Article

Healthy Dietary Patterns and Risk of Mortality and ESRD in CKD: A Meta-Analysis of Cohort Studies

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Abstract

Background and objectives Patients with CKD are advised to follow dietary recommendations that restrict individual nutrients. Emerging evidence indicates overall eating patterns may better predict clinical outcomes, however, current data on dietary patterns in kidney disease are limited.

Design, setting, participants, & measurements This systematic review aimed to evaluate the association between dietary patterns and mortality or ESRD among adults with CKD. Medline, Embase, and reference lists were systematically searched up to November 24, 2015 by two independent review authors. Eligible studies were longitudinal cohort studies reporting the association of dietary patterns with mortality, cardiovascular events, or ESRD.

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 (3983 events; adjusted relative risk, 0.73; 95% confidence interval, 0.63 to 0.83; risk difference of 46 fewer (29–63 fewer) events per 1000 people over 5 years). There was no statistically significant association between healthy dietary patterns and risk of ESRD (1027 events; adjusted relative risk, 1.04; 95% confidence interval, 0.68 to 1.40).

Conclusions 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 grain, and fiber intake, and reduced red meat, sodium, and refined sugar intake could be effective tools to lower mortality in people with kidney disease.
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Introduction

CKD affects about 10%–13% of adults (1) and represents a public health challenge because of the substantially increased risks of death and cardiovascular disease among affected people (2,3). Patients who have CKD 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 given on the basis of individual nutrients or food groups instead of whole eating patterns, despite being 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 health care 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, whereas 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 end points, in order to establish the potential role of dietary patterns among people with CKD.

Materials and Methods

Our primary aim was to assess the association of healthy dietary patterns with the risk of mortality and ESRD in adults with CKD. This systematic review

followed a prespecified review protocol, was prospectively registered in the International Prospective Register of Systematic Reviews (21) and was reported using the preferred reporting items for systematic reviews and meta-analysis (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 CKD on November 24, 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 (95% CIs). We used definitions of CKD according to international clinical practice guidelines (4).

Data Extraction and Quality Assessment

Two authors (J.T.K. and S.N.W.) 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 that was 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 methodology to rate the quality of the evidence for mortality as high, moderate, low, or very low (24). Observational studies began as low quality evidence, but could be rated upward to moderate or high quality evidence if they collectively demonstrated a large magnitude of effect, or a dose–response gradient. Outcomes were death, health-related quality of life, ESRD, major cardiovascular events, BP, serum cholesterol, and major adverse events.

Data Synthesis and Analysis

We carried out analyses according to a predefined protocol to compare healthy eating patterns (generally higher intake of fruit, vegetables, cereals, legumes, whole grains, fiber, and fish, and lower intake of red meat, salt, and refined sugar) with 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 were calculated as a risk difference on

the basis of a 5-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 $<25\%$ considered as low heterogeneity and $>75\%$ 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 those involving adults with ESRD. We planned subgroup analyses on the basis of sex, duration of follow-up, study quality, and geographical region. Analyses were performed using Stata 13, with 95% CIs, 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 CKD (Table 1) (17,26–31). The participants were followed for between 4 and 13 years on average, totaling approximately 91,000 person-years of follow-up. All but one study involved people with CKD defined as an eGFR$<$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, 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 ESRD 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 the Grading of Recommendations Assessment, Development, and Evaluation (directness, precision, consistency, and study limitations) recommendations were considered, the evidence quality for all-cause mortality was considered low on the basis of the nonrandomized 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, 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% CI, 0.63 to 0.83) (Figure 2). There was no
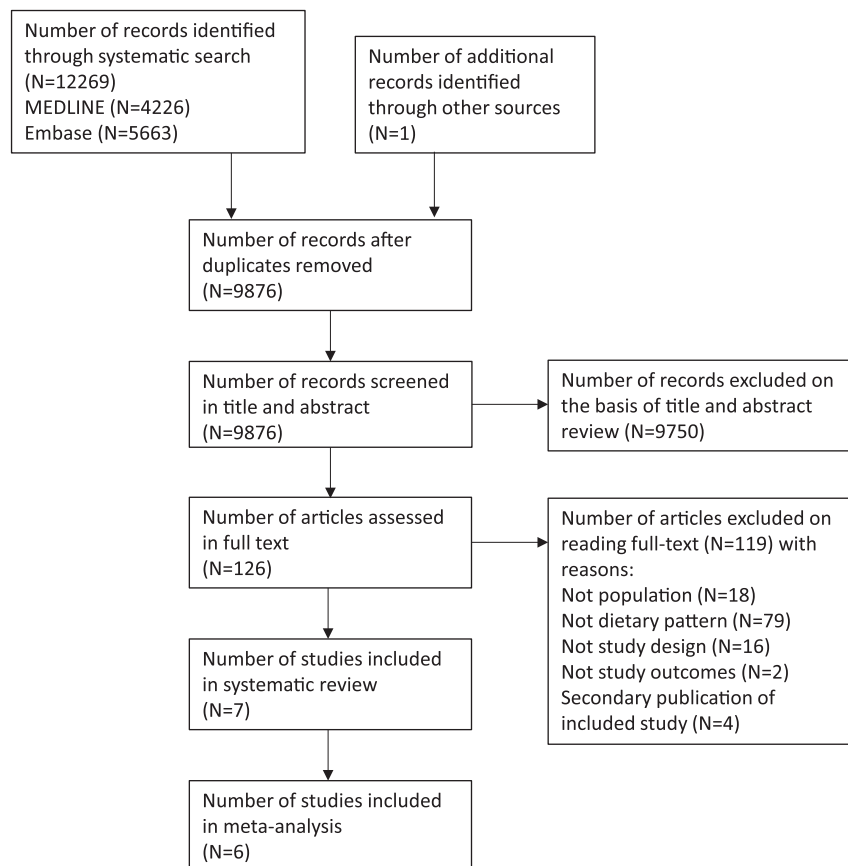
Figure 1. | **Flow chart describing process of study selection.**

