# Effect of Dietary Potassium Restriction on Serum Potassium, Disease Progression, and Mortality in Chronic Kidney Disease: A Systematic Review and Meta-Analysis

Morris, A., Krishnan, N., Kimani, P. K. & Lycett, D.



**Original citation & hyperlink:**
Morris, A, Krishnan, N, Kimani, PK & Lycett, D 2020, 'Effect of Dietary Potassium Restriction on Serum Potassium, Disease Progression, and Mortality in Chronic Kidney Disease: A Systematic Review and Meta-Analysis', Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation, vol. 30, no. 4, pp. 276-285. https://dx.doi.org/10.1053/j.jrn.2019.09.009

DOI 10.1053/j.jrn.2019.09.009
ISSN 1051-2276

Publisher: Elsevier

**Effect of dietary potassium restriction on serum potassium, disease progression, and mortality in chronic kidney disease: a systematic review and meta-analysis**

Mr. Andrew Morris MRes[1,2], Prof. Nithya Krishnan MD[2], Dr. Peter K. Kimani PhD[3], Prof. Deborah Lycett PhD[1]

**Authors' affiliations**

[1]Faculty of Health and Life Sciences, Coventry University, Priory Street, Coventry, CV1 5FB, UK ; [2] Renal Department, University Hospital, Clifford Bridge Road, Coventry, CV2 2DX, UK; [3]Warwick Medical School, University of Warwick, Coventry, CV4 7AL, UK.

**Authors' correspondence to:**

Mr Andrew Morris, Faculty of Health & Life Sciences, Coventry University,

Richard Crossman Building, Jordan Well, Coventry, CV1 5RW Telephone: +44 24 7765 5800, Email: ac5129@coventry.ac.uk

**Authors' contributions**

Research idea and study design: AM, DL; data acquisition: AM, DL, PKK; data analysis/interpretation: AM, DL PKK, NK; statistical analysis: AM, DL, PKK; academic supervision: DL; clinical supervision: NK. Each author contributed important intellectual content during manuscript drafting or revision.

## Abstract

### Objective

Low potassium diets are recommended to reduce serum potassium and prevent complications of chronic kidney disease (CKD); but evidence underpinning this recommendation has not been systematically reviewed and synthesised. We conducted a systematic review comparing change in serum potassium, CKD progression and mortality between those on a low versus unrestricted potassium diet.

### Methods

We searched Medline, AMED, PsychInfo, CINALH, Cochrane Central Register of Controlled Trials and Clinicaltrials.org from inception to 3 April 2018. We included randomised and observational studies that compared these outcomes in CKD adults who ate a restricted versus unrestricted amount of dietary potassium. We pooled mean change in serum potassium and adjusted hazard ratios of disease progression and mortality using random effects meta-analyses.

### Results

We identified 5563 articles of which seven studies (3489 participants) met our inclusion criteria. We found very low quality evidence that restricted (1295mg/d) versus unrestricted (1570mg/d) dietary potassium lowered serum potassium by -0.22mEq/L (95% CI: [-0.33, -0.10] $I^2$=0%). Lower (1725mg/d) versus higher (4558mg/d) dietary potassium was not significantly associated with disease progression (HR; 1.14, 95% CI: [0.77, 1.70] $I^2$= 57%). Lower (1670mg/d), compared with higher (4414mg/d) dietary potassium intake was associated with a 40% reduction in mortality hazard (HR; 0.60, 95% CI: [0.40, 0.89] $I^2$= 56%)].

### Conclusions

Very low quality evidence supports consensus that dietary potassium restriction reduces serum potassium in normokalaemia, and is associated with a reduced risk of death in those with CKD. High quality randomised controlled trials are needed.

**Introduction**

Serum potassium (Sk) > 5.5 mEq/L usually denotes hyperkalemia[1] although outlying thresholds of >6.0mEq/L or >7.0mEq/L exist. Hyperkalaemia, a common symptom of chronic kidney disease (CKD), affects 14 to 20% of the 30 million people worldwide with CKD;[2] it can lower resting cardiac membrane potential and increase cardiac conduction velocity, thereby increasing cardiac arrest risk.[3] Evidence suggests hyperkalaemia (≥ 5.5 and <6.0 mg/dl) in CKD is associated with an increase in one-day mortality risk (OR; 5.40 [95% CI: 4.72, 6.18]) ,[4] increased mortality risk after 15 years (RR 2.15, 95% CI [1.17-3.96])[5] and for every 0.1mEq/L rise in Sk ≥6.0 mEq/l, mortality risk may increase by 28%, although this association was not statistically significant to 1.28 (95%CI: [0.99-1.64]).[6]

Dietary potassium restriction assumes dietary potassium directly affects Sk level and is recommended around the world to treat hyperkalaemia in CKD.[7] However several inconsistencies exist.

Although laboratory studies on renal insufficient animals' demonstrate cardiac arrest with hyperkalemia from high potassium exposure [8] and dietary potassium restriction reduces serum potassium in hyperkalemia,[9] randomised controlled trial (RCT) evidence showing dietary potassium restriction causes a reduction in Sk appears limited. Case studies suggest that hyperkalemia (Sk >7.3mEq) is unrelated to a modified dietary potassium intake (58 mEq/day); but due to increased renal Sk secretion,[10] whereas cross-sectional studies suggest a positive association between dietary potassium and Sk.[11] As a result of this, clinical recommendations for dietary potassium restriction CKD are often opinion based; and

inconsistent across countries. For example, actual body weight (1mEq/K+/kg/ ABW),[12] ideal body weight (1mEq/K+/kg/IBW),[13] and a set range of 2000-2500mg/day (50-65mmol/day) are all used to calculate individual dietary potassium.[14] Hyperkalaemia threshold levels for dietary potassium management CKD stages also differ, for example, stage 4 interventions vary; from Sk >5.5mEq/L in the UK[15] to 6.0mEq/L in Australia.[16] Such inconsistencies raise the question as to how effective and necessary dietary potassium restriction in CKD actually is? This is particularly important, as a qualitative synthesis of evidence shows that dietary potassium restriction is detrimental to quality of life,[17] is difficult to follow, even when supported by renal dietitians,[18] and is consistently associated with poor general well-being and psychological stress.[19-22]

The objectives of this review were to assess the effect of dietary potassium restriction on serum potassium, and the association of potassium intake with CKD progression and mortality in CKD

