	Estimated glomerular filtration rate <60ml/min/1.73m^2	20 years or older (not reported)	101 ± 20 (quartile 1)	All-cause mortality (633)
Gutiérrez et al, 2014[27]	Plant based	United States	Reasons for Geographic and Racial Differences in Stroke (REGARDS) study	3972 men and women	6.4 years (25,421)	Estimated glomerular filtration rate <60ml/min/1.73m^2 or urine albumin: creatinine ratio >30mg/g	45 years or older (67.1-69.8 years)	68.1 (standard error 0.8) (quartile 1)	All-cause mortality (816); end-stage kidney disease (141)
Huang et al, 2013[28]	Mediterranean diet	Sweden	Uppsala Longitudinal Study of Adult Men	506 men	9.9 years (4648)	Estimated glomerular filtration rate <60ml/min/1.73m^2	Approximately 70 years	51.9 (median) (interquartile range 46.3-56.6)	All- cause mortality (168)
Muntner et al, 2013[29]	Diet score (fish; fruit/vegetables, sodium, sugar fiber, carbohydrate)	United States	Reasons for Geographic and Racial Differences in Stroke (REGARDS) study	3093 men and women	4 years (12,372)	Estimated glomerular filtration rate <60ml/min/1.73m^2	45 years or older (72.2 years)		All-cause mortality (610); end-stage kidney disease (160)
Ricardo et al, 2015[17]	American Heart Association	United States	Chronic Renal Insufficiency Cohort (CRIC) Study	3006 men and women	4 years (12,024)	Estimated glomerular filtration rate 20-70ml/min/1.73m^2.	21 to 74 years (58 years)	43.39 ± 13.34 (diet score 0)	All-cause mortality (437); chronic kidney disease progression (50% decrease in eGFR or end-stage kidney disease) (726); atherosclerotic events (355)

First author	Dietary pattern	Country	Study name	No. of participants	Years of follow-up (person-years) *	Definition of kidney disease	Age at entry (mean or median)	Estimated GFR, mean ± SD (ml/min/1.73 m^2)	Endpoints (no. of events)
Ricardo et al, 2013[30]	Healthy Eating Index based on Food Guide Pyramid	United States	Third National Health and Nutrition Examination Survey (NHANES III)	2288 men and women	13 years (29,744)	Estimated glomerular filtration rate <60ml/min/1.73m^2 or urine albumin: creatinine ratio >30mg/g	20 years or older (59 years)	88.4 ± 1.7 (standard error of mean) (healthy lifestyle score quartile 1)	All-cause mortality (1319);
Tsuruya et al, 2015[31]	Meat, fish and vegetable intake	Japan	Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS)	1355 men and women	Not reported	Hemodialysis	Not reported (61.4 years)	Dialysis	All-cause mortality or hospitalization due to cardiovascular disease (not reported)

Table 2: Characteristics of dietary exposures used in meta-analyses

Study	Dietary pattern	Dietary exposure	Exposure category	Reference category	Covariates included in risk ratio
Chen et al, 2016[26]	Plant versus animal protein	Plant protein ratio quartiles (grains, fruits, vegetables, legumes, nuts, and seeds)	Quartile 4 >43.5% plant protein ratio	Quartile 1 <25.3% plant protein ratio	Total protein intake, age, sex, race, smoking, alcohol use, calorie intake, exercise, body mass index, hypertension, cancer, myocardial infarction, congestive heart failure, stroke and diabetes
Gutiérrez et al, 2014[27]	Plant based	Plant based defined using principal component analysis (fruits, vegetables, fish)	Quartile 4 (highest)	Quartile 1 (lowest)	Age, gender, race, geographic region, energy intake, lifestyle factors (self-reported frequency of exercise; current smoking), comorbidities (heart disease; hypertension), educational achievement, family income, urinary albumin to creatinine ratio, estimated glomerular filtration rate
Huang et al, 2013[28]	Mediterranean diet	Mediterranean diet score (polyunsaturated fats/saturated fatty acids >0.34; vegetables and legumes >69 day; fruit >115 g/day; cereals and potatoes >361 g/day; fish >25 g/day; meat and meat products <92 g/day; milk and milk products <328 g/day; alcohol moderate	High adherence (dietary score 6-8)	Low adherence (dietary score 1-2)	Body mass index, physical activity, smoking status, education, hypertension, hyperlipidemia, and diabetes
Muntner et al, 2013[29]	Diet score	Healthy diet score based on fish (≥ servings/week), fruit and vegetable consumption (≥4.5 cups/day) and sodium (<1500 mg/day), sugar (<450 kcal/week), fiber/carbohydrate ratio intake (>0.1)	Intermediate dietary score (2-3 components)	Poor dietary score (0-1 components)	Age, race, sex, geographic region, income, education, history of stroke and coronary heart disease.
Ricardo et al, 2015[17]	American Heart Association	Healthy diet score (American Heart Association; fruits/vegetables>2.8 cups/day; fish >1.3 oz/week; whole grains >0.88 oz/day; 24-hour urine sodium excretion <152 mEq/day; sweets/sugar-sweetened beverages <571 ml/week	Ideal (healthy diet score 4-5	Dietary score 0-3	Clinical center; age, sex, race/ethnicity, education, diabetes, dyslipidemia, hypertension, any cardiovascular disease, angiotensin-converting enzyme/angiotensin receptor blocker use; estimated glomerular filtration rate, urine protein excretion.
Ricardo et al, 2013[30]	Healthy Eating Index based on Food Guide Pyramid	Healthy Eating Index based on 10 dietary components (grains, vegetables, fruits, milk, meat, total fat, saturated fat, cholesterol, sodium, and dietary variety)	Healthy Eating Index score 73.1-100	Healthy Eating Score <54.5	Age, sex, race/ethnicity, annual household income, education, estimated GFR, microalbuminuria, diabetes, cardiovascular disease, cancer, systolic blood pressure, serum cholesterol, use of statin, use of angiotensin-converting enzyme inhibitor.
Tsuruya et al, 2015[31]	Meat, fish and vegetable intake	Consumption of approximately equal amounts of food from meat, fish, and vegetable groups.	Well-balanced	Unbalanced	Age, gender, dialysis duration, serum albumin, body mass index, energy intake, diabetes, coronary heart disease, cerebrovascular disease and peripheral vascular disease.

GFR = glomerular filtration rate.

Figure 1: Flow chart describing process of study selection

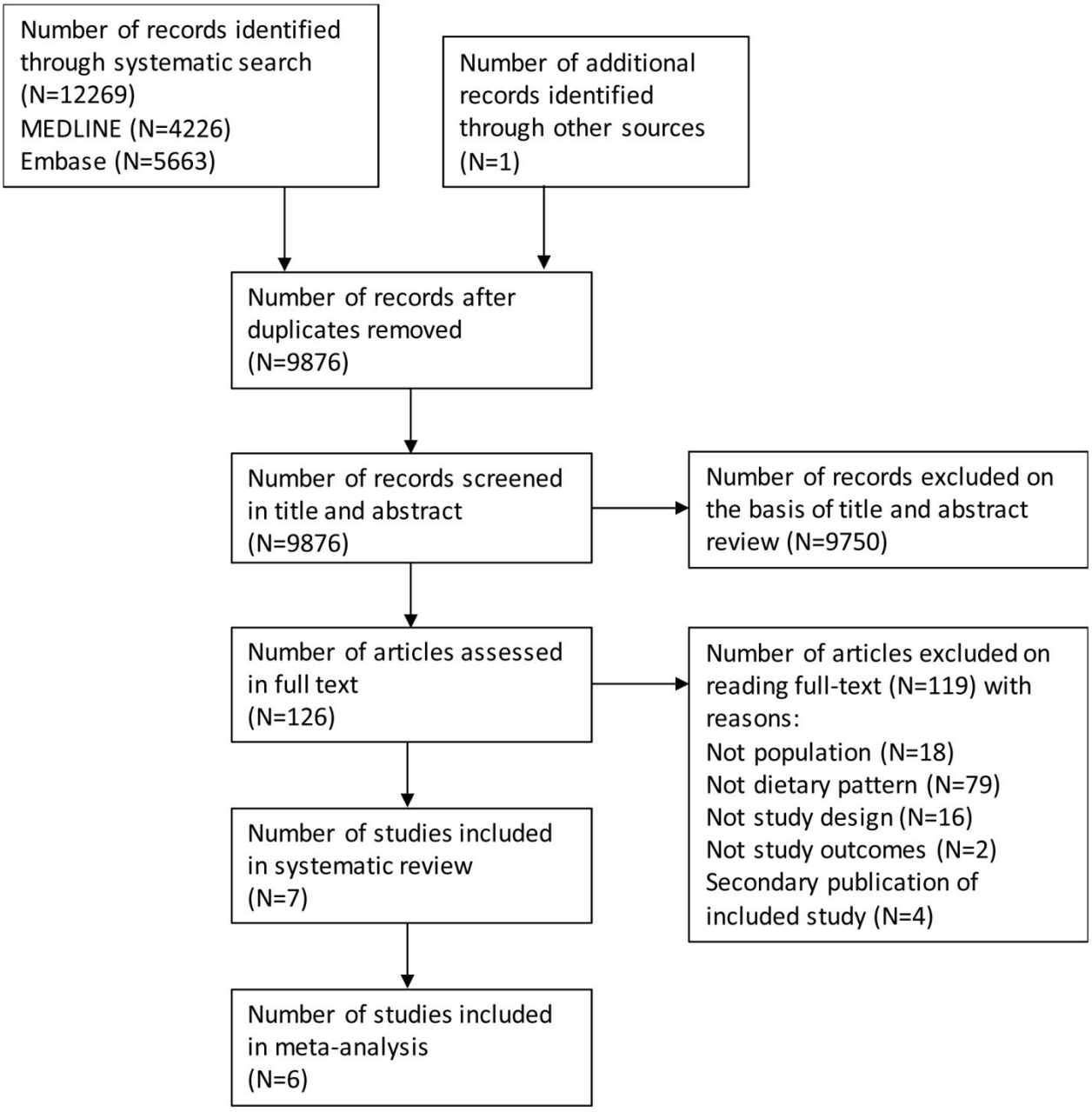


Figure 2: Risk of all-cause mortality associated with healthy dietary patterns among adults with chronic kidney disease

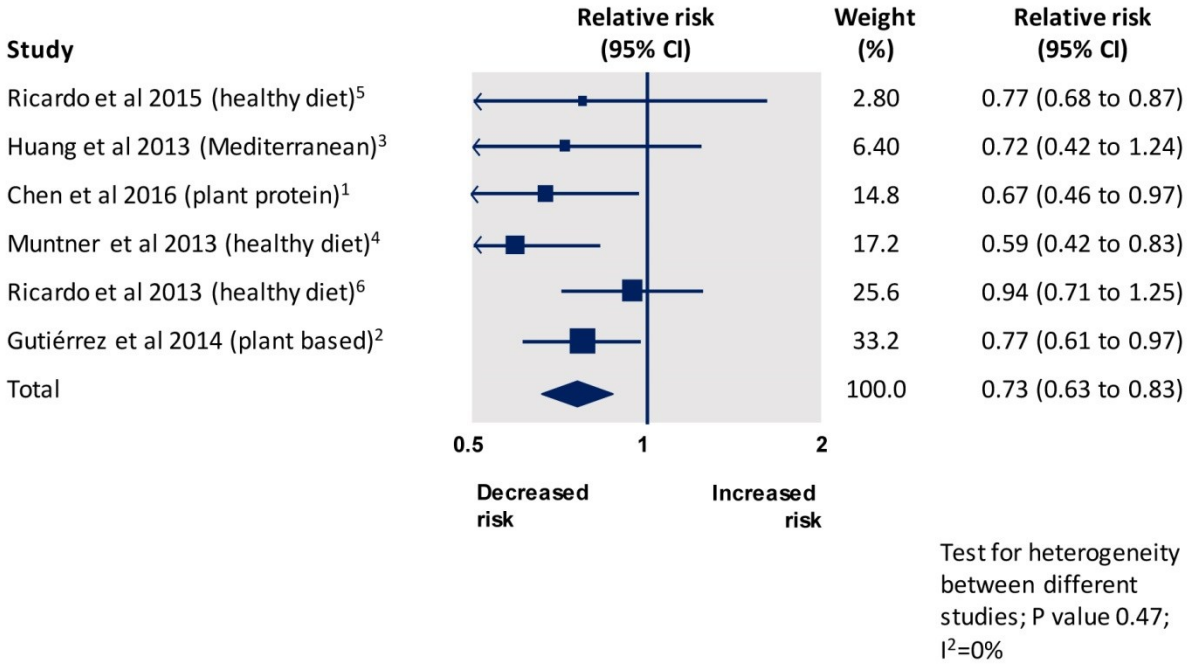
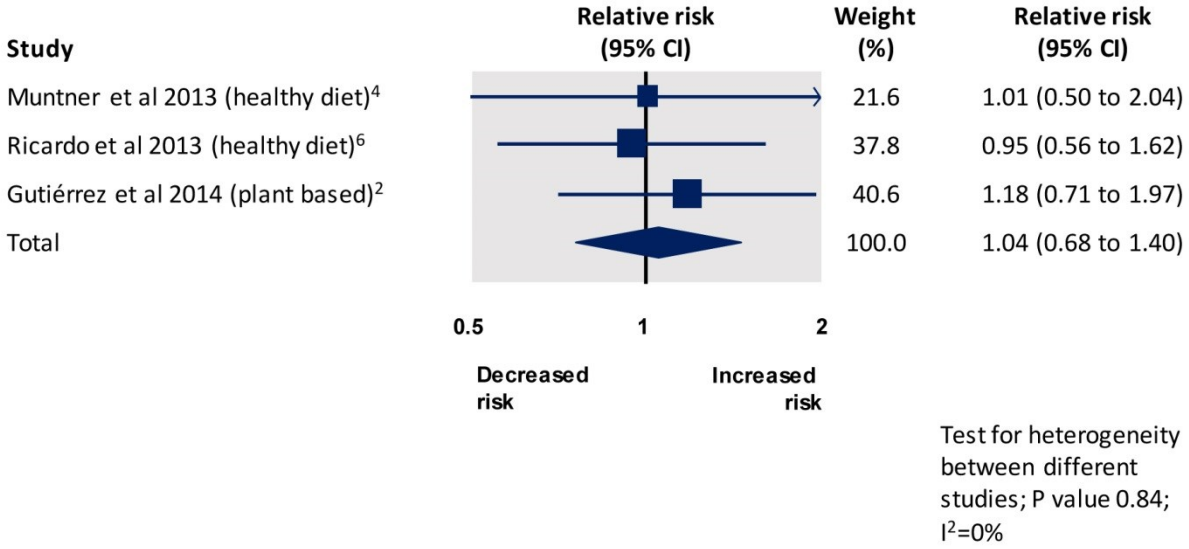


Figure 3: Risk of end-stage kidney disease associated with healthy dietary patterns among adults with chronic kidney disease



CHAPTER II: NUTRITION AND DIETARY INTAKE AND THEIR ASSOCIATION WITH MORTALITY AND HOSPITALISATION IN ADULTS WITH CHRONIC KIDNEY DISEASE TREATED WITH HAEMODIALYSIS: PROTOCOL FOR DIET-HD, A PROSPECTIVE, MULTINATIONAL, COHORT STUDY

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Abstract

Introduction

Adults with end stage kidney disease (ESKD) treated with haemodialysis experience mortality rates of between 15% and 20% each year. Effective interventions that improve health outcomes for long-term dialysis patients remain unproven. Novel and testable determinants of health in dialysis are needed. Nutrition and dietary patterns are potential factors influencing health in other health settings that warrant exploration in multinational studies in men and women treated with dialysis. We report the protocol of the "DIETary intake, death and hospitalisation in adults with end-stage kidney disease treated with haemodialysis (DIET-HD) study", a multinational prospective cohort study. DIET-HD will describe associations of nutrition and dietary patterns with major health outcomes for adults treated with dialysis in several countries.

Methods and Analysis

DIET-HD will include at least 6000 adults who have ESKD treated within a collaborative network of clinics in Argentina, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden, and Turkey administered by a single dialysis provider. Nutritional intake and dietary patterns will be measured using the Global Allergy and Asthma European Network (GA^2LEN) food frequency questionnaire. The primary dietary exposures will be n-3 and n-6 polyunsaturated fatty acid consumption. The primary outcome will be cardiovascular mortality and secondary outcomes will be all-cause mortality, infection-related mortality and hospitalisation.

Ethics and dissemination

The study has been approved by the relevant Ethics Committees in Argentina, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden, and Turkey. All participants will provide written informed consent and will be free to withdraw their data from the study at any time. Data will be handled securely and anonymously. The findings of the study will be disseminated through peer-reviewed journals, national and international conference presentation. We expect that the DIET-HD study will inform large pragmatic trials of nutrition or dietary interventions in the setting of advanced kidney disease.

Introduction

Long-term dialysis treatment for end-stage kidney disease is associated with an annual mortality of between 15% and 20%, a proportion in excess of many cancers.[1] Healthcare interventions have not been generally shown to improve clinical outcomes for adults treated with dialysis and additional testable strategies for improving mortality and morbidity are needed.

Nutritional intake and dietary patterns are potential determinants of health outcomes in dialysis patients. Dietary restrictions aimed at keeping fluid, serum phosphorus and potassium levels within range often results in limited food choices and unappetising meals.[2] The accumulation of uraemic metabolites, metabolic acidosis, inflammation and additional frequent comorbidities, including cardiac dysfunction, can suppress appetite, decrease protein and energy intake, and increase catabolic processes in this population.[3] Malnutrition (commonly referred to as protein-energy wasting[4]) affects 20 to 70% of dialysis patients and increases with duration of dialysis treatment;[5-7] Approximately 5 to 10% of people treated with dialysis experience severe protein-energy malnutrition.[8]

Premature death in people with end-stage kidney disease is strongly associated with low body mass, low serum cholesterol and other markers of impaired nutrition. Several studies have shown a consistent association between low serum albumin, low height-adjusted body weight and malnutrition (assessed by subjective global assessment) and total and cardiovascular-specific mortality in the dialysis population.[9-11] In addition, protein-energy wasting (incorporating both malnutrition and other metabolic derangements in patients with end-stage kidney disease, such as inflammation) is a strong risk factor for premature death.[3] Data for 5058 adults in the United States Renal Data System (USRDS) indicated that dialysis patients who were considered malnourished by their physicians had a 27% greater risk of cardiovascular death. Similarly, a Dialysis Outcomes and Practice Patterns Study (DOPPS) cohort study comprising 7719 adult haemodialysis patients reported that severe malnutrition (evaluated by a modified subjective global assessment, recent weight loss, poor dietary intake, gastrointestinal symptoms and visual assessment of subcutaneous fat) was linked to a 33% higher mortality risk.[11] [12]

Serum n-3 and n-6 polyunsaturated fatty acid profiles are additional potential determinants of cardiovascular outcomes in adults treated with haemodialysis. N-3 polyunsaturated fatty acids such as eicosapentaenoic acid and docosahexaenoic acid may favourably influence oxidative stress, inflammation and thrombosis.[13] [14] Dialysis patients have a decreased ratio of n-3 to n-6

PUFAs, which independently predicts accelerated cardiovascular disease.[15] However, data for dietary polyunsaturated fatty acid intake and associations with mortality in this clinical setting are sparse although n-3 polyunsaturated fatty acid supplementation may lower mortality and hospital admissions in other settings of chronic disease,[16] including earlier stages of chronic kidney disease.[17]

Other dietary and nutrition factors have potential clinical effects in the setting of end-stage kidney disease. The Mediterranean diet, characterised by high intake of olive oil fruit, nuts, vegetables and cereals, moderate fish and poultry intake and lower consumption of dairy foods, red and processed meats and sweets, prevents cardiovascular events,[18] although prognostic data in the setting of kidney disease are rare. The average blood levels of biologically important trace elements including selenium and zinc (antioxidant molecules) differ in people with end-stage kidney disease.[19] Lower zinc levels in end-stage kidney disease patients are associated with increased oxidative stress, lipid peroxidation and inflammation.[20] Since deficiency or excess of trace elements is potentially harmful, the hypothesis that trace element supplementation might influence clinical outcomes is worthy of evaluation. Similarly, vitamin C is an antioxidant with several immune and regulatory functions, and levels are often depleted in end-stage kidney disease patients by up to 50%. A recent Cochrane review of trials investigating the use of antioxidants for people with chronic kidney disease found that antioxidant therapy does not reduce cardiovascular or all-cause death but due to the suboptimal quality of existing studies, a clinically important benefit cannot be excluded.[21]

The quality and quantity of food intake is thought to play a major role in cardiovascular and infective complications of dialysis and have prognostic implications through mechanisms independent of overall nutrition status (lipid levels, blood pressure, thrombotic tendency, cardiac rhythm, endothelial function, insulin sensitivity, oxidative stress).[22 23] However, data evaluating the association between diet and clinical outcomes in people treated with dialysis are limited and largely derive from small, single-centre, retrospective studies.[24-27]

The prospective study described in this protocol will be the first large scale multinational cohort study to evaluate the association between nutrition and health outcomes in adults with end-stage kidney disease treated with haemodialysis. The study will assess the short and long term morbidity and mortality associated with dietary intake (total energy, fat (including mono- and n-3 and n-6 polyunsaturated fatty acids; cholesterol), carbohydrates (including total sugars), protein, fibre,

folate, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, fluid), and specific food types (fruit, vegetable, nuts, fish, pulses)) in adults treated with haemodialysis. The study will also evaluate nutrient and non-nutrient antioxidants, specific food groups related to Mediterranean or other regionally distinctive diets, and the intake of processed food and fresh fruit and vegetables.

Methods

Study design summary

The "DIETary intake, death and hospitalisation in adults with end-stage kidney disease treated with HaemoDialysis (DIET-HD) study" is a multinational, prospective, cohort study designed to evaluate the association between nutrition and dietary patterns and health outcomes in prevalent adult haemodialysis patients in Europe and South America.

Target population, setting and inclusion/exclusion criteria

The DIET-HD population will involve at least 6000 adults treated with long-term haemodialysis treatment at clinics within a multinational collaborative dialysis network administered by Diaverum, a provider of renal services. The clinics included in this study will be from dialysis communities in which the local investigators have committed to providing high quality data in Argentina, France, Germany, Hungary, Italy, Poland, Portugal, Romania, Spain, Sweden, and Turkey.

Participants will be eligible for DIET-HD if they meet the following inclusion criteria: (1) have end-stage kidney disease; (2) are treated with long-term haemodialysis for at least the previous 90 days; (3) are 18 years or older; (4) their treating team agrees to the patient's involvement in the study; and (5) the participant is willing to provide written and informed consent. We will exclude potential participants from DIET-HD if they have: (1) significant neurocognitive disability or medical comorbidity that would preclude them from understanding the dietary questionnaire even if assisted; (2) a life expectancy less than 6 months according to their treating physician; (3) planned kidney transplantation within 6 months of baseline, or (4) anticipated recovery of kidney function.

Study exposures and outcomes

The primary exposure variables will be dietary consumption of n-3 and n-6 polyunsaturated fatty acids. The primary outcome will be cardiovascular mortality. Secondary outcomes will be all-cause mortality, death due to infection, and all-cause and cause-specific hospitalisation. Key secondary nutritional exposure variables will dietary total energy, fat (including monounsaturated fatty acids; cholesterol), carbohydrates (including total sugars), protein, fibre, folate, β-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium, zinc, fluid), and specific food types (fruit, vegetable, nuts, fish, pulses).

Study procedures

Assessment of dietary intake (food frequency questionnaire)

Consecutive eligible patients in a convenient sample of selected clinics will be given a food frequency questionnaire to complete during dialysis treatment. The usual dietary intake will be ascertained using the Global Asthma and Allergy Network of Excellence (GA^2LEN) food frequency questionnaire (FFQ).[28] The GA^2LEN was initially translated into 12 languages to be used as a single instrument in all the European centres participating in the GA^2LEN follow-up survey. The FFQ has been tested in a sub-sample of adults from five European countries and shown to be a reliable instrument to estimate dietary intake in different countries.[28] Translations of the FFQ have been carried out following the standard operating procedure of the World Health Organization. Forward translation from English into relevant participant languages was carried out by local research team members. Back translation was then carried out by an independent translator who had not seen the original English version. During this stage, local foods were incorporated into each of the FFQs. The GA^2LEN has been adapted to mirror the local and staple foods of each participant country in this study without affecting the international comparability structure of the FFQ. The FFQ provides information on the frequency of a wide range of foods, which have been classified using the European Food Group Classification Method designed by Ireland and colleagues.[29] This is an international classification based on the European Food Consumption Survey Method (EFCOSUM) designed to "define a minimum set of dietary components which are relevant determinants of health and to define a method for the monitoring of food consumption in national representative samples of all age-gender categories in Europe in a comparable way."[30]

Nutrient estimates

Nutrient intake will be calculated using national Food Composition Tables from each participating country. For analyses comprising the entire study sample, we will implement the methodological approach used by GA^2LEN,[28] which employed the British Food Composition Table to describe nutrient composition, including data from country-specific Food Composition Tables, to calculate nutrient estimates of traditional or staple foods of specific countries. Current analyses in the GA^2LEN Nutrition study show that the British Food Composition Table is the most comprehensive table in terms of number of nutrient data available. We have access to all the latest data within Food Composition Tables in European countries facilitated by EuroFir (European Food Network of Excellence)[31] which, as GA^2LEN, was an EU funded Network. This is now a non-profit consortium

that fosters the advancement in the knowledge of food composition in Europe and other countries.

The standard food portion sizes used in the FFQ will be obtained from Food Standard Agency Food Portion Sizes Guidelines in the UK. The frequency of consumption will be converted into grams per day and then into nutrient estimates. The FFQ is designed to be answered by the participants (self-administered). However, depending on the country and the needs of the research team, as well as of the participants, some centres will prefer to have the FFQ interviewer-administered, when necessary, or have interviewers on hand in the clinics to either administer the FFQ (for participants who have literacy limitations) or to verify that the FFQ has been answered in full. Participants will complete the dietary questionnaire during a haemodialysis treatment.

We will calculate intake of the following macro- and micro- nutrients using estimates of the EuroFir Food Composition Tables: energy (kJ/day), fat (including mono- and polyunsaturated fat; n-3 polyunsaturated fatty acids; n-6 polyunsaturated fatty acids; *trans*-fatty acids; cholesterol), carbohydrate, glycaemic index, total sugar, protein (including sources (animal versus vegetable sources)), fibre, folate, beta-carotene, retinol, thiamine, riboflavin, phosphorus, magnesium, calcium and zinc. We will also estimate the intake of specific food groups including fruit, vegetable, nuts, fish and pulses. Research assistants will be trained using a step-by-step practical overview of the process that is to be followed in administration of the questionnaires. The protocol emphasises the need for assistants to avoid non-verbal cues indicating surprise or disapproval at the participant's eating patterns.

FFQ responses will be evaluated by members of the research team who are unaware of the participants' identities. All FFQs with missing values will be checked and corrected for any data errors. After data cleaning, if more than 10% of the questionnaire remains incomplete, then the participant will be excluded. In addition, individuals for whom energy intake is in the upper or lower 2% of the intake will then checked for data entry and coding accuracy and errors will be corrected, if identified. Data from the FFQ will be entered into an electronic database using optical character recognition (OCR) and analysed using software that facilitates the collection of food recalls in a standardised fashion.[32]

Demographic and clinical data

Demographic, clinical, laboratory and dialysis-related data will be obtained from a patient database within one month of enrolment. Relevant data will be obtained from clinical databases linked to the participant via a standardised identification code. Standardised data will include age, gender, race, country of residence, clinic attended, education, marital and occupational status, family income, financial stress, housing, alcohol intake, smoking history, physical activity, menopausal status, body mass index, protein catabolic rate, cause of kidney disease, existence of cardiovascular comorbidity, diabetes, or hypertension, medication prescription, dialysis prescription, and serum levels of haemoglobin, phosphorus, parathyroid hormone, calcium, ferritin, albumin, and total cholesterol.

Outcomes

Measurement time points

After baseline dietary evaluation, we will measure clinical outcomes using linked data at 12 months and thereafter at yearly intervals up to 10 years. Data for total and cause-specific hospitalisation and mortality are obtained through data linkages to a centralised database administered by Diaverum. In this database, every change in participant status is updated by the managing clinician on a monthly basis, including change in survival status or hospitalisation, with causes of death or hospital admission.

Outcomes

The primary study outcome will be cardiovascular mortality. Secondary outcomes will all-cause mortality, infection-related mortality, and all-cause and cardiovascular related hospitalisation. A cardiovascular-related death or hospitalisation will include death or hospitalisation attributed to acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary oedema, congestive cardiac failure, cerebrovascular accident including intracranial haemorrhage, ischemic brain damage including anoxic encephalopathy, or mesenteric infarction or ischemic bowel. An infection related death will include septicaemia due to internal vascular access, central nervous system infection (brain abscess, meningitis, encephalitis), septicaemia due to peripheral vascular disease or gangrene, cardiac infection (endocarditis), pulmonary infection (pneumonia or influenza), abdominal

infection (peritonitis, perforated bowel, diverticular disease, gallbladder infection), or genito-urinary infection (urinary tract infection, pyelonephritis, renal abscess).

Sample size

The sample size for this study will be at least 6000 participants. Based on an anticipated mortality of 14% to 15% each year and a cardiovascular mortality rate of 6% per annum, we anticipate that recruitment and evaluation of at least 6000 participants will allow the study, with a type 1 error α= 0.05 and power of 80% to detect a hazard ratio of at least 1.10 for each 1 standard deviation decrease in n-3 polyunsaturated fatty acid intake. When adjusting for the complete set of potentially confounding variables, assuming an $R^2 = 0.30$, the same sample size will detect a hazard ratio of at least 1.12 for each standard deviation decrease in the primary exposure.

Statistical analysis

The initial data analysis will be descriptive. Participants' baseline characteristics (country, clinic, demographics, clinical characteristics, dialysis treatment, etc.) will be described using frequencies for categorical variables and mean, median, range, standard deviation for continuous variables. Characteristics of specific dietary components will also be calculated as mean, median, range, and standard deviation. To evaluate associations between each individual nutrient of interest and the outcomes, we will conduct multivariate regression analyses using Cox proportional hazards analysis fitted using a shared frailty model to account for clustering within countries. Participants will be censored within survival analyses if they emigrate from the dialysis network, are transplanted, or experience recovery of their kidney function.

Given the large number of nutritional exposures, we will control for potential false discoveries using the Simes' procedure allowing for a 5% false discovery rate while controlling for potential confounding variables. Similarly we will explore associations between groups of foods (e.g., vegetables or fruits) and nutrients using similar techniques. We will then explore the association between dietary or nutritional exposures (foods, single or grouped or nutritional components) with the outcomes of interest within countries using logistic or linear regression adjusted by confounding variables) and then combine data from all countries using meta-analysis. We will also calculate weighting of the sample to make it representative of the source population within each country. We will conduct analyses in STATA (www.stata.com) using existing routines available for the GA^{2}LEN study.

Ethics and dissemination

Ethical considerations

DIET-HD has received ethics approval from the following responsible Human Research Ethics Committees in France, Germany, Hungary, Portugal, Romania, Spain, Sweden, and Turkey. Ethics approval was not required for this type of study in Argentina, Italy or Poland. The study is based on informed written consent, and participants can withdraw from the study at any point in time. The study is non-invasive and imposes no significant risks to participants. Data material will be managed confidentially and anonymously.

Dissemination

The findings of the study will be disseminated through peer-reviewed journals, national and international conference presentations and to the participants through communication within the dialysis network in which this study is conducted.

Discussion

We have designed DIET-HD to evaluate whether dietary patterns and nutritional intake are associated with mortality and hospitalisation in adults with end-stage kidney disease treated with haemodialysis. This study will generate potential testable diet and nutrition targets for evaluation in pragmatic multicentre trials and meta-analyses.

Our study design, while incorporating data from several countries and using validated and robust multinational dietary analysis tools from the GA^{2}LEN network collaboration, has potential limitations. To ensure sufficient data from a broad range of participants, we have used a convenient sample of clinics within the participating countries to maximise recruitment without stratification by key clinic demographic or clinical characteristics. This may limit our ability to provide data representative of source populations but will still be the largest in depth nutritional survey of adults treated with haemodialysis to date. Mortality and other endpoint data will be obtained using linkages to a data registry. There will not be adjudication of clinical endpoints by personnel blinded to exposure and there will be some misclassification of clinical outcomes.

Effective strategies to improve health outcomes in this population are scarce and urgently needed. We expect that the results of the DIET-HD study will inform large pragmatic trials of nutrition or dietary interventions in the setting of advanced kidney disease.

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CHAPTER III: DIETARY N-3 POLYUNSATURATED FATTY ACID INTAKE AND ALL-CAUSE AND CARDIOVASCULAR MORTALITY IN ADULTS ON HEMODIALYSIS: THE DIET-HD MULTINATIONAL COHORT STUDY

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Abstract

Background & Aims: Patients on hemodialysis suffer from high risk of premature death, which is largely attributed to cardiovascular disease, but interventions targeting traditional cardiovascular risk factors have made little or no difference. Long chain n-3 polyunsaturated fatty acids (n-3 PUFA) are putative candidates to reduce cardiovascular disease. Diets rich in n-3 PUFA are recommended in the general population, although their role in the hemodialysis setting is uncertain. We evaluated the association between the dietary intake of n-3 PUFA and mortality for hemodialysis patients.

Methods: The DIET-HD study is a prospective cohort study (January 2014-June 2017) in 9757 adults treated with hemodialysis in Europe and South America. Dietary n-3 PUFA intake was measured at baseline using the GA^{2}LEN Food Frequency Questionnaire. Adjusted Cox regression analyses clustered by country were conducted to evaluate the association of dietary n-3 PUFA intake with cardiovascular and all-cause mortality.

Results: During a median follow up of 2.7 years (18,666 person-years), 2087 deaths were recorded, including 829 attributable to cardiovascular causes. One third of the study participants consumed sufficient (at least 1.75 g/week) n-3 PUFA recommended for primary cardiovascular prevention, and less than 10% recommended for secondary prevention (7-14 g/week). Compared to patients with the lowest tertile of dietary n-3 PUFA intake (<0.37 g/week), the adjusted hazard ratios (95% confidence interval) for cardiovascular mortality for patients in the middle (0.37 to <1.8 g/week) and highest (≥1.8 g/week) tertiles of n-3 PUFA were 0.82 (0.69-0.98) and 1.03 (0.84-1.26), respectively. Corresponding adjusted hazard ratios for all-cause mortality were 0.96 (0.86-1.08) and 1.00 (0.88-1.13), respectively.

Conclusions: Dietary n-3 PUFA intake was not associated with cardiovascular or all-cause mortality in patients on hemodialysis. As dietary n-3 PUFA intake was low, the possibility that n-3 PUFA supplementation might mitigate cardiovascular risk has not been excluded.

Introduction

Approximately 1 in 10 people on dialysis die every year, and 40% of these deaths are attributable to cardiovascular disease (1-3). The pathogenesis of cardiovascular disease is different in dialysis patients from for the general population, driven largely by non-traditional risk factors, including oxidative stress, inflammation, endothelium dysfunction and altered mineral metabolism leading to medial arterial calcification (4-7). Consequently, the benefits of interventions targeting traditional cardiovascular risk factors, such as statins, blood-pressure lowering, and anti-platelet therapy, have been shown to have lower effectiveness for preventing adverse cardiovascular outcomes in hemodialysis patients (8-12).

Long chain n-3 polyunsaturated fatty acids (n-3 PUFA) are recommended to prevent cardiovascular disease in the general population (13-15). n-3 PUFA, present mostly in oily fish and in smaller amount in meat, eggs and dairy products, have potential anti-thrombotic, anti-oxidative, anti-inflammatory and anti-arrhythmic effects on cardiac myocytes (16-19). Informed by a number of randomized controlled trials and systematic reviews (20-25), the current recommendations by the American Heart Association and World Health Organization suggest an intake of at least 1.75 grams per week of n-3 PUFA (achieved by at least two servings of fish per week, especially oily fish) for primary cardiovascular prevention and 7-14 grams per week (which could require supplementation) for secondary prevention (13-15).

In patients on hemodialysis, data for the effects of n-3 PUFA on mortality are sparse and limited to small-scale observational studies (26-33). Results to date have been inconclusive. Accordingly, recommendations for n-3 PUFA intake in the hemodialysis population have been extrapolated from evidence in the general population (34).

The aim of this study was to ascertain the association of dietary n-3 PUFA intake with cardiovascular and all-cause mortality among adult patients on hemodialysis (35).

Methods

The "DIETary intake, death and hospitalization in adult with end-stage kidney disease treated with HemoDialysis" (DIET-HD) study is a multinational, prospective, cohort study to evaluate the association between nutrition and dietary patterns with major health outcomes in prevalent adult patients treated with hemodialysis. The study protocol has been detailed elsewhere (35). This study is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (36).

Study Population

Consecutive patients were invited from a convenience sample of clinics within a private dialysis provider network in Europe (France, Germany, Italy, Hungary, Poland, Portugal, Romania, Spain, Sweden, and Turkey) and South America (Argentina). Eligible patients were 18 years or older with end-stage kidney disease treated with hemodialysis (any number of treatments per week and any duration per treatment) for at least the previous 90 days. Patients were excluded if they had significant neurocognitive disability that precluded them from completing the Food Frequency Questionnaire (FFQ), a life expectancy less than six months, or anticipated kidney transplantation within six months of baseline data collection. Ethics approval was obtained from all relevant institutional ethics committees and the study was conducted in accordance with the Declaration of Helsinki. All participants provided written and informed consent.

Covariates of interests

Socio-demographic, clinical and dialysis characteristics at baseline were obtained from an administrative database that stored relevant data on incident patients requiring hemodialysis within all facilities of the private dialysis provider. This database was linked to the participants via a unique identification code. All participating clinics used the same standard operating procedures to assess and record baseline variables including age, gender, country of treatment, education attainment, marital status and living situation, occupation, smoking history, physical activity, Body Mass Index,comorbidities (including diabetes and previous cardiovascular disease), use of medications, laboratory parameters (including hemoglobin, albumin, phosphorus and calcium) and dialysis-related data(including time on dialysis and Kt/V).

Exposures

The dietary intake of n-3 PUFA was ascertained using the Global Allergy and Asthma European Network (GA^2LEN) Food Frequency Questionnaire (FFQ) (37). During the dialysis treatment, participants answered the FFQ, either independently or assisted by an interviewer, depending on the severity of their clinical condition. Data from the FFQ were entered into an electronic database using optical character recognition and linked to the baseline and outcomes data via a unique identification code. The GA^2LEN FFQ was specifically designed as the first single, standardized instrument to assess dietary intake across countries and was particularly validated for n-3 PUFA dietary intake. Patients reported how often they had consumed the foods over the previous year, using eight predefined options (rarely or never, 1-3 times per month, once, 2-4, or 5-6 times per week, once, 2-3 or 4 or more times per day). Standard food portion sizes were used to quantify the intake following the recommendations from the UK's Food Standards Agency, and daily food intake (grams) was calculated. Macro- and micronutrient intake were derived using the latest available McCance & Widdowson's Food Composition Tables.

Outcomes

The primary outcome was time to death due to cardiovascular causes. Cardiovascular mortality was defined as sudden death or death attributed to acute myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, cardiac arrhythmia, cardiac arrest, valvular heart disease, pulmonary edema, or congestive cardiac failure. Outcomes data were obtained from data linkage with the administrative database and adjudicated by the participants' treating clinicians, who were unaware of the dietary n-3 PUFA intake. The secondary outcome was death from any cause.

Statistical analysis

The a priori sample size calculation has been reported in detail in the published study protocol (35). Participants were excluded if their FFQ contained erroneous or missing identification code (after optical character recognition) that prevented the data linkage with their clinical baseline and outcomes data, 20% or more missing answers, or biologically implausible values for total energy intake (above or below 3 standard deviations from the log transformed mean).

Baseline variables were calculated as mean and standard deviation or median and interquartile range for continuous variables, depending upon their distribution, and as frequencies and

percentages for categorical variables. Restricted cubic splines were used to determine the linearity between n-3 PUFA intake and mortality (no evidence of non-linearity was identified). The follow-up period was defined from the time of the inclusion in the study to the time of cardiovascular or all-cause mortality. Patients who left the dialysis network, underwent kidney transplantation, were transferred to peritoneal dialysis, withdrew dialysis, had kidney function recovery, went on vacation, were lost to follow-up or survived until the end of the follow-up period were censored. Univariate and multivariate Cox proportional hazard regression analyses were fitted using a random effects shared frailty model and stratified by country to account for clustering of mortality risk and dietary exposure within countries. Dietary intake of n-3 PUFA was entered as tertiles in the random effect shared frailty model and as continuous variable in the analysis stratified by country. Results were expressed as a hazard ratio and the associated 95% confidence interval. The proportional hazards assumption in Cox models was assessed by fitting log (time)-dependent covariates in the multivariable model and no deviation from the assumption was found. Effect modification between dietary n-3 PUFA intake and covariates were tested in the multivariable model and no effect modification was observed.