heterogeneity between studies (I^2=0%) and no evidence of small study effects (Supplemental Figure 2). On the basis of an estimated 5-year mortality of 17% in people with CKD (25), the risk difference with a healthy dietary pattern compared with other dietary patterns was 46 fewer deaths per 1000 people (29–63 fewer) over 5 years.

ESRD. There was no evidence of an association between a healthy dietary pattern and risk of ESRD in three studies (*n*=10,071 people), with follow-up ranging from 4 to 6.4 years. The risk of ESRD among people with CKD was 1.04 (95% CI, 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, and BP. 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 (adjusted relative risk, 1.01; 95% CI, 0.47 to 2.18) (17). In a single study among 1355 dialysis patients, an "unbalanced dietary pattern" of high sodium and vegetable intake and lower fish and meat intake was associated with a higher risk of a composite of hospitalization because of cardiovascular disease or death because of any cause (31).

There was no reporting of health-related quality of life, cardiovascular-related death, adverse events, or hyperkalemia as individual end points. There was no information about

the effects of healthy dietary patterns on BP 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 on the basis of country of origin, age, duration of follow-up time, or quality of studies (Supplemental Table 3).

Discussion

This meta-analysis, comprised of 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 lower mortality in people with CKD. Existing cohort studies provide evidence of the association of healthy dietary patterns with risk of ESRD, major cardiovascular complications, and health-related quality of life, although there is considerable uncertainty in the results for these outcomes because of wide confidence intervals from meta-analyses that included few studies. To our knowledge, this is the first cumulative assessment of whole dietary patterns and

Table 1. Characteristics of included studies

First Author	Dietary Pattern	Country	Study Name	No. of Participants	Yr of Follow-Up (Person-yr)	Definition of Kidney Disease	Age at Entry, (Mean or Median)	eGFR, Mean±SD, ml/min per 1.73 m²	End Points (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 (6603)	eGFR<60 ml/min per 1.73 m²	20 yr 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 (25,421)	eGFR<60 ml/min per 1.73 m² or urine albumin-to-creatinine ratio >30 mg/g	45 yr or older (67.1–69.8 yr)	68.1 (SEM 0.8) (quartile 1)	All-cause mortality (816); ESRD (141)
Huang et al. 2013 (28)	Mediterranean diet	Sweden	Uppsala Longitudinal Study of Adult Men	506 men	9.9 (4648)	eGFR<60 ml/min per 1.73 m²	Approximately 70 yr	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, and carbohydrate)	United States	Reasons for Geographic and Racial Differences in Stroke (REGARDS) study	3093 men and women	4 (12,372)	eGFR<60 ml/min per 1.73 m²	45 yr or older (72.2 yr)		All-cause mortality (610); ESRD (160)
Ricardo et al. 2015 (17)	American Heart Association	United States	Chronic Renal Insufficiency Cohort (CRIC) Study	3006 men and women	4 (12,024)	eGFR of 20–70 ml/min per 1.73 m²	21–74 yr (58 yr)	43.39±13.34 (diet score 0)	All-cause mortality (437); CKD progression (50% decrease in eGFR or ESRD) (726); atherosclerotic events (355)
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 (29,744)	eGFR<60 ml/min per 1.73 m² or urine albumin-to-creatinine ratio >30 mg/g	20 yr or older (59 yr)	88.4±1.7 (SEM) (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 yr)	Dialysis	All-cause mortality or hospitalization because of cardiovascular disease (not reported)