## Methods

### Search strategy and selection criteria

This review was conducted and reported in accordance with published guidelines [23,24] using a pre-specified protocol and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines.[23] The search strategy (available in the supplementary table S1) was created by two experienced review authors (AM, DL). We searched Medline, CINAHL, AMED, PsychInfo, Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials and Clinicaltrials.org databases since inception to 4 April 2018. Medical subject headings (MeSH) terms, and keywords including: (Food or Diet or Nutrition or Nutritional Therapy) and (Potassium or Hyperkalemia or Hypokalemia) and (Renal or Kidney or Kidney Diseases, or Kidney Transplantation) were used. The search strategies

were adapted for each database. The search was limited by study type to include reviews, clinical trials and cohort studies. No language limitation was applied. Clinical trial databases were searched for unpublished literature. Conference abstracts were included and where there was no full publication, authors were contacted to provide data. Conference abstracts were rejected if we could not obtain the full text article from authors. We manually searched reference lists of relevant articles and clinical guidelines identified in the previous step and conducted a forward citation search of narrative reviews on dietary potassium in CKD. Two investigators reviewed each article to confirm eligibility using a study protocol. A third investigator was consulted where there was disagreement so consensus could be achieved.

We included studies on adults with any stage of CKD including dialysis or transplantation. We excluded studies where there was no intentional difference between dietary potassium intake or urinary potassium (Uk) level in the intervention and control group, or between exposure conditions. Eligible interventions/exposures provided potassium from food, oral nutritional supplements, enteral nutrition, or any combination of these. RCTs, non-randomised clinical trials and cohort study designs were included. We excluded adults with acute kidney injury, animal studies, laboratory studies, qualitative studies, and case studies. The outcomes were serum potassium, disease progression and all-cause mortality. We excluded studies that did not report these outcomes.

**Data Extraction**

Two investigators extracted the data independently using a data extraction form (supplementary form S1). The results of the data abstraction were compared by a third investigator after the review of the articles was complete. The investigators were not blinded to the authors and the institution of the studies undergoing review. Data extracted from intervention studies included: study type, population characteristics, description of

intervention and control conditions, number of patients included, baseline and follow-up of outcomes of interest. Data was only used once if several studies published data from the same participants. From observational studies we collected data on cohort characteristics, time to follow-up, dietary or urinary potassium, details of adjusted confounders, and outcomes, disease progression and mortality events in the lowest and highest dietary potassium exposure groups. For some studies, the reference category for the log hazard ratio inference was an intermediate category, rather than the lowest or the highest category. In such cases, the standard error (SE) for the log hazard ratio between the lowest and highest exposure groups was approximated as the square root of the sum of the squares of the two SEs for the log hazard ratios comparing the reference category to the lowest and highest groups. This assumes log hazard ratio estimates are independent.

We requested any relevant missing information from original study authors. Risk of bias and quality of the included studies were assessed by using the RCT /Non-RCT Cochrane review risk of bias criteria.[25] For RCTs the risk of bias identified as high, low or unclear was assessed for the method of sequence generation, allocation concealment, blinding, selective reporting, loss to follow-up, and completeness of reporting outcome data. The ROBINS-I tool was used to assess risk of bias in observational studies as per published guidelines.[25] The certainty of the overall evidence related to each outcome was assessed by two investigators using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[26] Certainty was assessed against the following domains: risk of bias, inconsistency, imprecision, indirectness and publication bias.

**Data synthesis**

We compared dietary potassium restriction to no dietary potassium restriction or low to high dietary potassium intakes or urinary potassium. Where a study had more than one intervention group or several levels of exposure we compared the lowest or most restricted potassium intake with the least restricted or highest intake. We estimated total dietary potassium intake assuming a 77% excretion rate of total dietary potassium intake per day. [27] For continuous outcomes (e.g. Sk change) we pooled the mean differences. For time to event outcomes (e.g. mortality) we pooled the log hazard ratios from models which adjusted for confounders. We used random effect models in all meta-analyses because of high heterogeneity between trial interventions meaning that exactly the same effect was not expected from each. One investigator input the data into Review Manager Software.[28] A second investigator checked the data entry for accuracy. We quantified heterogeneity using the $I^2$ metric and used the chi-squared to test if the heterogeneity was statistically significant. $I^2$ >75% alongside a statistically significant heterogeneity was considered to indicate substantial heterogeneity.[25] A priori sub-analysis grouping similar interventions, study type, population (dialysed or not) and time to follow-up were considered. Sensitivity analysis to examine the effect of removing studies at high risk of bias from the analysis was also considered. Results were taken as statistically significant at $p<0.05$.

**Results**

Our search yielded 5,563 publications (figure 1) that included key words. Of these, 5,558 studies were identified by the electronic search strategy and five from the reference lists of narrative reviews. After removing duplicate publications, irrelevant publications and studies that did not meet the inclusion criteria, 580 articles were examined in further detail, of which 573 were excluded at full text stage.

**Figure 1: Study selection**

Two RCTs [29,30] and five observational studies[31-35] were included, with a total of 3489 adults with CKD stages 3, stage 4, and stage 5 on heamodialysis, and post-transplant ≥ one year. At the first visit from enrolment Sk were all within normal biochemical range i.e. no studies reported baseline hyperkalaemia. One RCT in CKD stage 3 prescribed an intervention of 1 mEq/kg/d of potassium over 24 months versus no dietary restriction in the control group, unless Sk>6mEq/L, then a restriction of 1mEq/L/kg/ IBW/d was prescribed.[29] The other RCT exposed participants with end-stage renal failure (ESRF) to highly controlled amounts of potassium, from the content of a renal specific oral nutritional supplements (250.5mg/ 220ml), which were used as a sole source of nutrition over three weeks and compared to generic oral nutritional supplements (296mg/ 220ml).[30] There was no intentional overlap between the amount of dietary potassium in the intervention and control conditions across these trials.

Norri et al.[31] observational cohort study reported four quartiles consuming potassium at 879 ±161 mg/d, 1342 ±109 mg/d, 1852 ±217 mg/d and3440 ±969 mg/d. Eisenga et al.[32] reported three urinary potassium quartiles over 3.1 years: 48.2±11.0 mEq/L/24h, 70.6± 7.8mEq/l/24h and 98.9± 16.7 mEq/L; He et al.[33] reported four quartiles over 5 years 30.5±6.6 mEq/L/24h, 45.9±3.7mEq/L/24h, 59.0±4.3mEq/L/24h and86.1±24.4mEq/L/24h; Leonberg-Yoo et al.[34] reported four baseline urinary potassium quartiles over 6.1 median follow-up years: 1.41± 0.27g/d, 2.01± 0.14g/d, 2.54± 0.20g/d and 3.60 ±0.66g/d; and Nagata et al.[35] compared <1.5g/d, 2.0-2.5g/d and 2.5-3.0g/d over 5.47 mean follow-up years. Further characteristics of included studies, with quartiles used in the meta-analyses and the estimated total dietary intake from Uk are listed in table 1.