Analyses of cardiovascular mortality were adjusted for gender, education (secondary versus none/primary), smoke (former or current versus never), diabetes, myocardial infarction, vascular access type (arterio-venous fistula versus graft/catheter), Body Mass Index (categories according to WHO), albumin (tertiles), Charlson comorbidity score (quartiles), age (standard deviation increase), phosphorus, calcium, haemoglobin, KTV (index to quantify hemodialysis treatment adequacy), fiber daily intake (tertiles) and energy intake (1000 kcal per day increase). Analyses of all-cause mortality were adjusted as above except for fiber intake and with the addition of time on dialysis and being wait-listed for renal transplantation. Variables included in the multivariate models were selected by backwards elimination retaining those (a part from energy intake and gender) that were significantly associated with mortality ($p < 0.05$) or changed the hazard ratio of mortality for dietary n-3 PUFA by a clinically relevant amount (≥ 10%). For each categorical variable, an extra category was included for missing data in the multivariate model, when necessary (education, smoking, diabetes, myocardial infarction, serum albumin, Body Mass Index). A complete-case analysis was also conducted including only those patients with complete data as sensitivity analyses. In subgroup analysis the association between dietary n-3 PUFA intake and cardiovascular mortality was assessed among patients achieving levels of n-3 PUFA recommended for secondary cardiovascular prevention. The potential relevance of competing events (death from

other causes and kidney transplantation for the analysis of cardiovascular mortality; kidney transplantation for the analysis of all-cause mortality) was considered using a stratified proportional sub-distribution hazard model. All analyses were conducted using SAS 9.4. (Inc, Gary 2014) and STATA version 14. A two tailed P <0.05 was considered to indicate statistical significance.

Results

Overall, 9757 patients on hemodialysis were enrolled from 5 January 2014 through 22 January 2015 in the DIET-HD study and followed through 27 June 2017. Of these, 8110 (83%) were included in the analysis. Patients with an erroneous or missing identification code to allow data linkage [n = 1224 (13%)] and those with insufficient or implausible dietary responses [n = 423 (4%)] were excluded (**Figure 1**).

Baseline characteristics

The mean age of the cohort was 63.1 years (standard deviation 15.0 years). Overall, 4691 (58%) were men, 2068 (33%) were former or current smokers, 934 (15%) engaged in daily physical activity, 2332 (32%) had diabetes, 838 (12%) had experienced myocardial infarction and 634 (9%) had experienced stroke. Participants had been treated with hemodialysis for a median period of 3.6 years (interquartile range 1.7 to 6.8) (**Table 1**).

The median intake of n-3 PUFA was 1.2 (0.3 to 2.4) grams per week. Overall, 31% of participants did not consume any fish on a weekly basis, 46% consumed ≤1 serving, and 23% ≥ 2 servings each week. There was substantial variability in the dietary intake of n-3 PUFA across countries (**Table 2**). The median weekly intake of n-3 PUFA ranged from 0.2 (0.1 to 0.6) grams in Argentina and 3.1 (2.1 to 4.3) grams in Sweden. The median country-level n-3 PUFA intake was lower than the minimum recommended value for cardiovascular prevention (1.75 grams per week) in nine out of eleven countries.

Cardiovascular and all-cause mortality

During a median follow up of 2.7 years (18,666 person-years), 2087 deaths (26%) were recorded, of which 829 (40%) were attributable to cardiovascular causes. The incidence of cardiovascular and all-cause mortality varied considerably by country and was highest among patients in Eastern European countries (Hungary, Poland, Romania, Turkey) and Argentina and lower among patients

in Northern, Central and Western European countries (Sweden, Germany, Portugal, Spain, France, Italy) (**Table 2**). In general, patients in countries with lower incidence of cardiovascular and all-cause mortality, such as Sweden (5 and 16 deaths per 100,000 person-days, respectively) and Portugal (7 and 26 deaths per 100,000 person-days) reported a higher median intake of n-3 PUFA (3.1 [interquartile range 2.1-4.3] and 2.4 [1.2-6.9] g per week, respectively), while patients in countries with higher incidence of cardiovascular and all-cause mortality, including Hungary (25 and 46 deaths per 100,000 person-days) and Argentina (16 and 38 deaths per 100,000 person-days) reported lower intake of n-3 PUFA (0.4 [0.2-1.3] and 0.2 [0.1-0.6] grams per week respectively) (**Figure 2**).

Association between dietary n-3 PUFA intake and cardiovascular mortality

There was no association between dietary intake of n-3 PUFA and cardiovascular mortality. The adjusted hazard ratio (95% CI) for cardiovascular death among patients in the highest (≥1.8 grams per week) and middle tertile (0.37 to <1.8 grams per week) of dietary n-3 PUFA intake was 0.99 (0.83 to 1.19) and 0.84 (0.71 to 1.00), respectively, compared with patients in the lowest tertile (<0.37 grams per week). Similar findings were observed when considering the competing risk of other causes of death and kidney transplantation on cardiovascular mortality (**Table 3**). In subgroup analysis including only patients (N=725) achieving levels of n-3 PUFA recommended for secondary prevention (≥ 7 grams per week), no significant association between n-3 PUFA and cardiovascular mortality was observed [adjusted hazard ratio among patients in the highest (≥8.9 grams per week) and middle tertile (7.5 to <8.9 grams per week) was 1.26 (0.58-2.72) and (1.16 (0.56-2.4) respectively, compared with patients in the lowest tertile (<7.5 grams per week)]. There was no association between dietary n-3 PUFA intake and cardiovascular mortality within individual countries (**Figure 3**). Risk factors for cardiovascular mortality included older age, lower education, smoking, presence of comorbidities and higher level of phosphorus and calcium. Arterio-venous fistula vascular access, dietary fiber, serum albumin, BMI, hemoglobin and Kt/V were inversely associated with cardiovascular mortality (**Table S1**).

Association between dietary n-3 PUFA intake and all-cause mortality

Compared with patients in the lowest dietary intake of n-3 PUFA, the adjusted hazard ratio (95% CI) for all-cause mortality among those in the highest and middle n-3 PUFA tertile was 1.00 (0.88 to 1.13) and 0.96 (0.86 to 1.08), respectively. Similar findings were observed when considering the competing risk of kidney transplantation on all-cause mortality (**Table 3**). There was no association

between dietary intake of either n-3 PUFA and all-cause mortality within countries (**Figure 3**). Risk factors for all-cause mortality were older age, being male, lower education, smoking, presence of comorbidities, longer time on dialysis and serum levels of phosphorus and calcium. Arterio-venous fistula vascular access, being wait-listed for renal transplantation, and higher levels of albumin, BMI, hemoglobin and Kt/V were associated with lower risks of all-cause mortality (**Table S1**).

Complete-case analysis

Similar findings were observed in complete-case analysis. 3981 participants had complete data for dietary n-3 PUFA, as ascertained by the FFQ, and for covariates and clinical outcomes, as collected within the administrative database. In this subsample of patients, the adjusted hazard ratio (95% CI) for cardiovascular death among patients in the highest and middle tertiles of n-3 PUFA intake was 1.12 (0.82 to 1.53) and 0.89 (0.66 to 1.18), respectively, compared with those in the lowest tertile. The adjusted hazard ratios (95% CI) for all-cause mortality among patients in the highest and middle tertiles of n-3 PUFA intake were 1.04 (0.87 to 1.25) and 1.02 (0.86 to 1.20), respectively, compared with those in the lowest tertile.

Discussion

In this large, multinational cohort study of dietary n-3 PUFA intake, dietary intake was generally below recommended levels for primary and secondary prevention of cardiovascular mortality. No association between the dietary n-3 PUFA intake with cardiovascular or all-cause mortality was observed among adults treated with hemodialysis. When considering an ecological approach, there was considerable variation in the dietary intake of n-3 PUFA among participating countries with an apparent inverse relationship between country-level median dietary intake of n-3 PUFA and mortality incidence. However, such ecological inferences between n-3 PUFA dietary intake and mortality were not present at the individual patient level, when controlling for clinical characteristics and energy intake.

The absence of an observed relationship between dietary n-3 PUFA intake and mortality has a number of possible interpretations, including insufficient power, duration of follow up, dietary n-3 PUFA intake below levels considered sufficient for mortality prevention, or the absence of a true relationship between n-3 PUFA dietary intake and mortality in the dialysis setting. Chief among these putative explanations may be the insufficient level of n-3 PUFA, particularly in hemodialysis patients whose mortality risk is similar in magnitude to those requiring secondary prevention and whose dietary n-3 PUFA intake in this cohort was lower than recommended for primary cardiovascular prevention. Previous interventions studies in the general population have suggested a threshold of at least 1.75 g per week of n-3 PUFA (achieved by at least two servings of fish per week) is needed to achieve any cardiovascular benefits (38) and higher doses n-3 PUFA supplementations (≥ 7 g per week) are required for secondary cardiovascular prevention strategy (20, 21). Only one third of the present study population consumed recommended levels of n-3 PUFA as to achieve primary cardiovascular prevention, and less than 10% of study participants achieved the level of n-3 PUFA recommended for secondary prevention. The risk of cardiovascular disease within the hemodialysis population is very high, and might therefore require higher dose n-3 PUFA, analogous to secondary prevention, and which could only be achieved through supplementation. Although no significant association between n-3 PUFA and cardiovascular mortality was observed in our subgroup analysis including patients with secondary prevention levels of n-3 PUFA, the number of observations within this subgroup was too small to exclude a beneficial effect of higher dose n-3 PUFA. Existing randomized controlled trials of higher dose n-3 PUFA supplementation in patients on hemodialysis have reported no significant effect on all-cause

mortality and arteriovenous fistula failure, but reduced risk of thrombosis in arteriovenous grafts and cardiovascular events (39-42). None have assessed the impact of n-3 PUFA supplementation on cardiovascular mortality as the primary outcome in this population (26, 27).

The finding of low dietary intake of n-3 PUFA in our cohort is consistent with previous studies reporting a lower intake of n-3 PUFA in the hemodialysis setting compared to the dietary guidelines for cardiovascular risk reduction (43, 44). Low dietary n-3 PUFA intake is also consistent with lower energy and other nutrient intake, including protein and fiber, by hemodialysis patients as compared to recommendations for cardiovascular prevention in the general population, and renal nutrition recommendations (45-47). Impaired appetite caused by uremia and comorbid illness (48), and financial constraints (49) experienced by hemodialysis patients can contribute to these deficiencies in nutritional intake.

The present study has several strengths. It is the primary analysis of the DIET-HD study, a large multinational prospective cohort study investigating putative determinants of adverse clinical outcomes for patients on hemodialysis. In particular, the DIET-HD study examines the role of diet in the hemodialysis setting that is an important area of research uncertainty prioritized by healthcare professionals and patients (50). The population was geographically diverse thereby enhancing the generalizability of the findings. To date, no data are available on dietary intake of n-3 PUFA and its association with mortality in hemodialysis patients across different countries using a common FFQ. This was the first FFQ specifically designed to allow international comparisons and that included local foods for each participant country.

Limitations of the study should be also considered. First, ascertainment errors were possible due to the use of a self-reported questionnaire. Second, despite the high response rate to the FFQ, the exclusion of patients with erroneous or missing identification code (13%) raised the potential for selection bias. Third, information regarding the potential consumption of PUFA supplementation was not available. In addition, the single baseline measurement of dietary n-3 PUFA intake may be not reflective of the actual cumulative intake over time both before the study commended and during follow up. Moreover, blood levels of n-3 PUFA were not measured and may reflect more accurately longer term consumption and myocardial n-3 PUFA composition. However, the correlation between dietary intake of n-3 PUFA ascertained by the GA^{2}LEN FFQ and corresponding levels in plasma has been validated in a previous pilot study (37) reporting results in agreement

with those of other validation studies of dietary n-3 PUFA intake from FFQs with plasma levels (51, 52).

In summary, the dietary intake of n-3 PUFA in adults treated with hemodialysis is below the recommended levels for primary and secondary cardiovascular prevention. At these levels of n-3 PUFA intake, there was no demonstrable association between dietary n-3 PUFA and mortality which may indicate either that n-3 PUFA does not improve cardiovascular outcomes in hemodialysis patients or that supplementation is required to improve clinical outcomes.

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Authors' Contributions

Conception and design: VMS, GW, MR, SCP, KC, VGL, JCC, and GFMS; Data acquisition: MR, PN, LG, AMM, MG, RG, EC, TE, AGB, DDC, DT, MT, ABS, JD, PS, SH, MH, EF, CW; Data analysis: VMS, GW, ATP, GFMS; Data interpretation: all authors; Study supervision and mentorship: GFMS, JCC, GW, SCP. Each author contributed important intellectual content during manuscript drafting or revision and gave final approval of the version to be submitted.

Conflict of interest

Authors have nothing to declare.

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Figure 1: Flow chart of participation

Figure 2: Unadjusted incidence (per 100,000 person-days) of cardiovascular and all-cause mortality plotted against dietary n-3 PUFA intake by country

Figure 3 Association between dietary n-3 PUFA intake and cardiovascular and all-cause

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Table 1: Baseline characteristics of participants

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Table 3: Mortality hazard ratios (95% confidence interval) by tertiles of weekly grams n-3 PUFA intake

Table 1: Baseline characteristics of participants

Variable	Overall (N=8110)
Demographics	
Age (years) (n=8110)	63.1 (15.0)
Male (n=8110)	4691(57.8)
Country (n=8110)	
Portugal	1777 (21.9)
Argentina	1204 (14.9)
Turkey	1107 (13.7)
Spain	1041 (12.8)
Romania	1000 (12.3)
Hungary	554 (6.8)
Italy	543 (6.7)
Poland	434 (5.4)
France	221 (2.7)
Germany	178 (2.2)
Sweden	51 (0.6)
Socio-economic characteristics	
Married/life partner (n=6095)	4127 (67.7)
Secondary education (n=6090)	2699 (44.3)
Daily physical activity (n=6199)	934 (15.1)
Wait-listed for transplant (n=8094)	1496 (18.5)
Current or former smoker (n=6280)	2068 (32.9)
Clinical characteristics	
Body-Mass Index (kg/m^2) (n=7872)	
Underweight (<18.5)	365 (4.6)
Normal range (18.5-24.9)	3309 (42.0)
Pre-obese (25.0-29.9)	2659 (33.8)
Obese (≥30.0)	1539 (19.6)
Hypertension (n=7317)	6219 (85.0)
Diabetes (n=7280)	2332 (32.0)
Congestive heart failure (n=7272)	1388 (19.1)
Myocardial infarction (n=7236)	838 (11.6)
Stroke (n=7230)	634 (8.8)
Pulmonary disease (n=8108)	940 (11.6)
Depression (n=7218)	757 (10.5)
Gastrointestinal disease (n=8108)	1763 (21.7)
Charlson comorbidity score (n=8108)	6 (4-8)
Laboratory variables	
Albumin, g/L (n=6167)	39.8 (3.8)
Phosphorus, mg/dL (n=7869)	4.7 (1.4)
Calcium, mg/dL (n=7870)	8.9 (0.7)
Hemoglobin, g/dL (n=7869)	11.1 (1.3)
Dialysis characteristics	
Arterio-venous fistula (n=8051)	6481 (80.5)
Time on dialysis (years) (n=8108)	3.6 (1.7-6.8)
Kt/V urea (n=7818)	1.7 (0.3)

Continuous data are expressed as mean (standard deviation), median (25th, 75th quartile) or number (percentage). Body Mass Index categories are defined according to the World Health Organization. Anti-hypertensive includes angiotensin converting enzyme or angiotensin II receptor blocker.

Table 2. Country-specific dietary n-3 PUFA intake and incidence (per 100,000 person-days) of cardiovascular and all-cause mortality

Country	Cardiovascular mortality	All-cause mortality	n-3 PUFA Median, grams per week (IQR)
Argentina	16	38	0.2 (0.1-0.6)
France	9	32	1.5 (0.5-2.5)
Germany	4	29	1.4 (0.3-2.2)
Hungary	25	46	0.4 (0.2-1.3)
Italy	8	27	1.4 (0.3-2.7)
Poland	15	35	1.3 (0.3-2.4)
Portugal	7	26	2.4 (1.2-6.9)
Romania	18	32	1.3 (0.2-1.8)
Spain	7	32	1.5 (0.5-3.4)
Sweden	5	16	3.1 (2.1-4.3)
Turkey	11	22	1.2 (0.3-1.5)

n-3 PUFA: long chain n-3 polyunsaturated fatty acids (calculated as sum of eicosapentaenoic acid, docosapentaenoic acid and docosahexaenoic acid). IQR: interquartile range.

Table 3: Mortality hazard ratios (95% confidence interval) by tertiles of weekly grams n-3 PUFA intake

	n-3 PUFA, grams per week		
Model	≤ 0.37	0.37 to <1.8	≥1.8
Cardiovascular mortality			
Univariate random effect	1.00	0.84 (0.71-1.00)	0.99 (0.83-1.19)
*Multivariate random effect	1.00	0.82 (0.69-0.98)	1.03 (0.84-1.26)
*Multivariate competing risk	1.00	0.82 (0.68-0.97)	1.05 (0.85-1.29)
All-cause mortality			
Univariate random effect	1.00	0.99 (0.89-1.10)	1.00 (0.89-1.12)
≠Multivariate random effect	1.00	0.96 (0.86-1.08)	1.00 (0.88-1.13)
≠Multivariate competing risk	1.00	0.97 (0.87-1.09)	1.01 (0.89-1.15)

*Adjusted for gender, education (secondary versus none/primary), smoke (former or current versus never), diabetes, myocardial infarction, vascular access type (arterio-venous fistula versus graft/catheter), Body Mass Index (categories according to WHO), albumin (tertiles), Charlson comorbidity score (quartiles), age (standard deviation increase), phosphorus, calcium, haemoglobin, KTV, fiber daily intake (tertiles), energy intake (1000 kcal per day increase). ≠As above but excluding fiber daily intake and plus time on dialysis and being wait-listed for transplant

Figure 1. Flow chart of participation

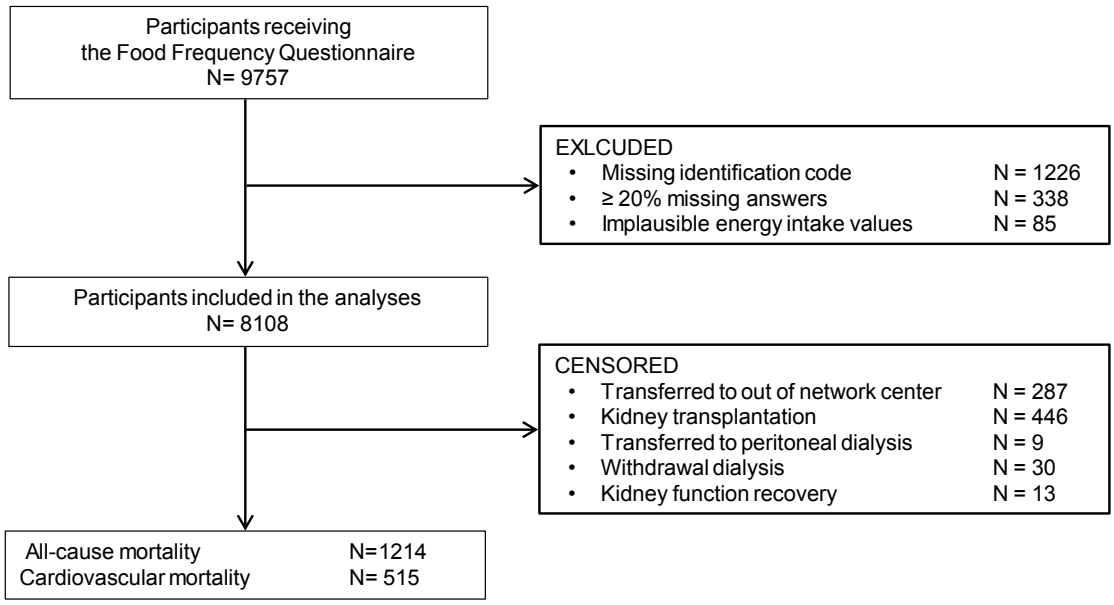
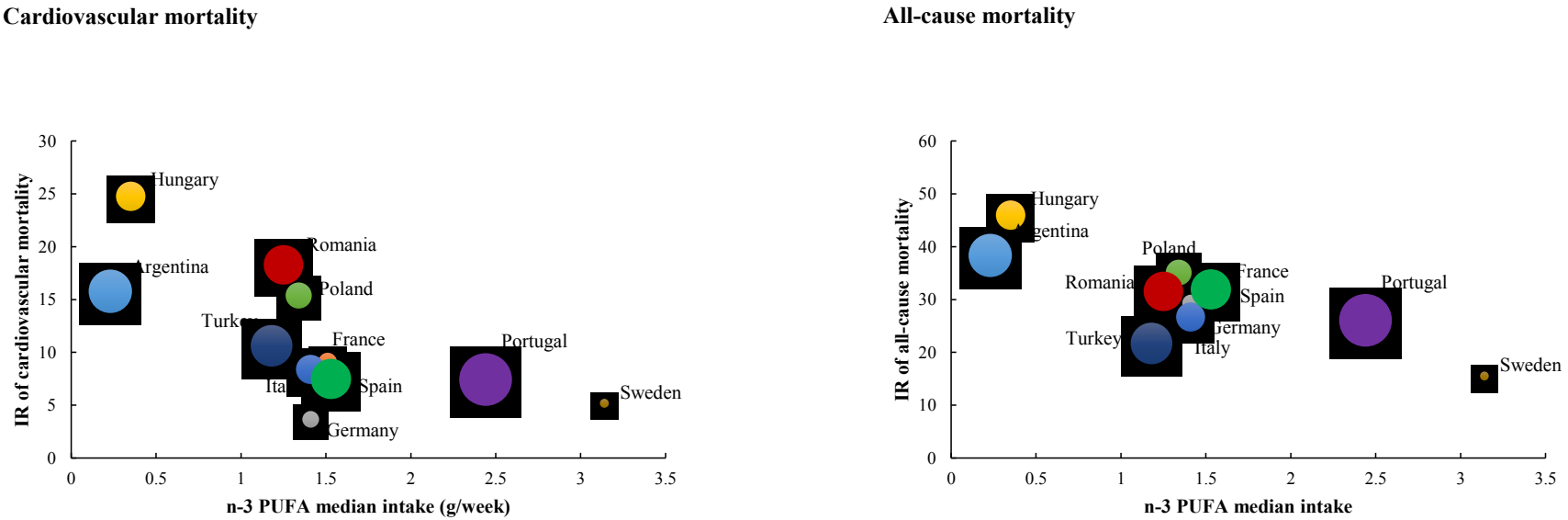
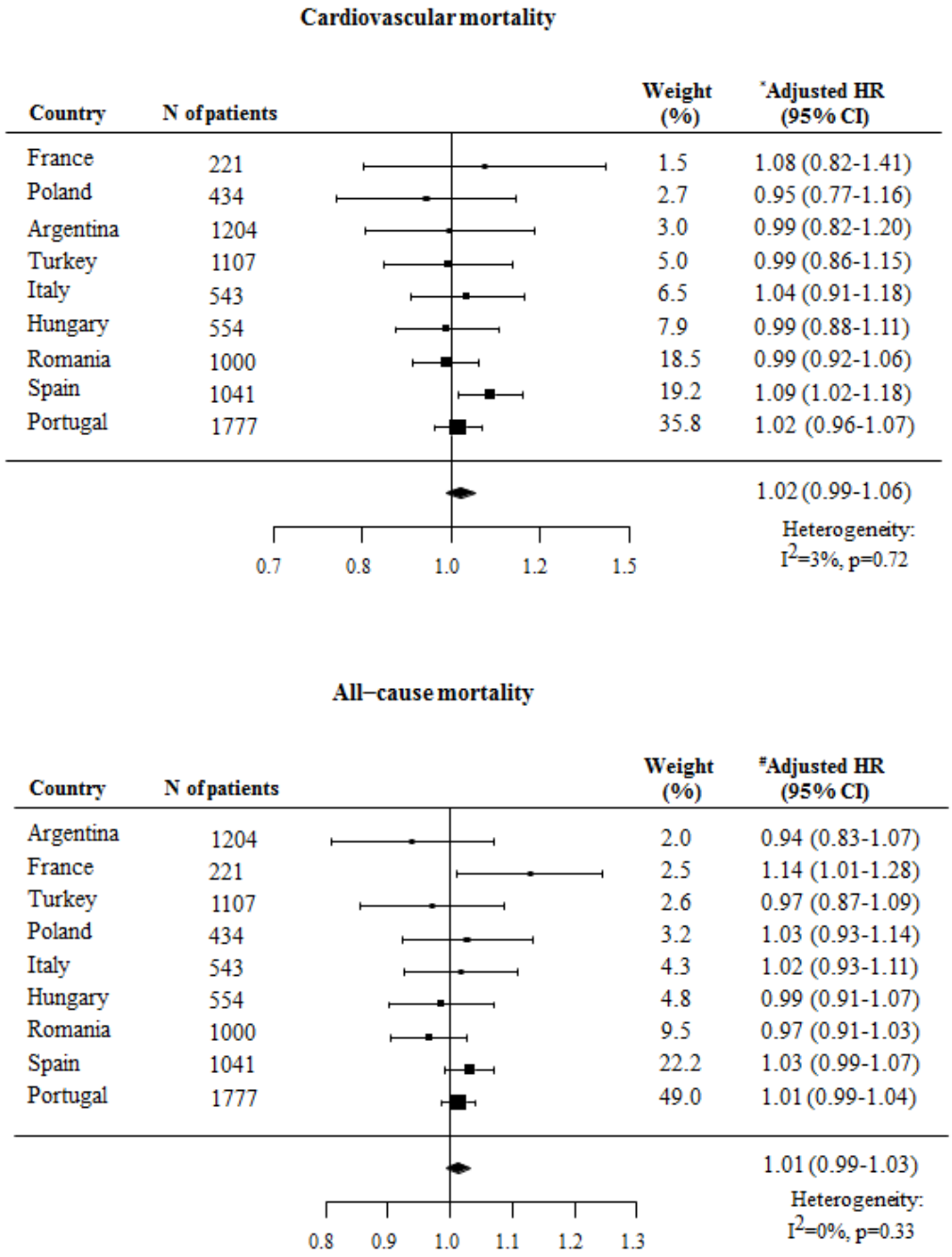


Figure 2. Unadjusted incidence (per 100,000 person-days) of cardiovascular and all-cause mortality plotted against dietary n-3 PUFA intake by country



IR: incidence rate per 100,000 person-days; n-3 PUFA: long chain n-3 polyunsaturated fatty acids (calculated as sum of eicosapentaenoic, docosapentaenoic and docosahexaenoic acids). The area of the circles is proportional to the number of participants in each country.

Figure 3. Association between dietary n-3 PUFA intake and cardiovascular and all-cause mortality by country



*Hazard ratio adjusted for gender, education (secondary versus none/primary), smoke (former or current versus never), diabetes, myocardial infarction, vascular access type (arterio-venous fistula versus graft/catheter), Body Mass Index (categories according to WHO), albumin (tertiles), Charlson comorbidity score (quartiles), age (standard deviation increase), phosphorus, calcium, haemoglobin, KTV, fiber daily intake (tertiles), energy intake (1000 kcal per day increase). #As above except for fiber daily intake and plus wait-listed for transplant and time on dialysis. CI: confidence interval.

Hazard ratios for Germany and Sweden were not estimable due to the low number of outcome events.

CHAPTER IV: PHOSPHATE-BINDING AGENTS IN ADULTS WITH CKD: A NETWORK META-ANALYSIS OF RANDOMIZED TRIALS

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Abstract

Background

Guidelines preferentially recommend non-calcium phosphate binders in adults with CKD. We compare and rank phosphate binder strategies for CKD.

Study Design

Network meta-analysis

Setting & Population

Adults with CKD

Selection Criteria for Studies

Randomized trials with allocation to phosphate binders.

Interventions

Sevelamer, lanthanum, iron, calcium, colestilan, bixalomer, nicotinic acid, magnesium.

Outcomes

The primary outcome was all-cause mortality. Additional outcomes were cardiovascular mortality, myocardial infarction, stroke, adverse events, serum phosphorus and calcium levels, and coronary artery calcification.

Results

77 trials (12,562 participants) were included. Most studies (62 trials in 11,009 patients) were performed in a dialysis population. Trials were generally of short duration (median 6 months) and had high risks of bias. All-cause mortality was ascertained in 20 studies during 86,744 patient-months of follow up. There was no evidence that any drug class lowered mortality or cardiovascular events when compared with placebo. Compared with calcium, sevelamer reduced all–cause mortality (odds ratio 0.39, 95% CI 0.21–0.74), while treatment effects of lanthanum (0.78, 0.16–3.72), iron (0.37, 0.09–1.60) and colestilan (0.55, 0.07–4.43) were not significant. Lanthanum caused nausea, while sevelamer posed the highest risk of constipation, and iron caused diarrhea. All phosphate binders lowered serum phosphorus to a greater extent than placebo, with iron ranked as the best treatment. Sevelamer and lanthanum posed substantially lower risks of hypercalcemia than calcium.

Limitations

Limited testing of consistency; short duration of follow up.

Conclusions

There is currently no evidence that phosphate binder treatment reduces mortality compared with placebo in adults with CKD. It is not clear whether the higher mortality with calcium versus sevelamer reflects whether there is net harm associated with calcium, net benefit with sevelamer, both, or neither. Iron-based binders show evidence of greater phosphate lowering that warrants further examination in randomized trials.

Introduction

Chronic kidney disease (CKD) caused 20 million years of life to be affected by premature mortality or meaningful disability in 2010.[1] CKD is characterized by premature vascular disease[2] in part due to accelerated vascular calcification. Phosphorus accumulation – due to impaired kidney excretion – drives transformation of vascular smooth muscle cells toward a phenotype similar to bone-forming osteoblasts.[3] Accordingly, oral phosphate binders are prescribed to reduce intestinal phosphorus uptake and lower serum levels. Guidelines recommend serum phosphorus levels within or toward the normal range.[4] In the United States, phosphate binders contribute $0.5 billion in health spend annually.[5]

Many different classes of phosphate binders are available. Although drugs have been compared head-to-head in randomized trials and meta-analyses,[6 7] uncertainty remains about which treatment option is the most effective at lowering mortality and cardiovascular complications, and whether drugs are better than placebo. A previous meta-analysis concluded that non-calcium binders reduced mortality compared to calcium-based treatments, but comparative effects of specific phosphate binder classes against each other or placebo could not be discerned due to a lack of head-to-head trials.[7] Current evidence has resulted in weak guideline recommendations[4] and considerable uncertainty about efficacy and harms of specific phosphate binders.

Network meta-analysis can evaluate all available phosphate binders within a coherent framework and rank treatments even when drugs have not been compared in head-to-head trials.[8] In this study, the effects of all phosphate binders were compared using network meta-analysis.

Methods

Study design

This systematic review with network meta-analysis was conducted according to a pre-specified protocol, and was reported using PRISMA guidelines.[9]

Search strategy and selection criteria

Cochrane, MEDLINE, and Embase databases were searched on May 18, 2016 without language restriction. Randomized trials from a previous Cochrane review were also included.[6] We included parallel-group randomized clinical trials (RCTs) with follow up of ≥4 weeks allocating adults with CKD to a phosphate binder, placebo, or standard care.

Study Selection and data extraction

Two reviewers (SP and SG) independently screened titles and abstracts of the retrieved citations and reviewed the full text of all citations considered potentially eligible. Reviewers resolved any disagreements through discussion. Two reviewers (SP and SG) extracted and double-checked data extraction.

Risk of bias assessment

Two reviewers (SP and SG) critically appraised risks of bias using the Cochrane tool.[10]

Statistical Analysis

The primary outcome was all–cause mortality. Secondary outcomes were cardiovascular mortality, myocardial infarction, stroke, nausea, abdominal pain, constipation, diarrhea, achievement of a serum phosphorus target, serum phosphorus levels, hypercalcemia, and coronary artery calcification.

First, random-effects pairwise meta-analysis was used to assess treatment effects.[11] Then, random-effects network meta-analysis in a frequentist environment was conducted. The following were evaluated when considering the appropriateness of combining studies for network meta-analysis: clinical setting, age, stage of kidney disease, follow up duration, and serum phosphorus. A fixed-effect model was to check for the robustness of the results for all-cause mortality. Binary outcomes were expressed as odds ratios and continuous outcomes were calculated as standardized mean differences, together with their 95% confidence intervals. A standardized mean difference of 0.2 is considered small, 0.5 moderate, and 0.8 large.[12]

The extent of network heterogeneity was estimated by comparing a common heterogeneity variance (tau [τ]) within each network with an empirical distribution of heterogeneity variances.[13] A loop-specific approach was then used to compare the difference between direct and indirect estimates for a treatment effect (inconsistency factor) within triangular or quadrilateral loops within a network.[14] The 'design-by-treatment' interaction model was also used to draw a single inference about the plausibility of assuming consistency within a network.[15] [16]

Pre-specified sensitivity analyses were restricted to studies in dialysis, younger patients (<60 years), follow up ≥12 months, and baseline serum phosphorus ≤1.8 mmol/l. Additional analyses were done removing one study at a time from the network for all-cause mortality and restricted to studies at low risk of bias for allocation concealment. A *post-hoc* analysis of the comparative effectiveness between sevelamer and calcium for all-cause mortality was done that included published longer term follow up of the Dialysis Clinical Outcomes Revisited (DCOR) study.[17]

All analyses were generated in Stata 13 using the *network* command[19] and previously reported routines.[20] To rank treatments according to their probability of being the best treatment for a specific outcome, the surface under the cumulative ranking (SUCRA) curve was estimated using the *network rank* command. We assumed that the relative effects of each intervention compared to placebo followed a multivariate normal distribution.[18] We generated 1000 relative effects and in each replicate, the treatment effects were ranked; finally, the percentages of assuming any of the possible ranks for all interventions was computed. Statistical testing was two-tailed. A p value <0.05 was taken to indicate statistical significance.

Role of the funding source

There was no funder for this study. SCP and GFMS had full access to all the data in the study and GFMS had final responsibility to submit for publication.

Results

Study characteristics

77 studies involving 12,562 adults were eligible (Figure 1 and Table S1). 62 trials involved 11,009 dialysis patients. Eight phosphate binder classes were evaluated: sevelamer (hydrochloride or carbonate), lanthanum carbonate, calcium (carbonate or acetate), iron (iron magnesium hydroxycarbonate, ferric citrate, SBR759, sucroferric oxyhydroxide), colestilan, bixalomer, nicotinic acid and magnesium carbonate. Median duration was three months (interquartile range [IQR], 1.8-6 months), with a median age of 56.7 years (IQR, 53.5-60.3), and median serum phosphorus of 6.5 mg/dl (IQR 5.3-7.7). The median (IQR) follow-up duration in months for each drug was: placebo 1.8 (1-3); sevelamer 3 (2-11); lanthanum 3 (1.5-9); calcium 6 (3-12); iron 1.8 (1-3); colestilan 3 (1-3); bixalomer 2 (1-3); nicotinic acid 1.9 (1.4-2.4). Twenty studies involving 6376 patients reported 770 deaths during 86,744 patient-months (Table 1).[21-39]

Risks of bias

The risks of bias were frequently high (Figures S1 and S2). 16 studies (20.8%) reported low risk methods for random sequence generation and eight (10.4%) adequately concealed allocation. 24 studies (31.1%) masked participants and investigators and two trials (3.0%) masked outcome assessment. 18 (23.3%) studies included 90% or more participants in analyses according to their randomized treatment allocation. 26 (33.8%) reported all clinically relevant outcomes (mortality and/or cardiovascular events and adverse events). Analyses were reported as intention–to–treat in 12 studies (15.6%) and adverse events were systematically captured in 14 (18.2%) studies. Published studies tended to favor newer drug classes (sevelamer, lanthanum, iron) for all-cause mortality (Figure S3).

Study consistency and heterogeneity

When considering potential effect modifiers in assessing consistency, nearly all studies (88%) included patients with end-stage kidney disease. 51 (76%) studies enrolled patients with a mean age between 50 and 70 years. Baseline serum phosphorus levels were variable (3.1-9.0 mg/dl) but less diverse in studies included in the network analysis for all-cause mortality (5.0-7.8 mg/dl). Dosing regimens for phosphate binders were similar among trials (Table S1). For studies reporting all-cause mortality, over half included follow up 12 months or longer (Table 1). Studies were deemed sufficiently comparable for key effect modifiers to justify the consistency assumption that meta-analysis was reasonable.

The network for cardiovascular mortality indicated the presence of substantial heterogeneity (τ=1.20), while networks for all-cause mortality (τ=0.74), hypercalcemia (τ=0.94) and diarrhea (τ=0.81) showed moderate-high heterogeneity, and networks for nausea (τ=0.55), abdominal pain (τ=0.41), constipation (τ=0.34), serum phosphorus target (τ=0.44), serum phosphorus values (τ=0.51), and coronary artery calcification (τ <0.001) showed low-moderate heterogeneity. Treatment estimates from direct and indirect evidence did not show loop-specific inconsistency except for serum phosphorus values, however, the results of testing were very imprecise in some cases and so inconsistency could not be excluded (Table S2). There was no evidence of global network inconsistency except for the outcome of diarrhea (Table S3).

Treatment outcomes

Overall results of pairwise meta-analyses for binary outcomes are given in the Table S4. Definitions of biochemical outcomes are described in Table S5.

All-cause mortality, cardiovascular mortality, stroke and myocardial infarction

The network for all-cause mortality is shown in Figure S4. Median follow up was 15 months for trials comparing sevelamer versus calcium, three months for sevelamer versus iron, and 12 months for lanthanum versus calcium.

There was no evidence of different odds of all-cause mortality between any phosphate binder and placebo (iron OR 0.45, CI 0.08−2.66, sevelamer 0.47, 0.08−2.56, colestilan 0.66, 0.10−4.31, lanthanum 0.93, 0.11−8.00, calcium 1.20, 0.21−6.75), although placebo-controlled trials were of short duration (4 weeks to 3 months) (Table 2).

Sevelamer appeared to reduce all-cause mortality compared with calcium (0.39, 0.21–0.74) and was ranked best for this outcome, while the effects of lanthanum (0.78, 0.16–3.72), iron (0.37, 0.09–1.60) and colestilan (0.55, 0.07–4.43) compared with calcium were not significant (Table 2). When a fixed effect model was used to estimate odds of all-cause mortality, the ORs for therapies when compared with calcium were 0.74 (0.62−0.89) for sevelamer, 0.67 (0.26−1.72) for iron, and 0.87 (0.16−4.76) for colestilan. The non-calcium binders did not differ statistically from each other for all-cause mortality.

Data for cardiovascular mortality, myocardial infarction and stroke were sparse due to few studies reporting these outcomes (Table S6 and Figure S5).

Side-effects (nausea, constipation, diarrhea, abdominal pain)

The networks for adverse events are shown in Figure S6. Lanthanum ranked as the treatment with the highest probability of causing nausea (Figure 2). Lanthanum increased nausea compared to calcium (2.18, 1.00–4.74) and iron (4.07, 1.15–14.3) (Table 3). Sevelamer increased constipation compared to calcium (2.12, 1.01–4.45), lanthanum (3.03, 1.31–7.02) and iron (3.15, 1.73–7.53) and was ranked worst for this side-effect (Table 4). Iron increased diarrhea compared with calcium (3.30, 1.02–10.8), but differences between all other phosphate binders were not significant (Table 4). No drug increased abdominal pain (Table 3).

Serum calcium and phosphorus

Networks for serum phosphorus and calcium are shown in Figure S7. Iron increased odds of achieving serum phosphorus targets compared with sevelamer, lanthanum, calcium, and placebo (Table 5). All phosphate binders except colestilan significantly lowered serum phosphorus levels compared to placebo (Table 5). Iron lowered serum phosphorus levels to a greater extent than lanthanum, sevelamer, and calcium, and was ranked as the best treatment (Figure 2). Sevelamer (0.14, 0.07–0.29) and lanthanum (0.09, 0.03–0.25) were associated with significantly lower odds of hypercalcemia compared with calcium.

Coronary artery calcification

Sevelamer reduced coronary artery calcification scores compared with calcium (SMD -0.20, -0.40 to -0.01) (Table S8 and Figure S8).