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

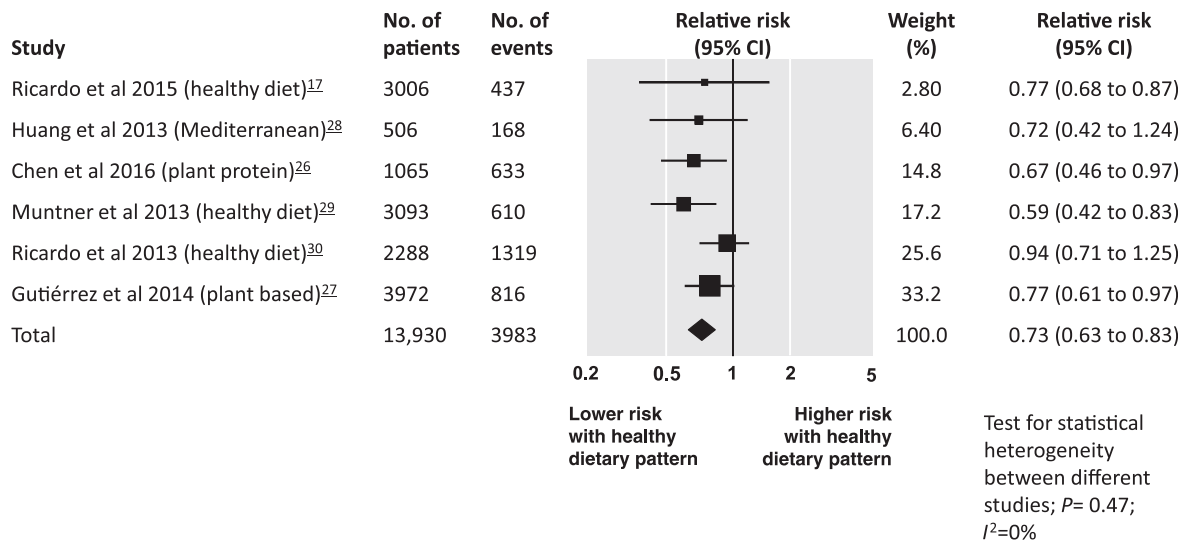| Study	Dietary Pattern	Dietary Exposure	Exposure Category	Reference Category	Covariates Included in Risk Ratio
Chen et al. 2016 (26)	Plant versus animal protein	Plant protein ratio quartiles (grains, fruits, vegetables, legumes, nuts, and seeds)	Quartile 4 >43.5% plant-to-protein ratio	Quartile 1 <25.3% plant-to-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, sex, 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, eGFR
Huang et al. 2013 (28)	Mediterranean diet	Mediterranean diet score (polyunsaturated fats/saturated fatty acids >0.34; vegetables and legumes >69 d; fruit >115 g/d; cereals and potatoes >361 g/d; fish >25 g/d; meat and meat products <92 g/d; milk and milk products <328 g/d; moderate alcohol intake >0.1)	High adherence (dietary score 6–8)	Low adherence (dietary score 1–2)	Body mass index, physical activity, smoking status, education, hypertension, hyperlipidemia, diabetes
Muntner et al. 2013 (29)	Diet score	Healthy diet score based on fish (≥servings/wk), fruit and vegetable consumption (≥4.5 cups/d), and sodium (<1500 mg/d), sugar (<450 kcal/wk), and fiber/carbohydrate ratio	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/d; fish >1.3 oz/wk; whole grains >0.88 oz/d; 24-hr urine sodium excretion <152 mEq/d; sweets/sugar-sweetened beverages <571 ml/wk)	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, eGFR, urine protein excretion
Ricardo et al. 2013 (30)	Healthy Eating Index based on Food Guide Pyramid	Healthy Eating Index based on ten 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, eGFR, microalbuminuria, diabetes, cardiovascular disease, cancer, systolic BP, 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, sex, dialysis duration, serum albumin, body mass index, energy intake, diabetes, coronary heart disease, cerebrovascular disease, peripheral vascular disease

Study	No. of patients	No. of events	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Ricardo et al 2015 (healthy diet)[17]	3006	437		2.80	0.77 (0.68 to 0.87)
Huang et al 2013 (Mediterranean)[28]	506	168		6.40	0.72 (0.42 to 1.24)
Chen et al 2016 (plant protein)[26]	1065	633		14.8	0.67 (0.46 to 0.97)
Muntner et al 2013 (healthy diet)[29]	3093	610		17.2	0.59 (0.42 to 0.83)
Ricardo et al 2013 (healthy diet)[30]	2288	1319		25.6	0.94 (0.71 to 1.25)
Gutiérrez et al 2014 (plant based)[27]	3972	816		33.2	0.77 (0.61 to 0.97)
Total	13,930	3983		100.0	0.73 (0.63 to 0.83)

0.2   0.5   1   2   5

Lower risk with healthy dietary pattern — Higher risk with healthy dietary pattern

Test for statistical heterogeneity between different studies; *P*= 0.47; I^2=0%

Figure 2. | **Risk of all-cause mortality associated with healthy dietary patterns among adults with CKD.** 95% CI, 95% confidence interval.

their association with mortality and clinical complications in people with CKD.

