Renal function in relation to sodium intake: a quantitative review of the literature

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We undertook a quantitative literature review to search for evidence underpinning current guidelines proposing a reduction of sodium intake to less than 2.4 g/d for the management of chronic kidney disease. We searched PubMed for peer-reviewed articles published from January 1980 through May 2016. Two investigators screened 5072 publications and extracted data from 36, including 11 cross-sectional and 5 longitudinal observational studies and 20 intervention trials. Within-study effect sizes were pooled and standardized to a sodium gradient of 100 mmol/d by using inverse-variance weighted random effects models. Among cross-sectional studies, the pooled odds ratio for albuminuria was 1.23 (95% confidence interval [CI], 0.92–1.64, $P = 0.16$), and the pooled mean difference in glomerular filtration rate amounted to 8.5 ml/min (CI, -2.3 to 19.2 ml/min; $P = 0.12$). In the cohort studies, the pooled relative risk of a renal endpoint was 1.08 (CI, 0.92–1.29; $P = 0.35$). In the intervention trials (median duration, 14 days [range, 4–186 days]), the mean differences in estimated glomerular filtration rate and albuminuria (high vs. low sodium intake) averaged 4.6 ml/min (CI, 3.4–5.8 ml/min; $P < 0.0001$) and 53% (CI, 21–84; $P = 0.001$), respectively. Cochran's Q statistic indicated significant heterogeneity among cross-sectional studies for both estimated glomerular filtration rate and albuminuria ($P < 0.0001$) and among intervention trials for albuminuria ($P = 0.04$). In conclusion, there is no robust evidence suggesting that long-term reduction of salt intake would prevent chronic kidney disease or delay its progression. However, our current findings, which were mainly obtained in people with slight renal impairment, cannot be extrapolated to patients with moderate or severe chronic kidney disease.

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Sodium chloride (NaCl), commonly known as table salt, consists of ~40% sodium and ~60% chloride. One level teaspoon of salt contains approximately 2.3 g of sodium. To convert a gram of sodium to a gram of salt, the gram of sodium is multiplied by 2.5. To convert millimoles of sodium to grams of sodium, the amount of sodium in millimoles is multiplied by 0.0231. To convert millimoles of sodium to grams of NaCl, the amount of sodium in millimoles is multiplied by 0.0585.

Chronic kidney disease (CKD) is a major health problem affecting millions of people and draining scarce health care resources. In the United States, CKD, defined as an estimated glomerular filtration rate (eGFR) of less than 60 ml/min per 1.73 m^2, increased from 10.0% in the years 1988–1994 to 13.1% in the years 1999–2004.[1] Furthermore, the Global Burden of Disease Study 2010 investigators estimated that of the nearly 50 million deaths occurring annually throughout the world, 0.40 million were attributable to CKD in 1990 and 0.74 in 2010, representing an increase of 82.3%.[2] Across all ages, over the same time span, the years lived with CKD increased by 57.1%, from 2.56 to 4.03 million,[3] and the disability-adjusted life years, a metric that captures both premature mortality and the prevalence of ill health, increased by 51.7%, from 13.9 to 21.1 million.[4]

Dietary interventions that could prevent CKD, delay its progression, or decrease disease-specific mortality might complement traditional strategies, such as controlling blood pressure and diabetes or inhibiting the renin-angiotensin-aldosterone system. Recent guidelines propose a dietary sodium intake of less than 2.4 g daily (6.0 g NaCl)[5] or less than 2.0 g daily (5.0 g NaCl) for patients with CKD.[6] In populations with or at increased risk of CKD, including African Americans, seniors (≥55 years), and patients with diabetes or hypertension, the recommendation is to decrease dietary sodium intake to less than 1.5 g/d (3.8 g NaCl).[7] On the other hand, a recent Institute of Medicine report, *Sodium Intake in Populations: Assessment of Evidence*,[8] failed to find robust evidence to support the aforementioned guidelines. Furthermore, the Institute of Medicine has cautioned against sodium intake of less than 1.5 g/d as being potentially

harmful. Based on the Institute of Medicine report, the revised American Guidelines[9] recommend a sodium intake of less than 2.3 g/d (5.8 g NaCl) for the general population. In view of this ongoing controversy, we undertook a quantitative review of the literature to assess the evidence on which recent guidelines[5–7,9] are based.

RESULTS

Our literature search generated 5072 PubMed hits. Figure 1 illustrates the selection of studies. Of the 247 full-text papers we read, 36 studies, including 73,482 participants, fulfilled the inclusion criteria and provided enough data to be included in at least one meta-analysis. Of these, 11 were cross-sectional studies,[10–20] 5 were longitudinal cohort studies,[21–25] and 20 were intervention trials.[26–45] The weighted means of sodium intake were similar among studies in which consumption was assessed by means of spot urine samples[13,16,17,19] (mean, 156 mmol/d; range, 96–209 mmol/d)[16,17] and 24-hour urine collections[10,11,14,15,20,22,24,25] (mean, 158 mmol/d; range across individual studies, 142 –180 mmol/d),[11,15] whereas the questionnaire approach including food frequency questionnaires[18,21,23] and 24-hour dietary recall[12] resulted in slightly lower estimates (mean, 128 mmol/d; range, 88–213 mmol/d; $P = 0.50$).[21,23]

Cross-sectional studies

The main characteristics of the cross-sectional studies are presented in Table 1. Seven studies were population based,[10,12,13,15–18] and 2 had been conducted in diabetic patients[14,19] or hypertensive subjects.[11,20] Sodium intake was estimated from spot urine samples in 4 studies,[13,16,17,19] from 24-hour urine collections in 5,[10,11,14,15,20] from a food frequency questionnaire in 1,[18] and from dietary recall in 1.[12] Of the 11 cross-sectional studies, 8 were focused on albumin excretion[12,14,15,19] or the urinary albumin-to-creatinine ratio[13,16–18] as a dichotomous[12–15,17–19] or continuous outcome.[16] Estimated GFR was reported in 6 cross-sectional studies.[10–14,20] The quality assessment of each study, according to the method proposed by the Agency for Healthcare Research and Quality,[46,47] is illustrated in Supplementary Table S1. All but 2 studies[14,15] had a high risk of bias for 1 or more items in the Agency for Healthcare Research and Quality checklist.