Sensitivity analyses

Treatment estimates were similar when restricted to studies reporting low risk methods of allocation concealment, involving dialysis patients, with longer duration of follow up, or with lower baseline serum phosphorus levels (Table S9). When removing one study at a time, the estimated odds of mortality with sevelamer compared to calcium was no longer significant when the INDEPENDENT study[26] was excluded (Table S10; 0.61, 0.37−1.01) and the heterogeneity tau in the mortality network with this study removed was reduced from 0.73 (moderate–high heterogeneity) to 0.35 (low heterogeneity). There was no evidence of treatment differences based on the individual phosphate binder formulation (sevelamer [hydrochloride or carbonate] or calcium [acetate or carbonate]) although there were frequently few observations leading to low power in the analyses (Table S11). The treatment estimates for all-cause mortality repeated including extended follow up for the DCOR study[17] were similar (sevelamer versus calcium, 0.39, 0.20 to 0.76).

Discussion

This systematic review included 77 studies involving 12,562 adults with CKD, predominantly in dialysis populations. There was no evidence that any phosphate binder lowered mortality compared with placebo. Sevelamer was associated with lower all-cause mortality when compared to calcium-based binders. Estimated effects of other non-calcium binding agents compared to calcium-based treatment were non-significant and there were no statistical differences in mortality risk between different non-calcium containing binders (sevelamer, lanthanum, iron). Overall, these data cannot establish whether there is net harm associated with calcium-based phosphate binders, net benefit associated with sevelamer, both, or neither. Existing trials of phosphate binders on all-cause mortality were of short duration with those evaluating iron-based treatment lasting generally 3 months or fewer. Coronary artery calcification (a putative mechanism for death related to high serum calcium and phosphorus) is not clinically apparent for most patients until at least 10 years of dialysis,[40] indicating that currently-available phosphate binder therapy trials may be of insufficient duration to provide definitive information about treatment effects on mortality, cardiovascular events, or vascular calcification, although sevelamer appeared to prevent coronary artery calcification compared with calcium binders in the short-term.

Lanthanum and colestilan had the highest probability of nausea, sevelamer ranked worst for constipation, and iron-based binders conferred greatest odds of diarrhea. Iron lowered serum phosphorus levels compared to other binders including sevelamer and lanthanum. All phosphate binders except colestilan lowered serum phosphorus compared with placebo. As expected, calcium was ranked as most likely to cause hypercalcemia.

These findings extend those of an previous pairwise meta-analysis[7] – which concluded that sevelamer or lanthanum should be first line therapy in the management of phosphorus in CKD – in three ways. First, by integrating direct and indirect evidence, the benefits of non–calcium binders in the previous review might have been principally attributable to sevelamer, whereas comparative effects of other non-calcium-based agents including lanthanum were not significant compared to calcium or placebo for mortality. In the previous pairwise meta-analysis, evidence for non-calcium based agents (sevelamer and lanthanum) were combined to identify a risk reduction in mortality with non-calcium binders of 22%, but study data were insufficient to evaluate treatment effects for individual drug classes. Importantly, due to a lack of placebo-controlled trials, comparisons of phosphate binders with placebo has not been previously possible. This network meta-analysis indicates that there is no evidence that any phosphate binder improves life expectancy when compared with placebo in trials of short

duration. Second, this review identifies adverse events attributable to phosphate binder classes that can facilitate decision-making aligned with patient preferences. Third, iron–based binders lowered serum phosphorus to a greater extent than other phosphate binder classes, indicating these are an important candidate intervention for larger studies against sevelamer and/or calcium, to evaluate impact on mortality and cardiovascular endpoints.

Proponents of non–calcium binders might argue that these findings indicating an association of sevelamer with lower all-cause mortality support the need to update existing guidelines, which cited insufficient comparative efficacy data on clinical outcomes rather than recommending a specific phosphate binder for patients with CKD.[4] However, there are several issues that preclude a preferential recommendation for sevelamer compared to other binders based on the current evidence. First, the available studies have important methodological limitations, meaning that bias could have affected the results. Smaller studies may have influenced the estimated benefit of sevelamer over calcium-based binders, indicated by the smaller benefit of treatment observed using a fixed-effect model and the absence of smaller trials with more favorable effects for calcium-based treatment. Second, after exclusion of a single study (the INDEPENDENT trial[26]), the reduction in all-cause mortality with sevelamer compared to calcium was no longer significant. Removing the INDEPENDENT study involving 466 incident dialysis patients substantially reduced heterogeneity between studies. It is not clear why the results of the INDEPENDENT study differed so markedly favoring sevelamer than other trials in this meta-analysis. Third, due to imprecision, it is possible that non–calcium binders other than sevelamer are also associated with better (or worse) associations with clinical outcomes compared to calcium. Finally, it is important to note that none of the available calcium or non–calcium agents lowered mortality compared with placebo – in other words whether calcium-based agents are harmful or non-calcium based agents are beneficial. Placebo-controlled trials lasted 3 months on average, precluding robust inferences about treatment effects.

Given the widespread use of phosphate binders in clinical practice, randomized trials are an urgent priority to support and inform the extensive prescribing of these medications. Such trials should include comparisons of phosphate binders with placebo (perhaps with rescue treatment for severe hyperphosphatemia and or hyperparathyroidism) and head–to–head comparisons between available agents – focusing on clinically relevant outcomes such as mortality and cardiovascular events. Given the significantly lower phosphorus levels associated with iron, and the potential association of sevelamer with lower mortality, future trials should focus on these two classes of agent, compared to placebo, calcium, or each other. Finally, the high absolute risk of adverse events with all binders suggests that there is value to considering

patient preferences when selecting an approach to phosphorus control in kidney patients, especially those who are concerned about treatment harms. Further, the failure of any agent to reduce mortality versus placebo suggests that a less aggressive approach to phosphate-lowering treatment may be entirely appropriate in all patients pending the availability of new evidence.

The results of this network meta–analysis contrasts with those of the largest randomized study to compare sevelamer with calcium (the Dialysis Clinical Outcomes Revisited (DCOR) trial), which found no effect of sevelamer compared with calcium on total death in hemodialysis patients treated for approximately 20 months.[35] First, it is possible that DCOR had insufficient statistical power to identify treatment benefit, particularly as about half of the 2103 randomized participants left the study early. The current meta–analysis potentially had greater power to discern a significant association for mortality between treatments due to a larger sample size, as well as draw inferences from both direct and indirect treatment comparisons. A second interpretation is that benefits of sevelamer might be limited to older participants as was identified in the DCOR study in participants who were 65 years or older in pre–specified subgroup analyses. However, it was unlikely that the reduction in mortality with sevelamer that was found in this meta-analysis was because of a preponderance of older participants as the mean age for participants in most included studies was 60 years or younger. Alternatively, it is possible that this meta-analysis found treatment benefits for sevelamer due to the inclusion of smaller studies at higher risk of bias for important methodological features within network meta-analyses, which may have resulted in overestimated effects on mortality that are discordant with the largest existing randomized trial. When the INDEPENDENT study was removed from analyses, the beneficial effect of sevelamer on all-cause mortality compared with calcium was not significant, indicating that evidence of efficacy for sevelamer in this analysis may be reliant on the results of this single study.[26]

The strengths of this meta-analysis include the use of network meta-analyses to draw inferences about the comparative effects of phosphate binders with clinical outcomes that have not been directly compared in existing randomized trials including against placebo and permit greater precision for treatment effects on mortality and adverse events than has previously been possible. The analyses are drawn from a highly-sensitive literature search and included assessments of study risks of bias.

The study has limitations which reduce the applicability of the findings to clinical practice, related principally to the extent and quality of information in individual trials. First, reporting risks of bias were often high or not reported sufficiently to make a judgment, lowering

confidence in the results of contemporary trials of phosphate binders. Lack of reporting of many outcomes in many studies was a potential limitation. Second, most contributing trials were of short duration. This was particularly the case for trials of iron-based binders, which were commonly continued for 3 months or less. Given the natural history of vascular calcification as clinically evident after many years of end-stage kidney disease,[40] it is likely that existing trials do not have sufficient longevity to identify definitive treatment effects, and trials of iron-based binders will need to be longer to identify treatment effects on hypercalcemia, adverse events (especially iron overload), and patient-level outcomes including mortality. Such trials may benefit from efficient trial design, such as follow up embedded within a data registry, to enable long-term follow up for sufficient numbers of participants. Trials of placebo were often of short duration (3 months or shorter). The longer-term benefits of treatment against placebo remain uncertain for many outcomes. Third, while meta-analysis assumes that contributing studies were sufficiently similar in most respects other than the treatments under study, statistical assessment of this assumption was limited by low power, although little evidence of network inconsistency was found. There was also no evidence of different treatment associations for individual drugs within binder classes, but few data reduced confidence in these assumptions. Fourth, data for cardiovascular events were rarely reported. As the assumed mechanism of benefit for these drugs is by reducing vascular calcification to prevent vascular injury, these outcomes must be considered as core outcomes in future trials and systematically captured in ongoing studies and prescribing surveillance. Finally, most studies involved participants with end-stage kidney disease. The findings of this review may not be generalizable across the full range of kidney function.

In conclusion, there is no evidence that phosphate binder treatment reduces mortality compared to placebo in adults with CKD. It is not clear whether the higher mortality with calcium versus sevelamer reflects whether there is net harm associated with calcium, net benefit with sevelamer, both, or neither. Iron lowered serum phosphate to the greatest extent, indicating future studies might prioritize evaluation of this treatment class. All available phosphate binders display distinct adverse event profiles that can inform treatment decisions for individual patients.

Contributors

SCP and GFMS had the idea for and designed the study. SCP and SG identified and acquired reports of trials and extracted data. DM provided statistical oversight. SCP did all data analyses, checked for statistical inconsistency and interpreted data. SG, JCC, MT, DM, DWJ, RF,

MR, and GFMS contributed to data interpretation. SCP drafted the report and all other authors critically reviewed the report. SCP obtained funding and GFMS supervised the study conduct.

Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. GFMS takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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Table 1. Trials ascertaining treatment effects on all-cause mortality

Study	Intervention drug (dose per day in milligrams)	Comparator drug(s) (dose per day in milligrams)	No. of participants	Location	Stage of chronic kidney disease at baseline	Mean age (SD), years	Serum phosphorus at baseline (SD), mmol/l	Duration of treatment (months)	Patient-months follow up for mortality*
Chertow 2002[41]	Sevelamer hydrochloride (mean 6500)	Calcium carbonate (mean 3900) or calcium acetate (4600)	200	United States, Germany and Austria	5D	57 (14)	2.5 (0.6)	12	2400
Sadek 2003[33]	Sevelamer hydrochloride (1200-4400)	Calcium carbonate (4800)	42	France	5D	N.I.	1.8 (0.2)	5	210
Block 2005[22]	Sevelamer hydrochloride (8000)	Calcium carbonate and/or calcium acetate (2300)	148	USA	5D	57 (15)	1.7 (0.5)	18	2286
DCOR study 2007[35]	Sevelamer hydrochloride (mean 6900)	Calcium carbonate (mean 4900) or calcium acetate (mean 5300)	2103	United States	5D	60 (14.7)	N.I.	20.3 (sevelamer) 19.6 (calcium)	42,690
BRiC study 2008[21]	Sevelamer hydrochloride (800-12000)	Calcium acetate (667-2028)	101	Brazil	5D	47 (13)	2.2 (0.7)	12	1212
CARE-2 study 2008[31]	Sevelamer hydrochloride (mean 7300)	Calcium acetate (mean 5500)	203	United States	5D	60.3 (12.1)	2.1 (0.5)	12	2436
INDEPENDENT study 2009[26]	Sevelamer hydrochloride (mean 4300)	Calcium carbonate (mean 2200)	466	Italy	5D	65.6 (14.8)	1.7 (0.5)	36	16,776
INDEPENDENT study 2012[25]	Sevelamer hydrochloride (mean 2184)	Calcium carbonate (2950)	212	Italy	3 and 4	57.9 (12.2)	1.6 (0.4)	24	5736

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Study	Intervention drug (dose per day in milligrams)	Comparator drug(s) (dose per day in milligrams)	No. of participants	Location	Stage of chronic kidney disease at baseline	Mean age (SD), years	Serum phosphorus at baseline (SD), mmol/l	Duration of treatment (months)	Patient-months follow up for mortality*
Chen 2011	Sevelamer hydrochloride (mean 4800)	SBR759 (mean 6200)	201	Japan and Taiwan	5D	59.6 (11.3)	N.I.	3	603
Wuthrich 2013[38]	Sevelamer hydrochloride (4800)	PA21 (1.25, 5, 7.5, 10, 12.5)	154	United States and Europe	5D	61.6 (11.2)	2.2 (0.5)	1.5	231
Floege 2014[27]	Sevelamer carbonate (4800-14400)	Sucroferric oxyhydroxide (1000--3000)	1055	Europe, the United States, Russia, Ukraine, and South Africa	5D	56 (15)	2.5 (N.I.)	6	6354
Locatelli 2014[29]	Sevelamer (2400-12000)	Colestilan (3000-15000)	336	Australia, Austria, the Czech Republic, France, Germany, Hungary, Italy, Poland, South Africa, Spain and the United Kingdom	5D	59.5 (13.8)	N.I.	3	1008
Spasovoski 2006[34]	Lanthanum carbonate (maximum 3000)	Calcium carbonate (maximum 4000)	20	Macedonia	5D	55 (10)	1.6 (0.2)	12	288
Touissant 2009[36]	Lanthanum carbonate (minimum 750)	Calcium carbonate (minimum 1800)	45	Australia	5D	56	1.9 (0.1)	18	810

Table 1. Trials ascertaining treatment effects on all-cause mortality

Study	Intervention drug (dose per day in milligrams)	Comparator drug(s) (dose per day in milligrams)	No. of participants	Location	Stage of chronic kidney disease at baseline	Mean age (SD), years	Serum phosphorus at baseline (SD), mmol/l	Duration of treatment (months)	Patient-months follow up for mortality*
Ohtake 2013[30]	Lanthanum carbonate (mean 1430.6)	Calcium carbonate (mean 3000)	42	Japan	5D	67.8 (6.3)	1.7 (0.5)	6	252
Wada 2014[37]	Lanthanum carbonate (mean 2130)	Calcium carbonate (mean 2730)	43	Japan	5D	65.57 (10.2)	1.6 (0.4)	12	516
Yokoyama 2014[39]	Ferric citrate (1500-6000)	Placebo	90	Japan	3 to 5	65.3 (10.2)	1.8 (0.2)	3	270
Locatelli 2013[28]	Colestilan (3000-15000)	Placebo	642	Hungary, Italy, Poland, Serbia, Macedonia, Ukraine, Russia, Malaysia	5D	49.1 (12.7)	2.4 (N.I.)	3	1926
Block 2015[23]	Ferric citrate (mean 5100)	Placebo	149	USA	3 to 5	66 (12)	1.5 (0.2)	2.75	409
Qunibi 2011[32]	Calcium carbonate (N.I.)	Placebo	110	United States	4 and 5	63.2 (11.7)	1.6 (0.4)	3	330

Abbreviations: CKD = chronic kidney disease. 5D = chronic kidney disease treated with dialysis. NI = not indicated. P = phosphorus. PTH = parathyroid hormone. *Patient-months follow up was estimated as the number of patients allocated with treatment multiplied by the duration of follow up in months.

Table 2: Network estimated odds ratios (95% confidence intervals) of phosphate binders on all-cause mortality

Sevelamer					
0.50 (0.09, 2.65)	**Lanthanum**				
<u>0.39</u> **<u>(0.21, 0.74)</u>**	0.78 (0.16, 3.72)	**Calcium**			
1.04 (0.27, 3.97)	2.08 (0.26, 16.5)	2.67 (0.63, 11.4)	**Iron**		
0.71 (0.09, 5.46)	1.42 (0.12, 17.4)	1.82 (0.23, 14.7)	0.68 (0.07, 6.40)	**Colestilan**	
0.47 (0.08, 2.59)	0.93 (0.11, 8.05)	1.20 (0.21, 6.77)	0.45 (0.08, 2.66)	0.66 (0.10, 4.29)	**Placebo**

The table should be read from left to right. The risk estimate is for the column-defining treatment compared with the row-defining treatment. An odds ratio <1 indicates the column treatment was associated with a lower odds of mortality than the row treatment. For example, sevelamer treatment lowered the odds of all-cause mortality compared to calcium treatment (odds ratio 0.39, 95% confidence interval 0.21, 0.74). Bold and underlined results are statistically significant. The heterogeneity tau (τ) for the network analysis was τ = 0.74 (indicative of moderate-high heterogeneity). There were 20 studies involving 6376 participants included in the network

Table 3. Network estimated odds ratios (95% confidence intervals) of phosphate binders on nausea and abdominal pain

	Abdominal pain						
Nausea	**Sevelamer**	0.93 (0.23, 3.74)	1.25 (0.46, 3.42)	0.52 (0.16, 1.69)	0.37 (0.05, 2.70)	1.00 (0.05, 18.4)	0.64 (0.23, 1.74)
	0.39 (0.13, 1.16)	**Lanthanum**	1.35 (0.42, 4.36)	0.56 (0.11, 2.83)	0.40 (0.05, 3.34)	1.07 (0.04, 27.1)	0.68 (0.19, 2.42)
	0.84 (0.34, 2.08)	**2.18 (1.00, 4.74)**	**Calcium**	0.41 (0.10, 1.70)	0.30 (0.04, 2.27)	0.80 (0.04, 17.4)	0.51 (0.17, 1.53)
	1.58 (0.61, 4.06)	**4.07 (1.16, 14.3)**	1.87 (0.59,5.93)	**Iron**	0.72 (0.09, 5.69)	1.93 (0.08, 44.9)	1.23 (0.38, 3.95)
	0.02 (0.00, 0.45)	0.05 (0.00, 1.05)	**0.02 (0.00, 0.50)**	**0.01 (0.00, 0.29)**	**Colestilan**	2.68 (0.08, 90.9)	1.71 (0.31, 9.42)
	1.00 (0.05, 20.0)	2.58 (0.11, 62.7)	1.19 (0.05, 27.1)	0.63 (0.03, 14.7)	52.6 (0.68, 4097)	**Bixalomer**	0.64 (0.03, 13.9)
	0.75 (0.27, 2.08)	1.92 (0.97, 3.81)	0.88 (0.38, 2.03)	0.47 (0.15, 1.46)	**39.2 (1.98, 779)**	0.75 (0.03,17.69)	**Placebo**

The lower part of the table reporting treatment estimates for nausea should be read from left to right. The risk estimate is for the column-defining treatment compared with the row-defining treatment. An odds ratio <1 indicated the column treatment was associated with a lower odds of nausea than the row treatment. For example, lanthanum-based treatment was associated with increased odds of nausea compared to calcium-based treatment (2.18, 1.00 to 4.74). The upper part of the table reporting estimates for abdominal pain should be read from left to right. The risk estimate was for the row-defining treatment compared with the column-defining treatment. An odds ratio <1 indicated the row treatment was associated with a lower odds of abdominal pain than the column treatment. For example, the odds of abdominal pain with sevelamer was 1.25 (0.46 to 3.42) compared with calcium treatment. Bold and underlined results are statistically significant. The heterogeneity tau (τ) for each network analysis was: nausea τ = 0.55 (indicative of moderate heterogeneity), abdominal pain τ = 0.41 (indicative of low-moderate heterogeneity). There were 26 trials involving 7265 patients in the network for nausea and 18 trials involving 3235 patients in the network for abdominal pain

Table 4 Network estimated odds ratios (95% confidence intervals) of phosphate binding agents on constipation and diarrhea

	Diarrhea								
Constipation	**Sevelamer**	0.93 (0.26, 3.30)	1.18 (0.38, 3.66)	**0.36 (0.15, 0.84)**	0.82 (0.11, 6.23)	3.06 (0.09, 106)	0.31 (0.01, 11.3)	0.20 (0.00, 9.06)	0.76 (0.26, 2.22)
	3.04 (1.31, 7.02)	**Lanthanum**	1.28 (0.42, 3.89)	0.39 (0.12, 1.28)	0.89 (0.12, 6.35)	3.30 (0.08, 143)	0.34 (0.01, 12.1)	0.22 (0.00, 9.50)	0.82 (0.32, 2.15)
	2.12 (1.01, 4.45)	0.70 (0.37, 1.30)	**Calcium**	**0.30 (0.09, 0.99)**	0.70 (0.09, 5.33)	2.58 (0.06, 107)	0.26 (0.01, 7.94)	0.17 (0.00, 7.71)	0.65 (0.22, 1.92)
	3.15 (1.73, 5.75)	1.04 (0.42, 2.57)	1.49 (0.62, 3.58)	**Iron**	2.30 (0.34, 15.7)	8.53 (0.22, 328)	0.87 (0.02, 32.0)	0.56 (0.01, 24.0)	2.13 (0.91, 5.03)
	3.73 (0.61, 22.9)	1.23 (0.20, 7.62)	1.76 (0.28, 11.1)	1.18 (0.19, 7.20)	**Colestilan**	3.70 (0.06, 220)	0.38 (0.01, 20.0)	0.24 (0.00, 13.8)	0.93 (0.17, 5.16)
	1.84 (0.64, 5.30)	0.61 (0.16, 2.27)	0.87 (0.24, 3.10)	0.59 (0.18, 1.93)	0.49 (0.06, 3.90)	**Bixalomer**	0.10 (0.00, 15.9)	0.07 (0.00, 12.0)	0.25 (0.01, 10.2)
	15.3 (0.49, 481)	5.04 (0.16, 155)	7.24 (0.25, 210)	4.86 (0.15, 158)	4.11 (0.09, 190)	8.30 (0.23, 303)	**Calcium + magnesium**	0.65 (0.00, 107)	2.45 (0.07, 87.8)
	--	--	--	--	--	**--**	--	**Nicotinamide**	3.80 (0.10, 147)
	7.39 (3.33, 16.4)	**2.43 (1.07, 5.51)**	**3.49 (1.49, 8.16)**	**2.34 (1.08, 5.08)**	1.98 (0.38, 10.1)	**4.01 (1.13, 14.2)**	0.48 (0.01, 15.5)	--	**Placebo**

The lower part of the table reporting treatment estimates for constipation should be read from left to right. The risk estimate is for the column-defining treatment compared with the row-defining treatment. An odds ratio <1 indicates the column treatment is associated with a lower odds of constipation than the row treatment. For example, sevelamer based treatment is associated with increased odds of constipation compared to calcium-based treatment (odds ratio 2.12, 95% confidence interval 1.01, 4.45). The upper part of the table reporting estimates for diarrhea should be read from left to right. The risk estimate is for the row-defining treatment compared with the column-defining treatment. An odds ratio <1 indicates the row treatment is associated with a lower odds of diarrhea than the column treatment. For example, sevelamer is associated with a lower odds of diarrhea than iron

treatment (odds ratio 0.30, 95% confidence interval 0.09, 0.99). Bold and underlined results are statistically significant. The heterogeneity tau (τ) for each network analysis was: constipation τ = 0.34 (indicative of low heterogeneity), diarrhea τ = 0.81 (indicative of moderate-high heterogeneity). There were 27 trials involving 7862 patients in the network for constipation and 23 trials involving 4894 patients in the network for diarrhea.

Table 5 Summary network treatment estimates of the comparative efficacy and safety of phosphate binding agents on serum phosphorus targets and hypercalcemia

	Achieving serum phosphorus target								
Hypercalcemia	**Sevelamer**	1.43 (0.56, 3.61)	1.64 (0.70, 3.89)	**0.55 (0.30, 0.99)**	0.82 (0.28, 2.39)	1.57 (0.31, 7.86)	1.14 (0.13, 9.79)	0.97 (0.11, 8.69)	6.92 (0.00, 15.9)
	1.61 (0.46, 5.61)	**Lanthanum**	1.15 (0.56, 2.36)	**0.38 (0.16, 0.94)**	0.57 (0.15, 2.12)	1.09 (0.17, 7.02)	0.80 (0.10, 6.48)	0.67 (0.06, 7.30)	**4.82 (2.79, 8.34)**
	0.14 (0.07, 0.29)	**0.09 (0.03, 0.25**	**Calcium**	**0.33 (0.14, 0.82)**	0.50 (0.14, 1.82)	0.96 (0.15, 5.93)	0.69 (0.10, 4.97)	0.59 (0.06, 6.22)	**4.20 (2.02, 8.74)**
	1.44 (0.12, 16.8)	0.90 (0.06, 14.1)	9.96 (0.77, 128)	**Iron**	1.48 (0.45, 4.85)	2.85 (0.51, 15.9)	2.08 (0.24, 18.1)	1.76 (0.18, 17.1)	**12.6 (5.79, 27.2)**
	--	--	--	--	**Bixalomer**	1.92 (0.28, 13.3)	1.39 (0.13, 14.8)	1.18 (0.10, 13.6)	**8.47 (2.45, 29.2)**
	--	--	--	--	--	**Nicotinic acid**	0.73 (0.05, 10.7)	0.62 (0.04, 9.38)	4.40 (0.72, 27.0)
	--	--	--	--	--	--	**Calcium + magnesium**	0.85 (0.04, 18.3)	6.05 (0.74, 49.4)
	0.52 (0.06, 4.33)	0.33 (0.03, 3.80)	3.62 (0.39, 33.6)	0.36 (0.01, 9.30)	--	--	--	**Sevelamer + calcium**	7.1 (0.68, 74.3)
	2.39 (0.20, 28.5)	1.48 (0.11, 19.7)	**16.4 (1.49, 181)**	1.66 (0.05, 54.5)	--	--	--	4.52 (0.18, 118)	**Placebo**

The lower part of the table reporting treatment estimates for hypercalcemia should be read from left to right. The risk estimate is for the column-defining treatment compared with the row-defining treatment. An odds ratio <1 indicates the column treatment is associated with a lower odds of hypercalcemia than the row treatment. For example, sevelamer based treatment is associated with lower odds of hypercalcemia compared to calcium-based treatment (odds ratio 0.14, 95% confidence interval 0.07, 0.29). The upper part of the table

reporting estimates for achieving a serum phosphorus target should be read from left to right. The risk estimate is for the row-defining treatment compared with the column-defining treatment. An odds ratio <1 indicates the row treatment is associated with lower odds of achieving a serum phosphorus target than the column treatment. For example, sevelamer is associated with lower odds of achieving a serum phosphorus target than iron treatment (odds ratio 0.55, 95% confidence interval 0.30, 0.99). Bold and underlined results are statistically significant. The heterogeneity tau (τ) for each network analysis was: hypercalcemia $\tau = 0.94$ (indicative of high heterogeneity), and achieving serum phosphorus target $\tau = 0.44$ (indicative of low-moderate heterogeneity). There were 21 trials involving 5159 patients in the network for hypercalcemia and 21 trials involving 2382 patients in the network for achieving target serum phosphorus levels.

Figure 1: Flow diagram of search results and selection of included studies

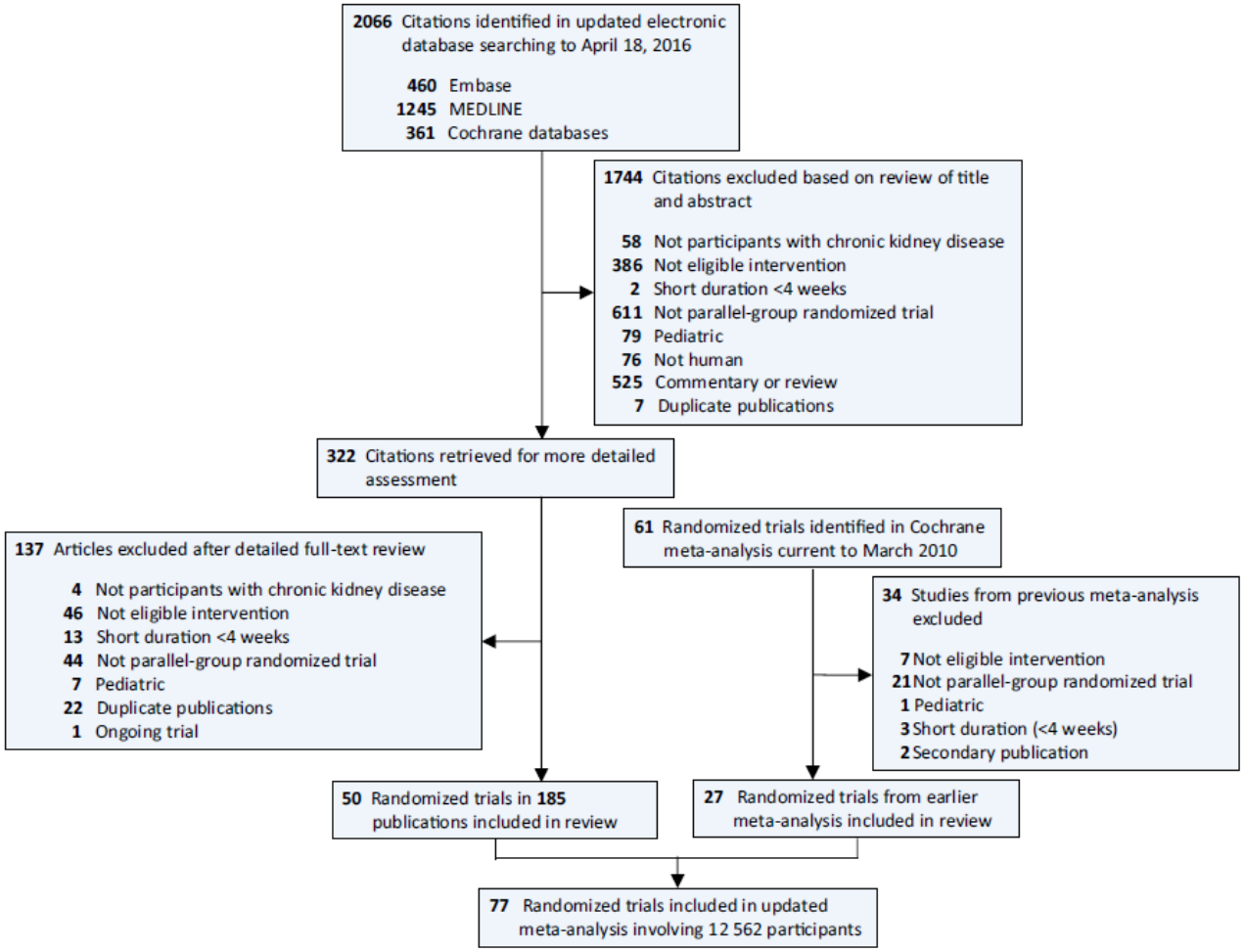
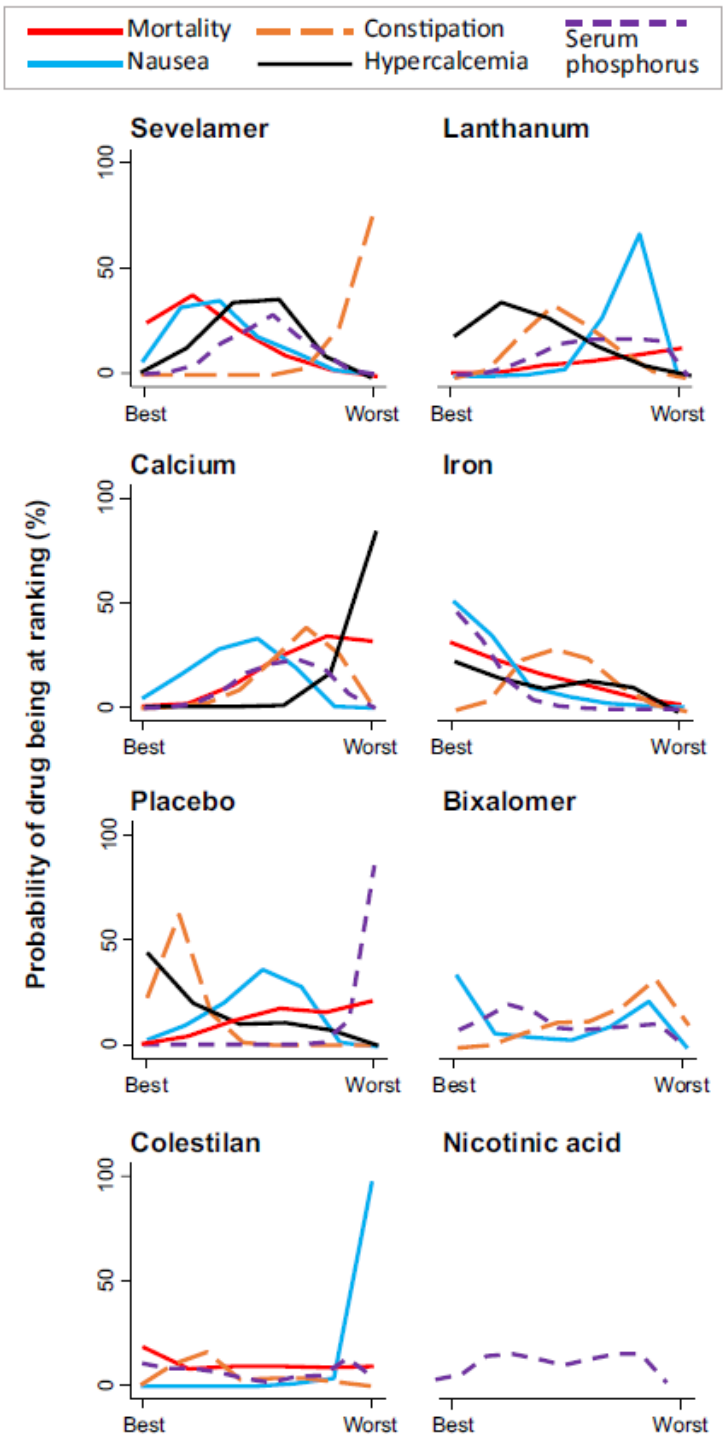


Figure 2: Rankings for efficacy and toxicity of phosphate binders



The graph displays distribution of probabilities for efficacy (all-cause mortality, serum phosphorus levels) and safety (nausea, constipation, hypercalcemia). Ranking indicates probability that drug class is first "best", second "best", etc. For example, sevelamer showed a 25.8% probability of ranking the best treatment for all-cause mortality, while calcium showed a 0.0% probability of ranking the best treatment for all-cause mortality.

CHAPTER V: COMPARISON OF CLINICAL OUTCOMES AND ADVERSE EVENTS ASSOCIATED WITH GLUCOSE-LOWERING DRUGS IN PATIENTS WITH TYPE 2 DIABETES. A META-ANALYSIS

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Abstract

Importance:

Numerous glucose−lowering drugs are used to prevent complications of type 2 diabetes.

Objective:

To estimate the relative efficacy and safety of glucose-lowering drugs including insulin.

Data Sources:

Cochrane, Medline, and EMBASE databases through March 21, 2016.

Study Selection:

Randomized clinical trials ≥24 weeks' duration.

Data Extraction and Synthesis:

Random-effects network meta-analysis.

Main Outcomes and Measures:

Cardiovascular mortality, all-cause mortality, serious adverse events, myocardial infarction, stroke, glycated hemoglobin (HbA1C), treatment failure (rescue treatment or lack of efficacy), hypoglycemia, and weight, as individual endpoints.

Results:

A total of 301 clinical trials (1,417,367 patient-months) were included; 177 trials (56,598 patients), drugs given as monotherapy; 109 trials (53,030 patients), drugs added to metformin (dual therapy); and 29 trials (10,598 patients), drugs added to metformin and sulfonylurea therapy (three-drug therapy). The association between drug classes and cardiovascular deaths was evaluated in 25 trials of drug monotherapy (14,477 patients; 67 events during 197,763 patient-months); 26 trials of dual therapy (20,690 patients; 45 events during 286,157 patient-months); and 5 trials of three drug therapy (3267 patients; 6 events during 37,223 patient-months). There were no differing associations between drug classes and cardiovascular or all-cause mortality. Compared with metformin, sulfonylurea (standardized mean difference (SMD) 0.18, 95% CI 0.01 to 0.34), thiazolidinedione (SMD 0.16, 0.00 to 0.31), DPP-4 inhibitor (SMD 0.33, 0.13 to 0.52), and alpha glucosidase inhibitor (SMD 0.35, 0.12 to 0.58) monotherapy were associated with higher HbA1C levels. Compared to metformin, SGLT-2 inhibitors were associated with lower odds of treatment failure (odds ratio (OR) 0.47, 0.31 to 0.71; risk difference (RD) -0.3%, -4% to 3%). Sulfonylurea (OR 3.13, 2.39 to 4.12; RD 10%, 7% to 13%) and

basal insulin (OR 17.9, 1.97 to 162; RD 10%, 0.08% to 20%) were associated with greatest odds of hypoglycemia. When added to metformin, drugs were associated with similar HbA1C levels, while SGLT-2 inhibitors offered the lowest odds of hypoglycemia (OR 0.12, 0.08 to 0.18; RD -22%, -27% to -18%). When added to metformin and sulfonylurea, basal insulin was associated with the lowest odds of treatment failure (OR 0.44, 0.20 to 0.99; RD -5%, -20% to 9%), while GLP-1 receptor agonists were associated with the lowest odds of hypoglycemia (OR 0.60, 0.39 to 0.94, RD -10%, -18% to -2%).

Conclusions and Relevance:

Among adults with type 2 diabetes, there were not significant differences in the associations between any of nine available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower HbA1C levels or no significant difference in HbA1C levels than any of the other drug classes. All drugs were estimated to be effective when added to metformin. These findings are consistent with ADA recommendations for using metformin monotherapy as initial treatment for patients with type 2 diabetes and selection of additional therapies based on patient-specific considerations.

Introduction

Diabetes was estimated to account for approximately 1.3 million deaths in 2010, with more than 80% of diabetes−related deaths occurring in low− and middle−income countries.[1,2] In addition, diabetes was estimated to cause disability (blindness, limb amputation, kidney failure, cardiovascular events) among 47 million people in 2010.[3] Lifestyle modification and glucose−lowering drug treatment are the mainstay of therapy to prevent and delay diabetes−related complications. A large number of glucose-lowering drug classes are approved for type 2 diabetes including metformin, insulins, sulfonylureas, thiazolidinediones, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium−glucose−linked cotransporter-2 (SGLT-2) inhibitors, glucagon−like peptide-1 (GLP-1) receptor agonists, meglitinides, and alpha−glucosidase inhibitors.

American Diabetes Association (ADA) guidelines suggest metformin as first−line drug treatment, and, if glycemic control is not achieved, the addition of a second drug (often sulfonylurea) is recommended.[4] Triple therapy with two drugs added to metformin is suggested when glycemic control is no longer sustained with two drugs. Annual drug expenditure for glucose-lowering therapy doubled to $12.5 billion between 2001 and 2007 in the United States, with most patients receiving at least dual therapy.[5] However, despite the widespread use of these drugs, the comparative effects of glucose−lowering strategies on hard clinical outcomes, especially mortality and cardiovascular events, are uncertain.[6,7] Emerging evidence suggests SGLT-2 inhibitors lower a composite of cardiovascular outcomes and death when the drug is added to standard care in high-risk patients.[8] However randomized clinical trials of diabetes medications have been generally insufficiently powered to establish the role of drug treatment on preventing cardiovascular death, limiting the ability of single studies to inform practice and policy.

Head−to−head trials and standard meta−analysis do not allow all treatments to be compared simultaneously, constraining the comparative assessment of longer term benefits and risks associated with available medications.[7] Therefore, a systematic review with network meta−analysis was conducted to compare and rank glucose−lowering treatments for type 2 diabetes.

Methods

Study design

A systematic review with network meta−analysis was conducted with a frequentist approach using a pre−specified study protocol. Additional post-hoc analyses and changes to the protocol are described in eMethods 1. The study was reported according to the PRISMA extension statement for network meta−analysis.[9]

Search strategy and selection criteria

Randomized clinical trials publically available on March 21, 2016 comparing two individual glucose−lowering drug classes for treatment of type 2 diabetes were identified. The Cochrane Library Central Register of Controlled Trials (CENTRAL), MEDLINE, and Embase were searched using a highly−sensitive search strategy developed by an experienced trials search coordinator for each database (eTable 1).

Study selection and data extraction

Parallel−group randomized clinical trials in which treatment was given for 24 weeks or longer were included. Comparisons of the following drug classes were considered: metformin, sulfonylurea, thiazolidinedione, dipeptidyl−peptidase-4 (DPP-4) inhibitor, sodium−glucose cotransporter-2 (SGLT2) inhibitor, glucagon−like peptide-1 (GLP-1) receptor agonist, basal insulin, meglitinide, and alpha−glucosidase inhibitor. Trials in which basal−bolus and prandial insulin regimens were compared with the specified drug classes of interest or placebo or standard therapy were also included. Trials were considered within separate analytical networks based on whether drugs were given as monotherapy, added to metformin (dual therapy), or added to metformin and sulfonylurea (triple therapy). Metformin plus sulfonylurea was chosen *a priori* as the baseline therapy for three−drug combinations, as this has been most widely used.[10] Studies evaluating treatments that were no longer available or withdrawn from the market (e.g., phenformin and troglitazone) were excluded, as were those that did not principally act to lower blood glucose. Studies evaluating treatment in children (age 18 years or younger) and pregnant women were ineligible.