The association of healthy dietary patterns with lower mortality in people with CKD is in contrast to the lack of association of restrictions of individual dietary components for food groups including serum phosphorus (7,32,33), sodium (6), and protein (34) intake with mortality, although individual studies addressing these questions have had small sample sizes and low power to discern the relative association of nutritional modifications on clinical outcomes. 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 on Mediterranean diet, a primarily plant-based diet including extra virgin olive oil or nuts, there was no statistical evidence of lower mortality alone in people at high risk of cardiovascular events, while a Mediterranean dietary pattern lowered the risk of a composite of nonfatal 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 end point (18,36,37). As in our study, there is limited evidence for the association of eating patterns with risk of ESRD in the literature, although cohort studies suggest dietary patterns rich in fruit and vegetables may lower risk of progression to CKD and decrease albuminuria and BP (38–42).

Recent research in CKD has seen a shift from the decades-long focus on assessing and modifying single nutrient components of diet among people with CKD, reflected in practice guidelines (4), to an increasing analysis of whole dietary patterns. As a result, this study shows accumulating evidence over the last 5 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 on 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 CKD in the community, data supporting specific dietary patterns potentially has an important public health impact, and warrants the prioritization
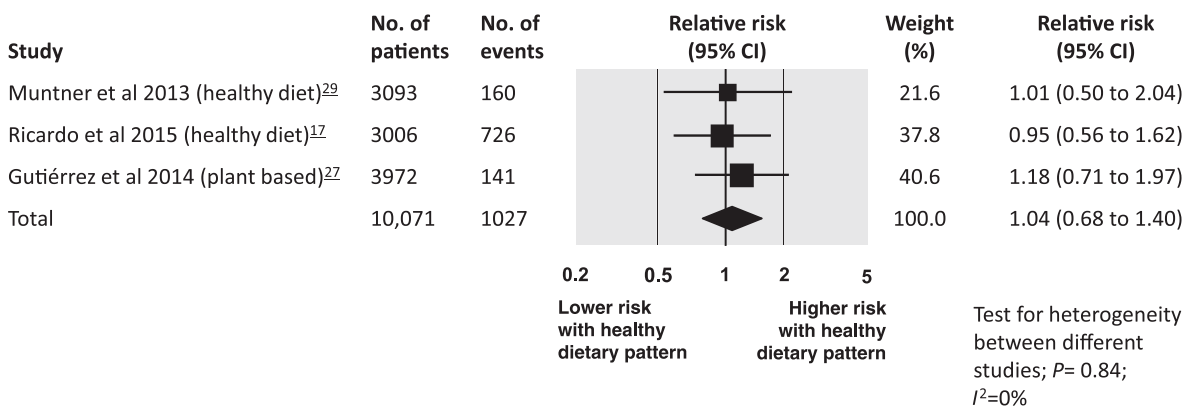
Study	No. of patients	No. of events	Relative risk (95% CI)	Weight (%)	Relative risk (95% CI)
Muntner et al 2013 (healthy diet)[29]	3093	160		21.6	1.01 (0.50 to 2.04)
Ricardo et al 2015 (healthy diet)[17]	3006	726		37.8	0.95 (0.56 to 1.62)
Gutiérrez et al 2014 (plant based)[27]	3972	141		40.6	1.18 (0.71 to 1.97)
Total	10,071	1027		100.0	1.04 (0.68 to 1.40)

0.2   0.5   1   2   5

Lower risk with healthy dietary pattern — Higher risk with healthy dietary pattern

Test for heterogeneity between different studies; *P*= 0.84; I^2=0%

Figure 3. | **Risk of ESRD associated with healthy dietary patterns among adults with CKD.** 95% CI, 95% confidence interval.

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 lower 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 ESRD, and lower risks when other sources of protein are substituted, further adds weight to the need to understand the association of whole food dietary patterns with clinical outcomes in the setting of kidney disease (44).

Although this study was prospectively planned and conducted independently by two authors, providing highly consistent findings among studies and precise risk estimates for the mortality end point, 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 on the basis of 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 eGFR<60–70 ml/min per 1.73 m^2 or albuminuria. Fourth, all of the studies included in meta-analysis for mortality were conducted in the 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 ESRD. ESRD is a rarer complication of CKD because of the competing risk of death; accumulated studies evaluating the associations of diet with 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 nonrandomized data, leading to the potential for the findings to be partly explained by residual confounding and leading to lower 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 lower mortality in people with CKD. 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, as well as the re-evaluation of dietary advice as a public health tool to lower mortality in people with kidney disease.

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