**Table 1: Study characteristics meeting the inclusion criteria**

There was low risk of bias for all key domains in one RCT[29] and unclear risk of bias was present across most domains in the other RCT[30]. Confounding bias and selection bias from study datasets were present in this RCT[30]. Across the four cohort studies reporting Uk outcome, there was serious risk of bias due to confounding, selection of participants, missing data and measurement of outcomes. There was moderate risk of bias across selection of reported results. There was severe to moderate risk of bias across one cohort study reporting long term mortality data.

Sk was stated as a primary outcome in both RCTs.[29,30] In one RCT,[29] a prescribed reduction of 1mmol/kg IBW/d dietary potassium resulted in a greater reduction from baseline at 24 month follow-up (-0.2 ±0.64mEq/L) when compared to an unrestricted diet (-0.05±0.64mEq/L). Within the intervention group, however, 47.6% of participants on a dietary restriction received a mean 19.8±7.8g/d sodium polystyrene sulfonate to maintain Sk ≤4.5mEQ/L over a mean time of 19.5±5.4 months. The second RCT was of short duration and at final follow up (22 days from baseline visit) the mean Sk was lower in the dietary restricted group taking lower potassium oral nutritional supplements (251mg/220ml) (total potassium intake on days 12-21was1128-1279mg/d) than the unrestricted group (total potassium intake on days 12-21 was 1390-1567mg/d) on standard oral nutritional supplements (296mg/220ml).[30] The intervention group showed a greater mean reduction from baseline by -0.5 mEq/L than the control group (-0.3mEq/L).

Pooling these results in a meta-analysis showed that at the final follow-up, the mean Sk in the restricted (1295 mg/d, see table S2 for estimation) was lower than the mean Sk in the non-

restricted (1570 mg/d) group (mean difference -0.22mEq/L, [95%CI:-0.33, -0.10], P=0.0002, $I^2$=0%).

**Figure 2: Change in serum potassium between baseline and follow- up in those restricting dietary potassium versus those eating an unrestricted diet**.

Adults consuming lower intakes (1725mg/d) were 14% more likely to experience a decline in kidney function (as measured by minimum reduction of 5% in eGFR) (HR 1.14; 95% CI: 0.77-1.70, P=0.5); compared to those with higher intakes (4558mg/d) at follow-up (figure 3); although this was not a statistically significant result.

**Figure 3: Meta-analysis of adjusted hazard ratios of CKD progression comparing lowest to highest urinary potassium between 3 to 5 year follow-up**

Participants consuming low levels of dietary potassium (1670mg/d) had 40% lower risk of death (HR 0.60; 95% CI: 0.4, 0.89, P=0.01) compared to those who consumed higher amounts of dietary potassium (4414mg/d) at follow-up between three to five years (figure 4).

**Figure 4: Meta-analysis of adjusted hazard ratios for risk of mortality comparing lowest to highest urinary and dietary potassium between 3 to 5 years**

Qualities of Evidence (GRADE) for three outcomes, analysed change in serum potassium, morbidity and mortality were analysed (table 2). Very low quality evidence from the RCTs comparing dietary potassium restriction to unrestricted diet favoured reducing baseline serum

potassium. Observational studies provided very low quality evidence that a lower intake of dietary potassium compared to a higher intake of dietary potassium is associated with a reduced mortality risk, but not with reduced disease progression. No details on the baseline confounding and selection of participants were reported in the observational studies to make an informed decision; therefore this evidence was downgraded by one.

**Table 2: GRADE quality of evidence summary**

## Discussion

Dietary potassium restriction may reduce baseline normokalaemic serum potassium levels, in those with CKD, when compared to a higher potassium intake. However, the effect we saw was driven by one RCT where dietary potassium was strictly controlled (33.2 ±3.37 mEq) and possibly unattainable eating normal foods as participants received a manufactured liquid diet as a sole source of nutrition. Nonetheless, the control diet was also a relatively low potassium intake (40.2±3.85 mEq) and was considered a low intake in the cohort studies, and within clinical practice. Therefore, the reduction in serum potassium may have been greater when compared with a truly unrestricted diet.

It is unclear whether restricting dietary potassium is associated with a reduced risk of CKD progression but our results suggest that they may be associated with a reduction in all-cause mortality in CKD. However these results are based on very low quality evidence and there is a high risk of uncertainty around them. Nonetheless, this is the first pooling of the evidence to date and suggests that the body of available evidence does support the practice of dietary potassium restriction in those with normokalemia in CKD. However, there are still no studies testing its effects in those with hyperkalemia.

Our meta-analyses results are in keeping with Kidney Disease Improving Global Outcomes clinical guideline that potassium supplementation cannot be recommended in any stage of CKD (non-dialysis) to reduce blood pressure, 36 due to the lack of definitive studies 37. We acknowledge though, that our meta-analysis is based on very low quality evidence. Our meta- analyses also offers support to current opinion that dietary potassium intakes should be limited to 2000-2500mg/d (50-65mmol/d) in CKD stage 5 on maintenance haemodialysis, to help maintain normokalemia.[14]

From the meta-analysis of these observational studies, we found little evidence to support the guidelines for reducing potassium intake in CKD stages 3-4 to prevent progression. However, we did find evidence to show dietary restriction may be associated with a reduction in all-cause mortality in those with CKD stages 3-5. In view of this we would recommend dietary potassium restriction continues to be practiced in these stages, however, this is informed by very low quality evidence. Furthermore, pathophysiological evidence that reducing potassium intake reduces the polarising effect of potassium on cardiac cells[3] remains controversial. Without further investigation the real effect of dietary restriction on serum potassium and all-cause mortality remains unknown

We note that our results were limited by the inclusion of a small number of studies each of which had their own limitations. Additionally pooling data resulted in heterogeneity; however this difference was not statistically significant as per our defined criteria ($I^2$>75%).