Two investigators screened the title and abstracts of retrieved citations independently (GDB and SP) to identify potentially eligible trials. Any discrepancies were discussed between researchers until a consensus occurred. Any potentially relevant citation was then retrieved in full−text and reviewed by the same two investigators against the eligibility criteria and decisions about eligibility were double−checked independently by a third author (VG).

Information in non−English language studies was formally translated before assessment. At least two investigators (SCP, DWJ, JM, VG, GDB, MR, PN, VS, SB, YC, AN, MB, LF, AL, NA, YL, and ST) independently reviewed the main reports and supplementary materials including data reported in the www.clinicaltrials.gov portal, and extracted study and patient characteristics, and treatment strategies. All extracted data were independently checked by two authors (SP, JM).

Outcomes

The association of drug treatment with cardiovascular mortality was the primary endpoint. Secondary individual efficacy endpoints were all−cause mortality, myocardial infarction, stroke, glycated hemoglobin (HbA1C), and treatment failure (lack of efficacy or need for rescue treatment). Secondary individual safety endpoints were serious adverse events, hypoglycemia, and body weight.

Quality assessment – risk of bias

Two investigators (JM, VG) used the Cochrane tool to assess study risks of bias.[11]

Statistical analysis

Detailed methods for statistical analysis were described in eMethods 1. The clinical setting and characteristics of the trials (considering age, proportion of men, HbA1C, body weight, duration of diagnosed diabetes, duration of follow-up, and year of publication) reporting each drug class were evaluated to consider whether the included trials were sufficiently similar that a network meta−analysis approach was appropriate. Treatment effects were then estimated by random−effects pair−wise meta−analysis.[12] The association between treatment and outcomes was estimated using standardized mean differences (SMD) for HbA1C and body weight and odds ratios (OR) for cardiovascular mortality, all−cause mortality, myocardial infarction, stroke, serious adverse events, treatment failure, and hypoglycemia, together with 95% confidence intervals. In general, a standardized mean difference of 0.2 is considered small, 0.5 medium, and 0.8 large.[13]

Frequentist network meta−analysis was then used to compare available treatment strategies within a single analytical framework.[14,15] Odds ratios were also accompanied by absolute risk differences (RD). Network meta−analysis was done in Stata version 13 (www.stata.com) using the network command and self−programmed Stata routines.[16,17] The relative ranking probability of each treatment was estimated and the treatment hierarchy of competing interventions was obtained using rankograms, surface under the cumulative ranking (SUCRA) curves, and mean ranks. The restricted maximum likelihood method was used to estimate

heterogeneity, assuming a common estimate for heterogeneity variance across different comparisons for a single clinical outcome.[18] The extent of heterogeneity in each network analysis was evaluated by comparing the magnitude of a common heterogeneity variance for the network (tau [τ]) with an empirical distribution of heterogeneity variances, considering the range of expected treatment estimates (odds ratios and standardized mean differences), in which values of τ from 0.1 to 0.5 were reasonable, 0.5 to 1.0 were considered fairly high, and above 1.0 represented fairly extreme heterogeneity.[19-21]

To explore for evidence of within−network inconsistency, the loop−specific approach was used initially.[22] To check the assumption of consistency in the entire analytical network, a 'design−by−treatment' approach was then used.[23] A comparison-adjusted funnel plot of treatment estimates for drug classes as monotherapy on cardiovascular mortality was used to assess for evidence of small-study effects. In addition, random−effects bivariable network meta−regression analyses were conducted to assess baseline HbA1C, body weight, duration of diabetes, and age as effect modifiers on estimates for end of treatment HbA1C, body weight, and hypoglycemia. *Post-hoc* sensitivity analysis was done to assess for intra-class variation in the effect of individual sulfonylurea drugs as monotherapy on odds of hypoglycemia. Additional *post-hoc* sensitivity analyses were conducted restricted to studies of monotherapy in which allocation concealment was at low risk of bias. Statistical testing was 2-sided with p values <0.05 considered to indicate statistical significance.

Results

Electronic searching through March 21, 2016 retrieved 9819 citations (Figure 1). Overall, 301 randomized clinical trials involving 118,094 patients were eligible for inclusion in the review. In 177 trials (56,598 patients), drugs were given as monotherapy, in 109 trials (53,030 patients), drugs were added to metformin, and in 29 trials (10,598 patients), drugs were added to metformin and sulfonylurea therapy (eTables 2-4). The number of patients allocated to each treatment in trials ranged between 8[24-26] and 1562[27] (median 104 adults, IQR 46−190). The mean HbA1C level at randomization was 8.2% (SD 1.1%) in monotherapy trials, 8.2% (SD 0.6%) in dual therapy trials, and 8.4% (SD 0.6%) in triple therapy trials. Mean body weight at baseline was 81.9 (SD 8.9) kilograms in monotherapy trials, 83.8 (SD 15.7) kilograms in dual therapy trials, and 84.1 (SD 9.5) kilograms in triple therapy trials. The median duration of diagnosed diabetes at randomization was 5.7 (IQR 3.3−7.0) years. Mean study follow-up ranged between 24 weeks and 76.8 months (median, 6 months, IQR 5.5 to 12 months). The clinical trials were deemed sufficiently similar on the basis of study-level age, gender, HbA1C, body weight, duration of diagnosed diabetes, and duration of follow-up that a network analysis was appropriate although newer drug classes (DPP-4 inhibitors, SGLT-2 inhibitors and GLP-1 receptor antagonists) were evaluated in trials published somewhat more recently (eFigure 1).

Risks of bias

Overall, the risk of bias was high or unclear for random sequence generation in 208 trials (69.1%), concealment of treatment allocation in 232 trials (77.1%), masking of participants and/or investigators in 96 trials (31.9%), masking of outcome assessment in 281 trials (93.4%), completeness of outcome reporting in 179 trials (59.5%) and selective reporting of outcomes in 172 trials (57.5%) (eTables 5-7). The trial sponsor was involved in authorship and/or data management in 190 trials (63.1%).

Network consistency

The networks of individual treatment endpoints are shown in Figure 2 and eFigure 2. Inconsistencies between direct and indirect evidence were noted for some drug comparisons (eFigures 3-5), assessing dual therapy (for treatment failure, hypoglycemia and body weight) and triple therapy (HbA1C and hypoglycemia). The design−by−treatment interaction model did not identify global inconsistency in treatment networks (except treatment failure with dual therapy and HbA1C with three-drug therapy) (eTable 8). However, the confidence intervals for inconsistency in loops of drug comparisons were often very wide and robust conclusions about inconsistency could not be drawn. When assuming a common heterogeneity variance within

treatment networks for binary outcomes, there was evidence of low levels of heterogeneity in all networks with the exception of HbA1C for dual therapy, in which there was evidence of fairly high network heterogeneity (tau, 0.5 to 1.0) (eTable 9). Definitions of treatment failure in the included studies were generally lack of efficacy or need for additional glucose-lowering therapy (eTable 10). Contributions of direct evidence to network analyses were reported in eTable 11.

Treatment outcomes

Treatment effects in pairwise meta-analyses are shown in eFigures 6-8.

Monotherapy

Primary outcome: cardiovascular mortality

25 studies involving 14,477 adults evaluated the association of drug classes as monotherapy with cardiovascular death, including a total of 67 events during 197,763 patient−months of follow-up (Figure 2). There were no significant differences in the associations between any drug class as monotherapy with odds of cardiovascular mortality (Table 1 and eTable 12). Data were absent for basal insulin and GLP-1 receptor agonist monotherapy and rankings of drug classes for cardiovascular mortality were very imprecise (Figure 3).

Secondary outcomes: all-cause mortality, serious adverse events, myocardial infarction, stroke, HbA1C, treatment failure, hypoglycemia, body weight

All monotherapies had uncertain comparative associations with all-cause mortality, serious adverse events, myocardial infarction, and stroke (Table 1 and eTable 12). All drug classes as monotherapy were associated with lower HbA1C levels than placebo (standardized mean difference (SMD) ranging from −0.66, CI -0.88 to -0.44 for alpha glucosidase inhibitors to -1.11, -1.44 to -0.77 for meglitinides). Compared to metformin, sulfonylurea (SMD 0.18, 0.10 to 0.34), thiazolidinedione (SMD 0.16, 0.00 to 0.31), DPP-4 inhibitor (SMD 0.33, 0.13 to 0.52), and alpha glucosidase inhibitor (SMD 0.35, 0.12 to 0.58) monotherapy were associated with higher HbA1C levels, while SGLT-2 inhibitors (SMD 0.18, -0.15 to 0.51), basal insulin (SMD 0.13, -0.24 to 0.51), GLP-1 receptor agonists (SMD -0.04, -0.31 to 0.23), and meglitinides (SMD -0.09, -0.42 to 0.24) showed no significant difference in HbA1C levels. There was limited confidence in hierarchical treatment rankings for HbA1C levels (Figure 3).[28]

Placebo was associated with the greatest odds of treatment failure (odds ratio (OR) *versus* metformin 3.83, 2.88 to 5.10; risk difference (RD) 11%, 8% to 14%), while DPP-4 inhibitor (OR 1.53, CI 1.16 to 2.01; RD 3%, 1% to 6%) and meglitinide (OR 2.58, 1.43 to 4.66; RD 5%, 1% to

9%) monotherapies were also associated with higher odds of treatment failure than metformin. SGLT-2 inhibitor (OR 0.47, 0.31 to 0.71; RD -0.3%, -4% to 3%) treatment was associated with the lowest odds of treatment failure.

Basal insulin (OR 17.9, 1.97 to 162; RD 10%, 0.08% to 20%) or sulfonylurea (OR 3.13, 2.39 to 4.12; RD 10%, 7% to 13%) monotherapy were hierarchically the worst for an association with hypoglycemia while placebo (OR 0.58, 0.40 to 0.83; RD -3%, -5% to -0.2%) was the only intervention associated with lower odds of hypoglycemia than metformin. Thiazolidinediones (OR 0.67, 0.50 to 0.88; RD -4%, -7% to -1%) and DPP-4 inhibitors (OR 0.69, 0.50–0.94; RD -1%, -4% to 1%) were also associated with a lower risk of hypoglycemia than metformin. Compared with metformin, GLP-1 receptor agonist monotherapy was associated with a lower body weight (SMD -0.28, -0.52 to -0.04) while sulfonylurea (SMD 0.19, 0.04 to 0.33) and thiazolidinedione (SMD 0.24, 0.04 to 0.43) monotherapy were associated with higher body weight.

Drugs added to metformin

Primary outcome: cardiovascular mortality

26 trials involving 20,690 adults evaluated dual therapy (drugs added to metformin) including 45 cardiovascular deaths during 286,157 patient−months of dual therapy (Figure 2). There was no significant association between any drug class and odds of cardiovascular mortality (Table 1 and eTable 13). Data for basal insulin or alpha glucosidase inhibitors added to metformin were absent and rankings of drug classes for cardiovascular mortality were very imprecise (Figure 3).

Secondary outcomes: all-cause mortality, serious adverse events, myocardial infarction, stroke, HbA1C, treatment failure, hypoglycemia, body weight

There were no significant differences between any drug class when added to metformin for odds of all−cause mortality, serious adverse events, myocardial infarction, or stroke (Table 1 and eTable 13) with the exception of a lower odds of stroke associated with DPP-4 inhibitor/metformin versus sulfonylurea/metformin (OR 0.47, 0.23 to 0.95; RD -0.2%, -0.4% to -0.04%). When considering efficacy, all drug classes as dual therapy regimens lowered HbA1C to a similar extent, although there was fairly high statistical heterogeneity in this network. Direct and indirect evidence tended to indicate similar results with the exception of the comparison between sulfonylurea and placebo therapy when added to metformin (eFigure 7). Compared with sulfonylurea/metformin, SGLT-2 inhibitor/metformin ranked the best for avoiding treatment failure (OR 0.68, 0.48 to 0.96; RD -3%, -6% to -0.8%) while alpha glucosidase inhibitor/metformin (OR 12.4, 1.84 to 83.3; RD 9%, 1% to 17%) and DPP-4

inhibitor/metformin (OR 1.37, 1.07 to 1.76; RD 1%, -1% to 3%) strategies were associated with higher odds of treatment failure.

All dual therapy classes were associated with lower odds of hypoglycemia than sulfonylurea/metformin dual therapy, with mean odds of hypoglycemia ranging from 0.56 (0.32 to 0.98; RD -4%, -12% to 5%) for basal insulin/metformin to 0.12 (0.08 to 0.18; RD -22%, -27% to -18%) for SGLT-2 inhibitor/metformin, which was ranked as the best option to avoid hypoglycemia (Figure 3). Sulfonylurea/metformin dual therapy was ranked worst for body weight. Compared with sulfonylurea/metformin treatment, DPP-4 inhibitor/metformin (SMD -0.58, -1.06 to -0.11), SGLT-2 inhibitor/metformin (SMD -0.96, -1.46 to -0.47) and GLP-1 receptor agonist/metformin (SMD -1.05, -1.54 to -0.57) were associated with significantly lower body weight at the end of treatment.

Drugs added to metformin and sulfonylurea: secondary outcomes

Primary outcome: cardiovascular mortality

Five trials involving 3267 adults evaluated triple therapy (drugs added to metformin and sulfonylurea) (Figure 2) including 6 cardiovascular deaths during 37,223 patients−months of triple therapy. There was no evidence of an association of any drug class with cardiovascular mortality (Table 1 and eTable 14). Data for meglitinides and alpha glucosidase inhibitors added to metformin and sulfonylurea were absent and rankings of drug classes cardiovascular death were very imprecise (Figure 3).

Secondary outcomes: all-cause mortality, serious adverse events, myocardial infarction, stroke, HbA1C, treatment failure, hypoglycemia, body weight

There was no evidence of significantly different associations with all-cause mortality or serious adverse events between any of the drug classes given as triple therapy (Table 1 and eTable 14). Insufficient observations were available to generate evidence networks for myocardial infarction or stroke.

As add-ons to metformin/sulfonylurea, alpha glucosidase inhibitors ranked worst for lowering HbA1C whereas thiazolidinediones or basal insulin were best (Figure 3 and eTable 14). Alpha glucosidase inhibitors were associated with higher HbA1C levels than thiazolidinediones (SMD 1.42, 0.57 to 2.26), GLP-1 receptor agonists (SMD 1.34, 0.37 to 2.32) and basal insulin (SMD 1.42, 0. 44 to 2.39) when added to metformin/sulfonylurea. Basal insulin plus metformin/sulfonylurea ranked best for avoiding treatment failure whereas DPP-4 inhibitor plus metformin/sulfonylurea was the worst (Figure 3 and Table 1). Compared with thiazolidinedione given as triple therapy, basal insulin was associated with lower odds of

treatment failure (OR 0.44, 0.20 to 0.99; RD -5%, -20% to 9%) while DPP-4 inhibitor plus metformin/sulfonylurea was associated with higher odds of treatment failure (OR 2.20, 1.32 to 3.68; RD 21%, 7% to 35%).

When added to metformin/sulfonylurea, GLP-1 receptor agonists were ranked best for avoiding hypoglycemia while thiazolidinediones ranked worst. GLP-1 receptor agonists were associated with lower odds of hypoglycemia than thiazolidinediones (OR 0.60, 0.39 to 0.94; -10%, -18% to 2%) in triple therapy. When added to metformin/sulfonylurea, SGLT-2 inhibitors were ranked best for minimizing weight gain while thiazolidinediones and basal insulin ranked worst. All other drug classes except basal insulin were associated with a lower body weight than thiazolidinediones when added to metformin/sulfonylurea (SMD ranging from -0.23, -0.46 to -0.00 for DPP-4 inhibitors and SMD -0.23, -0.39 to -0.06 for GLP-1 receptor agonists to SMD -0.33, -0.59 to -0.07 for SGLT-2 inhibitors).

Meta-regression and sensitivity analysis

Network meta-regression analyses were used to assess whether treatment effects for HbA1C, hypoglycemia and body weight were modified by study−level age, HbA1C, body, duration of diagnosed diabetes and duration of treatment. Generally, regression analyses were non−significant or had limited associations with estimated treatment effects (eTable 15). There was no evidence of different associations between drug classes as monotherapy between small and large trials for the primary outcome of cardiovascular mortality (Figure 4). In additional analyses, all sulfonylureas as monotherapy ranked similarly and among the worst treatments for odds of hypoglycemia (eTable 16 and eFigure 9). There were no substantive differences in the findings for drug classes as monotherapy when analyses were restricted to trials at low risk of bias from allocation concealment (eTable 17). DPP-4 inhibitors were associated with moderately higher HbA1C levels than metformin and higher odds of treatment failure, while being association with lower risks of hypoglycemia. Sulfonylurea monotherapy was associated with higher odds of hypoglycemia compared with metformin. Treatment estimates for mortality and cardiovascular events in high quality trials were uninterpretable due to wide confidence intervals.

Discussion

This network meta−analysis evaluated the association with efficacy and safety endpoints of nine classes of glucose-lowering drugs for type 2 diabetes. Considering cumulative trial data from 114,962 adults, there was no evidence of differences in the associations between any of the available drug classes (alone or in combination) on cardiovascular mortality, all-cause mortality, serious adverse events, myocardial infarction, or stroke (with the exception of a lower association of DPP-4 inhibitor therapy with stroke compared with sulfonylurea treatment when added to metformin). Considerable uncertainty about the association of drug treatment with cardiovascular mortality occurred largely because of the small number of events, despite evidence networks that included 15,000 to 20,000 patients.

All monotherapies were associated with large proportional reductions in HbA1C levels compared with placebo (standardized mean differences ranging between -0.66 and -1.11), while metformin was associated with small to moderately lower HbA1C levels versus sulfonylurea, thiazolidinedione, DPP-4 inhibitor, and alpha glucosidase inhibitor monotherapy (standardized mean differences ranging between -0.16 and -0.35). All drugs were associated with less treatment failure than placebo. Compared with metformin, SGLT-2 inhibitors performed the best with significantly lower odds of treatment failure, although this translated to a small and non-significant absolute risk difference of -0.3%. Basal insulin and sulfonylurea monotherapy were associated with greatest odds of hypoglycemia with absolute risk difference of 10% compared with metformin. Individual sulfonylurea drugs as monotherapy were associated with similar odds of hypoglycemia. Metformin was associated with small relative reductions in body weight compared with sulfonylurea (-0.19) and thiazolidinedione (-0.24) treatment but moderately higher body weight than GLP-1 receptor agonists (0.28), which performed the best. Metformin was a reasonable first−line agent for type 2 diabetes, while sulfonylureas and basal insulin might be avoided in patients for whom hypoglycemia was particularly hazardous. SGLT-2 inhibitors might be considered as an alternative first−line agent given lower odds of treatment failure compared to other available drug classes.

When drug classes were added to metformin as dual therapy, all were associated with large reductions in HbA1C levels (mean differences ranging between -0.67 and -2.07), although heterogeneity in this network lowered confidence in the results. SGLT-2 inhibitors had the highest probability of avoiding treatment failure; SGLT-2 inhibitors were associated with lower odds of treatment failure than sulfonylureas with an absolute risk reduction of 3%. Sulfonylurea therapy added to metformin was associated with the greatest odds of hypoglycemia and performed significantly worse than all other treatments, while SGLT-2

inhibitors added to metformin ranked the best. SGLT-2 inhibitors and GLP-1 receptor agonists added to metformin had the highest probabilities of being the best treatment for body weight while sulfonylurea therapy as dual treatment was the worst. Considering the balance of treatment benefits and harms, adding SGLT-2 inhibitors to metformin among patients needing additional glucose−lowering therapy might be the preferred treatment option to offer the lowest odds of treatment failure and minimize risks of hypoglycemia and weight gain. Otherwise, addition of basal insulin to metformin appeared to be a reasonable alternative. In contrast, although it is commonly used, sulfonylurea treatment added to metformin was associated with the least favorable side effect profile. Given the lack of evidence that any regimen was superior for hard clinical outcomes, decision−makers (especially within lower−resource settings) may consider whether the advantages of SGLT-2 inhibitors outweigh their generally higher costs compared to sulfonylureas or basal insulin.

When efficacy and safety of available agents used as part of a three−drug regimen added to metformin plus sulfonylurea were compared, alpha glucosidase inhibitors were associated with highest HbA1C levels while there were no significant differences in HbA1C levels between any other treatment classes. Basal insulin ranked the best for avoiding treatment failure while DPP-4 inhibitors were the worst. GLP-1 receptor agonists as three-drug therapy posed the lowest risks of hypoglycemia, associated with a 10% absolute risk reduction compared with thiazolidinedione therapy, although due to rare events for some treatments, this risk difference was not significant. SGLT-2 inhibitors were the best ranked for weight gain. Thiazolidinediones posed the greatest risks of hypoglycemia and were ranked worst for body weight. Considering these results, SGLT-2 inhibitors, GLP-1 receptor agonists and basal insulin might be considered as preferred options when adding a third agent to metformin and sulfonylurea, while alpha glucosidase inhibitors and thiazolidinediones might be less favorably considered.

A central finding in this meta−analysis was that despite over 300 available clinical trials involving nearly 120,00 adults and 1.4 million patient-months of treatment, there was little or no evidence that specific glucose−lowering drugs as one, two, or three drug regimens prolonged life−expectancy or prevented cardiovascular−related deaths or events. This finding might have been due to the lack of statistical power in available trials, with only approximately 70 cardiovascular deaths reported among monotherapy trials. Although recruitment to several large and principally placebo−controlled studies is ongoing,[6] all of these studies plan composite primary outcomes that include cardiovascular mortality, myocardial infarction, and stroke, and may not draw definitive conclusions about the individual components of the combined patient

outcomes. In addition, it also remained possible that there were no clinically important comparative differences between specific glucose−lowering drugs on mortality risk. A recent trial involving 14,671 adults adding sitagliptin or placebo to existing therapy over 3 years observed no difference in the risk of cardiovascular mortality between treatment groups,[29] while a placebo−controlled trial of saxagliptin among nearly 17,000 adults observed no differences in mortality with treatment.[30] Notably, the EMPA-REG OUTCOME trial[8] evaluating the SGLT-2 inhibitor empagliflozin was not eligible for this meta-analysis because background treatment that included other antidiabetic therapies. Together, our findings and EMPA-REG OUTCOME concluding that 3 years of SGLT-2 inhibitor treatment reduced cardiovascular and all-cause mortality in adults with diabetes and cardiovascular disease, suggested that future trials should compare the risk of mortality for SGLT-2 inhibitors against metformin or basal insulin or in dual therapy regimens. Cumulative network meta−analysis of any available additional studies should be conducted as results become available to ensure any evidence for survival benefits or harms is rapidly identified.

The finding that metformin monotherapy was an appropriate first−line pharmacological treatment for initial treatment of type 2 diabetes was consistent with the American Diabetes Association (ADA) recommendations.[4] However, these guidelines also suggested a patient−centered approach – considering efficacy, weight gain, hypoglycemia, and comorbidities – when selecting treatment. Therefore, clinicians and patients may prefer to avoid sulfonylurea or basal insulin as initial therapy to avoid hypoglycemia, choose GLP-1 receptor agonists when weight management is a priority, or consider SGLT-2 inhibitors based on a favorable combined safety and efficacy profile. When considering the addition of a second agent to metformin (one of six treatment options of sulfonylurea, thiazolidinedione, DPP-4 inhibitor, SGLT2 inhibitors, GLP-1 receptor agonist, or basal insulin), the present findings suggested a potential treatment hierarchy with sulfonylurea therapy least preferred (due to an unfavorable side effect profile); SGLT-2 inhibitors can be suggested for patients wishing to avoid hypoglycemia; and SGLT-2 inhibitors or GLP-1 receptor agonists for those in whom weight gain is a higher priority. There was little evidence to guide the choice of third drug in triple therapy regimens, although clinicians might consider SGLT-2 inhibitors, GLP-1 receptor agonists, or basal insulin based on efficacy and safety, while thiazolidinediones might be less favored due to their side effect profile, and alpha glucosidase inhibitors lack efficacy. In addition, metformin plus sulfonylurea as the two−drug basis for a third agent appeared to be least favorable, and three−drug combinations that use other oral agents (particularly metformin plus SGLT-2 inhibitor) warranted further evaluation.

The present systematic review and network analysis extended findings from a 2011 pairwise meta−analysis of 166 randomized clinical trials and observational studies examining medications for type 2 diabetes that included assessments of one− and two−drug combinations.[7] The network approach allowed greater statistical power to compare all single and two−drug treatments with each other, confirmed the hazards of sulfonylureas alone and when combined with metformin for hypoglycemia, and indicated the beneficial associations of GLP-1 receptor agonists on body weight. The network analysis extended understanding about comparative effectiveness and safety for all other treatment options and combinations, based on metformin as initial treatment, even though these have not been directly evaluated in head−to−head trials. The consistency of many findings between the two reviews despite the differing analytical methods strengthened the conclusions of both studies.

Thiazolidinediones (including rosiglitazone and pioglitazone) have been linked to increased edema and heart failure without evidence of a corresponding excess in cardiovascular mortality in previous meta−analyses.[31,32] This increased risk is recommended as being considered when patients make treatment decisions about dual therapy for type 2 diabetes.[4] Because of limited trial data for heart failure was not included as an outcome in this analysis, and network analysis did not demonstrate different comparative effects between thiazolidinediones and other drug classes on other cardiovascular complications such as myocardial infarction and stroke.

The strengths of this review included the comprehensive systematic search that considered trials published in languages other than English and those published only as conference proceedings, the use of a pre−specified protocol, and double−checking of data extraction. However, there were several limitations. First, analyses were limited by the amount of data in the included studies. While cardiovascular mortality was included as an outcome because of its central clinical importance and the ongoing uncertainty about drug effectiveness for this endpoint, only a minority of studies reported this outcome and most had few or zero events. Meta-analysis resulted in treatment estimates with wide confidence intervals for this and other outcomes, leading to low confidence in drug effects and non-significant absolute risk differences. In the network analysis for cardiovascular mortality for monotherapy, the mortality rate was considerably lower than that in a recent pragmatic trial among adults with previously undetected diabetes,[33] suggesting future trial investigators need to consider drug evaluations in real−world settings with higher morbidity and mortality risks. Randomized trials of sufficient duration and with adequate statistical power are needed to detect treatment effects of diabetes drugs on mortality,[6] and include consideration of disruptive trial designs

such as registry−based trials to maximize trial efficiency and feasibility. In addition, statistical inconsistency between direct and indirect comparisons in some networks, including dual therapy associations with HbA1C levels, diminished the ability to draw confident conclusions for some treatment effects. Second, triple therapy regimens evaluated in this study were limited to individual drugs added to metformin and sulfonylurea therapy and the comparative effectiveness of other three−drug combinations were not assessed. Third, analyses have not been adjusted for baseline kidney function, and thus findings may not have been applicable to patients who have chronic kidney disease. A recent trial of empagliflozin added to standard therapy (EMPA-REG OUTCOME)[8] which included a subgroup of nearly 2000 adults who had chronic kidney disease found no evidence of different risks of cardiovascular death with treatment among people with kidney failure.[8] Fourth, many of the trials were conducted in higher income countries. Medication use in lower resource settings may be limited by cost and drug availability. Fifth, most studies were short−term and the longer term safety of the available drugs alone and in combination was incompletely understood. Finally, while there were no clinically important associations between drug effects and patient or study characteristics, there was limited power in these analyses.

Conclusions

Among adults with type 2 diabetes, there were not significant differences in the associations between any of nine available classes of glucose-lowering drugs (alone or in combination) and the risk of cardiovascular or all-cause mortality. Metformin was associated with lower HbA1C levels or no significant difference in HbA1C levels than any of the other drug classes. All drugs were estimated to be effective when added to metformin. These findings are consistent with ADA recommendations for using metformin monotherapy as initial treatment for patients with type 2 diabetes and selection of additional therapies based on patient-specific considerations.

Contributors

SCP, AN, and GFMS had the idea for and designed the study. SCP, DWJ, JM, VG, GDB, MR, PN, VS, SB, YC, AN, MB, LF, AL, NA, YL, and ST identified and acquired reports of trials and extracted data. DM provided statistical advice and input. SCP did all data analyses, checked for statistical inconsistency, and interpreted data. DM, AN, DWJ, MT, JCC, GDB, and GFMS contributed to data interpretation. SCP drafted the report and all other authors critically reviewed the report.

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Table 1: Summary effects of glucose-lowering interventions in people with type 2 diabetes

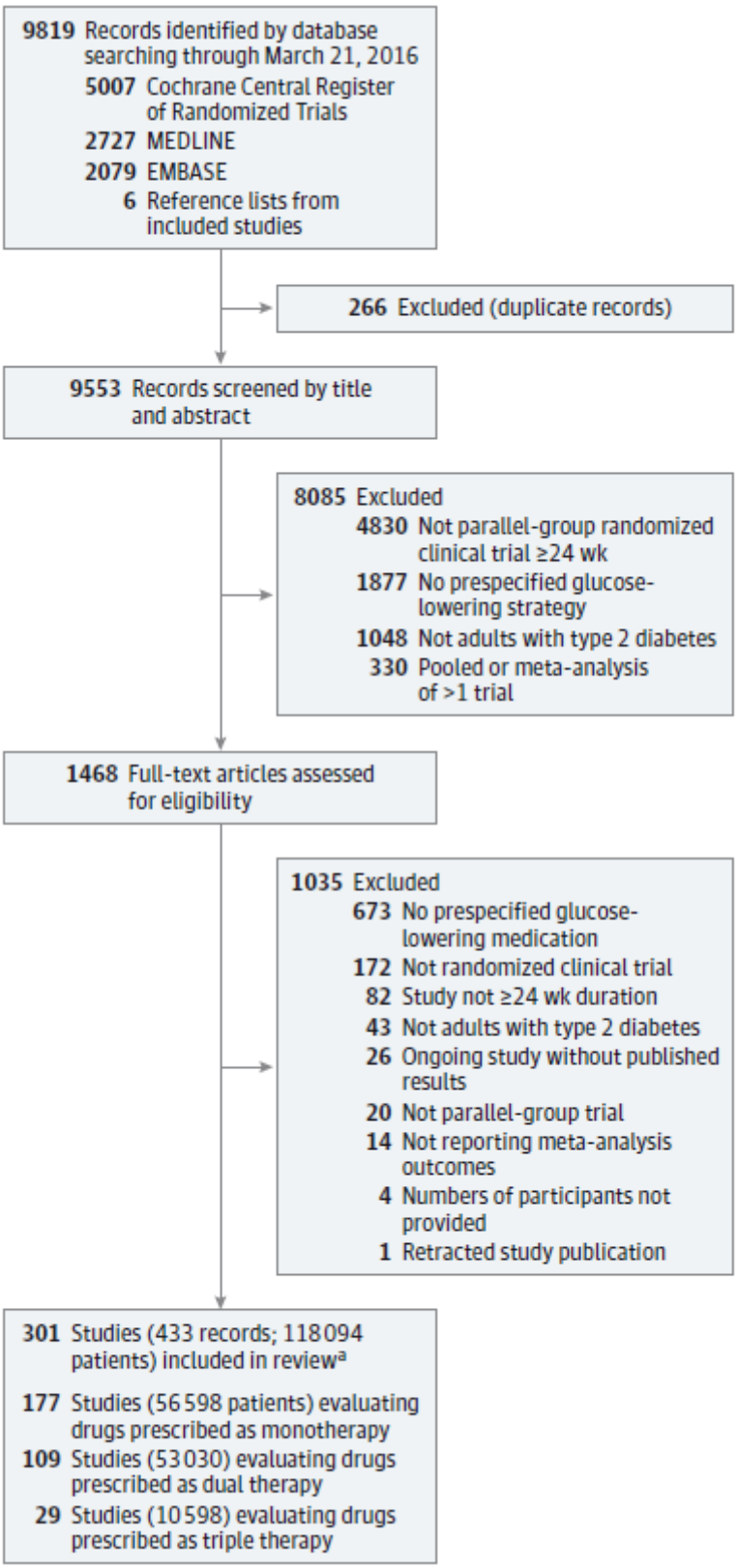
	Drugs given as monotherapy									
Outcome	**Metformin**	**Sulfonylurea**	**Thiazolidinedione**	**DPP-4-inhibitor**	**SGLT-2-inhibitor**	**Basal insulin**	**GLP-1 receptor agonist**	**Meglitinide**	**Alpha glucosidase inhibitor**	**Placebo**
Cardiovascular mortality	Referent	1.25 (0.59 to 2.67)	0.87 (0.30 to 2.49)	1.00 (0.37 to 2.65)	0.75 (0.14 to 3.96)	--	--	0.55 (0.07 to 4.61)	0.92 (0.13 to 6.38)	1.38 (0.41 to 4.72)
All-cause mortality	Referent	1.19 (0.81 to 1.75)	1.09 (0.72 to 1.65)	0.73 (0.41 to 1.30)	0.84 (0.22 to 3.21)	--	0.91 (0.18 to 4.46)	1.10 (0.17 to 7.05)	0.79 (0.17 to 3.79)	1.09 (0.44 to 2.75)
Serious adverse event	Referent	0.96 (0.83 to 1.12)	1.00 (0.86 to 1.16)	1.08 (0.87 to 1.34)	1.24 (0.81 to 1.92)	--	0.86 (0.62 to 1.20)	1.65 (0.82 to 3.30)	0.73 (0.31 to 1.71)	1.05 (0.79 to 1.39)
Myocardial infarction	Referent	0.94 (0.58 to 1.50)	0.99 (0.62 to 1.59)	0.90 (0.36 to 2.23)	0.63 (0.06 to 6.24)	--	0.80 (0.15 to 4.17)	--	0.87 (0.03 to 26.4)	1.15 (0.35 to 3.74)
Stroke	Referent	1.08 (0.67 to 1.76)	1.04 (0.60 to 1.80)	1.43 (0.50 to 4.09)	0.70 (0.05 to 9.71)	--	0.74 (0.17 to 3.21)	--	--	1.35 (0.33 to 5.46)
HbA1C	Referent	**0.18 (0.01 to 0.34)**	**0.16 (0.00 to 0.31)**	**0.33 (0.13 to 0.52)**	0.18 (-0.15 to 0.51)	0.13 (-0.24 to 0.51)	-0.04 (-0.31 to 0.23)	-0.09 (-0.42 to 0.24)	**0.35 (0.12 to 0.58)**	**1.01 (0.84 to 1.18)**
Treatment failure	Referent	1.18 (0.86 to 1.65)	1.21 (0.87 to 1.67)	**1.53 (1.16 to 2.01)**	**0.47 (0.31 to 0.71)**	0.22 (0.01 to 5.51)	0.62 (0.37 to 1.04)	**2.58 (1.43 to 4.66)**	2.54 (0.67 to 9.60)	**3.83 (2.88 to 5.10)**
Hypoglycemia	Referent	**3.13 (2.39 to 4.12)**	**0.67 (0.50 to 0.88)**	**0.69 (0.50 to 0.94)**	0.63 (0.30 to 1.32)	**17.9 (1.97 to 162)**	1.06 (0.74 to 1.52)	2.16 (1.49 to 3.12)	0.65 (0.37 to 1.13)	**0.58 (0.40 to 0.83)**
Body weight	Referent	**0.19 (0.04 to 0.33)**	**0.24 (0.04 to 0.43)**	0.12 (-0.09 to 0.32)	-0.06 (-0.22 to 0.08)	0.07 (-0.45 to 0.60)	**-0.28 (-0.52 to -0.04)**	-0.09 (-0.30 to 0.13)	0.03 (-0.18 to 0.23)	0.09 (-0.05 to 0.24)
	Drugs given as dual therapy (in addition to metformin)									
		Sulfonylurea	**Thiazolidinedione**	**DPP-4-inhibitor**	**SGLT-2-inhibitor**	**Basal insulin**	**GLP-1 receptor agonist**	**Meglitinide**	**Alpha glucosidase inhibitor**	**Placebo**

Cardiovascular mortality		Referent	2.10 (0.48 to 9.15)	0.81 (0.36 to 1.82)	0.86 (0.14 to 5.27)	--	0.52 (0.08 to 3.43)	1.03 (0.10 to 10.9)	--	1.60 (0.35 to 7.37)
All-cause mortality		Referent	1.29 (0.39 to 4.23)	0.75 (0.45 to 1.24)	0.83 (0.37 to 1.86)	3.76 (0.30 to 47.2)	0.87 (0.39 to 1.91)	1.20 (0.25 to 5.72)	--	1.12 (0.45 to 2.78)
Serious adverse event		Referent	1.23 (0.92 to 1.65)	0.94 (0.82 to 1.07)	0.92 (0.73 to 1.15)	1.13 (0.66 to 1.92)	1.13 (0.91 to 1.41)	0.87 (0.46 to 1.63)	2.11 (0.73 to 6.09)	0.93 (0.73 to 1.17)
Myocardial infarction		Referent	1.59 (0.43 to 5.91)	0.59 (0.32 to 1.09)	0.42 (0.12 to 1.48)	0.22 (0.01 to 5.70)	0.89 (0.35 to 2.22)	--	--	1.00 (0.36 to 2.79)
Stroke		Referent	0.81 (0.20 to 3.29)	**0.47 (0.23 to 0.95)**	2.75 (0.76 to 10.0)	1.58 (0.06 to 42.1)	0.88 (0.26 to 2.97)	--	--	1.40 (0.50 to 3.89)
HbA1C		Referent	0.03 (-0.36 to 0.41)	-0.02 (-0.43 to 0.39)	0.17 (-0.49 to 0.82)	0.07 (-0.75 to 0.88)	0.10 (-0.41 to 0.62)	-0.83 (-1.80 to 0.14)	0.58 (-0.22 to 1.37)	**1.24 (0.76 to 1.72)**
Treatment failure		Referent	1.18 (0.70 to 1.98)	**1.37 (1.07 to 1.76)**	**0.68 (0.48 to 0.96)**	0.10 (0.01 to 1.89)	0.84 (0.54 to 1.30)	1.16 (0.59 to 2.26)	**12.4 (1.84 to 83.3)**	**3.43 (2.50 to 4.72)**
Hypoglycemia		Referent	**0.14 (0.09 to 0.24)**	**0.12 (0.10 to 0.16)**	**0.12 (0.08 to 0.18)**	**0.56 (0.32 to 0.98)**	**0.19 (0.13 to 0.27)**	**0.55 (0.32 to 0.93)**	**0.13 (0.05 to 0.40)**	**0.14 (0.10 to 0.21)**
Body weight		Referent	-0.25 (-0.65 to 0.13)	**-0.58 (-1.06 to -0.11)**	**-0.96 (-1.46 to -0.47)**	-0.99 (-2.14 to 0.16)	**-1.05 (-1.54 to -0.57)**	--	-0.63 (-1.65 to 0.40)	**-0.63 (-1.05 to -0.21)**
	Drugs given as triple therapy (in addition to metformin + sulfonylurea)									
			Thiazolidinedione	**DPP-4-inhibitor**	**SGLT-2-inhibitor**	**Basal insulin**	**GLP-1 receptor agonist**	**Meglitinide**	**Alpha glucosidase inhibitor**	**Placebo**
Cardiovascular mortality			Referent	0.73 (0.00 to 136)	3.69 (0.05 to 258)	2.13 (0.04 to 108)	2.13 (0.04 to 108)	--	--	2.42 (0.15 to 39.1)
All-cause mortality			Referent	0.44 (0.02 to 11.6)	2.16 (0.10 to 45.2)	0.69 (0.02 to 19.3)	0.15 (0.01 to 2.22)	--	--	1.37 (0.27 to 6.94)
Serious adverse event			Referent	0.62 (0.32 to 1.20)	0.53 (0.27 to 1.06)	0.73 (0.42 to 1. 27)	0.64 (0.39 to 1.07)	--	--	0.93 (0.54 to 1.62)

Myocardial infarction			Referent	--	--	--	--	--	--	--
Stroke			Referent	--	--	--	--	--	--	--
HbA1C			Referent	0.23 (-0.62 to 1.08)	0.12 (-1.12 to 1.35)	0.00 (-0. 61 to 0.61)	0.107 (-0.55 to 0.70)	--	**1.42 (0.57 to 2.26)**	**0.86 (0.25 to 1.48)**
Treatment failure			Referent	**2.20 (1.32 to 3.68)**	0.78 (0.39 to 1.57)	**0.44 (0.20 to 0.99)**	0.95 (0.60 to 1.50)	--	--	**4.66 (3.04 to 7.17)**
Hypoglycemia			Referent	0.87 (0.50 to 1.51)	0.86 (0.48 to 1.54)	0.95 (0.60 to 1.52)	**0.60 (0.39 to 0.94)**	--	--	**0.37 (0.24 to 0.57)**
Body weight			Referent	**-0.23 (-0.46 to -0.00)**	**-0.33 (-0.59 to -0.07)**	0.16 (-0.36 to 0.68)	**-0.23 (-0.39 to -0.06)**	--	**-0.28 (-0.48 to -0.08)**	**-0.26 (-0.50 to -0.02)**

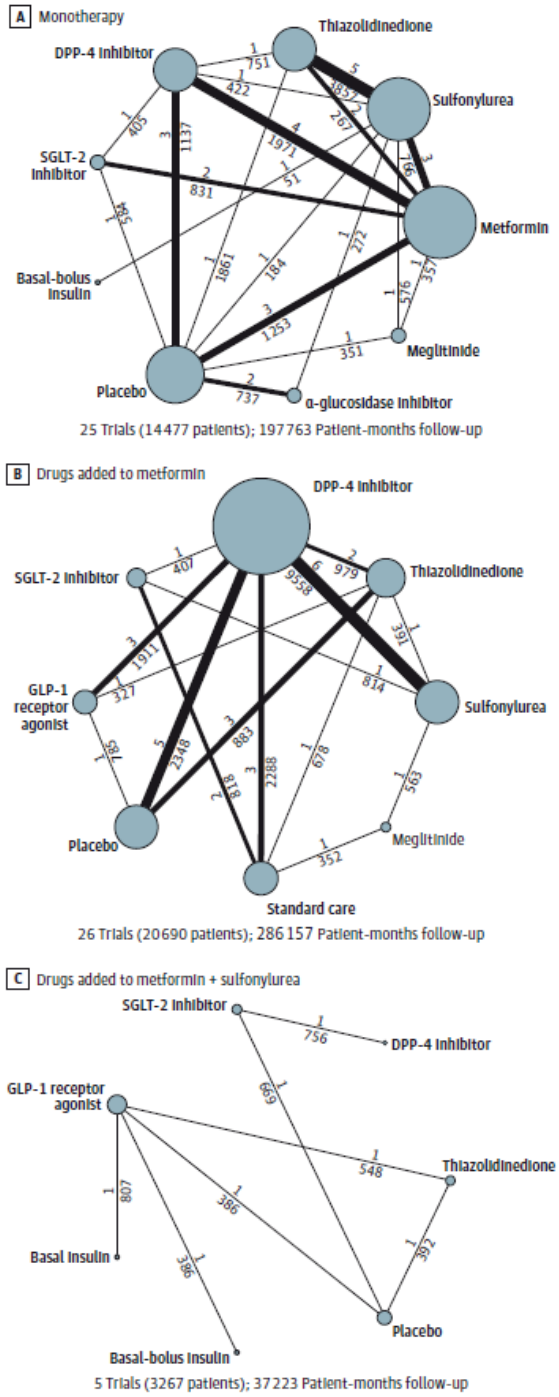
Treatment effects are shown as odds ratios from indirect and direct evidence (all-cause mortality, cardiovascular mortality, serious adverse effects, myocardial infarction, stroke, hypoglycemia, or treatment failure) or standardized mean differences (HbA1C or body weight) together with the corresponding 95% confidence intervals. An odds ratio >1 indicates the outcome is more likely with treatment than the reference intervention. An SMD above 0 indicates a higher body weight or HbA1C at end of treatment with the drug being considered compared to the reference treatment. Standardized mean difference of 0.2 is considered to indicate a small difference between treatments, 0.5 a moderate difference, and 0.8 a large difference. For example, sulfonylurea monotherapy was associated with a small increase in mean HbA1C levels (standardized mean difference 0.18) compared to metformin monotherapy, and this difference had a 95% probability of ranging between 0.01 and 0.34. The statistically significant results are shown in bold and underlined. -- indicates treatment effects were not estimable due to an insufficient number of observations. Insufficient data were available to generate networks for drug classes used as triple therapy and outcomes of myocardial infarction and stroke. Mean odds ratios or standardized mean differences with wide confidence intervals should be interpreted with caution (e.g., the estimated odds of hypoglycemia associated with basal insulin compared to metformin was 17.9 and included a confidence interval of 1.97 to 162). The true odds of hypoglycemia associated with treatment might be considerably different than the mean estimated effect (odds ratio 17.9) and range from a small increase in hypoglycemia (odds ratio 1.97) to a very high odds of hypoglycemia (odds ratio 162). Wide confidence intervals were present for many drug comparisons and outcomes.

Figure 1: Summary of study retrieval and identification for network meta-analysis



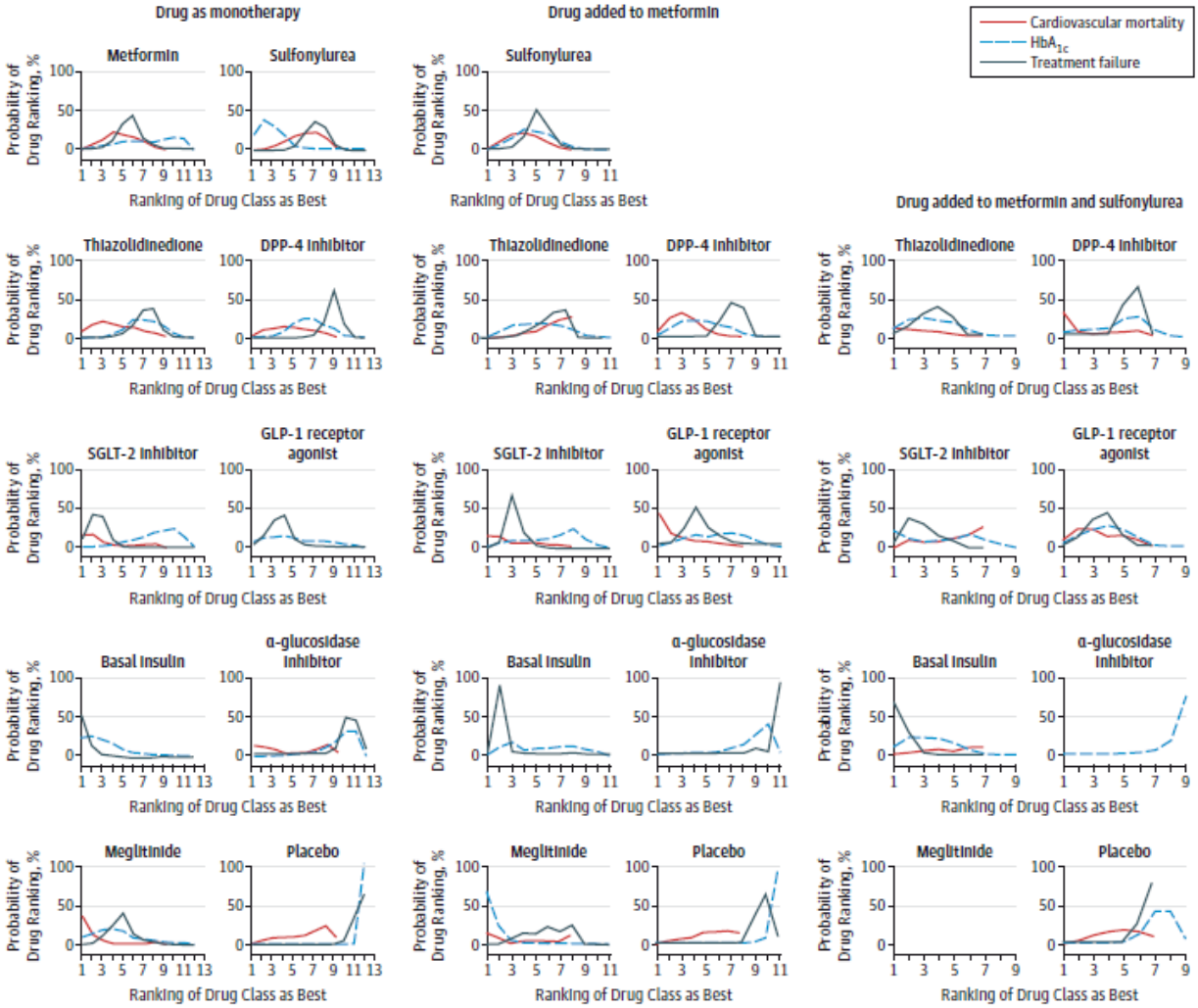
*Fourteen studies evaluated glucose–lowering strategies as both monotherapy and dual therapy.

Figure 2: Graphic representation of available glucose-lowering drugs on cardiovascular mortality in clinical trials involving people with type 2 diabetes.



Nodes indicate the drug treatments which are evaluated in clinical trials. Lines represent head-to-head comparisons of the two drug classes indicated by the connected nodes. Numbers on the connecting lines between nodes represent the number of studies/number of adults in trials directly comparing the two treatments. The thickness of the line connecting two nodes is proportional to the number of clinical trials directly evaluating the two connected drug classes. For example, the most common head-to-head drug comparison for monotherapy is a sulfonylurea compared with a thiazolidinedione. The size of the node is proportional to the number of trials evaluating the treatment. For example, the most commonly evaluated monotherapy for glucose–lowering in adults with diabetes was metformin, followed by sulfonylurea, then placebo.

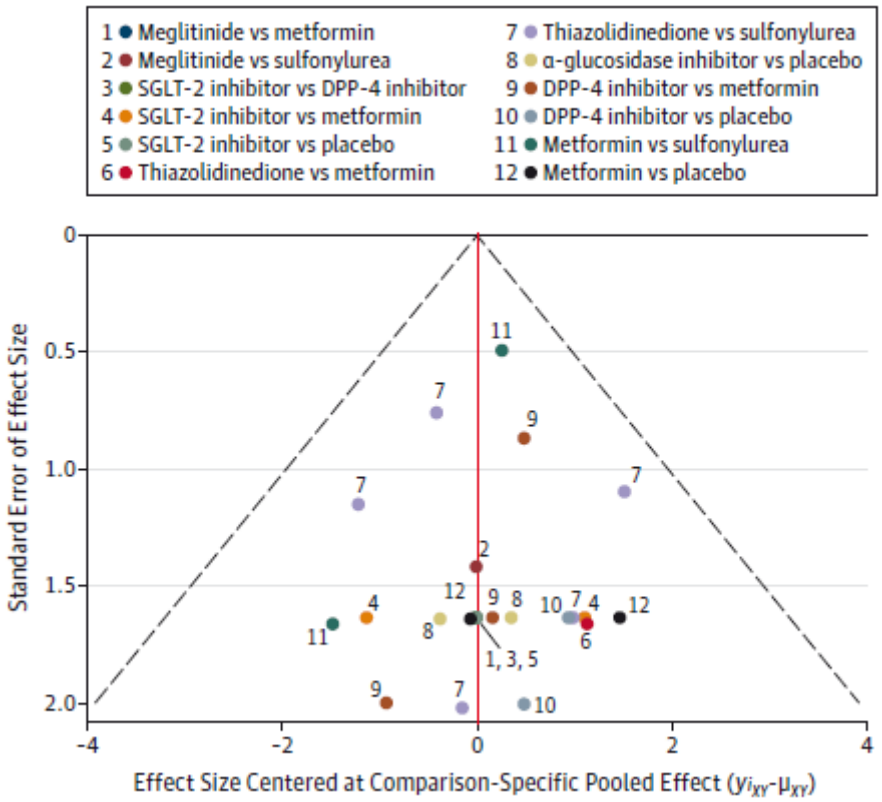
Figure 3: Rankings of available glucose-lowering drugs for treatment of type 2 diabetes.



Drug classes are stratified according to administration as monotherapy, as dual therapy in addition to metformin, or as triple therapy in addition to metformin and sulfonylurea. The upper panel (A) indicates drug rankings for efficacy (cardiovascular mortality, treatment failure, and HbA1C levels). The lower panel (B) indicates drug rankings for adverse effects (serious adverse effects, hypoglycemia, and weight gain). The lines show the probability of the drug ranking for each outcome between best and worst (ranking 1st, 2nd, 3rd, etc.) and the peak indicates the ranking with the highest probability for the corresponding drug class. For example, for treatment failure, SGLT-2 inhibitor monotherapy demonstrates a higher probability of ranking best than thiazolidinedione (TZD) monotherapy. Basal insulin monotherapy has a 50% probability of ranking as the best drug for avoiding treatment failure and a 100% probability of ranking the worst (13th best) for hypoglycemia. Rankogram lines without marked peaks (for example for all drug classes as monotherapy and their association with odds of cardiovascular mortality) indicate similar probabilities of all rankings and lower confidence in comparative ranking of the relevant drug class for that outcome. Rankograms showing no data indicate observations were insufficient to generate a rankogram for the drug class for the corresponding outcome. For example, there were insufficient data for meglitinides as triple therapy to infer drug rankings for any outcome. Similarly, there were insufficient data to infer drug rankings for alpha glucosidase inhibitor treatment in triple therapy for the outcome of cardiovascular mortality. The peak of the rankogram curve can be used to assess probabilities of drug classes between best and worst (for example, for treatment failure, SGLT-2 inhibitors and GLP-1 receptor agonists were most likely to be among the best treatments and had similar ranking).

Abbreviations: AGI = alpha glucosidase inhibitor. BASAL = basal insulin. DPP-4-i = dipeptidyl peptidase-4 inhibitor. GLITINIDE = Meglitinide. GLP-1RA = glucagon-like peptide-1 agonist. MET = metformin. PCO = placebo. SGLT-2-i = sodium-glucose linked transporter-2 inhibitor. SU = sulfonylurea. TZD = thiazolidinedione.

Figure 4: Funnel plot for cardiovascular mortality when glucose-lowering drugs were used as monotherapy.



The red line represents the null hypothesis that the study-specific effect sizes do not differ from the respective comparison-specific pooled effect estimates. The two black dashed lines represent a 95% confidence interval for the difference between study-specific effect sizes and comparison-specific summary estimates. yixy is the noted effect size in study i that compares x with y. µxy is the comparison specific summary estimate for x versus y. The treatments are ordered by the surface under the cumulative ranking curve (SUCRA). A=GLITINIDE; B=SGLT-2-I; C=TZD; D=AGI; E=DPP-4-i; F=MET; G=SU; H=PCO; I=BASAL-BOLUS.

A funnel plot is a scatterplot of the study effect size versus some measure of its precision, in this the standard error. A funnel plot which is asymmetrical with respect to the line of the summary effect (vertical red line) implies there are differences between the estimates derived from small and large studies. The studies are ordered from “best” to “worst” according to effects on cardiovascular mortality. Missing (small) studies lying on the right side of the zero line suggest that small studies tend to exaggerate the effectiveness of higher ranked treatments compared to lower ranked treatments. The cause of any small study effects is explored by meta-regression and is not necessarily due to publication bias (the absence of small negative studies in the available literature).

CHAPTER VI: DIETARY INTERVENTIONS FOR ADULTS WITH CHRONIC KIDNEY DISEASE

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Abstract

Background

Dietary changes are routinely recommended in people with chronic kidney disease on the basis of randomised evidence in the general population and non-randomised studies in chronic kidney disease that suggest certain healthy eating patterns may prevent cardiovascular events (CVE) and lower mortality. People who have kidney disease have prioritised dietary modifications as an important treatment uncertainty.

Objectives

This review evaluated the benefits and harms of dietary interventions among adults with CKD including people with end-stage kidney disease (ESKD) treated with dialysis or kidney transplantation.

Search methods

We searched the Cochrane Kidney and Transplant Specialised Register (up to 31 January 2017) through contact with the Information Specialist using search terms relevant to this review. Studies contained in the Specialised Register are identified through search strategies specifically designed for CENTRAL, MEDLINE, and EMBASE; handsearching conference proceedings; and searching the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Selection criteria

Randomised controlled trials (RCTs) or quasi-randomised RCTs of dietary interventions versus other dietary interventions, lifestyle advice, or standard care assessing mortality, cardiovascular events, health-related quality of life, and biochemical, anthropomorphic, and nutritional outcomes among people with CKD.

Data collection and analysis

Two authors independently screened studies for inclusion and extracted data. Results were summarised as risk ratios (RR) for dichotomous outcomes or mean differences (MD) or standardised MD (SMD) for continuous outcomes, with 95% confidence intervals (CI) or in descriptive format when meta-analysis was not possible. Confidence in the evidence was assessed using GRADE.

Main results

We included 17 studies involving 1639 people with CKD. Three studies enrolled 341 people treated with dialysis, four studies enrolled 168 kidney transplant recipients, and 10 studies enrolled 1130 people with CKD stages 1 to 5. Eleven studies (900 people) evaluated dietary counselling with or without lifestyle advice and six evaluated dietary patterns (739 people), including one study (191 people) of a carbohydrate-restricted low-iron, polyphenol enriched diet, two studies (181 people) of increased fruit and vegetable intake, two studies (355 people) of a Mediterranean diet and one study (12 people) of a high protein/low carbohydrate diet. Risks of bias in the included studies were generally high or unclear, lowering confidence in the results. Participants were followed up for a median of 12 months (range 1 to 46.8 months).

Studies were not designed to examine all-cause mortality or cardiovascular events. In very-low quality evidence, dietary interventions had uncertain effects on all-cause mortality or ESKD. In absolute terms, dietary interventions may prevent one person in every 3000 treated for one year avoiding ESKD, although the certainty in this effect was very low. Across all 17 studies, outcome data for cardiovascular events were sparse. Dietary interventions in low quality evidence were associated with a higher health-related quality of life (2 studies, 119 people: MD in SF-36 score 11.46, 95% CI 7.73 to 15.18; I^2 = 0%). Adverse events were generally not reported.

Dietary interventions lowered systolic blood pressure (3 studies, 167 people: MD -9.26 mm Hg, 95% CI -13.48 to -5.04; I^2 = 80%) and diastolic blood pressure (2 studies, 95 people: MD -8.95, 95% CI -10.69 to -7.21; I^2 = 0%) compared to a control diet. Dietary interventions were associated with a higher estimated glomerular filtration rate (eGFR) (5 studies, 219 people: SMD 1.08; 95% CI 0.26 to 1.97; I^2 = 88%) and serum albumin levels (6 studies, 541 people: MD 0.16 g/dL, 95% CI 0.07 to 0.24; I^2 = 26%). A Mediterranean diet lowered serum LDL cholesterol levels (1 study, 40 people: MD -1.00 mmol/L, 95% CI -1.56 to -0.44).

Authors' conclusions

Dietary interventions have uncertain effects on mortality, cardiovascular events and ESKD among people with CKD as these outcomes were rarely measured or reported. Dietary interventions may increase health-related quality of life, eGFR, and serum albumin, and lower blood pressure and serum cholesterol levels.

Based on stakeholder prioritisation of dietary research in the setting of CKD and preliminary evidence of beneficial effects on risks factors for clinical outcomes, large-scale pragmatic RCTs to test the effects of dietary interventions on patient outcomes are required.

Background

Description of the condition

Chronic kidney disease (CKD) is a disorder resulting from structural changes to the kidney (cysts, loss of tissue, or masses) and/or urinary tract leading to changes in the composition of the urine, reduced kidney function or both. The kidney is a target organ injured in diseases primary to the kidney (such as glomerulonephritis or polycystic kidney disease) and secondary diseases (including cardiovascular disease, metabolic syndrome, diabetes (predominantly type 2), obesity, and arterial hypertension). Secondary causes of kidney failure now dominate the global epidemiology of kidney disease - diabetes and hypertension are the leading causes of CKD in middle and higher income countries worldwide, accounting for approximately 35% and 25% of kidney disease (Jha 2013). Kidney tissue in systemic diseases is injured by accelerated vascular damage, glomerular hypertension, and increased cellular glycosylation and oxidation.

Overall, CKD affects an estimated 10% to 15% of people around the world (Chadban 2003; Singh 2009; Zhang 2012) and leads to poorer health outcomes for affected individuals and communities. Among people who have moderate to severe CKD, early death and cardiovascular complications are two to three times more likely than for people without kidney disease and quality of life is reduced (Go 2004; Hemmelgarn 2010; Wyld 2012).

Description of the intervention

Dietary modifications (dietary intake of whole foods rather than single dietary nutrients, such as sodium or protein) may play an important and complex role in the aetiology and progression of CKD, in part through modification of systemic disease processes affecting kidney function (arterial hypertension, tissue glycosylation, glomerular injury, and macrovascular and microvascular diseases) and in part through altering the risks of non-communicable diseases such as diabetes that play such an important role in the prevalence of kidney disease in developed and developing nations. Individual dietary components may influence blood lipid levels, oxidative stress, insulin sensitivity, blood pressure, systemic inflammatory responses, pro fibrotic processes, thrombosis risk, and endothelial function to modify clinical outcomes (Abiemo 2012; Nakayama 1996; Peters 2000; Stamler 1996; van Dijk 2012).

How the intervention might work

While the exact mechanisms through which dietary modifications might act to prolong life expectancy and kidney function are likely to be multifactorial, there is emerging evidence

showing the impact of dietary changes on risk factors for kidney injury and cardiovascular disease. In recent Cochrane reviews of dietary advice in primary and secondary prevention studies - predominantly through reduction of salt and fat intake and increased fruit, vegetables, and fibre intake - dietary changes reduced arterial blood pressure by up to 10 mm Hg on average, as well as serum cholesterol and sodium excretion (Hartley 2013; Rees 2013a; Rees 2013b).

Combined dietary and exercise interventions among people at risk of diabetes, many of whom have kidney disease, reduce weight and body mass and have modest effects on blood lipids and blood pressure, while altered carbohydrate or energy intake plus exercise improves glycaemic control in people with type 2 diabetes (Nield 2008; Orozco 2008). Intensive advice and support to reduce salt intake may have small and unsustained effects on blood pressure (Adler 2014) of uncertain clinical importance. Among people at high cardiovascular risk, a Mediterranean diet increases circulating anti-oxidant levels, which has been proposed as one possible mechanism for improved survival (Zamora-Ros 2013). Whether dietary alteration of risks factors for cardiovascular events including blood pressure, serum lipids, or anti-oxidant levels modify clinical outcomes for people with CKD remains uncertain.

Why it is important to do this review

Although numerous randomised controlled trials (RCTs) in people with CKD have evaluated single nutrient management (such as protein intake or salt intake), there is relatively less information about the impact of whole dietary modifications - for example, the Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) diet - on clinical outcomes in people with CKD. Clinical studies in this area have been largely restricted to modifying protein, sodium, and phosphorus dietary intake as well as antioxidant supplementation (Fouque 2009; Jun 2012; Liu 2015; McMahon 2015). Among people with CKD, lowered dietary salt intake reduced blood pressure and the amount of protein excreted by the kidney (an indicator of cardiovascular risk) (McMahon 2015), although there was no high-quality evidence this translated to slower kidney disease progression or fewer cardiovascular complications. Although dietary interventions in the setting of CKD have commonly focused on protein restriction as a mechanism to slow kidney failure, there is limited evidence that this dietary strategy is effective and safe and the impact of different protein sources on clinical outcomes is poorly understood (Robertson 2007; Fouque 2009).

Global clinical guidelines recommend dietary strategies in the management of CKD (KDIGO 2012). Specifically, guidelines suggest lower protein intake with appropriate education and

avoiding high protein intake for people at risk of kidney disease progression, lower salt intake, and increased physical activity (aiming for at least 30 minutes, 5 times/week). Guidelines recommend that people with CKD receive dietary advice and information in the context of an education program that is tailored to the severity of their CKD and the need to modify salt, phosphate, potassium, and protein intake. Given these guidelines, up to date evidence of the benefits and harms of dietary management is needed to inform practice and policy.

In addition, patients, caregivers and health professionals consider the effects of dietary management as important and a priority treatment uncertainty in CKD (Manns 2014). When speaking about dietary changes, some patients experience dietary restrictions as an intense and unremitting burden (Palmer 2015), while at the same time offering them greater self-efficacy in the management of their CKD. In general, patients value better understanding of the role of lifestyle management as a research priority (Tong 2015). Dietary management is therefore an important potential intervention for improving clinical outcomes in CKD that aligns with patient priorities.

Objectives

This review evaluated the benefits and harms of dietary interventions among adults with chronic kidney disease including people with end-stage kidney disease treated with dialysis or kidney transplantation.

Methods

Criteria for considering studies for this review

Types of studies

We included RCTs and quasi-RCTs (in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth, or other predictable methods) measuring the effect of dietary interventions in adults with CKD.

Types of participants

Inclusion criteria

Adults with any stage of CKD (any structural kidney or urine abnormality with or without reduced glomerular filtration rate below 60 mL/min/1.73 m^2 as defined by the Kidney Disease: Improving Global Outcomes (KDIGO 2012)) including people with end-stage kidney disease treated with dialysis, kidney transplantation or supportive care.

Exclusion criteria

Pregnant women and children younger than 18 years.

Types of interventions

Inclusion criteria

We evaluated the following dietary modifications (including dietary advice or lifestyle management) compared with any other dietary pattern or standard care (including lifestyle advice).

- Dietary patterns (e.g. DASH diet; Mediterranean diet, American Heart Association diet)
- Nutritional counselling and education about food-based dietary interventions

We included studies evaluating interventions for at least one month and studies in which concomitant *non-randomised* interventions such as antihypertensive medication, sodium restriction, or other co-interventions including supplements were used during the study period (e.g. specific blood pressure targets), providing that these interventions were administered to all treatment groups. We included studies of dietary modifications regardless of whether other dietary changes such as salt or phosphorus dietary intake were adjusted. We did not include differing levels of energy intake as interventions in the review.

Exclusion criteria

We excluded dietary interventions that were "single-nutrient" or nutrient-focused interventions (including supplementation). This included the following dietary management interventions.

- Dietary management of specific dietary factors including sodium, phosphorus, and protein (as these are evaluated in other Cochrane reviews (Fouque 2009; Jun 2012; Liu 2015; McMahon 2015))
- Probiotics, prebiotics or synbiotics
- Implementation strategies for dietary or lifestyle management

Types of outcome measures

We categorised outcomes according to length of follow up (< 6 months and ≥ 6 months). We extracted and analysed data for shorter (< 6 months) and longer (≥ 6 months) term outcomes separately.

Primary outcomes

1. All-cause mortality
2. Major adverse cardiovascular events (as defined by study investigators)
3. Health-related quality of life (as defined and measured by investigators)

Secondary outcomes

1. Withdrawal from dietary intervention
2. Cause-specific death (cardiovascular mortality, sudden death, infection-related mortality)
3. Progression to ESKD (as defined by the investigators including estimated glomerular filtration rate below 15 mL/min/1.73 m^2 or requiring treatment with long-term dialysis or kidney transplantation)
4. Participant adherence to intervention
5. Myocardial infarction
6. Kidney function measures (creatinine clearance or estimated glomerular filtration rate, doubling of serum creatinine, serum creatinine)
7. Serum lipids (total cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides)

8. Blood pressure
9. Blood glucose control (glycated haemoglobin; fasting plasma glucose)
10. Global measures of nutritional status (body mass index; body weight; waist circumference; subjective global assessment; malnutrition screening tool; mini nutritional assessment; skin-fold measurements; bioelectrical impedance analysis; albumin; prealbumin)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Kidney and Transplant Specialised Register (up to 12 January 2016) 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.

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 search strategy was used to obtain titles and abstracts of studies that might have been relevant to the review. The titles and abstracts were screened independently by at least two authors (SP and JM), who discarded studies that were not eligible; however, studies and reviews that might have included relevant data or information on studies were retained initially. Two authors (SP and JM) independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria. Any uncertainties about study eligibility were discussed between authors and if necessary with a third author (KC).

Data extraction and management

Data extraction was carried out independently by two authors using pre-specified standard data extraction forms. Studies reported in non-English language journals were electronically translated before assessment. Where more than one publication of one study exists, study reports were grouped together and the publication with the most complete data was used in the analyses. Where relevant outcomes are only published in earlier publications of the study, these data were used. Any discrepancy between published versions were evaluated and highlighted.

Assessment of risk of bias in included studies

The following reporting items were independently assessed by two authors (SP and JM) using the Cochrane risk of bias assessment tool (Higgins 2011):

- 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? These were pre-specified as: baseline imbalance, interim reporting, deviation from study protocol in a way that does not reflect clinical practice, pre-randomisation administration of an intervention that could enhance or diminish the effects of a subsequent randomised intervention, contamination, occurrence of 'null bias' due to interventions being insufficiently well delivered or overly wide inclusion criteria, selective reporting of subgroups, reporting of trial registration, reporting of funding source(s), publication as full journal report, and fraud.

Measures of treatment effect

For dichotomous outcomes (total and cause-specific mortality, myocardial infarction, progression to ESKD, doubling of serum creatinine, participant adherence, withdrawal from intervention), the treatment effects of dietary management were expressed as a risk ratio (RR) together with 95% confidence intervals (CI). Where continuous scales of measurement are used to assess the effects of dietary management (health-related quality of life, blood pressure, lipids (total cholesterol, LDL cholesterol, triglycerides), kidney function (serum creatinine, creatinine clearance, glomerular filtration rate), body composition (weight, waist circumference, body mass index)), the mean difference (MD) between treatment groups were used, or the standardised mean difference (SMD) if different measurement scales have been reported. A standardised mean difference of 0.2 indicated a small difference, 0.5 a moderate difference and 0.8 a large difference. We evaluated mean end of treatment values for continuous outcomes together with the reported standard deviation in meta-analyses for these continuous outcomes.

Unit of analysis issues

Studies with more than two interventions were evaluated in this review. We used recommended methods for data extraction and analysis described by the Cochrane Collaboration (Higgins 2011).

Cross-over studies

There were no cross-over studies included in this meta-analysis.

Studies with more than two interventions

Studies with multiple intervention groups were included. When a study was a 'multi-arm' study, and all treatment arms provided data for eligible interventions, the study was described and included in the systematic review. If there were adequate data from the study, then

treatment arms relevant to the treatment comparisons of interest were included in applicable meta-analyses.

Cluster randomised studies

We planned to include information from cluster randomised studies. We planned to divide the effective sample size for each data point by a quantity called the design effect calculated as 1 + (M - 1) ICC, where M was the average cluster size and ICC was the intra-cluster correlation coefficient. In this calculation, a common design effect was assumed across all intervention groups. The intra-cluster coefficient (ICC) is seldom available in published reports. We therefore planned to adopt a common approach to use external estimates obtained from similar studies. For dichotomous outcomes, we planned to divide the number of participants and the number experiencing the event by the design effect. For continuous endpoints only the sample size was planned to be divided by the design effect with means and standard deviations remaining unchanged.

Dealing with missing data

Any further information required from the original author was requested by electronic mail and any relevant information obtained in this manner was included in the review. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population were carefully performed. Attrition rates, for example drop-outs, losses to follow-up and withdrawals were investigated. Issues of missing data and imputation methods (for example, last-observation-carried-forward) was critically appraised (Higgins 2011).

Assessment of heterogeneity

Statistical heterogeneity in treatment effects among studies was 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). We considered I^2 values of 25%, 50% and 75% as corresponding to low, medium and high levels of heterogeneity.

Assessment of reporting biases

There were insufficient data to generate funnel plots to assess for the potential existence of small study bias for the outcome of all-cause mortality.

Data synthesis

We grouped studies by dietary modifications into similar interventions (e.g. counselling; Mediterranean; fruits and vegetables). Treatment estimates for the specified were

summarised within groups of dietary modifications and treatment effects were summarised using random-effects meta-analysis. Effects were reported as the relative risk (RR) and 95% confidence interval (CI) for binary outcomes and mean difference (MD) and 95% CI for continuous outcomes.

We summarised information for outcomes in which meta-analysis is not possible due to insufficient observations using narrative tables. Narrative outcome reporting included health-related quality of life domains described in the studies and nutrition assessments. The dietary interventions and associated implementation strategies were described using the "Better reporting of interventions: Template for Intervention Description and Replication (TIDieR) checklist and guide" (Hoffmann 2014) and tabulated in the review.

Subgroup analysis and investigation of heterogeneity

There were insufficient extractable data to conduct subgroup and univariate meta-regression analysis to explore the following variables as possible sources of heterogeneity: mean study age, mean proportion of men, energy intake, study-level mean blood pressure or cholesterol at baseline, proportion with diabetes, adequacy of allocation concealment, sample size, and duration of follow up (< 12 months versus ≥ 12 months).

Sensitivity analysis

There were insufficient extractable data to perform the following sensitivity analyses in order to explore the influence of the following factors on effect size:

- Repeating the analysis excluding unpublished studies
- Repeating the analysis taking account of risk of bias, as specified above
- Repeating the analysis excluding any very long or large studies to establish how much they dominated the results
- Repeating the analysis excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), and country.

'Summary of findings' tables

We presented the main results of the review in a 'Summary of findings' table for the outcomes of all-cause mortality, cardiovascular mortality, end-stage kidney disease, and health-related quality of life. 'Summary of findings' 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 (Schunemann 2011a). The 'Summary of findings' tables

also included 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 (Schunemann 2011b).

Results

Description of studies

Results of the search

The electronic search strategy of the Cochrane Kidney and Transplant specialised register on January 11, 2016 identified 824 records (Figure 1). On title and abstract screening, 754 records were excluded (seven were not related to people with chronic kidney disease, 732 did not evaluate a dietary pattern, 10 were not randomised clinical trials, and five were duplicate publications). Seventy records were evaluated in full-text detail. Fifty-eight were excluded (21 were not in people with chronic kidney disease, 33 were not evaluating dietary patterns, three were not randomised clinical trials and one was of short duration (<1 month of follow up).

Included studies

Overall, 17 studies reported in 20 publications involving 1639 people with chronic kidney disease were eligible (Campbell 2008; Chanwikrai 2012; DIRECT 2012; Facchini 2003; Flesher 2011; Goraya 2013; Goraya 2014; Leon 2006; Mekki 2010; Orazio 2011; Riccio 2014; Stachowska 2005; Sutton 2007; Teng 2013; Tzvetanov 2014; Whittier 1985; Zhou 2011b). The study characteristics are summarised in Table 1. Studies were published between 2003 and 2014, with all but five (Facchini 2003; Leon 2006; Stachowska 2005; Sutton 2007; Whittier 1985) of the studies published since 2008.

Three studies involved 341 people treated with long-term dialysis (1 in haemodialysis and 2 in peritoneal dialysis), four studies involved 168 recipients of a kidney transplant, and 10 studies involved 1130 people with chronic kidney disease stages 1 to 5. In the studies involving people with chronic kidney disease, the average estimated glomerular filtration rate ranged between 21.6 and 75 ml/min per 1.73 m^2. Most participants with chronic kidney disease had an estimated GFR below 60 ml/min per 1.73 m^2.The mean study eGFR ranged between 22.8 and 70 ml/min per 1.73 m^2. In people with a kidney transplant, the estimated glomerular filtration rate at baseline in the 2 studies reporting this was between 48 and 54 ml/min per 1.73 m^2 on average. Studies had generally small sample sizes (including a median 73 participants, range 12 to 318 patients). Participants were followed up for between 1 month and 3.9 years (median 12 months).

All studies that reported funding received funding from governmental or healthcare organisations.

One study was conducted in Algeria (Mekki 2010), two in Australia (Campbell 2008; Orazio 2011), one in Canada (Flesher 2011), one in China (Zhou 2011b), one in Israel (DIRECT 2012), one in Italy (Riccio 2014), one in Poland (Stachowska 2005), one in Taiwan (Teng 2013), one in Thailand (Chanwikrai 2012), one in the United Kingdom (Sutton 2007), and six in the United States (Facchini 2003; Goraya 2013; Goraya 2014; Leon 2006; Tzvetanov 2014; Whittier 1985).

The mean age in the included studies ranged between 41 years (Stachowska 2005) and 69.5 years (Campbell 2008). The mean body mass index at baseline ranged between 22.8 and 38.6 kg/m^2(median 28.5 kg/m^2).

Dietary interventions

Dietary interventions included dietary counselling with or without physical activity and lifestyle advice in ten studies (860 patients) (Campbell 2008; Chanwikrai 2012; Flesher 2011; Leon 2006; Orazio 2011; Riccio 2014; Sutton 2007; Teng 2013; Tzvetanov 2014; Zhou 2011b), a Mediterranean diet in three studies (395 patients) (DIRECT 2012; Mekki 2010; Stachowska 2005), increased fruit and vegetable intake in two studies (179 participants) (Goraya 2013; Goraya 2014), and a carbohydrate-restricted, low-iron available, polyphenol enriched (CR-LIPE) diet in one study (191 patients) (Facchini 2003) and a high protein/low carbohydrate diet in one study (Whittier 1985). A high fruit and vegetable intake was compared with oral bicarbonate supplementation in the setting of chronic kidney disease. A Mediterranean diet was compared with a control diet, a low fat diet, or a low carbohydrate diet. In general, dietary modifications tended to include increased intake of fish and poultry, fruit and vegetables, olive oil, and nuts, and lower intake of carbohydrates, red meat, sodium, and sugars.

The aims of the dietary counselling studies were generally to assess whether dietary advice could improve nutritional status and body composition (Campbell 2008; Zhou 2011b), slow progression of chronic kidney disease (Chanwikrai 2012; Flesher 2011) or decrease biochemical derangement in kidney disease (Riccio 2014; Teng 2013). Studies of dietary patterns were primarily aimed at assessing effects of dietary intake on kidney function (DIRECT 2012; Facchini 2003; Goraya 2013; Goraya 2014) or dyslipidaemia (Mekki 2010). Among people treated with dialysis, the interventions were aimed at increasing serum albumin levels (Leon 2006), supporting adjusted energy intake (Sutton 2007) and improving under nutrition (Zhou 2011b). Dietary interventions for transplant recipients aimed to modify cardiovascular risk factors (Orazio 2011; Stachowska 2005), provide lifestyle advice including nutrition guidance (Tzvetanov 2014), or reduce cushingoid side-effects.

Two studies reported three treatment groups. In the DIRECT 2012 study, a calorie restricted Mediterranean diet was compared with a calorie restricted low fat diet or calorie unrestricted low carbohydrate diet. In the Goraya 2014 study, increased fruit and vegetable intake was compared with oral bicarbonate supplementation and standard care.

Excluded studies

The one study which meet our population and intervention criteria was excluded as it was only for a short duration (10 days) (Parillo 1988).

Risk of bias in included studies

Reporting of details of study methodology was incomplete for most studies. The summary risks of bias are shown in Figure 2.

Allocation (selection bias)

Three studies reported adequate (low risk) random sequence generation (Campbell 2008; Leon 2006; Sutton 2007). The risk of bias from random sequence generation methods was unclear in the remaining 14 studies.

Blinding (performance bias and detection bias)

Dues to the nature of the interventions, performance bias was judged as high risk in all 17 studies. Detection bias was judged to be low risk in DIRECT Study 2013 and high in Zhou 2011b. Risk of detection bias was unclear in the remaining 15 studies.

Incomplete outcome data (attrition bias)

Attrition bias was low risk in seven studies (Campbell 2008; Chanwikrai 2012; DIRECT Study 2013; Facchini 2003; Flesher 2011; Teng 2013; Zhou 2011b) and high risk in three studies (Leon 2006; Sutton 2007; Tzvetanov 2014). Risks from attrition bias were unclear in the remaining seven studies.

Selective reporting (reporting bias)

Three studies were at low risk of reporting bias (Campbell 2008; Facchini 2003; Flesher 2011), and the remaining 14 studies were at high risk of reporting bias.

Other potential sources of bias

Eight studies were judged to be at low risk of other potential biases (Campbell 2008; Flesher 2011; Goraya 2013; Goraya 2014; Mekki 2010; Orazio 2011; Teng 2013; Whittier 1985); five studies were judged to be high risk of bias (Chanwikrai 2012; DIRECT Study 2013; Leon 2006;

Riccio 2014; Stachowska 2005), and risks of bias were unclear in four studies (Facchini 2003; Sutton 2007; Tzvetanov 2014; Zhou 2011b).

Effects of interventions

Data for health-related quality of life are shown in Table 2. Adverse event data are reported in Table 3. Adverse events were rarely reported.

Primary outcomes

No included studies were designed to examine effects of dietary interventions on all-cause mortality or major cardiovascular events. The confidence in the results for these outcomes was very low.

All-cause mortality

Five studies (Campbell 2008; Facchini 2003; Flesher 2011; Leon 2006; Sutton 2007) reported the number of deaths. Of these, four studies (Campbell 2008; Flesher 2011; Leon 2006; Sutton 2007) reported deaths as part of the information provided about participant recruitment or attrition from study follow-up which lasted between 12 weeks and 12 months. Dietary counselling had uncertain effects on all-cause mortality (Analysis 1.1.1 (4 studies, 371 participants): RR 1.59, 95% CI 0.60 to 4.21; I^2 = 0%).

In one study comparing a low-iron-available, polyphenol enriched carbohydrate-restricted (CR-LIPE) diet with control over 3.9 years (Facchini 2003), mortality was reported as a patient outcome. A CR-LIPE diet had uncertain effects on all-cause mortality compared with standard care (Analysis 1.1.2 (1 study, 170 participants): RR 0.50, 95% CI 0.22 to 1.12). The confidence in the evidence for all-cause mortality was very low (Summary of findings table 1).