Measurement of dietary potassium is problematic due to the known inaccuracies of self-reported dietary data.[27] However we compared the highest with the lowest exposures and

were careful to remove studies where there was no actual difference between exposures to dietary potassium.

We also ensured that the urinary potassium quartiles did not overlap which offered some reassurance that dietary exposure was different, between the lowest and highest group. Taking urinary potassium as a surrogate marker of dietary potassium intake has limitations too; Uk may not be an exact match for dietary intake, and it may not reflect total body potassium stores.[38] A fractional absorption rate of 77% in healthy adults has been reported,[27] but the rate in CKD is less well known, although one included observational study reported Uk and dietary potassium intake correlated well in CKD ($r=0.44$, $p<0.001$).[32]

Nonetheless, these limitations are characteristic of all such studies and not a unique limitation to our study. However, publication bias was not assessed using funnel plot asymmetry due to the small number of included studies. We therefore assumed bias was present when considering the overall quality of evidence.

While we suggest, based on current available evidence, it is prudent to continue to restrict dietary potassium in individuals with CKD, there are important questions that remain unanswered and a definitive trial is needed. Such a trial would include a clear difference between dietary potassium intake in the control and intervention groups. Dietary advice would need to be achievable in 'free-eating' individuals and adherence checked by also measuring urinary potassium. As well as the need for this in those with normokalaemia, investigating the effects in those with hyperkalemia is also urgently required.

**Practical Application**

Dietary potassium restriction does seem a prudent approach in normokalaemic chronic kidney disease to keep potassium levels low and reduce mortality risk, but this is based on very low quality evidence. With no quality of life quantitative data around following dietary potassium restrictions to inform practice, it would seem sensible to check for any reported adverse impact of a low potassium diet on a person's lifestyle, and discuss alternative approaches to achieving the desired level of dietary potassium.

**Conflict of interest**

We declare no competing interests.

**Funding Sources**

The National Institute of Health Research was not involved in the study design; collection, analysis, and interpretation of data; writing the report; and the decision to submit the report for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

**References**

(1) Alfonzo A, Soar J, MacTier et al. Treatment of Acute Hyperkalaemia in Adults. 2014 UK Renal Association.

(2) Gilligan S, Raphael KL. Hyperkalemia and Hypokalemia in CKD: Prevalence, Risk Factors, and Clinical Outcomes. ADV CHRONIC KIDNEY DIS 2017; 24(5):315-318

(3)Kovesdy CP. Management of hyperkalemia: an update for the internist. The American journal of medicine. 2015 Dec 1; 128(12):1281-7.

(4)Einhorn LM, Zhan M, Walker LD, Moen MF, Seliger SL, Weir MR, Fink JC. The frequency of hyperkalemia and its significance in chronic kidney disease. Archives of internal medicine. 2009 Jun 22; 169(12):1156-62.

(5)Iseki K, Iseki C, Ikemiya Y, Fukiyama K. Risk of developing end-stage renal disease in a cohort of mass screening. Kidney Int 1996; 49(3):800-805.

(6)Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study. American journal of nephrology. 2016; 44(3):179-86.

(7)Turakhia MP, Blankestijn PJ, Carrero JJ, Clase CM, Deo R, Herzog CA, Kasner SE, Passman RS, Pecoits-Filho R, Reinecke H, Shroff GR. Chronic kidney disease and arrhythmias: conclusions from a kidney disease: improving global outcomes (KDIGO) controversies conference. European heart journal. 2018 Mar 7;39(24):2314-25.

(8) Hiatt N, Katayanagi T, Miller A. Cardiac sensitivity to hyperkalemia in adrenalectomized dogs. Proceedings of the Society for Experimental Biology and Medicine. 1975 May;149(1):168-71.

(9) Segev G, Fascetti AJ, Weeth LP, Cowgill LD. Correction of hyperkalemia in dogs with chronic kidney disease consuming commercial renal therapeutic diets by a potassium-reduced home- prepared diet. Journal of veterinary internal medicine. 2010 May; 24 (3):546-50.

(10) Berlyne GM, Janabi KM, Shaw AB. Dietary treatment of chronic renal failure. Proc R Soc Med 1966; 59(7):665-667.

(11) Sanlier N, Demircioğlu Y. Correlation of dietary intakes and biochemical determinates of nutrition in hemodialysis patients. Ren Fail 2007; 29(2):213-218.

(12) Thomas B, Bishop J. Manual of dietetic practice. Blackwell publishing; 2007.

(13) Wiggins KL. Guidelines for Nutritional Care of Renal Patients, 3rd Edn. Renal Dietitians Dietetic Practice Group, American Dietetic Association. Chicago: American Dietetic Association; 2002.

(14) European Guidelines for the Nutritional Care of Adult Renal Patients. 2003. European Dialysis and Transplantation Nurses Association/ European Renal Care Association (Edtna/Erca) Journal, 29(1), s1-s23.

(15)Wright M, Jones, C. Nutrition in CKD. UK renal Association 5th Edition. 2010

(16)Ash S, Campbell K, MacLaughlin H, McCoy E, Chan M, Anderson K, Corke K, Dumont R, Lloyd L, Meade A, Montgomery- Johnson R. Evidence based practice guidelines for the nutritional management of chronic kidney disease. Nutrition & Dietetics. 2006 Sep; 63: S33-45.

(17)Palmer SC, Hanson CS, Craig JC, Strippoli GF, Ruospo M, Campbell K, Johnson DW, Tong A. Dietary and fluid restrictions in CKD: a thematic synthesis of patient views from qualitative studies. American Journal of Kidney Diseases. 2015 Apr 1;65(4):559-73.

(18)St-Jules DE, Woolf K, Pompeii ML, Sevick MA. Exploring problems in following the hemodialysis diet and their relation to energy and nutrient intakes: The BalanceWise Study. Journal of Renal Nutrition. 2016 Mar 1; 26(2):118-24.

(19)Morris A, Love H, van Aar Z, Liles C, Roskell C. Integrating renal nutrition guidelines into daily family life: a qualitative exploration. Journal of Human Nutrition and Dietetics 2018; 31(1):3-11.

(20)Morris A, Love H, van Aar Z, Liles C, Roskell C. The problematic world of following a renal diet outside the home. Journal of renal care 2015; 41(4):253-259.

(21)Hollingdale R, Sutton D, Hart Facilitating dietary changes in renal disease: investigating patients' perspectives. Journal of Renal Care 2008; 34(3):136-142.