Major adverse cardiovascular events

Campbell 2008 death from cardiovascular causes was described by investigators when reporting study loss to follow-up during the 12 month study. Dietary counselling had very uncertain effects on cardiovascular mortality (Analysis 1.2.1 (1 study, 62 participants): RR 6.58, 95% CI 0.35 to 122.21). The confidence in the evidence for cardiovascular events was very low (Summary of findings table 1).

Health-related quality of life

Only six studies included quality of life measures (Table 3). Of these, four studies used the Kidney Disease Quality of Life questionnaire and/or the Short Form-36 (Campbell 2008; Leon 2006; Tzvetanov 2014; Zhou 2011b). In two studies (Tzvetanov 2014; Zhou 2011b), dietary

counselling was associated with a higher score on the SF-36 questionnaire than standard care (Analysis 1.3.1 (2 studies, 119 participants): MD 11.46, 95% CI 7.73 to 15.18; I^2 = 0%). The confidence in the evidence for health-related quality of life was low (Summary of findings table 1).

Secondary outcomes

End-stage kidney disease

No included studies were designed to examine ESKD or risks of doubling of serum creatinine. The confidence in the results for ESKD was very low. Two studies reported the number of participants experiencing ESKD (Campbell 2008; Facchini 2003). In one of these studies comparing dietary counselling with standard care, the number of people starting dialysis was reported as part of participant progression in the 12-week study (Campbell 2008). In one study, a CR-LIPE diet had uncertain effects on ESKD compared with standard care. In the two studies combined, dietary interventions did not have statistically significant effect on risks of ESKD ((Analysis 1.4 (2 studies, 232 participants): RR 0.53, 95% CI 0.26 to 1.07; I^2 = 0%). The confidence in the evidence for ESKD was very low (Summary of findings table 1).

Doubling of serum creatinine

Facchini 2003 reported that a CR-LIPE diet was associated with lower risks of doubling of serum creatinine ((Analysis 1.5 (1 study, 170 participants): RR 0.53, 95% CI 0.33 to 0.86).

Employment

Dietary counselling had uncertain effects on employment during a single 12 month study involving recipients of a kidney transplant (Analysis 1.6 (1 study, 17 participants): RR 6.22, 95% CI 0.96 to 40.22).

Dietary adherence

Dietary counselling had uncertain effects on dietary adherence compared with standard care, in a single study (Analysis 1.7 (1 study 54 participants): RR 1.58, 95% CI 0.97 to 2.58).

Worsening nutrition

In two studies, the proportion of participants with worsening nutritional status was measured using subjective global assessment (SGA) (Campbell 2008; Leon 2006). Compared with usual care, dietary counselling had uncertain effects on nutritional status as measured by SGA (Analysis 1.8.1 (2 studies, 230 participants): RR 0.40, 95% CI 0.05 to 3.37; I^2 = 57%).

Kidney function

eGFR

Dietary intervention was associated with a higher eGFR (Analysis 1.9 (5 studies, 219 participants): SMD 1.08; 95% CI 0.20 to 1.97; I^2 = 88%) than standard care, although there was very marked heterogeneity in treatment effects between the four studies evaluating dietary counselling and this may have been due to the different strategies used in participant counselling.

Fruits and vegetables had uncertain effects on the eGFR compared with oral bicarbonate supplementation (Analysis 3.1 (2 studies, 143 participants); MD 0.84 mL/min/1.73 m^2, 95% CI -0.84 to 2.53; I^2 = 0%).

Serum creatinine

Dietary interventions had uncertain effects on serum creatinine when compared to control (Analysis 1.10 (3 studies 112 participants): MD 0.83 µmol/L, 95% CI -16.57 to 18.23; I^2 = 0%).

In Goraya 2013, fruits and vegetables had very uncertain effects on serum creatinine compared with oral bicarbonate supplementation (Analysis 3.2 (1 study, 71 participants): MD -9.00 µmol/L, 95% CI -39.11 to 21.11).

Blood pressure

Systolic blood pressure

Dietary interventions lowered systolic blood pressure compared with standard care (Analysis 1.11 (3 studies, 167 participants): MD -9.26 mm Hg, 95% CI -13.48 to -5.04; I^2 = 80%). There was heterogeneity in the effects between the two different dietary approaches (I^2=88.7%).

Fruits and vegetables lowered systolic blood pressure compared to oral bicarbonate supplementation (Analysis 3.3 (2 studies, 143 participants): MD -5.81 mm Hg, 95% CI -8.84 to -2.77) although there was high heterogeneity between studies (I^2 = 79%).

Diastolic blood pressure

Dietary counselling lowered diastolic blood pressure compared with standard care (Analysis 1.12 (2 studies, 95 participants): MD -8.95 mm Hg, 95% CI -10.69 to -7.21; I^2 = 0%)

Energy intake

Different dietary interventions had statistically heterogeneous effects on energy intake and therefore the results of all available dietary approaches compared with standard care were not combined within a single analysis.

Dietary counselling had uncertain effects on energy intake compared to standard care (Analysis 1.13.1 (4 studies, 340 participants); SMD 1.54, 95% CI -0.87 to 3.95). There was very high heterogeneity in this analysis (I^2 = 99%) likely due to the differing counselling approaches in the included studies.

A Mediterranean diet was associated with higher energy intake than standard care in Mekki 2010 (Analysis 1.13.2 (1 study, 40 participants): SMD 1.86, 95% CI 1.11-2.61).

A high nitrogen and low carbohydrate diet had uncertain effects on energy intake in Whittier 1985 (Analysis 1.13 (1 study, 12 participants): SMD -0.65, 95% CI -1.82 to 0.53).

Body weight, body mass index, waist circumference, waist-to-hip ratio and arm circumference

Body weight

Dietary interventions had uncertain effects on body weight compared with control (Analysis 1.14 (6 studies, 454 participants): MD -0.44 kg, 95% CI -1.46 to 0.58; I2 = 15%).

A higher fruit and vegetable intake was associated with a lower body weight than oral bicarbonate supplementation (Analysis 3.4 (2 studies, 143 participants):; MD -5.09 kg, 95% CI -7.73 to -2.44; I2 = 56%).

BMI

Dietary interventions had uncertain effects on BMI compared with control (Analysis 1.15 (2 studies, 119 participants): MD -1.70 kg/m2, 95% CI -5.23 to 1.82; I2 = 14%).

Waist-to-hip ratio, waist circumference, and arm circumference

In Orazio 2011, dietary interventions had uncertain effects on waist-to-hip ratio compared with control (Analysis 1.16 (1 study, 82 participants): MD -1.05, 95% CI -5.92 to 3.82). In the same study, dietary interventions had uncertain effects on the waist circumference (Analysis 1.17 (1 study, 82 participants): MD -0.46 cm, 95% CI -2.05 to 1.13).

Dietary interventions had uncertain effects on arm circumference compared with control (Analysis 1.18 (2 studies, 149 participants): MD 0.37 cm, 95% CI -0.39 to 1.12; I2 = 0%).

Serum albumin

Dietary interventions increased serum albumin levels compared with control (Analysis 1.19 (6 studies, 541 participants): MD 0.16 g/dL, 95% CI 0.07 to 0.24; I2 = 26%).

Serum low density lipoprotein cholesterol

In Mekki 2010, a Mediterranean diet lowered serum LDL cholesterol levels compared with a control diet (Analysis 1.20.1 (1 study, 40 participants): MD -1.00 mmol/L, 95% CI -1.56 to -0.44).

In Facchini 2003, a CR-LIPE diet had uncertain effects on serum LDL cholesterol levels compared with a control diet (Analysis 1.20.2 (1 study, 148 participants): MD 0.21 mmol/L, 95% CI -0.38 to 0.81).

In Stachowska 2005, a Mediterranean diet lowered serum LDL cholesterol levels compared with a low fat diet (Analysis 2.1 (1 study, 38 participants): MD -0.60 mmol/L, 95% CI -1.15 to -0.05).

Investigation of publication bias, sub-group analyses and sensitivity analyses

Investigation of publication bias, sub-group analyses and sensitivity analyses were not possible due to a lack of data observations. In particular there were insufficient data observations to test whether effects of dietary interventions were modified by stage of kidney disease.

Discussion

Summary of main results

This review summarises 17 studies of dietary interventions involving 1639 people with CKD that took place in a wide variety of global regions and health systems. Dietary interventions were evaluated for a median of 12 months. Dietary interventions were counselling, or a dietary pattern (Mediterranean; low fat; low carbohydrate; high fruit and vegetable; carbohydrate-restricted, low-iron available, polyphenol-enriched; low carbohydrate-high nitrogen) compared with standard care, low protein intake, low fat or low carbohydrate intake, or oral bicarbonate supplementation. The studies included people with stages 1-5 CKD, kidney transplant recipients, and people with ESKD requiring dialysis. There was considerable heterogeneity in dietary interventions and their implementation, together with differences in tailoring of dietary management to individual requirements and methods to support adherence. Risks of bias in the included studies were often high or unclear, and these risks combined with imprecision in effect estimates led to low or very low confidence in the results.

Studies were not designed to assess dietary effects on risks of death or cardiovascular events. As a result there was considerable uncertainty about the effects of dietary approaches on these outcomes including risks of myocardial infarction or stroke. This finding is particularly relevant as many people with CKD will die from cardiovascular causes before requiring treatment with dialysis or kidney transplantation.

Dietary effects on health-related quality of life were infrequently reported and were documented using different tools, limiting the ability of studies to be combined. In low quality evidence, dietary interventions may have clinically-important increases in the SF-36 quality of life score. There was evidence that dietary modification impacted risks of ESKD, although dietary interventions may increase GFR compared with standard care. Dietary interventions lowered systolic and diastolic blood pressure by nearly 10 mm Hg on average and increased serum albumin levels.

Overall, these data suggest that current evidence for dietary interventions in the setting of CKD is of very low quality and insufficient to guide clinical practice. Possible beneficial effects of dietary modifications on risk factors for disease in this review, the association of healthy eating patterns with lower mortality in non-randomised studies (Chen 2016; Gutierrez 2014; Muntner 2013), and the priority placed on dietary restrictions in research (Tong 2015a) suggest dietary interventions remain an important research and clinical uncertainty in the setting of kidney disease.

Overall completeness and applicability of evidence

The strengths of this review comprehensive systematic searching for eligible studies, rigid inclusion criteria for RCTs, and data extraction and analysis by two independent investigators. We aimed to evaluate the effectiveness of dietary modification for range of food groups for people with CKD. This review included a small number of studies with heterogeneous interventions and implementation strategies. We could not robustly assess the effect of dietary pattern on endpoints such as mortality or cardiovascular events in people with CKD as there were few studies of sufficient size or duration to examine these outcomes. Despite preliminary evidence for improved blood pressure and serum cholesterol with some dietary patterns, evidence for the longer-term effects of dietary pattern on patient-level outcomes remains to be determined. There was a lack of consistency in estimating health-related quality of life among the available studies. Given the patients report dietary requirements and restrictions as a sometimes intense burden (Palmer 2015a), this aspect of dietary interventions remains important for future exploration. Reporting of health-related quality of life using tools validated for CKD would be helpful in future research studies.

Quality of the evidence

We assessed the quality of study evidence using standard risks of bias domains within the Cochrane tool together with GRADE methodology. Confidence in evidence for all-cause mortality, major cardiovascular events and health-related quality of life was very low or could not be estimated, meaning future studies might offer different results. No study had low risk methods for allocation concealment and none of the participants or study investigators was masked to treatment allocation. We downgraded for the possibility of publication bias due to the very low numbers of data observations for each outcome, precluding formal testing.

Data summary was also difficult due to the variable methods of reporting in the individual studies. Particularly relevant was the heterogeneous manner of reporting GFR and serum creatinine concentrations. Some studies did not report an estimate of variance (SE or SD) and some provided data in descriptive or figure format only.

Potential biases in the review process

Potential biases in this review relate to the data availability in the individual studies. First, there was heterogeneity in treatment interventions and comparisons; due to the small number of data observations, robust statistical estimates of heterogeneity could not be estimated. Second, we could not assess for potential reporting bias due to the small number of studies in the review. Third, while most participants had moderate CKD (stage 3 or 4), there was wide

variation in the definition of kidney disease for inclusion in eligible studies. Fourth, studies were frequently at high risks of bias, but poorer quality studies could not be excluded from sensitivity analyses due to the limited number of data observations. Fifth, the treatment endpoints were principally surrogate markers of health (blood pressure, serum cholesterol, serum albumin) and the effects of dietary interventions on longer term outcomes remains uncertain. Sixth, adverse event reporting in the available studies was infrequent and inconsistent. Finally, selective outcome reporting was a limitation across the included studies.

Agreements and disagreements with other studies or reviews

A recently published Cochrane review (McMahon 2015) evaluated salt restriction among patients with CKD. While the intervention decreased blood pressure, as in this review there were insufficient data available to assess the impact of salt restriction on all-cause mortality or cardiovascular mortality. Similarly, in a Cochrane review of dietary interventions for mineral and bone disorder in CKD, there was low quality evidence that calcium enriched bread might influence biochemical parameters, and data were insufficient to identify treatment effects on clinical outcomes including cardiovascular mortality and fracture (Liu 2015). In a Cochrane review of low protein diets among people with CKD, a delay in progression of CKD was observed with a low protein intake (Fouque 2009). A recent meta-analysis of eight non-randomised of eating patterns among 15,285 people with CKD, healthy eating was associated with lower risks of all-cause mortality (RR 0.73, 95% CI 0.63 to 0.83), but no effect on ESKD was detected (personal communication). The possible reasons for differences between the findings of that review and the present meta-analysis could include the non-randomised nature of the data, with the possibility of residual confounding accounting for the results, or a larger sample size providing greater statistical power to observe differences between treatment groups. A non-randomised study conducted in the general population reported a dietary pattern rich in whole grains, fruit, and low-fat dairy foods was associated with lower urinary albumin to creatinine ratio (Nettleton 2008). Albumin to creatinine ratio is used as a proxy marker for possibility of development of kidney disease in the general population and is also suggestive of increased risk of cardiovascular disease in patients with diabetes and hypertension. The finding that a study in this review showing a diet pattern with lower red meat and carbohydrates and higher olive oil content was associated with lower risks of kidney failure suggests larger studies evaluating dietary patterns on progression of CKD are clinically relevant.

Authors' conclusions

Implications for practice

Overall, these data suggest that current evidence for dietary interventions in the setting of CKD is of very low quality and insufficient to guide clinical practice. Possible beneficial effects of dietary interventions include clinically-important increases in health-related quality of life, lower blood pressure and serum LDL cholesterol levels and higher kidney function and serum albumin levels. These preliminary findings represent potential mechanisms for benefit of dietary modifications in larger studies, but the longer term impact of dietary changes need to be examined.

Due to variation in dietary implementation and content, the range of clinical settings in the studies, and the lack of evidence for clinical outcomes, specific dietary recommendations or counselling cannot be currently recommended in the care of CKD or people treated with dialysis or a kidney transplant. As patients report dietary changes to be frequently confronting and intrusive and challenging to implement, patient input into future study design could strengthen the quality and acceptability of tested interventions. Not all areas of the world have health systems where dietitians are able to provide patient-centred care or patients have access to food types used in the studies in this review, and food availability and health service funding might be important barriers to future clinical studies.

Implications for research

Questions remain about the impact of dietary patterns on long-term clinical outcomes in the setting of CKD. Dietary restrictions are a priority uncertainty in CKD for patients and clinicians. This review highlights potential intermediary mechanisms (lowering blood pressure or serum cholesterol) through which dietary counselling or specific dietary patterns might act to benefit long-term health outcomes among people with CKD.

Given existing non-randomised studies suggest benefits of healthy, plant-based dietary patterns on lowering mortality in CKD (Chen 2016; Gutierrez 2014), and large RCTs show the Mediterranean diet lowers cardiovascular complications among people at risk of cardiovascular disease (Estruch 2013), further research is needed to evaluate the impact of dietary patterns on hard clinical outcomes including mortality and cardiovascular endpoints in CKD. Qualitative data are available about the impact of dietary restrictions on patient well-being (Palmer 2015a) that might be considered when designing dietary strategies and their implementation. Given that existing studies have generally small sample sizes and insufficient power to determine effects on mortality and cardiovascular events, consideration of a

pragmatic study design to ensure efficient participant recruitment, such as a registry-trial design, might assist with study feasibility and cost.

Future research should pay specific attention to outcomes that have been relatively under-researched, but are important causes of significant morbidity. Due to the considerably higher risk of death and cardiovascular events compared to ESKD, future studies should be powered to assess dietary effects on these outcomes. We plan to add these to the review outcomes in future review updates if they become available. There were no studies incorporating economic analyses; we suggest future studies should include analyses of the relative costs and benefits of dietary management. Dietary studies involving participants in resource-constrained settings should be considered.

Given the variation in outcome measures routinely collected and reported in nephrology studies including studies in the present review, a core (minimum) data set, such as that being generated by the SONG collaboration (Tong 2015b), together with a validated measure of health-related quality of life would facilitate development of clinically-relevant studies and useful meta-analyses of dietary interventions.

Future studies in this area would benefit from drawing on a framework for studies of complex interventions, which explicitly requires theoretical modelling between processes and outcomes in the pre-trial stage, and a process evaluation of the study (Anderson 2008). All studies should provide greater description of intervention and standard models of care being assessed (Hoffmann 2014) and include process evaluations of how they are being implemented (Moore 2014), using reporting guidelines for complex interventions.

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Table 1. Summary of included studies

Study ID	Treatment	Control	CKD stage	GFR (mL/min)	Mean age	% men	Mean GFR (mL/min)	Mean BMI (kg/m^2)	Detailed inclusion criteria
					Counselling				
Campbell 2008	Dietary counselling	Written material	4-5	≤ 30	69.5 (11.7) 70.9 (11.6)	61	23.1 (7.2) 21.6 (6.1)	26.8 (4.7) 27.6 (5.2)	> 18 years; eGFR < 30 mL/min/1.73 m^2; CKD not previously seen by a dietitian for stage 4 CKD; absence of communication or intellectual impairment; absence of malnutrition from a cause other than CKD; not expected to require RRT within 6 months
Chanwikrai 2012	Dietary counselling	Standard care	3-5	--	--	--	--	--	CKD stage 3-5
Flesher 2011	Dietary counselling + exercise	Standard care	3-4	20-60	63.4 (12.1) 63.4 (11.8)	53	37.2 (3.2) 38.4 (3.0)	--	eGFR 20 to 60 mL/min for ≥3 months; presence of urinary protein; adult (≥ 19 years); hypertension or taking at least 1 antihypertensive medication; physician approval to exercise
Leon 2006	Dietary counselling and targeting nutritional barriers	Standard care	5 (HD)	Dialysis	62 60	42	--	29.0 27.9	18 to 85 years; receiving dialysis for at least 9 months; mean serum albumin level for previous 3 months < 3.70 g/dL (bromcresol green method) or < 3.40 g/dL (bromcresol purple method)
Orazio 2011	Dietary counselling	Standard care	Transplant	Transplant	54.9 (9.9) 54.7 (11.8)	61	54 (20) 48 (17)	29 (5) 29 (6)	Kidney transplant > 6 months
Riccio 2014	Dietary counselling	Low protein diet	--	--	--	--	--	--	CKD not requiring dialysis

Sutton 2007	Dietary counselling + physical activity	Standard care	5 (PD)	Dialysis	60.7 (15.5) 58.5 (15.4)	55	--	25.4 (3.8) 25.7 (3.4)	Treatment with CAPD for 3 months or longer; not diabetic
Teng 2013	Dietary counselling + exercise	Standard care	1-3	--	62.1 (14.0) 65.7 (11.2)	71	53.7 (18.3) 49.5 (13.3)	24.4 (3.9) 25.3 (3.1)	20 years or older; communicate in Mandarin or Taiwanese; aware of CKD diagnosis; GFR range 30 to 106.7 mL/min/1.73 m^2
Tzvetanov 2014	Dietary counselling + exercise	Standard care	Transplant	Transplant	46 (6.9) 45 (19)	47	--	--	Kidney transplant; obese
Zhou 2011b	Dietary counselling	Standard care	5 (PD)	Dialysis	57.8 (12.8) 59.9 (13.6)	71	--	23.3 (4.5) 22.8 (6.2)	18 to 70 years; receiving long-term dialysis > 3 months
Mediterranean diet									
DIRECT Study 2013	Mediterranean diet (restricted calorie)	Low-fat (restricted calorie) diet Low-carbohydrate (unrestricted calorie) diet	3	30-60	52.5 (6.2)	99	52.6 (5.9)	30.9 (3.4)	40 to 65 years with BMI ≥ 27 kg/m^2; individuals with type 2 diabetes or coronary heart disease were eligible regardless of age. Post-hoc analysis among participants with eGFR 30 to 60 mL/min/1.73 m^2
Mekki 2010	Mediterranean diet	Standard care	2-3	60-89	60 (10) 59 (12)	53	70 (10) 75 (15)	26.9 (3.9) 25.1 (4.2)	eGFR 60 to 89 mL/min/1.73 m^2; dyslipidaemia
Stachowska 2005	Modified Mediterranean diet	Low fat diet	Transplant	Transplant	41 (12.5) 46 (9.5)	68	--	25.0 (4.1) 26.2 (4.2)	Stable transplant function
Increased fruit and vegetables									
Goraya 2013	Increased fruit and vegetable intake	Oral bicarbonate	4	15-29	53.9 (6.9) 54.2 (5.3)	54	22.8 (4.9) 23.0 (3.5)	--	Non-malignant hypertension; eGFR 15 to 29 mL/min/1.73 m^2; plasma TCO_2< 22 mM; no diabetes or cardiovascular disease; two or more

									primary care physician visits in previous year; age ≥ 18 years
Goraya 2014	Increased fruit and vegetable intake	Oral bicarbonate Standard care	3	30-59	53.5 (5.2) 53.9 (4.8)	44	42.3 (7.1) 42.6 (7.6)	--	Non-malignant hypertension, eGFR 30 to 59 mL/min/1.73 m^2; plasma TCO_2< 25 mM; macroalbuminuria; able to tolerate angiotensin-converting inhibition; non-smoking for ≥ 1 year; no diabetes or cardiovascular disease; 2 or more primary care physician visits in previous year; ≥ 18 years
Carbohydrate-restricted, low-iron, polyphenol enriched (CR-LIPE) diet									
Facchini 2003	CR-LIPE diet	Protein restriction	2-5	15-75	59 (10) 60 (12)	51	64 (28) 62 (32)	28 (5) 28 (5)	Type 2 diabetes; referred to nephrology clinic for kidney failure (15 ± 75 mL/min); otherwise unexplained proteinuria (350 ± 12,000 mg/d); kidney disease attributed to diabetes
High-nitrogen, low-carbohydrate diet									
Whittier 1985	High-nitrogen, low carbohydrate diet	Standard care	Transplant	Transplant	33 32	75	--	--	Kidney transplant; no diabetes

Table 3. Narrative description of health-related quality of life outcomes

Study ID	Tool	Description
		Dietary counselling
Campbell 2008	Kidney Disease Quality of Life Short Form Version 1.3 (combining the SF-36 with a kidney-disease specific module)	"There was a clear trend for a mean increase in ratings from the intervention group with a clinically significant mean improvement in 13 of the 18 sub-scales from baseline to week 12, indicated by an effect size of 0.2 or greater...". There was a statistically significant difference in mean change for scores of symptoms of kidney disease (7.1 (0.1-14.1) P = 0.047); cognitive functioning (14.6 (5.4-23.7) P = 0.003); and vitality (12.0 (4.6-19.5) P = 0.002) in favour of the intervention."
Chanwikrai 2012	--	Not reported
Flesher 2011	Self-Management Questionnaire	"Overall, the experimental group showed 'improvement' in exercise frequency, concern over health condition, and frequency of visits to health providers or hospitalisation. Overall the control group answers indicated an improvement in their communication with health providers in asking question and discussing personal issues."
Leon 2006	Kidney Disease Quality of Life questionnaire (combining the SF-36 with a kidney-disease specific module)	"There were no differences between intervention and control patients in quality-of-life subscales, including general health, physical functioning, emotional well-being, social function, pain, and dialysis-related symptoms."
Orazio 2011	--	Not reported
Riccio 2014	--	Not reported
Sutton 2007	--	Not reported
Teng 2013	52-item HPLP-IIC questionnaire	Intervention had a significant effect on health responsibility and physical activity, but not stress management, interpersonal relations, spiritual growth or nutrition
Tzvetanov 2014	SF-36	"The mean SF-36 score at 6 months was significantly higher in the intervention group compared with the control group (583±13 vs 436±22, P = 0.008), reflecting an improved perception of health status. ... The intervention group had improvements compared with the control group in the domains of vitality and general health."

Zhou 2011b	Kidney Disease Quality of Life Short Form Version 1.3 (combining the SF-36 with a kidney-disease specific module)	"Prior to intervention, the differences in KDTA and SF-36 scores were not statistically significant in both groups (P >0.05 for all). After intervention, both KDTA and SF-36 scores were improved in the study group, but decreased in the control group. The difference in KDTA (P = 0.001) and SF-36 scores (P = 0.001) before and after intervention were statistically significant in both groups (Table 2)."
	Mediterranean diet	
DIRECT Study 2013	--	Not reported
Mekki 2010	--	Not reported
Stachowska 2005	--	Not reported
	Increased fruit and vegetables	
Goraya 2013	--	Not reported
Goraya 2014	--	Not reported
	Carbohydrate-restricted, low-iron-available, polyphenol-enriched diet	
Facchini 2003	--	Not reported
	High-protein, low carbohydrate diet	
Whittier 1985	--	Not reported

Table 2. Adverse events

Study	Adverse events reported in study
Campbell 2008	Mortality; need for dialysis.
Chanwikrai 2012	None reported
DIRECT 2012	None reported
Facchini 2003	None reported
Flesher 2011	None reported
Goraya 2013	No participants meeting eGFR and plasma potassium criteria developed plasma potassium concentration >5.0 mEq/L.
Goraya 2014	None reported
Leon 2006	None reported
Mekki 2010	None reported
Orazio 2011	None reported
Riccio 2014	None reported
Stachowska 2005	None reported
Sutton 2007	Mortality; transfer from peritoneal dialysis to haemodialysis.
Teng 2013	None reported
Tzvetanov 2014	None reported
Whittier 1985	Dialysis due to elevated blood urea and potassium concentrations.
Zhou 2011b	None reported

Summary of findings table - Dietary intervention versus control

Dietary modifications (counselling or dietary change) compared with control for chronic kidney disease

Patient or population: People with chronic kidney disease
Intervention: Dietary modifications
Comparison: Control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk Standard care	Corresponding risk Dietary intervention				
Death	**High risk population**		Not estimable	539 (5 studies)	+- - - very low[1,2,3]	Studies were not designed to measure effects of dietary interventions on mortality.
	150 per 1000	Not estimable				
	Medium risk population					
	25 per 1000	Not estimable				
Major cardiovascular event	**High risk population**		Not estimable	Insufficient data observations	No studies were available for this outcome.	Studies were not designed to measure effects of dietary interventions on cardiovascular events. 0 studies reported major cardiovascular events.
	150 per 1000	Not estimable				
	Medium risk population					
	45 per 1000	Not estimable				
Progression to end-stage kidney disease Measured as requiring dialysis treatment in people with chronic kidney disease	0.6 per 1000	0.3 per 1000	RR 0.53 (0.26 to 1.07)	242 (2 studies)	+- - - very low[1,2,3,4]	29 participants developed end-stage kidney disease in these studies. 0 studies included recipients of a kidney transplant.
Health related quality of life Health-related quality of life measured using the Short Form-36 scale from 0 to 100.	The mean SF-36 score ranged across control groups from 43.6 to 48.8.	The mean SF-36 score in the intervention groups was 11.46 higher (95% CI 7.73 to 15.18)		119 (2 studies)	++- - low[1,3]	0 studies included recipients of a kidney transplant. None of the studies were blinded.

*The basis for the assumed risk of mortality (e.g. the median control group risk across studies) was obtained from the absolute population risk estimated from previously published cohort studies or data registries (Johnson 2011; Weiner 2006). The corresponding risk (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 quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Footnotes

1 Study limitations were due to high or unclear risks of bias

2 Confidence interval includes range of plausible values that include substantial benefit or harm

3 Based on few events and/or participants across all studies

4 Data not available for recipients of a kidney transplant

Figure 1. Flow diagram of study selection

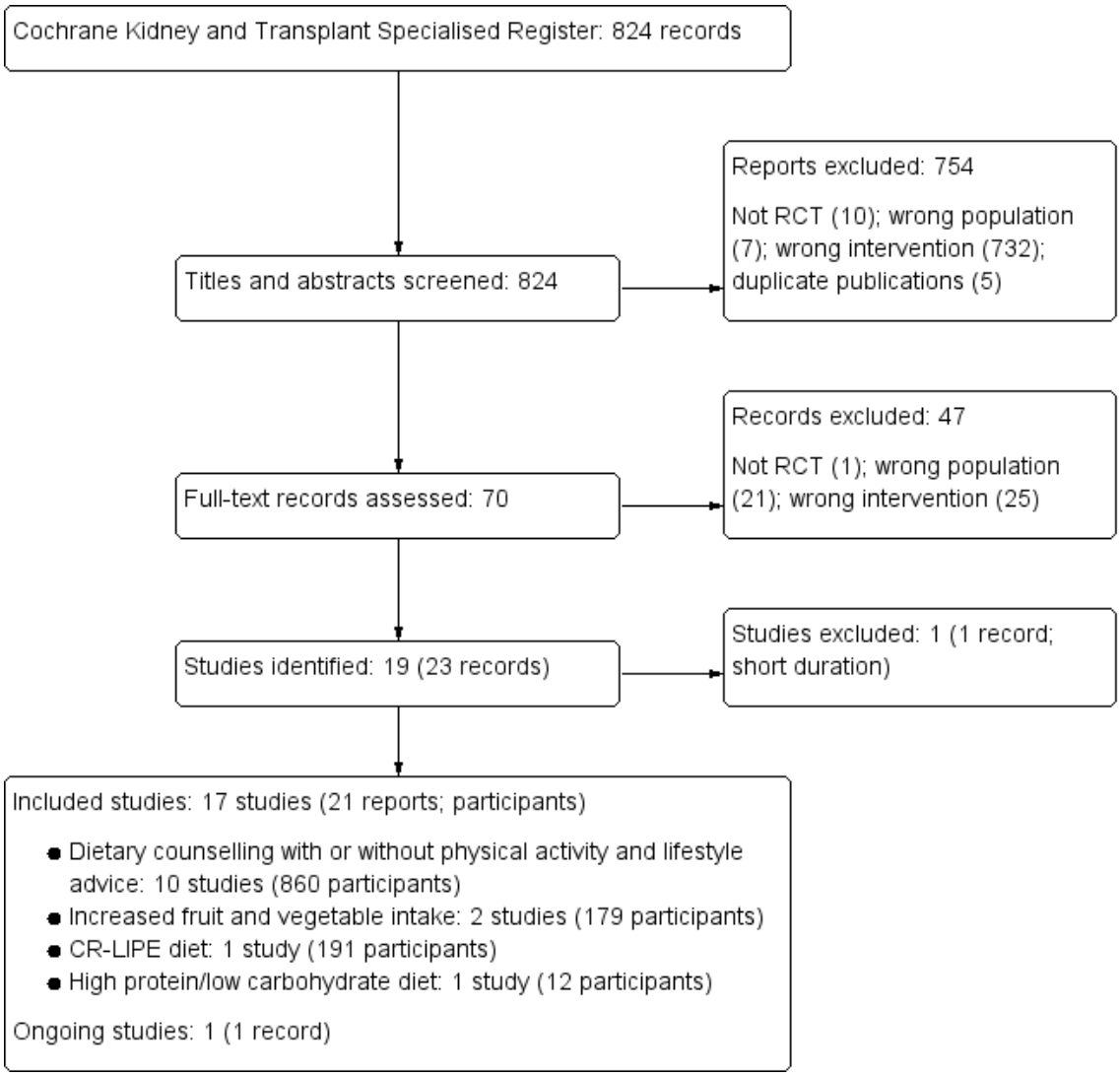
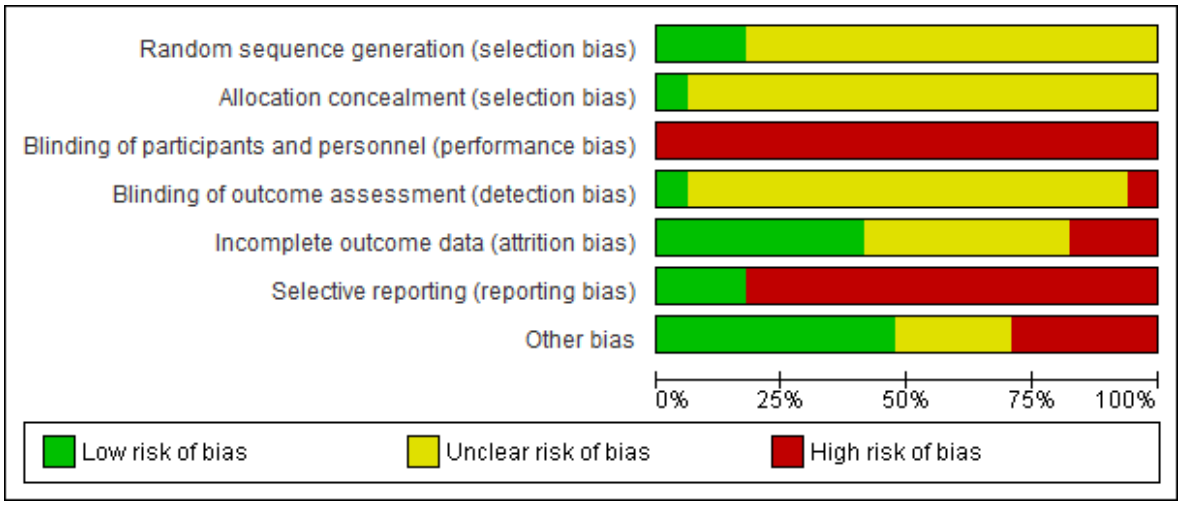
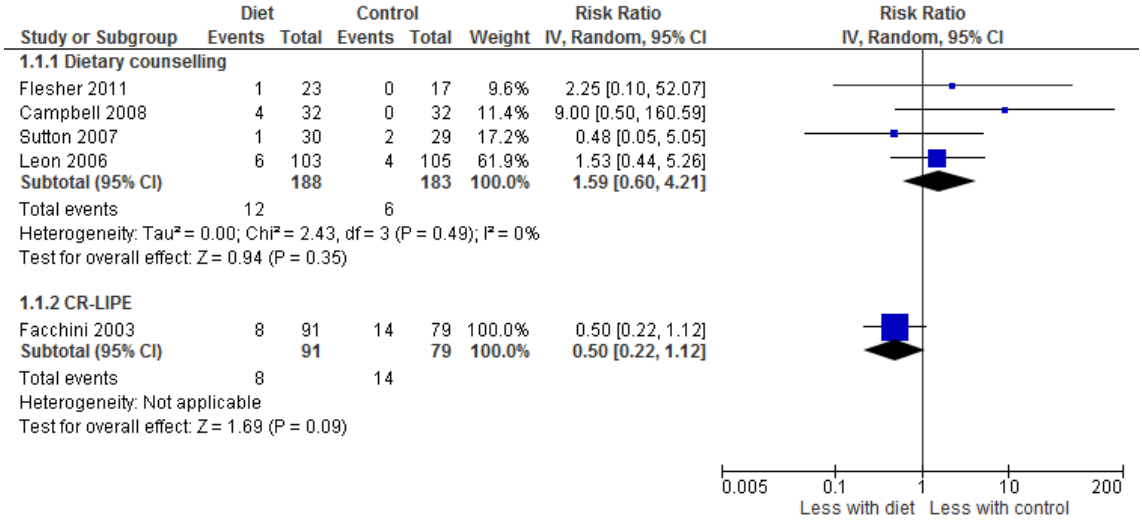


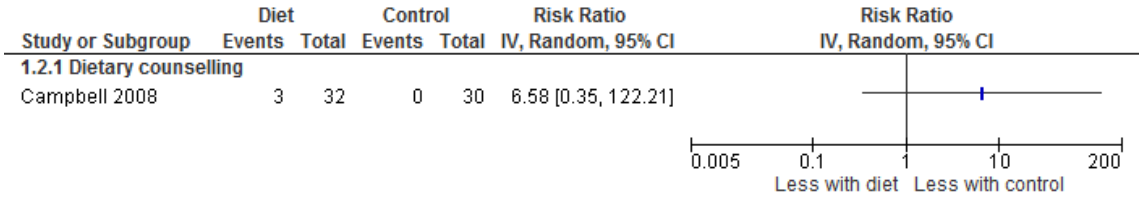
Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



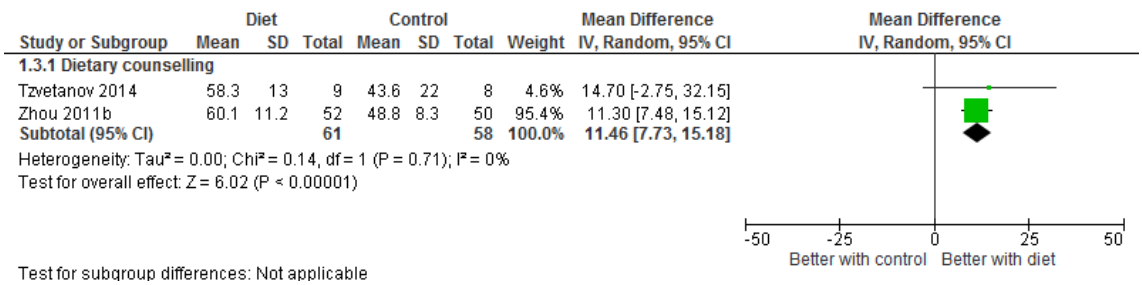
Analysis 1.1 Forest plot of comparison: Dietary intervention versus control, outcome: All-cause mortality



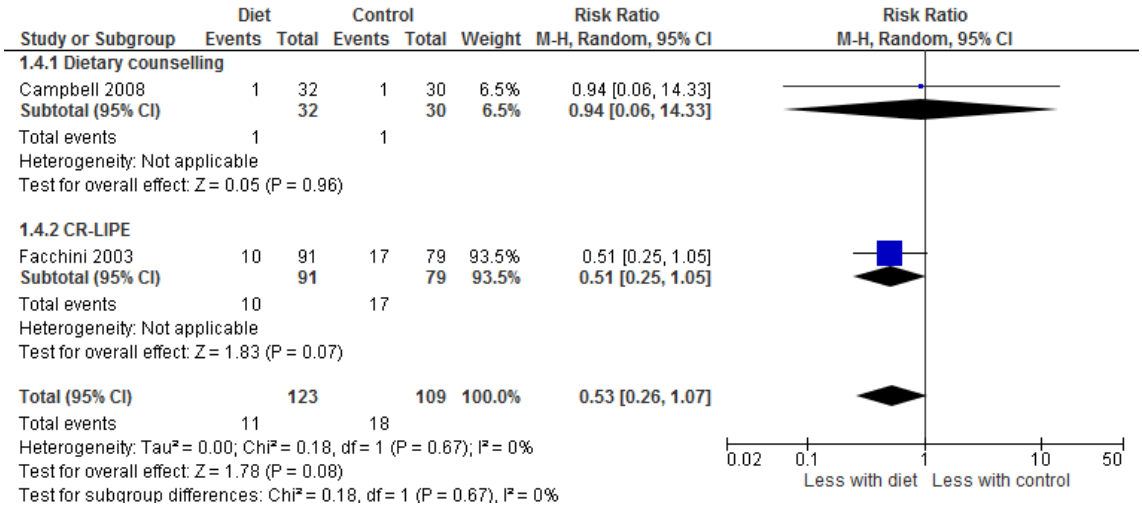
Analysis 1.2 Forest plot of comparison: Dietary intervention versus control, outcome: Cardiovascular mortality



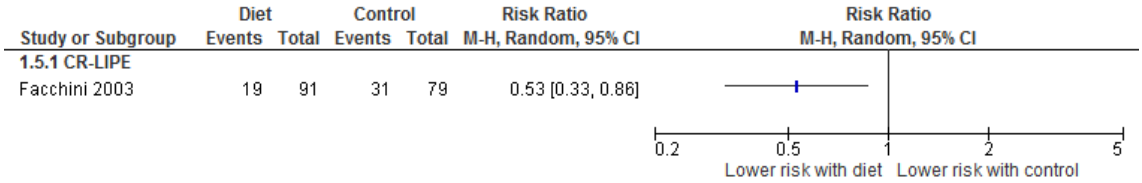
Analysis 1.3 Forest plot of comparison: Dietary intervention versus control, outcome: Health-related quality of life (SF-36) score



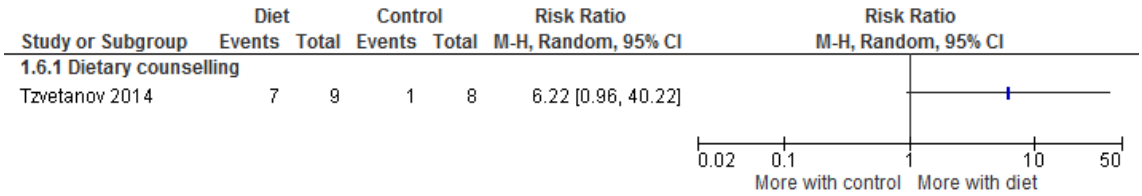
Analysis 1.4 Forest plot of comparison: Dietary intervention versus control, outcome: ESKD



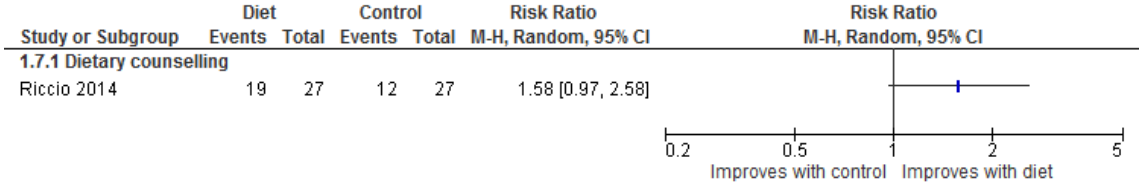
Analysis 1.5 Forest plot of comparison: Dietary intervention versus control, outcome: Doubling of serum creatinine



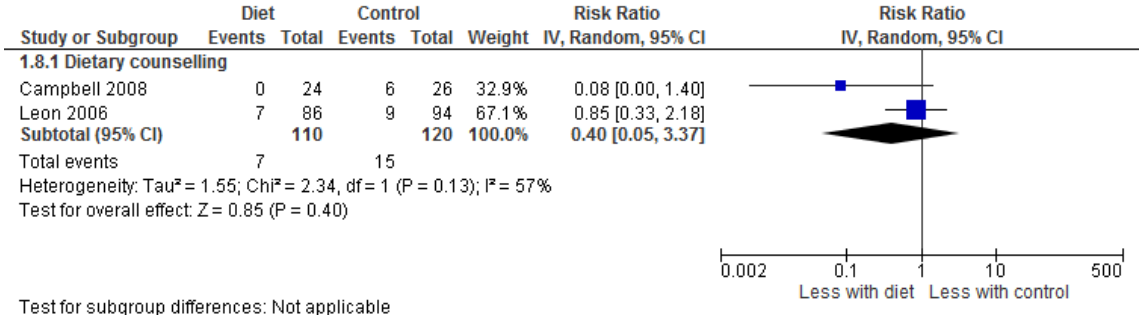
Analysis 1.6 Forest plot of comparison: Dietary intervention versus control, outcome: Employment



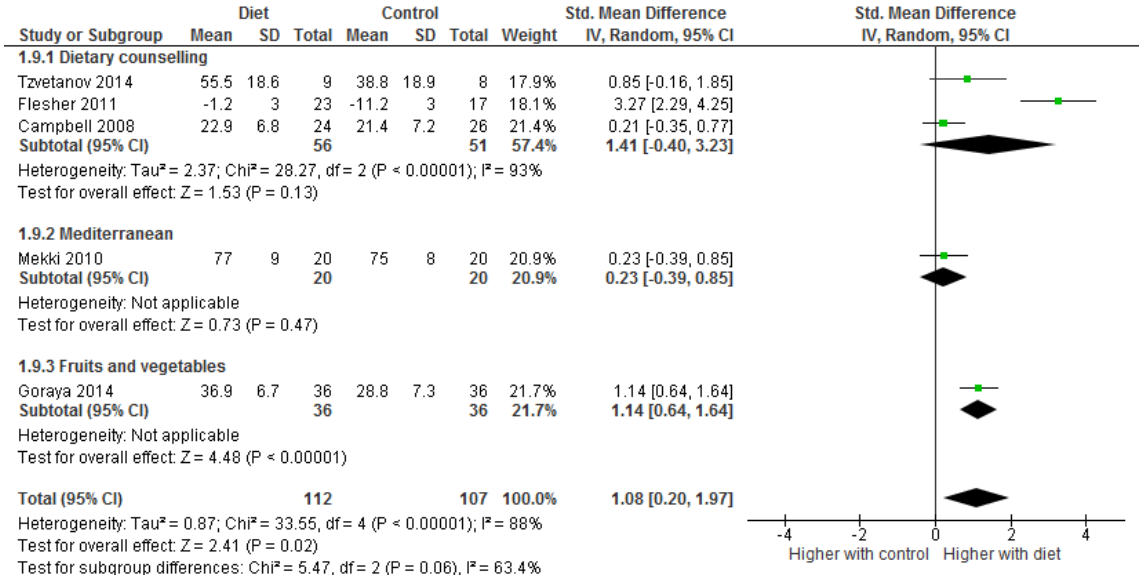
Analysis 1.7 Forest plot of comparison: Dietary intervention versus control, outcome: Dietary adherence



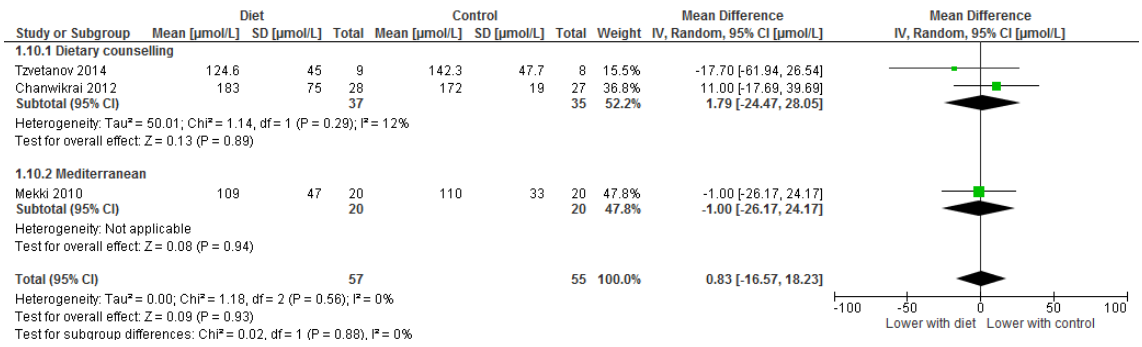
Analysis 1.8 Forest plot of comparison: Dietary intervention versus control, outcome: Worsening nutrition



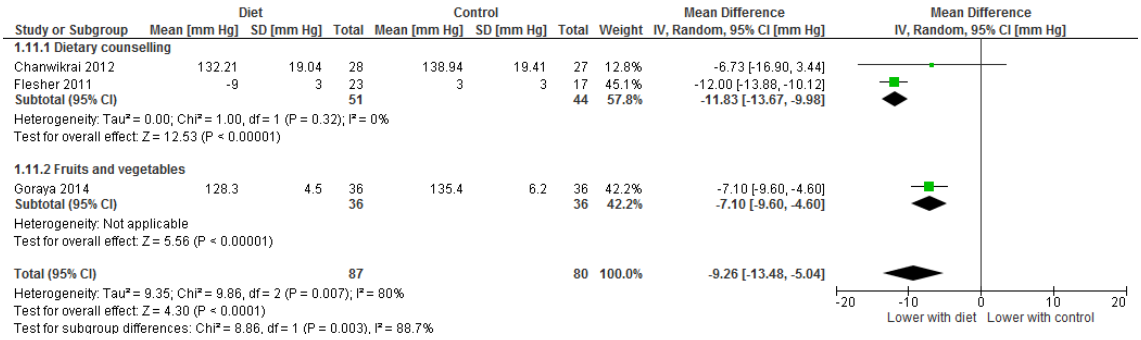
Analysis 1.9 Forest plot of comparison: Dietary intervention versus control, outcome: eGFR



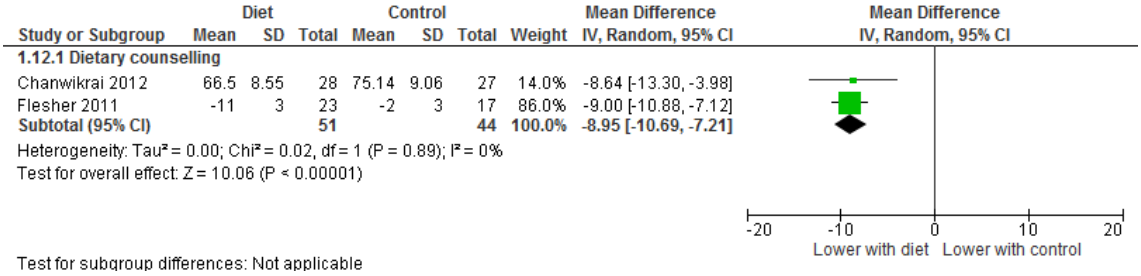
Analysis 1.10 Forest plot of comparison: Dietary intervention versus control, outcome: Serum creatinine



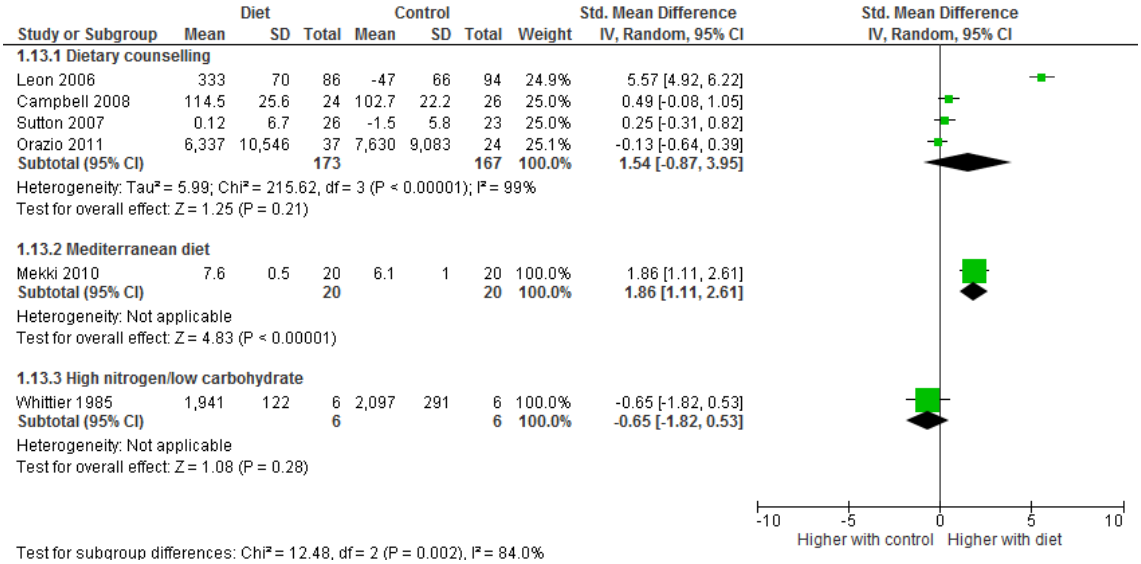
Analysis 1.11 Forest plot of comparison: Dietary intervention versus control, outcome: Systolic blood pressure



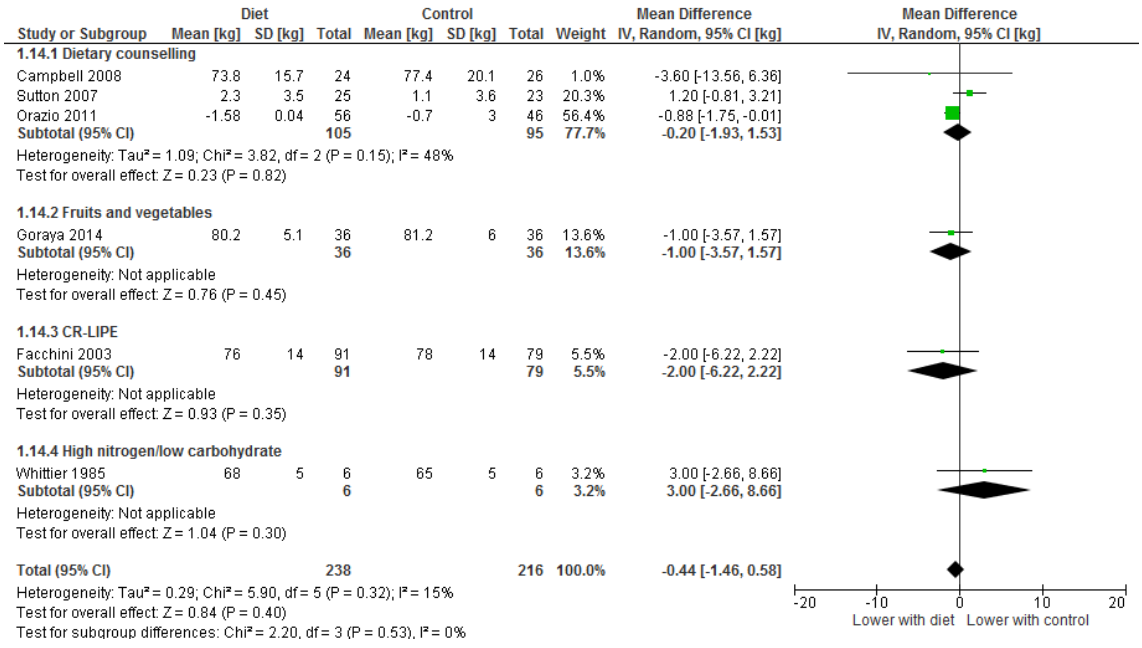
Analysis 1.12 Forest plot of comparison: Dietary intervention versus control, outcome: Diastolic blood pressure



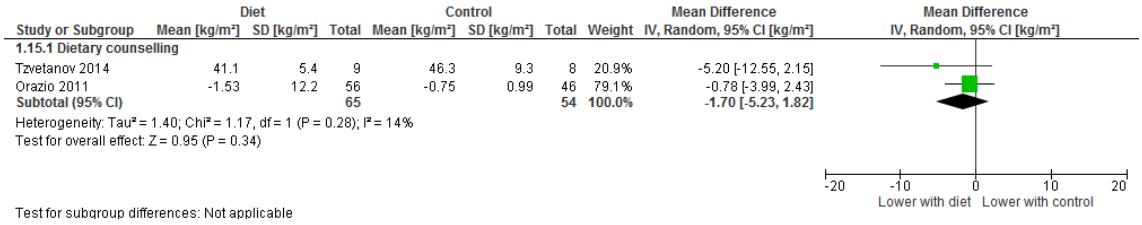
Analysis 1.13 Forest plot of comparison: Dietary intervention versus control, outcome: Energy intake



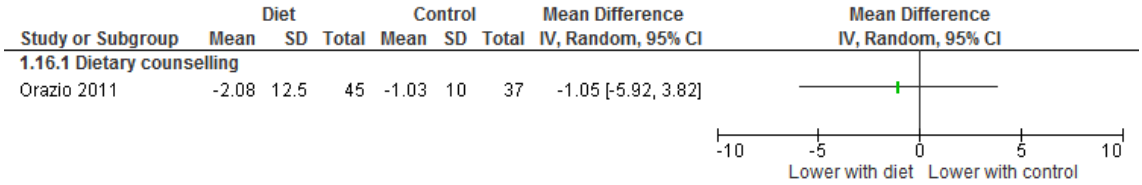
Analysis 1.14 Forest plot of comparison: Dietary intervention versus control, outcome: Body weight



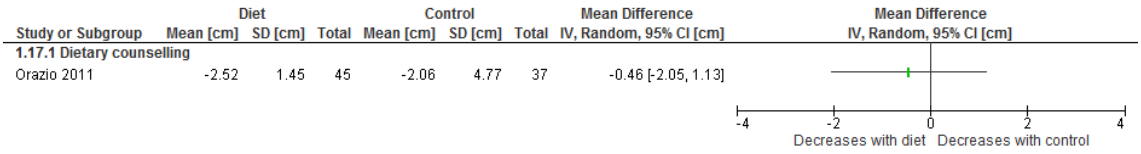
Analysis 1.15 Forest plot of comparison: Dietary intervention versus control, outcome: BMI



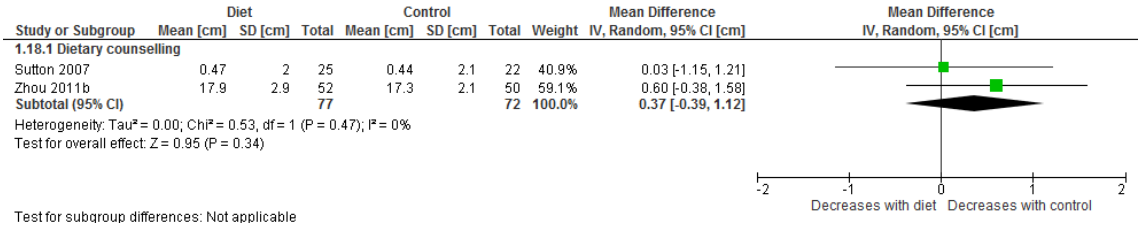
Analysis 1.16 Forest plot of comparison: Dietary intervention versus control, outcome: Waist-hip ratio



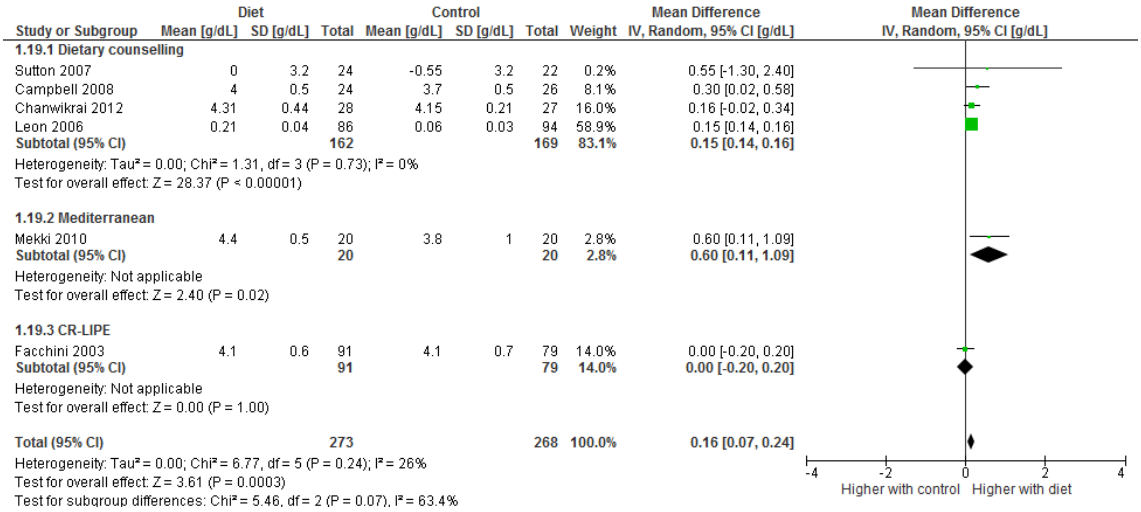
Analysis 1.17 Forest plot of comparison: Dietary intervention versus control, outcome: Waist circumference



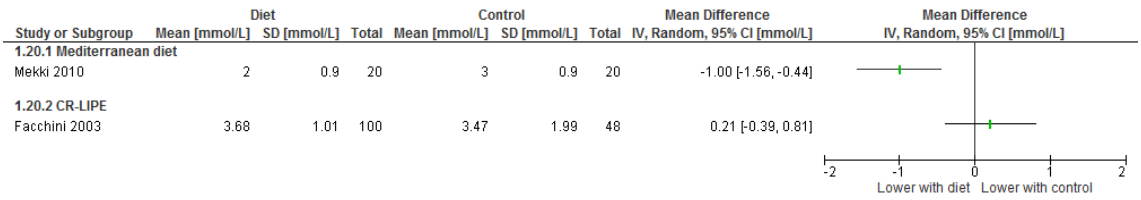
Analysis 1.18 Forest plot of comparison: Dietary intervention versus control, outcome: Arm circumference



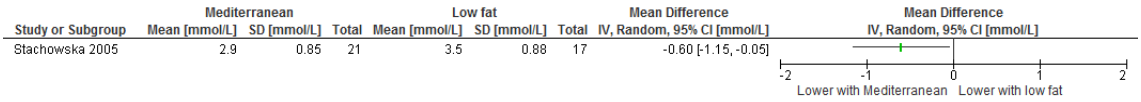
Analysis 1.19 Forest plot of comparison: Dietary intervention versus control, outcome: Serum albumin



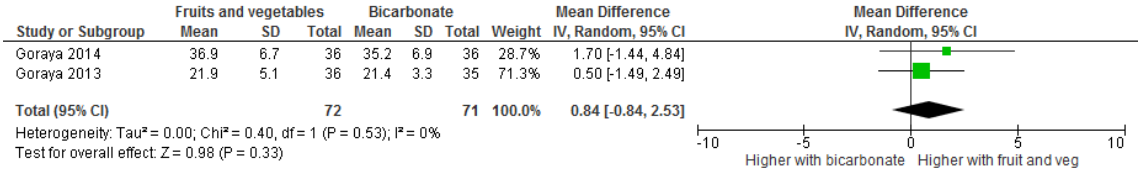
Analysis 1.20 Forest plot of comparison: Dietary intervention versus control, outcome: Serum LDL cholesterol



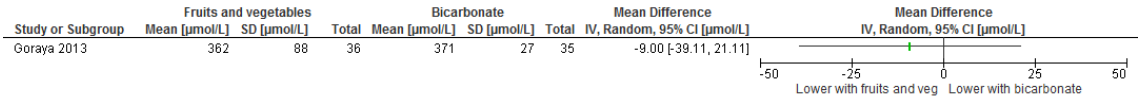
Analysis 2.1 Forest plot of comparison: Mediterranean diet versus low fat, outcome: Serum LDL cholesterol



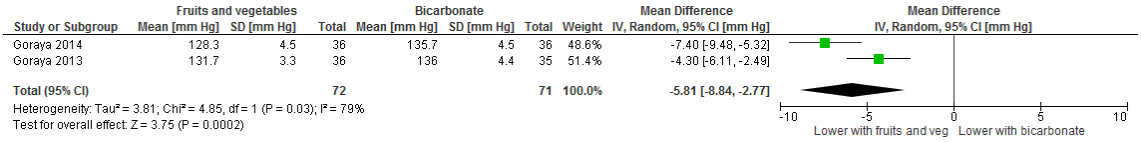
Analysis 3.1 Forest plot of comparison: Fruits and vegetables versus bicarbonate, Outcome: eGFR



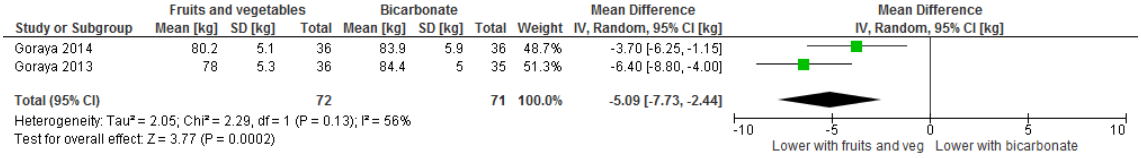
Analysis 3.2 Forest plot of comparison: Fruits and vegetables versus bicarbonate, Outcome: Serum creatinine



Analysis 3.3 Forest plot of comparison: Fruits and vegetables versus bicarbonate, Outcome: Systolic blood pressure



Analysis 3.4 Forest plot of comparison: Fruits and vegetables versus bicarbonate, Outcome: Body weight



CHAPTER VII: DIETARY AND FLUID RESTRICTIONS IN CKD: A THEMATIC SYNTHESIS OF PATIENT VIEWS FROM QUALITATIVE STUDIES

Suetonia C. Palmer, Camilla S. Hanson, Jonathan C. Craig, Giovanni F.M. Strippoli, Marinella Ruospo, Katrina Campbell, David W. Johnson, and Allison Tong.

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Abstract

Background: Managing the complex fluid and diet requirements of chronic kidney disease (CKD) is challenging for patients. We aimed to summarize patients' perspectives of dietary and fluid management in CKD to inform clinical practice and research.

Study design: Systematic review of qualitative studies.

Setting and population: Adults with CKD who express opinions about dietary and fluid management.

Search strategy and sources: MEDLINE, Embase, PsycINFO, CINAHL, Google Scholar, reference lists and PhD dissertations were searched to May 2013.

Analytical approach: Thematic synthesis

Results: We included 46 studies involving 816 patients living in middle- to high-income countries. Studies involved patients treated with facility-based and home hemodialysis (33 studies; 462 patients), peritoneal dialysis (10 studies; 112 patients), either hemodialysis or peritoneal dialysis (3 studies; 73 patients), kidney transplant recipients (9 studies; 89 patients) and patients with CKD stages 1-5 (not treated with dialysis) (5 studies; 80 patients). Five major themes were identified: preserving relationships (interference with roles, social limitations, and being a burden), navigating change (feeling deprived, disrupting held truths, breaking habits and norms, overwhelmed by information, questioning efficacy, and negotiating priorities), fighting temptation (resisting impositions, mental invasion, and withstanding physiological needs), optimizing health (accepting responsibility, valuing self-management, preventing disease progression, preparing for and protecting a transplant), and becoming empowered (comprehending paradoxes, finding solutions, and mastering change and demands).

Limitations: Limited data in non-English languages, low-income settings and for adults with chronic kidney disease not treated with hemodialysis.

Conclusions: Dietary and fluid restrictions are disorienting and an intense burden for patients with CKD. Patient prioritized education strategies, harnessing patients' motivation to stay well for a transplant or to avoid dialysis, and viewing adaptation to restrictions as a collaborative journey are suggested strategies to help patients adjust to dietary regimens in order to reduce their impact on quality of life.

Introduction

CKD causes water, sodium, potassium and phosphorus retention, which contributes to cardiovascular events, intra-dialysis symptoms, breathlessness and edema. Obesity is a risk factor for end-stage kidney disease,[1] while malnutrition is endemic in people with advanced CKD and is associated with mortality.[2] However, adherence to dietary regimens in CKD is challenging due to the burden of constant choices about food and drink, the adaptation to complex eating patterns, existing cultural practices, and the competing demands of CKD and related illnesses.[3-6]

Guidelines recommend that individuals with CKD receive dietary advice to intervene in salt, phosphate, potassium and protein intake and emphasize the importance of dietary counseling.[7] While dietary interventions are considered central to management of CKD, health professionals cite insufficient time to implement recommendations[8] and inclusion of patient experiences and perceptions of dietary treatment in CKD guidelines are limited.[7]

We aimed to summarize patients' perspectives and choices of dietary and fluid management in CKD provided in existing qualitative studies to inform clinical practice and research.

Methods

We conducted this review using the Enhancing Transparency of Reporting the Synthesis of Qualitative research (ENTREQ) framework.[9]

Selection criteria and literature search

We included qualitative data for adults aged 18 years or older who had CKD and who expressed opinions about diet or fluid management. We included CKD stages 1-5, kidney transplant recipients (5T), and people treated with dialysis (5D).[7]

Data sources and searches

Electronic databases and reference lists of included studies were searched at May 7, 2013 (Item S1). Two authors (SP, GS) screened all records and discarded those that were not eligible. The full text of the remaining citations was then examined to identify qualitative data.

Comprehensiveness of reporting

SP and CH independently assessed the comprehensiveness of reporting using the consolidated criteria for reporting qualitative research (COREQ) framework.[10]

Synthesis of findings

We identified descriptive themes in primary data and used thematic synthesis to generate analytical themes, which are a higher level of abstraction of concepts, understandings or hypotheses.[11] We imported text of each primary source into HyperRESEARCH (www.researchware.com). One author (SP) performed line-by-line coding, conceptualized the data, and inductively identified concepts relating to patient perspectives, experiences and values. Similar concepts were grouped into themes and subthemes. Conceptual linkages between themes were used to generate a thematic schema. To ensure that coding captured the relevant ideas and reflected data from the primary studies, researcher triangulation was done where two authors (SP, AT) discussed the primary themes and analytical framework. Revisions of the themes and concepts were discussed and these were incorporated into the final synthesis.

Results

Characteristics of the studies

Forty-six studies (involving 816 patients) were included (Figure 1 and Table 1). Studies involved patients treated with facility-based and home hemodialysis (33 studies; 462 patients), peritoneal dialysis (10 studies; 112 patients), either hemodialysis or peritoneal dialysis (3 studies; 73 patients), kidney transplant recipients (9 studies; 89 patients) and patients with CKD stages 1-5 (not treated with dialysis) (5 studies; 80 patients).

Study appraisal

The comprehensiveness of study reporting was variable (Table 2).

Synthesis

Five major themes conceptualized patients' experiences: preserving relationships, navigating change, fighting temptation, optimizing health, and becoming empowered (Table 3). Quotations to illustrate each theme are provided in Table 4.

Preserving relationships

Interference with roles (23 studies):

Patients, principally those on dialysis, experienced challenges to their roles with others. They felt infantilized and scolded about their diet. Family members policed their diet intake[12,13] and searched for food they thought that patients had hidden.[12] Patients on dialysis resented unsolicited advice particularly in social situations.[13] Some patients felt patronized by medical staff for not following food advice[12] and others told of eating restricted foods in secret to avoid being lectured by clinicians.[5,14]

Social limitations (14 studies):

Food and fluid management stopped many dialysis patients from socializing. It became too difficult to explain food restrictions to others for fear of 'social stigma', [15] or that refusing food or drink would offend their hosts.[14-16] Some preferred not to be with others as eating restrictively drew attention to their disease[15,17] and they became 'afraid of seeing people.'[5] After declining invitations previously, some were subsequently excluded from social occasions.[5] Some patients decided to eat and drink normally in social situations and 'pay for it' later with symptoms due to fluid overload or itch.[5,15,18] For first-generation immigrants from Bangladesh in the United Kingdom, dietary changes were embarrassing as reducing some foods, including salt, could be interpreted as a sign of poverty.[19]

Being a burden (11 studies):

Some patients on dialysis depended on family for preparing meals in accordance with their dietary restrictions. They felt guilty that family members had to adopt the restrictive renal diet.[20] Some female Bangladeshi patients were concerned that if they omitted salt from meals their families would resent them[19] while some patients chose to be vigilant about their dietary regimen to stay well and avoid becoming a burden to their family or wasting their nurses' and doctors' time.[14]

Navigating change

Feeling deprived (27 studies):

In addition to experiencing severe illness, diet and fluid restrictions were perceived as a further deprivation. Patients viewed diet recommendations as externally imposed and more difficult to accept than if they had been a personal choice.[5,13,15,21,22] Patients spoke about having life's pleasures removed and how food had become bland and tasteless.[12,13,21,23] Some patients on dialysis described their restrictions using nihilistic or violent terms such as 'having no life at all',[24] 'having a meaningless existence',[5] or as like being a prisoner, being condemned to death or being tied up.[25] Some anticipated they would 'live again; feel reborn!...and enjoy life again' after a kidney transplant!'[26] while those who have received a kidney transplant expressed delight at the freedom from their dietary restrictions; 'I was excited about eating something I hadn't eaten in a while.'[27]

Disrupting held truths (12 studies):

Dietary restrictions were counterintuitive and disorienting. Dietary advice contradicted a 'healthy diet'[20] and patients felt lethargic, malnourished and starved if they followed the diet as instructed.[5] Some patients from an ethnic minority felt that recommended diets did not consider traditional foods, with one patient from Barbados in the US suggesting 'something could be done to help put some back home foods on the list and let the dieticians learn about our foods, …'[28]

Breaking habits and norms (21 studies):

Patients were angry about having to take on a new food and liquid regimen in addition to changes to their daily schedules and recreational activities imposed on CKD. Some patients on dialysis were ambivalent about the transformation of so many aspects of their lives that were

previously worry-free.[25] Patients admitted forgetting the dietary recommendations particularly when they had a change or a break in their routine.[15]

Overwhelmed by information (18 studies):

When learning about diet management, patients described being 'bombed' with information [23] that was sometimes not relevant to their cultural background or existing food preferences;[19] '[the clinicians] speak in a Latin tongue…and…just jibber, jibber, jibber'.[29] Patients spoke of listed permissible foods as being unfamiliar to them.[28] Comorbid conditions (diabetes and heart disease) led to conflicting advice.[20] Patients reported not understanding the advice, when they were still in 'emotional turmoil' after learning about their CKD diagnosis or just having had a dialysis catheter implanted.[5] Patients 'preferred to receive advice from a renal dietician who could support the rules with a clear rationale and practical advice to help them implement any changes'.[20] Kidney transplant recipients expressed a lack of knowledge about appropriate ways to follow dietary freedoms in a healthy way.[27]

Questioning efficacy (17 studies):

Patients felt that taking the advice about food and fluid was a personal choice.[5] Some patients had a sense that restrictions had few immediate or longer term benefits or even caused harm [18] or alternatively that the dialysis could compensate for any excessive intake.[29] For this reason, some returned to a regular food or fluid intake[28] or lacked faith in doctors who advised strict restrictions as patients considered them unnecessary.[5]

Negotiating priorities (23 studies):

Patients struggled with making choices between getting pleasure from food and fluid versus staying in control and keeping well. Some spoke about 'cheating' on their diet by learning how to get away with eating treats in moderation.[12,13] 'It isn't though I don't ever cheat on my diet, everyone does. I cheat in a way that I know from experience will be safe for me'.[12] They tested the boundaries of dietary restrictions: 'I try my best to adhere to dietary restrictions. I only eat a little bit in secret when I really can't refrain. … But I don't do that often.'[5] Others perceived there was no choice other than to stick to the diet.[5,22]

Fighting temptation

Resisting impositions (15 studies):

For some patients, the dietary and fluid advice was seen as unreasonable. One described having a list of 'forbidden foods' that occupied 'four sheets of A4-sized paper' and which was

impossible to incorporate into daily life.[5] Consuming food in restricted amounts was unfeasible and impractical. 'When I eat banana, I've to eat just half. Where do I put the remaining half then? It'd be better to eat the remaining half as well.'[5] Some saw the dieticians' role as ideally not to impose change but to support patients in their adaptation to new diet and fluid habits.[30]

Mental invasion (14 studies):

Some patients on hemodialysis were tormented by unrelenting thoughts of food and drink.[31] Compulsive thoughts about fluid provoked 'mirages' that made them look for water even when it was not present[32] or experience 'visions…such as a mountain with fresh water gushing forth'.[25] Patients would consider the need to drink as 'stronger than me' describing themselves as 'tortured',[14] 'fixated',[25] 'obsessed'[14] or 'addicted'.[24,25] Thirst was distressing[4] and for some could never be satiated.[33]

Withstanding physiological needs (15 studies):

Food and fluid were seen as a physical need which were 'indispensable elements for life'.[25] Patients couldn't conceive of how medical advice leading to dehydration could be beneficial.[25] Some recipients of a kidney transplant found it impossible to control their appetite: 'the larger the dose of prednisone, my appetite just got bigger and bigger' while another mentioned that he 'never got full'.[27] Dietary restrictions were both 'fighting nature' and 'fighting against themselves' against thirst or appetite.[14]

Optimizing health

Accepting responsibility (22 studies):

Adherence to diet and fluid restrictions became more manageable once they learned to accept responsibility for their treatment and recognized the potential consequences of their behavior on their future health. Some learned to cope better over time and by being 'grown up' and simply what they had to tolerate.[31] Some accepted that food and fluid changes were 'part of the deal'[14] and having taken charge no longer allowed diet to be a dominating concern in their lives.[20]

Valuing self-management (31 studies):

For some patients, diet and fluid advice was part of the suite of specific actions they could do to care for themselves[12] to feel better.[5] Some wanted to tell other patients to persevere on diet and fluid advice to improve quality of life based on their own critical experiences such as severe fluid overload.[25,29] Some patients gained confidence in their own dietary strategies by

regulating their diet according to blood test results:[6] 'I've kept my chemistries at a level and I know that if it goes up, I know how to bring it down'.[34]

Preventing chronic kidney disease progression (5 studies):

Some patients sought comprehensive guidance about how to prevent the progression of their disease[18] and wished in hindsight that they had taken more heed of dietary advice if they had known it might have slowed down the rate of their CKD progression.

Preparing for and protecting transplant (8 studies):

Some patients on dialysis harnessed the prospect of a transplant as motivation to keep themselves healthy,[5,13,21] while viewing not getting a transplant as equivalent to giving up hope.[13] Some African American patients on dialysis believed that weight loss was difficult if not impossible while on dialysis and were angry they might be excluded from getting a transplant without weight loss.[35] Kidney transplant recipients refrained from foods they feared might cause transplant rejection.[36]

Becoming empowered

Comprehending paradoxes (21 studies):

Through a process of adaptation and negotiation, patients learned how to incorporate complicated dietary ideals into their lives.[3] By adjusting to the counterintuitive idea that many 'healthy' foods were now off limits and making decisions based on how their symptoms responded to their choices, patients learned to navigate through complex clinical instructions until it became second nature.[13] Once they had 'grappled' with the many adjustments needed to adapt to dialysis treatment, some felt confident to share their experiences with their peers.[12]

Finding solutions (23 studies):

Some dialysis patients used practical responses to cope with dietary restrictions, such as buying cookbooks and learning to read nutritional labels to identify sodium-free products.[12] They developed libraries of foods that were high in potassium, phosphorus and sodium[19] and valued regular contact with renal dieticians and their peers to consolidate their learning and build confidence.[15] Patients believed that the person who did the shopping and cooking for their household should also be invited to attend education sessions. They expressed a preference for a repeated problem-solving approach rather than didactic teaching methods when learning how to manage their food and fluid intake.[20]

Mastering change and demands (25 studies):

Gaining and keeping control of diet and fluid was one way of finding meaningful ways to stay alive and feel good and that surviving their chronic disease was worth the effort. They saw that quality of life 'was within their own reach and under their control'.[21]

Discussion

In this review, we found that dietary and fluid management is a disorienting challenge and intense burden for patients when adapting to and coping with different stages of CKD. The substantial number and complexity of restrictions on food and fluid exacerbates the impaired quality of life caused by CKD and has a profound impact on patients' relationships with others. Patients experience unresolved conflict between their medical team who advocate strongly for a narrow window of diet and fluid choices on the basis of 'improved health', and their own sense of well-being which is undermined by what they perceive as an unrealistic and unpalatable diet devoid of taste and interest. Studies reveal that patients avoid social situations and are overwhelmed by a confusing array of advice that seems contrary to their normal cultural beliefs and which is difficult to implement fully. In sparse data, kidney transplant recipients find it difficult to readjust to normal eating patterns and cope with an increased appetite despite considerable relief at renewed freedom from restrictions. Thus, some fear their lack of knowledge about diet may contribute to transplant rejection. Patients indicate that information about appropriate diet management is frequently difficult to comprehend due to reliance on didactic one-off education sessions and thus prefer multiple problem-solving and collaborative approaches to learning in partnership with their dieticians and families. Some patients find feedback from blood tests helpful in their own self-management. This review finds that over time, individual patients draw on the strength of achieving incremental dietary changes, motivations of a future kidney transplant, slowing CKD progression or feeling better as ways of sustaining dietary and fluid recommendations in their lives.

This thematic integration from studies across a range of clinical and cultural contexts highlights three potential factors that might be relevant to helping patients learn and incorporate dietary restrictions. Our review suggests that 1) approaches to education, 2) harnessing patient motivation, and 3) identifying adaptation as a journey might be ways of helping patients positively adapt to dietary recommendations.

Patients desire knowledge about diet and fluid but may be counselled at a difficult time, such as when they are adapting to dialysis or transplantation or comprehending a diagnosis. In diabetes, patients who receive dietary counselling soon after diagnosis with consultation offered every three months and monthly nursing support show improved glycemic control, lower body weight and less use of diabetes drugs, suggesting that continued support over the months after diagnosis is helpful to generate meaningful dietary changes in other settings and are possibly applicable to CKD.[37] This also aligns with CKD patients' preference to form an

alliance with their clinical team rather than feeling they are being scolded or patronized for not adhering to advice.