(22)Stevenson J, Tong A, Gutman T, Campbell KL, Craig JC, Brown MA, Lee VW. Experiences and Perspectives of Dietary Management among Patients on Hemodialysis: An Interview Study. Journal of Renal Nutrition. 2018 Apr 22.

(23)Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151(4):264-269.

(24)University of York. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. : University of York, Centre for Reviews & Dissemination; 2009.

(25) Green S, Higgins J. Cochrane handbook for systematic reviews of interventions. 2005

(26) Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008; 336(7650):924-926.

(27) Holbrook JT, Patterson KY, Bodner JE, Douglas LW, Veillon C, Kelsay JL, Mertz W, Smith Jr JC. Sodium and potassium intake and balance in adults consuming self-selected diets. The American journal of clinical nutrition. 1984 Oct 1;40(4):786-93.

(28) Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

(29) Arnold R, Pianta TJ, Pussell BA, Kirby A, O'Brien K, Sullivan K, et al. Randomized, controlled trial of the effect of dietary potassium restriction on nerve function in CKD. Clinical Journal of the American Society of Nephrology 2017; 12(10):1569-1577.

(30)Cockram DB, Hensley MK, Rodriguez M, Agarwal G, Wennberg A, Ruey P, et al. Safety and tolerance of medical nutritional products as sole sources of nutrition in people on hemodialysis. Journal of Renal Nutrition 1998;8(1):25-33.

(31) Noori N, Kalantar-Zadeh K, Kovesdy CP, Murali SB, Bross R, Nissenson AR, et al. Dietary potassium intake and mortality in long-term hemodialysis patients. Am J Kidney Dis 2010;56(2):338-347.

(32) Eisenga MF, Kieneker LM, Soedamah-Muthu S, den Berg Ev, Deetman PE, Navis GJ, et al. Urinary potassium excretion, renal ammoniagenesis, and risk of graft failure and mortality in renal transplant recipients. Am J Clin Nutr 2016; 104(6):1703-1711

(33) He J, Mills KT, Appel LJ, Yang W, Chen J, Lee BT, Rosas SE, Porter A, Makos G, Weir MR, Hamm LL. Urinary sodium and potassium excretion and CKD progression. Journal of the American Society of Nephrology. 2016 Apr 1;27(4):1202-12.

(34) Leonberg-Yoo AK, Tighiouart H, Levey AS, Beck GJ, Sarnak MJ. Urine potassium excretion, kidney failure, and mortality in CKD. American Journal of Kidney Diseases. 2017 Mar 1;69(3):341-9.

(35) Nagata T, Sobajima H, Ohashi N, Hirakawa A, Katsuno T, Yasuda Y, Matsuo S, Tsuboi N, Maruyama S. Association between 24h urinary sodium and potassium excretion and estimated glomerular filtration rate (eGFR) decline or death in patients with diabetes mellitus and eGFR more than 30 ml/min/1.73 m2. PloS one. 2016 May 2;11(5):e0152306.

(36) Kidney Disease: Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO Clinical Practice Guideline for the Management of Blood Pressure in Chronic Kidney Disease. Kidney inter., Suppl. 2012; 2: 337–414.

(37) Taler SJ, Agarwal R, Bakris GL, Flynn JT, Nilsson PM, Rahman M, Sanders PW, Textor SC, Weir MR, Townsend RR. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for management of blood pressure in CKD. Am J Kidney Dis. 2013 Aug;62(2):201-13

(38) Sandle GI, Gaiger E, Tapster S, Goodship TH. Evidence for large intestinal control of potassium homoeostasis in uraemic patients undergoing long-term dialysis. Clinical science. 1987 Sep 1;73(3):247-52.

**Tables, Figures, and Supplements**

Table

| **Studies** | **Population** (Mean baseline eGFR) | **Study type** | **Length of study** | **Patients on a reduced potassium intake (outcome: (Sk) serum potassium, (Uk) urinary potassium)** | **Amount of dietary potassium consumed per day on a reduced intake (estimated from urinary potassium * or actual intake)** | **Patients exposed to higher potassium intakes (outcome: (Sk) serum potassium, (Uk) urinary potassium)** | **Amount of dietary potassium consumed per day on a higher intake (estimated from urinary potassium*or actual intake)** |
|---|---|---|---|---|---|---|---|
| Arnold et al (2017) | Adults with CKD stage 3 and 4, 47-73 years, eGFR 27-43 ml/min per1.73m² | Randomised controlled trail | 24 months intervention | n=21(Sk)<br>diet prescription of 1mEq/kg/IBW | 3248±204mg/24hour | n=21(Sk)<br>no dietary prescription unless >6mEq/L | 4029±178mg/24hour |
| Cockram et al (1998) | Adults with CKD stage 5 on heamodialysis, 44-56 years. | Randomised controlled trial | 3 weeks intervention | n=52(Sk)<br>oral nutritional supplements (251mg/K+/220ml) | 1129.5-±125.5mg/24hour** | n=27(Sk)<br>oral nutritional supplements (296mg/K+/220ml) | 1361.6±148mg/24hour** |
| Eisenga et al (2016) | Adults with CKD stage 3 who had received a renal transplant >1 year previously, 40-66 years, e GFR 32-72ml/min per 1.73m² | Observational study | 37 months follow-up | n=235 (Uk)<br>Urinary potassium excretion 48.5±11.0mEq/24hour | 2453.1±553.8mg/24hour | n=235 (Uk)<br>urinary potassium excretion 98.9±16.7mmol/24hour | 5007.6±842.4mg/24hour |
| He et al (2016) | Adults with CKD stage 3, 21-74 years | Observational study | 48 month follow-up | n=939 (Uk)<br>excretion 30.5±6.6mEq/24 hour | 1544.4±179.4mg/24hour | n=940 (Uk)<br>excretion 86.1±24.4mmol/24hour | 4360.2±1232.4mg/24hour |
| Leonberg-Yoo et al (2017) | Adults with CKD stage 3, 18-70 years | Observational study | CKD progression median follow-up 6.1 years (3.5-11.7) , mortality follow-up 19.2 (10.8-20.6) | n=209 (Uk)<br>excretion 1.41±0.27g/d = 1410±270mg/d = 36.1±6.9mEq/24hour | 1825.2±347.1mg/24 hour | n=200 (Uk)<br>excretion 3.60±0.66g/d =3600±660mg/ 24hour = 92.3±16.9mEq/24hour | 4672.2±854.1mg/24hour |
| Nagata et al (2016) | Adults with eGFR <60ml/min/1.73m but >30ml/min/1.73m mean age 62.2(±10.9) years | Observational study | 65.6 month mean follow-up | n=242 (Uk)<br>excretion 1.23±0.21g/d =1230±210g/d =31.5±5.3mEq/24hour | 1595.1±460.2mg/24hour | n= 144 (Uk)<br>excretion 3.64±0.62g/24hour =3640±620mg/24hour =93.3±15.8mEq/24hour | 4722.9±799.5mg/24hour |
| Noori et al (2010) | Adults with ESRF on maintenance heamodialysis | Observational study | 60 month follow-up | n= 56 (Sk)<br>dietary intake 879±161 mg/24hour | 879±161 mg/24hour | n=56 (Sk)<br>dietary intake 3,440±969 mg/24hour | 3440±969 mg/24hour |

**Table 1 : Characteristics of included studies**

**Notes**
* Assuming 77% of total dietary potassium intake is excreted (Holbrook et al.1984)
** The combined mean and SD from day 8 to 21 were calculated. Both EN-9528 and EN-9529 were pooled as lowest potassium intakes. Pooled SD were calculated used Cohen (1988) method
**Conversions**
Mg converted to mEq of potassium by dividing by atomic mass of potassium (taken as 39)

**Table 2: GRADE summary of evidence**

| Certainty assessment | | | | | | | № of patients | | Effect | | Certainty | NNT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| № of studies | Study design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | Dietary potassium restriction | No dietary potassium restriction | Relative (95% CI) | Absolute (95% CI) | | Numbers needed to treat |
| **Change in serum potassium** | | | | | | | | | | | | |
| 2 | randomised trials | very serious [a] | not serious | not serious | not serious | publication bias strongly suspected [b] | 45 | 46 | - | MD **0.22 mEq lower** (0.33 lower to 0.1 lower) | ⨁◯◯◯ VERY LOW | - |
| **CKD progression (assessed with urinary potassium)** | | | | | | | | | | | | |
| 4 | observational studies | serious [c] | serious [d] | very serious [e] | serious [f] | publication bias strongly suspected [g] | 401/1625 (24.7%) | 265/1519 (17.4%) | **HR 1.14** (0.77 to 1.70) | **22 more per 1,000** (from 37 fewer to 104 more) | ⨁◯◯◯ VERY LOW | **NNT 14** |
| **Mortality (assessed with urinary potassium and dietary potassium)** | | | | | | | | | | | | |
| 4 | observational studies | serious [c] | serious [h] | very serious [e] | serious [f] | publication bias strongly suspected [i] | 234/1439 (16.3%) | 242/1431 (16.9%) | **HR 0.60** (0.33 to 0.89) | **64 fewer per 1,000** (from 110 fewer to 17 fewer) | ⨁◯◯◯ VERY LOW | **NNT 167** |

**CI:** Confidence interval; **MD:** Mean difference; **HR:** Hazard Ratio

## Explanations

a. Cockram et al. 1998 influenced the overall effect but did not report how participants were selected, allocated to groups. There was an intentional difference in dietary exposure, however, both groups could have been exposed to the same amount of dietary potassium. Blinding of participants may have been possible as the cartons of nutritional supplements may have been generic, but it is not known. Blinding of outcome assessment was unknown. Arnold et al. (2017) >40% of the intervention group received potassium binding medication to achieve the target serum potassium level.
b. Both studies have reported that a lower potassium intake results in a greater change from baseline in the intervention groups.
c. All studies had serious risk of bias across 5 domains (bias due to confounding, bias in selection of participants, bias due to deviations from intended interventions, bias due to missing data/ lost to follow-up and bias in measurement of outcomes).
d.Heterogeneity substantial as per GRADE ($I^2$= 57%)
e. Urinary potassium used as a surrogate of dietary potassium intake
f. Large confidence intervals around effect size
g. Publication biased not assessed - bias assumed.
h. Substantial heterogeneity as per GRADE ($I^2$= 56%)
i. Assumed publication bias as too few studies to complete funnel plot. All three urinary studies report the same effect.