Partners and families are important sources of support who can shop for appropriate foods and make food palatable as well as 'take on the stress and concern of planning meals'.[20] This review suggests care-givers might be routinely involved in dietary education, as involvement of caregivers in nutrition counseling improves recall on messages about foods and food preparation information.[38] Advice about reading nutritional labels and building a personal library of foods to minimize or avoid relevant to cultural practices are helpful for patients in this review. In addition, the opportunity for patients to learn about and respond to regular blood test results aligns with existing data showing patients with diabetes experience improved glycemic control in response to immediately available blood results.[39] Patient experiences in our review are also supported by evidence showing education to avoid foods high in phosphorus additive at the time when patients purchase groceries or go to a fast-food restaurant lowers serum phosphorus levels.[40] Some patients prefer group education sessions where they can support each other and discuss their concerns and find solutions. Patients favor problem-based learning on multiple occasions to build their confidence and gradually adapt to diet changes. This preference is supported by CKD data showing that individualized fortnightly dietary counselling with ongoing follow-up is more effective than written materials[41] and a nonrandomized study showing that regular 6-monthly dietetic review and intensive follow-up targeted to specific nutritional parameters is associated with improved nutrition, serum potassium and phosphorus levels, and fluid overload.[42]

This review indicates that kidney transplant recipients need ways to manage their increased appetite and advice to stay well and be reassured about their dietary approaches and the risk of transplant rejection. To support this need, a small exploratory study showed that body weight was increased by about 6% in the first months after transplantation without measurable changes in dietary intake.[43] While regular dietary consultations and multidisciplinary care-modified dietary patterns might slow weight gain,[44] effects of lifestyle modification on patient-relevant outcomes in solid-organ transplantation are lacking.[45] Patients with earlier stages of CKD wish to address dietary approaches specifically targeted at preventing CKD progression, which aligns with evidence showing patients prioritize diet as an intervention to prevent CKD progression when asked.[46]

Patients often find changing their diet and fluid habits unacceptable as they view the restrictions as externally imposed and additional to other losses associated with CKD. Once patients experienced an increased sense of responsibility for food and fluid management as

'part of the deal', they became empowered and the dietary changes were much less important to their lives. Therefore, the key experiences of patients in this review might be used to inform decisional balance activity (patients and health workers exploring the pros and cons of changing and not changing health practices)[47] to help assist patients to incorporate dietary changes by better articulating the perceived benefits of change (feeling better; hope for better CKD, dialysis and transplantation outcomes; reducing burden to others) and costs of not changing (fluid overload, itch, not gaining self-management) against their reasons to remain the same (inadequate information and understanding, ambivalence over efficacy, unsustainability of the changes needed, competing priorities in CKD). Some patients who had found internal motivation to sustain dietary adjustments were keen to tell their peers about what they had learned so that others might shorten the time it took to adopt the restrictions. Meeting patient peers to discuss care has been suggested previously in the setting of CKD as inspirational and a 'powerful and persuasive method for patients to gain knowledge about their treatment options' and may be widely applicable for people with CKD who face treatment that is complex and demanding and has been shown to have a positive influence on diet self-management in other settings.[48,49]

While we conducted a thematic synthesis drawing on a broad and comprehensive search of the literature, considering a coding and analytical framework agreed between multiple researchers and evaluating the comprehensiveness of reporting in primary studies, this review has limitations that need to be considered. First, we did not include non-English research and while studies were situated within different cultural settings or reflected on the impact of culture on patient experiences, we cannot infer the applicability of our findings to all cultural and clinical contexts. As studies including patients treated by facility hemodialysis dominated the primary literature, the experiences of kidney transplant recipients, home dialysis patients and those with CKD may have been underestimated. All studies were conducted in middle- and high-income countries and conclusions may not be appropriate for patients in low-income regions.

In conclusion, dietary and fluid restrictions have a powerful negative impact on the experiences of patients with CKD that require time for adaptation and patient and family-centered care. The burden of dietary and fluid management may be alleviated through new approaches to patient education, harnessing patient motivations for change, and viewing adaptation to dietary and fluid management as a collaborative journey for patients, families, peers, and clinicians.

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Table 1. Characteristics of included studies

Study	Country	Patients (n)	Age range (years)	Treatment	Methodology (as reported by authors)	Data collection	Analysis (as reported by authors)	Principal experiences explored
Munakata 1982[50]	Japan	23	Not stated	Outpatient hemodialysis	Not stated	Interviews	Not stated	Self-care behaviors for diet
Hume 1984[4]	Canada	25	29-79	Peritoneal dialysis	Not stated	Interviews	Not stated	Dietary adherence
Berg 1989[3]	USA	23	17-78	Hemodialysis	Not stated	Interviews	Not stated	Knowledge and choices about foods
Beer 1995[36]	UK	12	22-64	Hemodialysis, peritoneal dialysis, transplant	Exploratory	Interviews	Thematic analysis	Body image with end-stage kidney disease and after transplantation
Bordelon 1997[12]	USA	20	Not stated	Hemodialysis	Naturalistic enquiry	Interviews	Not stated	Empowerment of dialysis patients within community of care
Fisher 1998[17]	UK	10	24-62	Hemodialysis, peritoneal dialysis, transplant	Exploratory	Interviews	Inductive approach	Quality of life before and after kidney transplantation
Ndlovu 1998[51]	South Africa	14	19-48	Transplant	Exploratory	Interviews	Thematic analysis	Kidney transplantation viewed by African recipients
Bass 1999[23]	USA	13	40-69	Hemodialysis, peritoneal dialysis	Exploratory	Focus groups	Content analysis	Quality of life
Costello 1999[13]	USA	11	45-78	Hemodialysis	Not stated	Focus groups	Not stated	Adaptation to end-stage kidney disease/chronic illness
Mayers 2000[28]	USA	5	22-50	Hemodialysis	Phenomenology	Interviews	Constant comparative method	Dietary restrictions

Study	Country	Patients (n)	Age range (years)	Treatment	Methodology (as reported by authors)	Data collection	Analysis (as reported by authors)	Principal experiences explored
Sussman 2001[30]	UK	8	20-68	Hemodialysis	Exploratory	Interviews	Thematic analysis	Dietary restrictions
King 2002[22]	UK	20	36-69	Chronic kidney disease	Phenomenology	Interviews	Template analysis	Adaptation to diabetic renal disease
Giles 2003[52]	Canada	4	Not stated	Home hemodialysis	Phenomenology	Interviews	Thematic analysis	End-stage kidney disease and home hemodialysis technology
Martin-McDonald 2003[53]	Australia	10	22-68	Hemodialysis, peritoneal dialysis	Narrative	Interviews	Thematic continua	Dialysis
Polaschek 2003[54]	New Zealand	6	20-60	Home hemodialysis	Critical interpretive approach	Interviews	Thematic analysis	Home hemodialysis
Pradel 2003[55]	USA	13	30-72	Potential transplant recipients, transplant	Phenomenology	Focus groups	Phenomenological analysis	Before and after kidney transplantation
Curtin 2004[34]	USA	18	33-86	Peritoneal dialysis	Exploratory/ descriptive	Interviews	Thematic analysis	Peritoneal dialysis
Dekkers 2005[56]	The Netherlands	7	55-82	Hemodialysis	Not stated	Interviews	Phenomenological analysis	End-stage kidney disease
Al-Arabi 2006[21]	USA	80	Not stated	Hemodialysis	Naturalistic enquiry	Interviews	Constant comparative method	Quality of life
Polaschek 2007[57]	New Zealand	20	24-77	Home hemodialysis, peritoneal dialysis	Interpretivist	Interviews	Thematic analysis	Home dialysis

Study	Country	Patients (n)	Age range (years)	Treatment	Methodology (as reported by authors)	Data collection	Analysis (as reported by authors)	Principal experiences explored
Russ 2007[58]	USA	43	70-93	Hemodialysis	Exploratory	Interviews	Grounded theory	Discontinuing treatment
Hollingdale 2008[20]	UK	20	Not stated	Chronic kidney disease, hemodialysis	Exploratory	Focus groups	Framework method	Conceptualization of diet
Duffy 2009[59]	USA	10	28-48*	Transplant	Phenomenology	Interviews	Inductive thematic approach	Sibling relationships during living donor kidney transplantation
Fex 2009[60]	Sweden	6	37-83	Home hemodialysis, peritoneal dialysis	Phenomenology	Interviews	Phenomenological analysis	Advanced medical technology at home
Namiki 2009[61]	Australia	4	60-75	Home hemodialysis	Exploratory	Interviews	Thematic analysis	Home hemodialysis for older people
Sinclair 2009[14]	Australia	7	39-82	Hemodialysis	Not stated	Interviews	Thematic analysis	Interdialytic weight gain
Tong 2009[18]	Australia	63	20-78	Chronic kidney disease, hemodialysis, transplant	Not stated	Focus groups	Thematic analysis	Chronic kidney disease
Ford-Anderson 2010[33]	USA	22	Not stated	Hemodialysis	Not stated	Open-ended survey questions	Content analysis	Adherence to hemodialysis regimen
Ismail 2010[26]	The Netherlands	50	27-74	Dialysis	Not stated	Focus groups	Thematic analysis	Living donor kidney transplantation among ethnic minorities
Smith 2010[29]	USA	19	28-82	Hemodialysis	Not stated	Focus groups	Content analysis	Self-care and adherence to fluid restrictions

Study	Country	Patients (n)	Age range (years)	Treatment	Methodology (as reported by authors)	Data collection	Analysis (as reported by authors)	Principal experiences explored
Cases 2011[62]	UK	6	48-74	Home hemodialysis	Not stated	Interviews	Phenomenological analysis	Home hemodialysis
de Brito-Ashurst 2011[19]	UK	20	Not stated	Chronic kidney disease	Not stated	Focus groups, vignettes, food diaries	Thematic analysis	Traditional and current diets and beliefs
Humphreys 2011[35]	USA	10	39-64	Hemodialysis	Not stated	Interviews	Grounded theory	Kidney transplant evaluation for African American patients
Lai 2012[32]	Singapore	13	39-63	Hemodialysis	Not stated	Interviews	Phenomenological analysis	Dialysis treatment
Lam 2012[5]	China	36	35-76	Chronic ambulatory peritoneal dialysis	Explanatory sequential design	Interviews	Content analysis	Adherence for Chinese patients
Rygh 2012[63]	Norway	11	23-82	Home hemodialysis, peritoneal dialysis	Not stated	Interviews	Inductive thematic approach	Home dialysis
Stanfill 2012[27]	USA	7	41-60+	Transplant	Not stated	Focus groups	Iterative thematic analysis	Weight gain after kidney transplantation
Tovazzi 2012[25]	Italy	12	37-77	Hemodialysis	Not stated	Interviews	Phenomenological analysis	Restricted fluid intake and adherence
Urstad 2012[64]	Norway	16	26-67	Transplant	Not stated	Interviews	Thematic analysis	Education following kidney transplant
Walker 2012[6]	UK	9	63-93	Chronic kidney disease	Exploratory	Interviews	Thematic analysis	Transition to CKD
Bennett 2013[24]	Australia	9	29-67	Hemodialysis	Visual image communication	Interviews	Thematic analysis	Adherence to fluid restrictions

Study	Country	Patients (n)	Age range (years)	Treatment	Methodology (as reported by authors)	Data collection	Analysis (as reported by authors)	Principal experiences explored
Griva 2013[15]	Singapore	37	Not stated	Hemodialysis	Exploratory	Interviews, focus groups	Inductive thematic approach	Treatment adherence
Karamanidou 2013[31]	UK	7	32-68	Hemodialysis	Phenomenology	Interviews	Phenomenological analysis	Illness, prescribed treatment and adherence
Krespi Boothby 2013[16]	Not stated	16	23-77	Hemodialysis	Not stated	Interviews	Template analysis	Dietary and/or fluid restrictions
Theofilou 2013[65]	Greece	10	Not stated	Hemodialysis	Not stated	Interviews	Phenomenological analysis	Hemodialysis
Xi 2013[66]	Canada	10	38-57	Quotidian dialysis	Phenomenology	Interviews	Iterative thematic analysis	Quotidian dialysis

*Age at time of kidney transplant. Abbreviations: USA, United States. Definitions: Constant comparative method, breaks the data into discrete phenomena and coding into categories; Content analysis, deductive methodology that involves identification of codes prior to searching for their occurrence in the data; Critical interpretivist approach/methodology, analytically disclosing meaning-making practices of people; Ethnography, to discover and describe individual social and cultural groups; Explanatory sequential design; collecting qualitative data to explore a phenomenon followed by collection of quantitative data to test an emergent theory or framework; Framework method, identifies commonalities and differences in qualitative data, before focusing on relationships between different parts of the data, thereby seeking to draw descriptive and/or explanatory conclusions clustered around themes; Grounded theory; discovery of theory through analysis of data; Iterative approach; similar to thematic analysis; Naturalistic enquiry, seeking to describe, understand or interpret daily life experiences and structures; Phenomenology, to study peoples' understanding and interpretations of their experiences in their own terms and emphasizing these as explanations for their actions; Template analysis; development of a coding template from a priori codes expected to be relevant to the analysis, which are modified or dispensed with if they are not relevant to the actual data examined; Thematic analysis, concepts and theories are inductively derived from the data.

Table 2. Comprehensiveness of reporting assessment

Reporting criteria	References of studies reporting each criterion	No. (%)
Characteristics of research team:		
Interviewer or facilitator identified	4-6,12,16,17,26,28,29,34,35,51,53,54,57-60,66	19 (41%)
Occupation	4-6,12,16,17,19,24,28,34,35,53,54,57,59,60	16 (35%)
Experience or training in qualitative research	5,12,15,20,23,24,26,55	8 (17%)
Research team relationship with participants:		
Relationship established prior to study commencement	4,12,20,24,26,35,36,59,63	9 (20%)
Participant selection:		
Selection strategy	4-6,12-19,22-29,32-36,51-55,57,59-61,63,64,66	36 (78%)
Method of approach or recruitment	4,5,12,15,16,18,21,24,26-28,30,32-36,51-55,57,59,60,62-64	28 (61%)
Sample size	3-6,12-36,50-66	100%
Number/ reasons for non-participation	5,13-16,18,22,27,31,33,51,55,63	13 (28%)
Setting:		
Venue of data collection	3-6,12,15,16,18-21,23-31,33-36,51-54,56-66	39 (85%)
Presence of non-participants (e.g. clinical staff)	5,16-18,20,21,23-25,29-31,35,56,63-66	18 (39%)
Description of the sample	3-6,12-20,22-36,51-53,55-66	43 (93%)
Data collection:		
Questions, prompts or topic guide	5,12-18,20,21,23,24,26-36,53,55,56,58,59,62-66	33 (72%)
Repeat interviews / observations	12,18,19,24,26,27,34,35,52-59,61,62	18 (39%)
Audio / visual recording	5,6,12,13,15-36,51,52,54-57,59-66	40 (87%)
Field notes	5,6,12,18,19,21,26,27,35,51,54,55,61,63,66	15 (33%)
Duration of data collection	3,5,6,13-17,19,23-27,29-32,34-36,51-54,56-58,60,62-66	34 (74%)
Protocol for data preparation and transcription	5,6,12,13,15,16,18-24,26,27,29-32,34-36,52,55,59-66	32 (70%)
Data (or theoretical) saturation	5,6,15,16,27-29,32,34,66	10 (22%)
Data analysis:		
Researcher/expert triangulation	5,6,13,15,18,21-27,29,31,32,34,35,55,62-66	23

Reporting criteria	References of studies reporting each criterion	No. (%)
		(50%)
Derivation of themes or findings	5,6,12-36,52-66	42 (91%)
Use of software	15,18,19,26,29,33,35,36,55,59	10 (22%)
Participant feedback on findings	12,13,21,27,28,34,35,53,61,62	10 (22%)
Reporting:		
Participant quotations or raw data provided	3,5,6,12-35,50,52-56,58,59,61-66	41 (89%)
Range and depth of insight into participant perspectives	5,6,12-20,22,24-36,51-66	41 (89%)

Table 3 Studies contributing to each theme

Themes	Munakata 1982	Hume 1994	Beer 1995	Berg 1989	Bordelon 1997	Fisher 1998	Ndlovu 1998	Bass 1999	Costello 1999	Mayers 2000	Sussman 2001	King 2002	Giles 2003	Martin-McDonald, 2003	Polaschek 2003	Pradel 2003	Curtin 2004	Dekkers 2005	Al-Arabi 2006	Polashek 2007	Russ 2007	Hollingdale 2008	Duffy 2009	Fex 2009	Sinclair 2009	Tong 2009	Ford-Anderson 2010	Ismail 2010	Namiki 2010	Smith 2010	Cases 2011	de Brito-Ashurst 2011	Humphreys 2011	Lai 2012	Lam 2012	Rygh 2012	Stanfill 2012	Tovazzi 2012	Urstad 2012	Walker 2012	Bennett 2013	Griva 2013	Karamanidou 2013	Krespi Boothby 2013	Theofilou 2013	Xi 2013
Preserving relationships																																														
Interference with roles	●	●		●	●	●			●	●	●	●		●						●		●			●	●				●		●			●			●		●	●	●	●	●		
Social limitations	●	●				●			●																●	●				●		●			●			●		●	●	●		●		
Being a burden						●			●	●		●							●			●			●										●					●		●		●		
Navigating change																																														
Feeling deprived	●	●		●	●	●		●	●	●	●	●							●	●		●			●	●	●			●		●		●	●		●	●			●	●	●	●	●	
Disrupting held truths				●	●		●		●	●												●					●					●			●			●				●	●			
Breaking habits/norms	●			●	●	●	●	●	●		●	●								●		●			●	●				●		●			●		●	●				●	●	●		
Overwhelmed by information		●		●				●	●	●	●	●										●				●				●	●	●	●		●		●	●	●			●				
Questioning efficacy	●			●			●		●	●					●							●				●				●		●			●			●		●	●	●	●	●		
Negotiating priorities		●		●	●		●	●	●			●			●				●	●	●	●				●	●			●	●	●			●			●			●	●	●	●		
Fighting temptation																																														

Themes	Munakata 1982	Hume 1994	Beer 1995	Berg 1989	Bordelon 1997	Fisher 1998	Ndlovu 1998	Bass 1999	Costello 1999	Mayers 2000	Sussman 2001	King 2002	Giles 2003	Martin-McDonald, 2003	Polaschek 2003	Pradel 2003	Curtin 2004	Dekkers 2005	Al-Arabi 2006	Polashek 2007	Russ 2007	Hollingdale 2008	Duffy 2009	Fex 2009	Sinclair 2009	Tong 2009	Ford-Anderson 2010	Ismail 2010	Namiki 2010	Smith 2010	Cases 2011	de Brito-Ashurst 2011	Humphreys 2011	Lai 2012	Lam 2012	Rygh 2012	Stanfill 2012	Tovazzi 2012	Urstad 2012	Walker 2012	Bennett 2013	Griva 2013	Karamanidou 2013	Krespi Boothby 2013	Theofilou 2013	Xi 2013
	Study																																												
Resisting impositions		•		•						•	•	•	•		•						•	•				•							•				•				•	•		
Mental invasion					•			•			•		•												•	•				•				•	•			•			•	•	•	•	
Withstanding physiological needs	•			•	•				•	•									•						•		•			•				•		•	•			•	•	•			
Optimizing health																																													
Accepting responsibility	•	•			•			•									•	•				•		•	•	•			•	•	•	•		•	•	•	•		•	•	•	•	•		
Valuing self-management	•	•			•				•		•	•			•	•	•		•		•	•	•	•	•	•	•	•	•	•	•	•		•	•	•	•	•	•		•	•	•		•
Preventing CKD progression		•														•						•				•								•											
Preparing for and protecting transplant		•	•																		•		•			•						•	•											
Becoming empowered																																													
Comprehending paradoxes	•	•		•	•			•	•	•	•	•										•			•	•	•			•		•		•			•		•	•	•	•		
Finding solutions		•		•	•				•	•	•						•		•			•		•	•		•			•		•		•	•		•		•		•	•	•	
Mastering change and demands	•	•		•	•			•	•	•	•	•					•		•			•		•	•	•	•			•		•		•			•		•		•	•	•	

Table 4 Quotations from participants and authors of primary studies to illustrate each theme

Themes	Quotations from participants in primary study
Preserving relationships	
Interference with roles	My kids accept it. They watch over me, you'd be surprised how they watch over. Family, you go out to eat with them and you order something, they say, 'You can't eat that'.[13]
	When I come in to treatment I will be looking at my tech like 'What is she going to say about me having all this fluid on?' I kind of look at her and see the look that she gives me like, 'Boy, you better stop that'.[14]
	You can't be sneaky. My son knows the routine: what type of medications I take, what I should be eating, and the like. I still like cashews. My husband and son look in all of my hiding places and find them…they always know when I'm eating them.[12]
Social limitations	No, it means that, you know, sometimes you go to someplace to eat and there's all this food laying around and you realize that if you don't eat, you know, you're either gonna not eating anything and/or, you know, offend somebody…Probably stuff I shouldn't eat, you know, but I'll eat it anyway just because he cooked it up for me you know.[13]
	People will think we are very poor and can't afford salt. They will think we are starving and have no money.[19]
	I don't have any social life now, although I could do but I don't trust myself to go to dinners or cocktail parties because of drinking and eating. I don't know what they are going to serve me up you know, could be very salty. So I dodge all this stuff. Far better you eat at home. You know that there is no salt in it.[16]
Being a burden	I want to have better health. I don't want to eat indiscriminately. If I do so, I'd suffer. It's okay if I can die, but I'd be a burden to others if I don t die. …I'd be a burden for the young [my children] because they'd have to come and visit me often. That would be a trouble.[5]
	With the fluid restriction, I think if I'm going to come here four hours, three times a week, and go home and drink what I want, eat what I want, then it's a complete waste of time. I'm wasting the nurses' time, I'm wasting the doctors' time, and I'm wasting my time, so while I'm on dialysis, I try to do the right thing.[14]
Navigating change	
Feeling deprived (dealing with loss)	It's not an easy diet by any means…its affects life's little pleasures.[23]
	Lots of changes...Well, my diet. It took away all my goodies.[13]
	Quitting isn't the most difficult. It's not being allowed to eat for the long term that's difficult. It's adhering to the dietary restrictions in every meal that's difficult. If you give me a time frame, such as telling me not to eat it for 1 month, that would be easy. If you say I'm not allowed to eat it for my whole life, that'd be difficult.[5]
	If I am going to live thirsty, I don't want to live.[24]

Themes	Quotations from participants in primary study
Disrupting held truths	I always tell dieticians that the dietary restrictions would make people starve. There are so many foods that I should eat just a little. …If I do as instructed by the dieticians, I'd die from starving.[5]
	I found my diet has been quite difficult… of all the healthy food I've been cooking it has had to stop.[20]
Breaking habits and norms	...it's a new life, an entire different life, new food, new intake of liquid and everything. Everything is different.[13]
	I feel cross being where I am at because I can't live my normal life like I used to. I can't just drink whatever I want to drink whenever I want to drink it...[14]
Overwhelmed by information	It's confusing. …The funniest thing is that they asked me what I ate because I didn't have any potassium. I told them I didn't eat those foods because they asked me not to eat them. They said I didn't have any potassium at all, and asked me to eat bananas because bananas contain potassium. Later, I had another blood test, after which they told me to stop eating bananas and eat like normal.[5]
	It is hard to know what to eat. They say less vegetables and fruits…I try to not eat soya beans no nuts…still high…still itchy…where am I going wrong?[15]
	I was so confused at the beginning but over years I learnt…[15]
Questioning efficacy	Not eating the foods before me doesn't mean that my test results would be better than if I ate them. With experience, you'd know and you'd continue eating.[5]
	Well the food they tell you to eat, it have no substance. It make you feel so weaky, weaky. If you could eat some of your back home food, maybe you could have a little strength in your body.[28]
	Doctors always tell me to follow restrictions more strictly whenever there's a problem. If that's always the case, anyone can be a doctor.[5]
Negotiating priorities	Half an hour I regret it but it happens again and again, and I struggle with that, and it becomes like a struggle between life and death.[24]
	I like to drink lots of water, even before I started dialysis. I try my best, but at the end of the day I'll be dead anyway.[24]
	I have the choice. I can choose to survive for 2 or 3 more years; I have to restrict my diet. I can also choose to neglect it if I don t want to survive. That's simple. If I want to be able to eat for a longer time, I should adhere to dietary restrictions. If not, I may as well choose to eat whatever I like. I'd suffer if I don t adhere to dietary restrictions. I wouldn't die immediately if I don t adhere, but it'd be even worse if I'm like half dead.[5]
Fighting temptation	
Resisting impositions	Just name anything, and you'd find out that I shouldn't eat it. There're too many foods that I shouldn't eat… It'd be impossible to refrain from eating those foods altogether, because there're too many of them. The list occupied four sheets of A4-sized paper, so you know how many there actually are.[5]
	My son says, ''Mama, that's not good.'' But I say, ''I'm 72, I'm going to eat what I want. It's not going to get better anyway. I'm so tired.[58]
	I was getting fed up of being told off, but I know she (the dietician) was doing good. Mum told me off about the diet and not sticking to it as well. It

Themes	Quotations from participants in primary study
	made me feel even more depressed so that I wanted to have something else.[30]
Mental invasion	And when I drink, I just don't like myself. When I have the water in my mouth then I don't want to swallow. You know when you are making love and you want to stop half way, how many people can control that. So when I have that water in my mouth it's like something is holding my hand, maybe god, and then I give up and I say, oh well I'll have it all.[24]
	I fail to resist, I am always thirsty, and my thoughts remain always fixed upon thirst and water… I can't resist, I can't find a way to avoid the drinking need; my thoughts are always fixated on the bottle, and I am always close to the fridge.[25]
	It's like fighting nature all the time because you want to drink all the time. You have to have a really strong will to do that... I get to the stage where I fantasize about it...[14]
Withstanding physiological needs	I think I will succeed in reducing fluid although I do not yet succeed in understanding: is not drinking beneficial for my body? Dehydration also derives from the fact that one doesn't drink. Do I have a problem with dehydration or not? Do you have this type of problem with your physiology?[25]
	I get so tired when I cut down on water.[50]
Optimizing health	
Accepting responsibility	I've taken actions such as being educated about dialysis, to take responsibility for my health and diet and I never miss my medications.[12]
	I love my food too and er…. I learnt the hard way, you know, er phosphates itching and you soon get fed up with that and learn the hard way if you like.[20]
	Every time I have follow-up, I ask the nurse to write them [the laboratory results] down for me as a reference, and tell me whether my sodium and phosphorus levels are high. If my sodium or potassium level is high, the doctor would warn me, and I'd adhere to dietary restrictions. …That s for my own reference, so I know how I should eat.[5]
Valuing self-management	If your attitude is right, I've got a, I've got a problem. I have a renal disease, but there's ways around it. I can go to dialysis, and if . . . I stick to the diet, and I do my treatment, and I take the medication, er, I can make a better quality of life for myself.[62]
	I oftentimes just think about me and what I need to do for me. Who is going to stop you from doing for you? Nobody. Help yourself.[29]
	… I don't have the prospect of a transplant, so I have to stay as well as possible. If I carry a regular weight I can hope to live another 10 years. This is the principal factor: to stay well with oneself, individual well-being.[25]
Preventing disease progression	I am very keen on controlling this quite fast, if I can, to avoid dialysis.[20]
Preparing for and protecting a transplant	I'm on the waiting list for a kidney transplant. Therefore, I must keep myself healthy. This is to ensure that when the hospital calls and tells me that there are kidneys for me, be immediately fit to undergo the operation. If my body can't tolerate the surgery or if I don t feel well when the hospital calls, I won't be allowed to undergo the surgery. I'll miss the chance then. That would be a pity because we've to wait for a very long time for a

Themes	Quotations from participants in primary study
	transplant.[5]
Becoming empowered	
Comprehending paradoxes	Well, I found it hard, what made it difficult for me was just getting myself adjusted to the regulations and so forth. Having to do things that had to be done. Of course, like, it was hard but then, all of a sudden, it became so customary, I more or less got used to it...I have found that you have to, because of the dialysis, you have to adjust yourself to the situation. Therefore, it automatically becomes more or less customary.[13]
	It's hard because I've to refer to it all the time. There're so many foods that I shouldn't eat. Now I've begun to get used to it.[5]
Finding solutions	I used to have a problem with potassium, but I think the dialyzers today are better and have largely solved that problem. I look at the blood work, and feel that the more I know the better I can juggle my diet.[12]
	That's when the nurses are really, really good at coming up with suggestions, alternatives and stuff like that. We had one patient that only ate like frozen meals. He didn't cook, he only had a microwave. And he would go and buy brands of, like, you know, those frozen TV dinners and that was basically his only source of nutrition. So, his primary nurse contacted the company to find out how much fluid they were putting in the gravy, how much potassium, how much sodium, how much whatever whatever each of his favorite meals was. And they, the company actually sent packets describing all of that so that the patient had a little library, like knowing which foods were high in phosphorous, potassium or sodium and that kind of stuff. So, that helped the patient adjust. Those sorts of things would help the patient adjust.[13]
Mastering change and demands	I don't know how you get people to stay on diets because it's all got to come from inside them and they've got to really want to do it and really, well, they've got to look after their health.[30]
	I've worked out what I can and can't do in certain stages of the dialysis cycle. So I just work around that.[14]

Figure 1: Results of search strategy and identification of publications included in the review

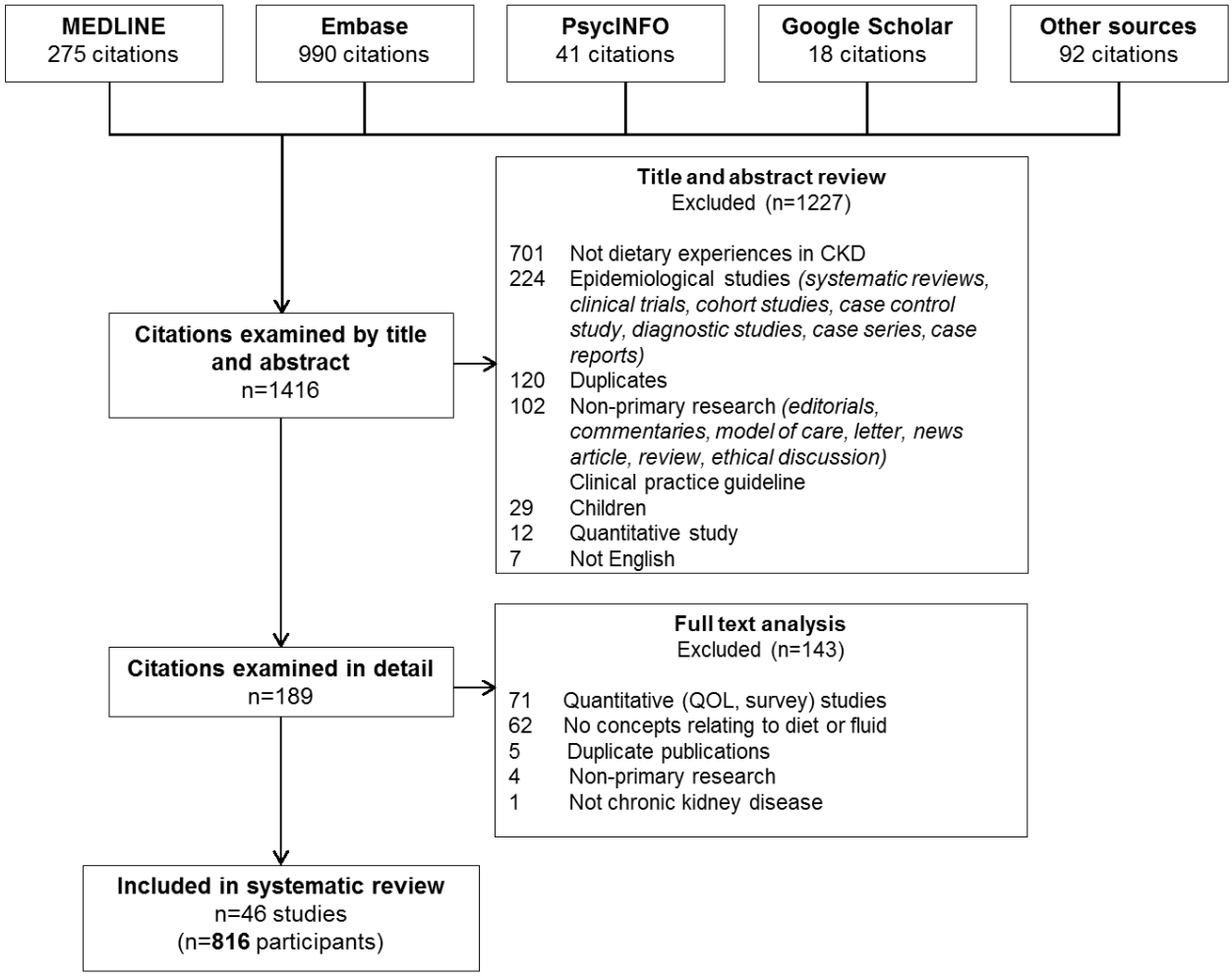
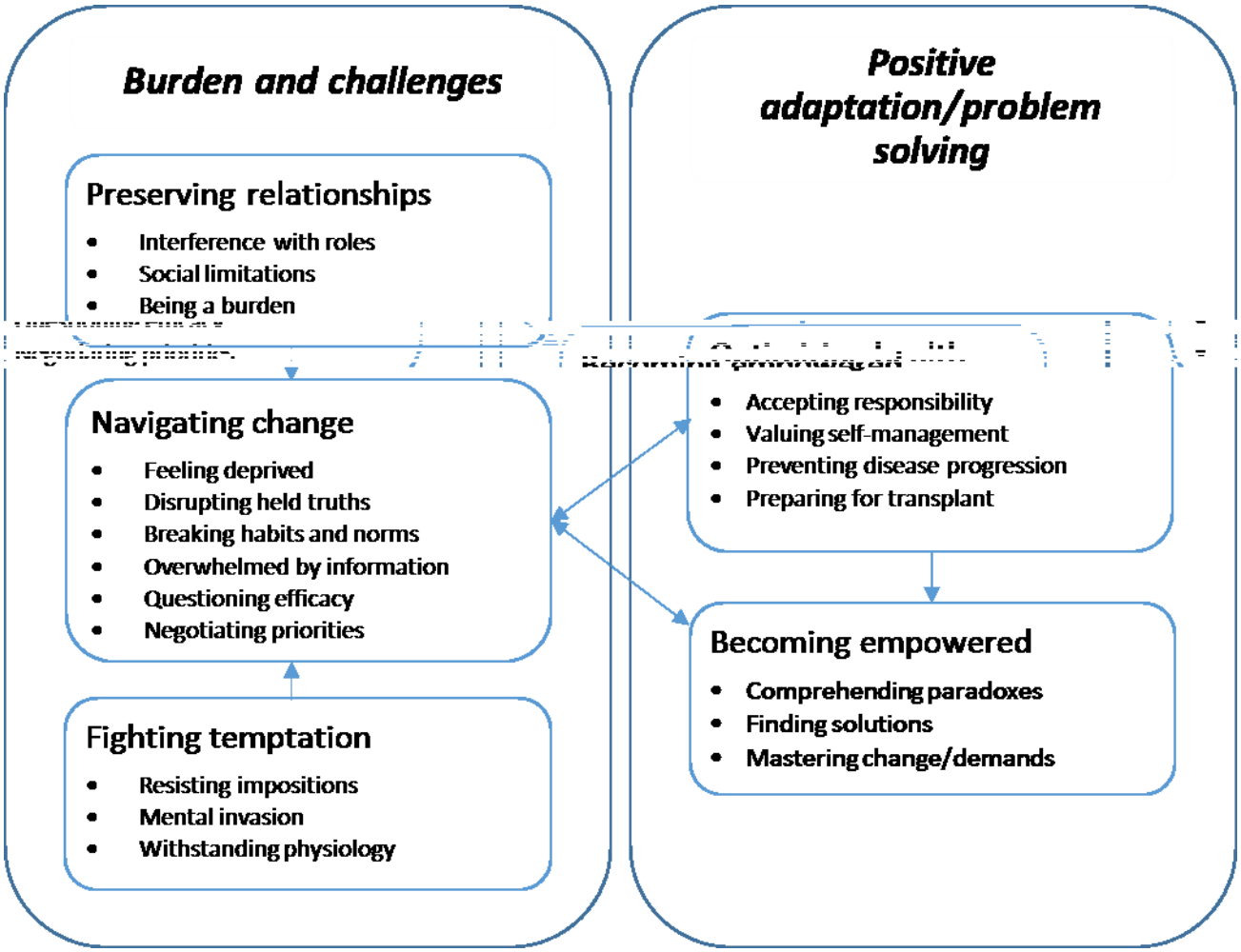


Figure 2: Conceptual framework for understanding patient's experiences of diet and fluid restrictions in chronic kidney disease



Conclusions and future perspectives

The aim of this body of work was to understand the impact of diet on CKD and ESKD and the association between nutrition and clinical adverse events in the setting of hemodialysis. The broader aim of the work of the research team in which I operate is to explore novel determinants of cardiovascular risk in people with CKD treated with hemodialysis, whose mortality is still very high and substantially unchanged during the past decades, despite introduction of multiple intervention, primarily but not only pharmaceutical.

The work done here has explored several factors related to nutrition in CKD and hemodialysis. Key findings have been generated, but also many studies confirmed the strong need for further research in the area, particularly in the form of primary studies, and namely intervention studies.

The first network meta-analysis run in the area of CKD/ESKD shows that there is insufficient evidence that any phosphate binding agent improves survival. Despite this, phosphate binding agents are broadly used in ESKD patients, their use is strongly promoted and advocated. There is a clear need for randomized trials to finally test the assumption that they would provide a survival advantage.

The second network meta-analysis, run in the area of diabetes management with glucose lowering agents, found no evidence of differences in the performance of any of the glucose lowering drugs (alone or in combination) on cardiovascular mortality, all-cause mortality, serious adverse events, myocardial infarction, or stroke, despite recommendations from global guidelines. This specific finding is reflective of the fact that even in an area where there is a strong development of new trials, these are primarily aimed at showing whether differences existing between drugs on surrogate biomarkers, while the data on survival remains scant. And, in general, there is no drug yet of proven superiority when it comes to survival, with the possible exception of SGLT2 inhibitors, proving that also this is a proper ground for further studies.

What this part of my thesis aimed to show is that even in areas of consolidated knowledge and practice, and related to nutrition (diabetes, phosphate control), the evidence remains suboptimal and guidelines provide strong statements which are and remain unsubstantiated by the evidence.

More specifically, the most relevant part of my PhD focused on dietary aspects related to CKD and ESKD/hemodialysis. The findings of the meta-analysis of cohort studies which opens this thesis showed that dietary patterns rich in vegetables and fruits, legumes, whole grains, and fiber

together with lower consumption of red meat, sodium, and refined sugars were consistently associated with reduced mortality in people with chronic kidney disease. This was the first cumulative assessment of whole dietary patterns and their impact on mortality and clinical complications in people with chronic kidney disease.

These associations, together with the possible beneficial effects of dietary modifications on risk factors for disease found in the review of randomized trials, suggested that dietary interventions remain an important research and clinical uncertainty in the setting of kidney disease. The data suggested that also the current evidence for dietary interventions in the setting of chronic kidney disease is of very low quality and insufficient to guide clinical practice.

When asking patients their perspectives about dietary and fluid management, our qualitative review showed that this is a disorienting challenge and intense burden for patients when adapting to and coping with different stages of CKD. The substantial number and complexity of restrictions on food and fluid exacerbates the impaired quality of life caused by CKD and has a profound impact on patients' relationships with others. This review found that over time, individual patients draw on the strength of achieving incremental dietary changes, motivations of a future kidney transplant, slowing CKD progression or feeling better as ways of sustaining dietary and fluid recommendations in their lives.

In all systematic reviews performed in this thesis, study quality was suboptimal, mortality was often an outcome not correctly evaluated and several methodological shortcomings were present. For this reason, we decided that our major contribution to the field of enquiry would be the design and conduct of a large primary study, the DIET HD prospective cohort study. This was designed and intended to be the largest multinational prospective cohort study investigating nutritional determinants of adverse clinical outcomes in hemodialysis. The study will include a large number of "a priori" defined analyses, of which the first I contributed to forms a fundamental part of this PhD. In the first analysis arising from the DIET study, there appeared to be no association between the dietary intakes of n-3 PUFA and cardiovascular and all-cause mortality among adults treated with hemodialysis, with only an apparent relationship between dietary intake of PUFA and mortality across countries. Mortality was inversely related to the national intake of n-3 PUFA. Furthermore, the lack of association between PUFA and mortality was consistent within individual countries.

All these findings together, and the ones we are further developing (individual investigators in our research team) support the design of primary intervention studies based around nutritional strategies in this population. The current evidence for dietary interventions is insufficient to guide clinical practice, as arised from the comprehensive systematic review of the existing literature, and possible beneficial effects of dietary interventions include clinically-important increases in health-related quality of life, lower blood pressure and serum LDL cholesterol levels and higher kidney function and serum albumin levels. These represent potential mechanisms for benefit of dietary modifications in larger trials, but the longer term impact of dietary changes needs to be examined.

Further research is needed to evaluate the impact of dietary patterns on hard clinical outcomes including mortality and cardiovascular endpoints in chronic kidney disease, focusing on outcomes that have been relatively under-researched, but are important causes of significant morbidity. Also, it is important to consider the variation in outcome measures routinely collected and reported in nephrology studies, which is intended to change, as the SONG initiative is currently exploring.

Future trials should be powered to assess dietary effects on these outcomes, together with a validated measure of health-related quality of life, to develop clinically-relevant studies and useful meta-analyses of dietary interventions, already planned as part of my post-doctoral work.