Figure 1

Figure 1 Study selection

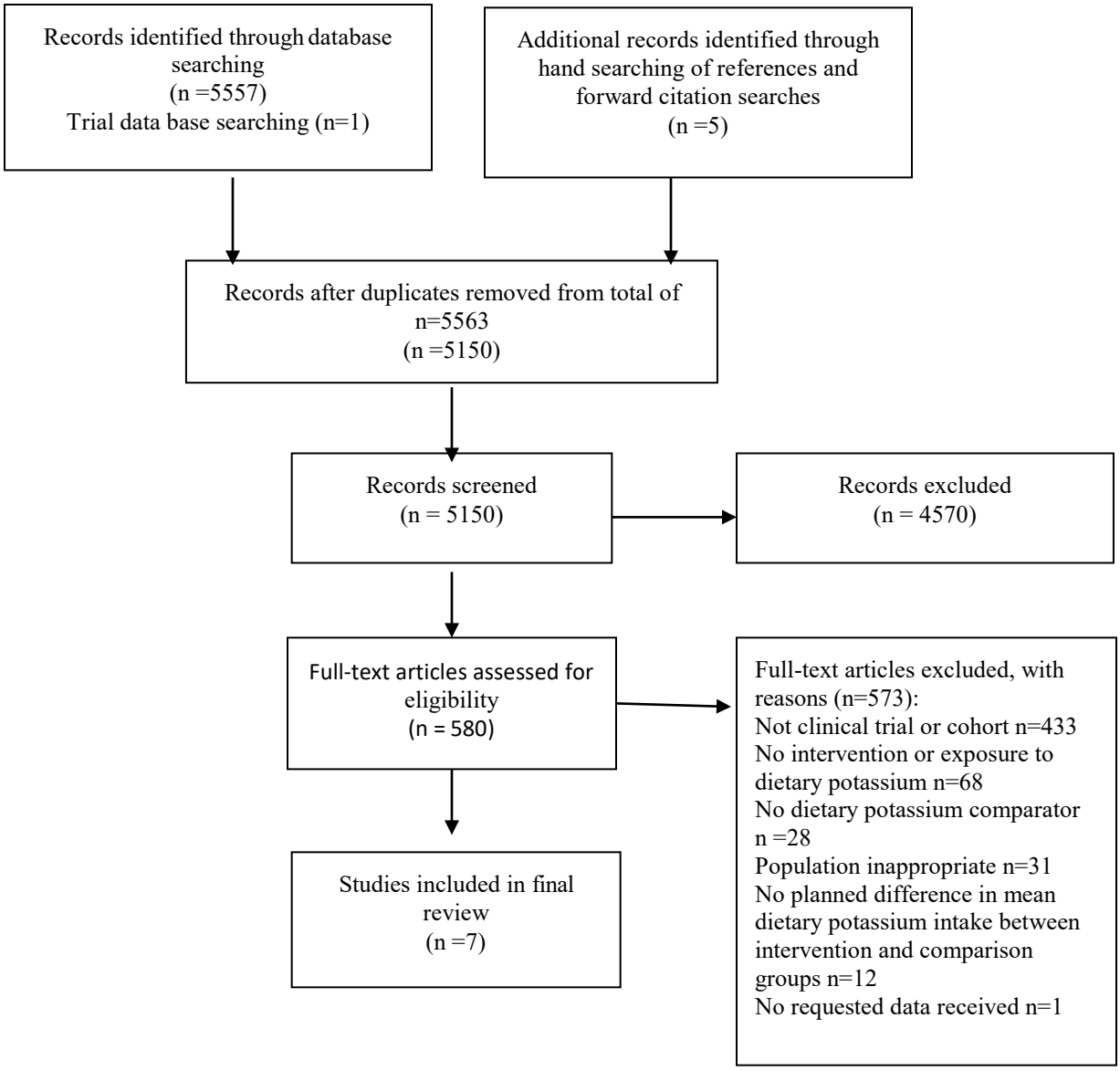


**Figure 2: Change in serum potassium between baseline and follow- up in those restricting dietary potassium versus those eating an unrestricted diet.**

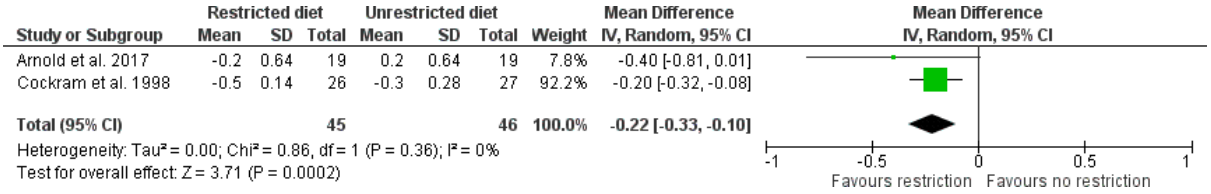
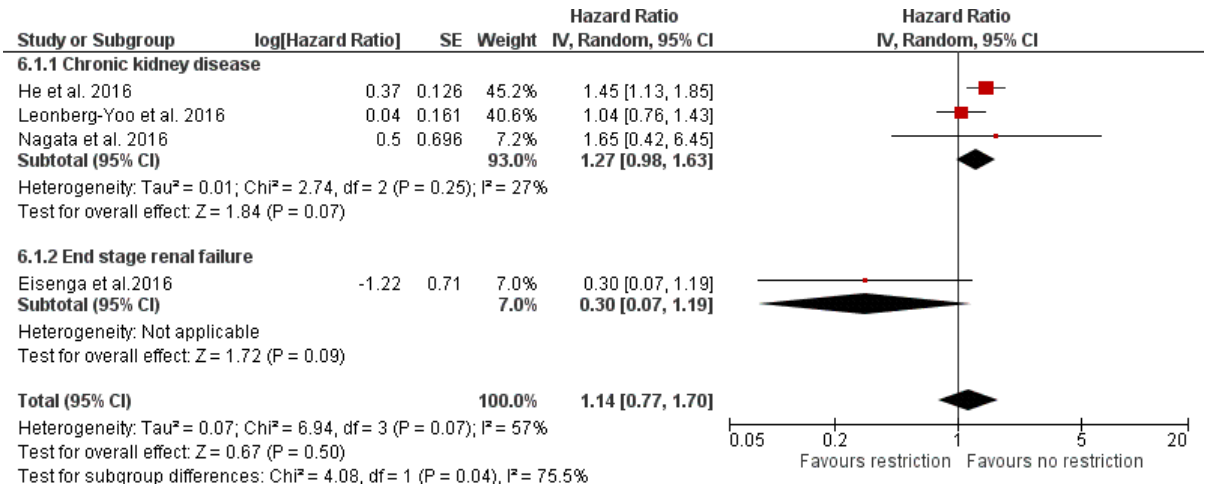



**Figure 3: Meta-analysis of adjusted hazard ratios of CKD progression comparing lowest to highest urinary potassium between 3 to 5 year follow-up**




Note: Nagata et al. contained deaths (n=2) within the morbidity data.

**Figure 4: Meta-analysis of adjusted hazard ratios for risk of mortality comparing lowest to highest urinary and dietary potassium between 3 to 5 years**

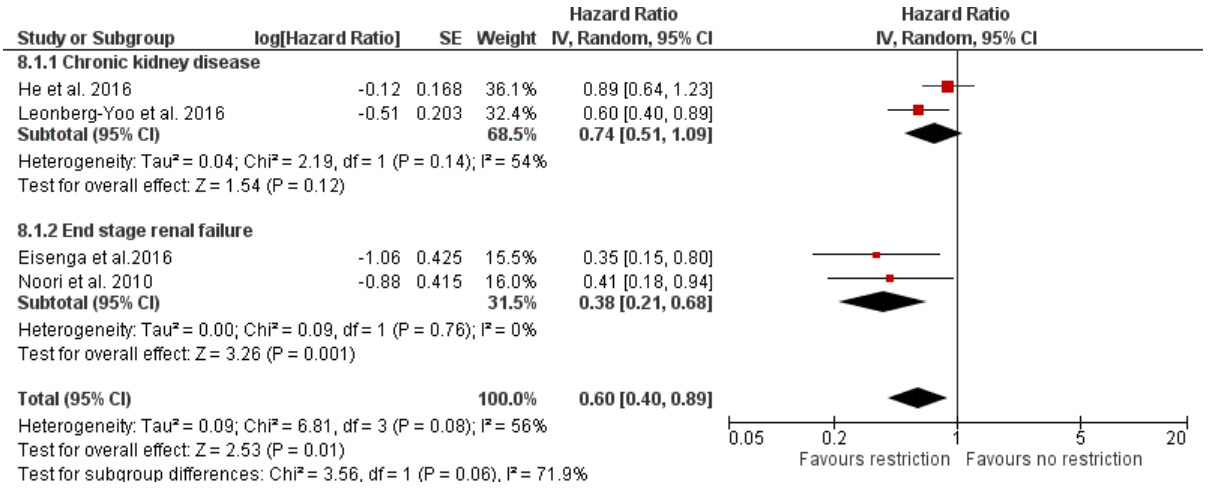


Table S1 Electronic Search Strategy

| | | | | |
|---|---|---|---|---|
| S13 | (S1 OR S2 OR S3 OR S4 OR S5 OR S6) AND ( S7 OR S8 OR S9) AND ( S10 OR S11 OR S12) | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 5,557 |
| S12 | (DE "KIDNEY") OR (DE "RENAL DIALYSIS") OR (DE "KIDNEY FAILURE CHRONIC") OR (DE "KIDNEY TRANSPLANTATION") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 155,724 |
| S11 | (MH "Kidney Diseases+") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 536,485 |
| S10 | renal* or kidney* | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 1,138,572 |
| S9 | (DE "POTASSIUM") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 17,295 |

| | | | | |
|---|---|---|---|---|
| S8 | (MH "Potassium")OR (MH "Hyperkalemia")OR (MH " Hypokalemia") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 113,736 |
| S7 | Potassium or Hyperkal* or Hypokal* | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 282,446 |
| S6 | (DE "NUTRITION") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 44,822 |
| S5 | nutrition* | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 659,455 |
| S4 | (DE "DIET")OR (DE "FOOD") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 216,524 |
| S3 | renal diet* | Search modes - Find all my | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; | 34,068 |

| | | | | |
|---|---|---|---|---|
| | | search terms | AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | |
| S2 | (MH "Diet+") OR (MH "Restricted Diet+") OR (MH "Renal Diet") OR (MH "Diet Therapy+") OR (MH "Diet Records") OR (MH "Nutrition Therapy+") OR (MH “Nutritional Requirements”) OR (MH "Nutritional Support") OR (MH "Enteral Nutrition") OR (MH "Parenteral Nutrition+")OR (MH "Food Preferences") | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 426,728 |
| S1 | Diet* or Food* | Search modes - Find all my search terms | Interface - EBSCOhost Research Databases<br>Search Screen - Advanced Search<br>Database - CINAHL Complete; AMED - The Allied and Complementary Medicine Database; MEDLINE; PsycINFO | 1,598,725 |

Table S2: Estimating dietary potassium intake and contribution to the pooled effect in the meta-analysis

| Study | % contribution to meta-analysis inclusion for change in baseline Sk | % contribution to meta-analysis of morbidity | % contribution to meta-analysis of mortality | Mean amount of dietary potassium consumed per day on a reduced intake (estimated from urinary potassium or actual intake) | Mean amount of dietary potassium consumed per day on a higher intake (estimated from urinary potassium or actual intake) | Weighted mean amount of dietary potassium consumed per day | | Weighted mean amount of dietary potassium consumed per day - morbidity | | Weighted mean amount of dietary potassium consumed per day - mortality | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Reduced intake | Higher intake | Reduced intake | Higher intake | Reduced intake | Higher intake |
| Arnold et al (2017) | 7.8% | | | 3248±204mg/24hr | 4029±178mg/24hr | 253.3mg/24hour | 314.2mg/24hr | | | | |
| Cockram et al (1998) | 92.2% | | | 1129.5-±125.5mg/24hr | 1361.6±148mg/24hr | 1041.4mg/24hr | 1255.4mg/24hr | | | | |
| Eisenga et al (2016) | | 7.0% | 15.5% | 2453.1±553.8mg/24hr | 5007.6±842.4mg/24 hr | | | 171.7 mg/24hr | 350.5 mg/24hr | 380.2mg/24hr | 776.2 mg/24hr |
| He et al (2016) | | 45.2% | 36.1% | 1544.4±179.4mg/24hr | 4360.2±1232.4mg/2 4hr | | | 697.9mg/24hr | 1970.8 mg/24hr | 557.5mg/24hr | 1574.0 mg/24hr |
| Leonberg -Yoo et al (2017) | | 40.6% | 32.4% | 1825.2±347.1mg/24hr | 4672.2±854.1mg/24 hr | | | 741.0mg/24hr | 1896.9 mg/24hr | 591.4mg/24hr | 1513.8 mg/24hr |
| Nagata et al (2016) | | 7.2% | | 1595.1±460.2mg/24hr | 4722.9±799.5mg/24 hr | | | 114.8 mg/24hr | 340.0 mg/24hr | | |
| Noori et al (2010) | | | 16.0% | 879±161 mg/24hr | 3440±969 mg/24hr | | | | | 140.6mg/24hr | 550.4 mg/24hr |
| Total weighted mean | | | | | | 1294.7mg/24 hr | 1569.7 mg/24hr | | | | |

Table S2: Estimating dietary potassium intake and contribution to the pooled effect in the meta-analysis

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Total weighted mean | | | | | | | 1725.5mg/24hr | 4558.3mg/24hr | | |
| Total weighted mean | | | | | | | | | 1669.7mg/24hr | 4414.4 mg/24hr |

Figure S1

**Data Extraction Form**

Date……..

Reviewer one or two (please circle)

**Study details**

Author

Publication type

Design (including intervention type, ethical approval, randomisation etc.)

Study duration

Participants (setting, recruitment, age, sex, race CKD stage, co-morbidities)

Country

**Study groups**

Please include description of intervention, number of groups receiving intervention, duration of intervention, delivery and timing of intervention and by whom, compliance, drop-outs, co-interventions e.g. K+ binding medication, laxatives, insulin etc.

Intervention group

Dietary potassium intervention group

Urinary potassium intervention group

Comparison group

Dietary potassium comparison group

Urinary potassium comparison group

**Outcomes**

Please include outcome name, time points measured and reported, units, validated collection tools/techniques, power calculation, missing data, and baseline population risk noted.

**Was there a true difference between exposure to dietary potassium between the intervention and comparison groups?**

Please provide evidence, e.g. show calculations if undertaken to inform your decision, confidence intervals with an explanation.

**Dietary potassium**

True difference in intervention

True difference in comparison

**Urinary potassium**

True difference in intervention

True difference in comparison

**Reviewer's decision**

Review inclusion decision

Inclusion/ exclusion rationale

Meta-analysis inclusion decision

Inclusion caveats, if applicable. If none, state NONE.

**Peer reviewer's decision**

Include/ exclude (please circle)

Rationale