Glomerular filtration rate. Figure 2 shows, for each study, the difference in mean eGFR between the high and low sodium exposure groups rescaled to a between-group difference in estimated sodium intake of 100 mmol/d. In three studies[10,12,13] eGFR was significantly higher in the high sodium exposure group as compared with the low sodium exposure group. The pooled difference in eGFR between high and low sodium intake did not reach statistical significance (weighted mean difference, 8.5 ml/min; 95% confidence interval [CI], -2.3 to 19.2 ml/min; $P = 0.12$. Both the Cochran Q (1269.8, $P < 0.0001$) and the I^2 statistics (99.6%) showed substantial heterogeneity between studies.

Albuminuria. As shown in Figure 3, the association between albuminuria and sodium intake was positive in

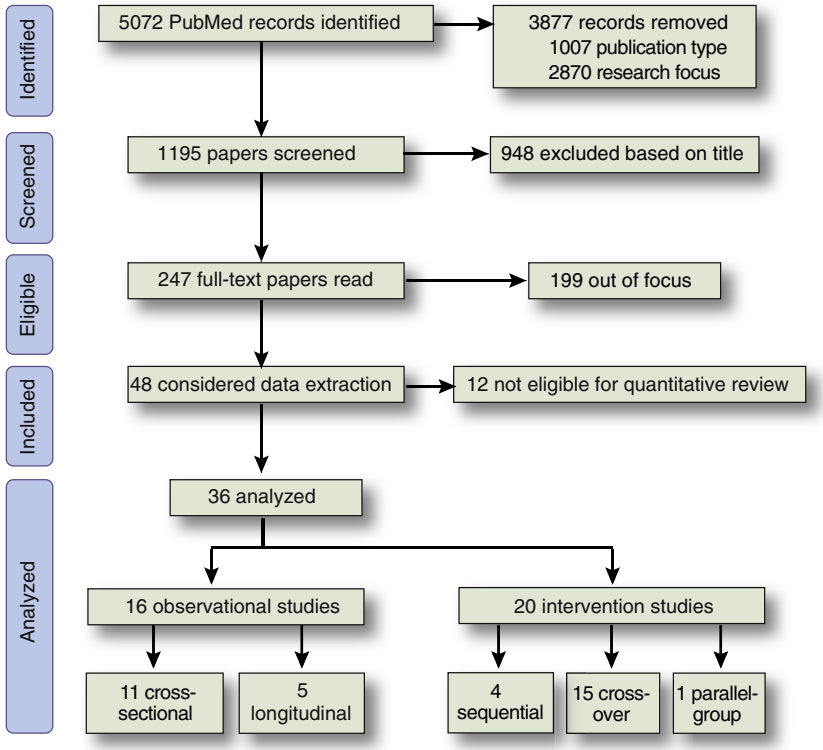

Figure 1 | Selection of studies.

Table 1 | Characteristics of cross-sectional studies

Study	Recruitment (country)[a]	No. of participants (% female)	Age, yr (range)[b]	GFR (ml/min)[c]	Sodium (mmol/d)[d]	Outcomes[e]	Covariables[f]
Verhave *et al.*[10]	P (Netherlands)	7,850 (47)	49 (28–75)	103	143 (24-h [1])	eGFR[g]; AE[g]	S, BMI, BP, WHR, LIP, DM, SMK, CCR, UE, MED
Daviglus *et al.*[15]	P (International)	4,381 (50)	49 (40–59)	…[h]	180 (24-h [2])	AE (<30 vs. 30–300 mg/d)	S, BMI, C, BP, SMK,
Fox *et al.*[16]	P (US)	2,700 (53)	58 (38–78)	≥60	96 (SU[63])	UACR (1st vs. 5th in quintile)	S, BP, SCR, DM, SMK, NA^+, ALDO, MED
Konta *et al.*[17]	P (Japan)	2,282 (56)	64 (43–83)	69	209 (SU[64])	UACR (<30 vs. 30–300 mg/g Cr)	BMI, HT, UA, SA, DM, SMK, ALC,
Aaron *et al.*[18]	P (US)	19,884 (55)	65 (45–85)	85	91 [FFQ]	UACR (<30 vs. ≥30 mg/g Cr)	E, S, HT, LIP, DM, SMK, ALC, SES, PA
Sakabe *et al.*[19]	T2DM (Japan)	270 (42)	64 (53–74)	80	152 (SU[64])	UACR (≤30 vs. >30 mg/g Cr)	S, BMI, BP, LIP, SCR, DM, SMK, ALC
Yilmaz *et al.*[11]	HT (Turkey)	224 (39)	52 (41–64)	90	142 (24-h [1])	eGFR[g]; AE[g]	S, BMI, BP, LIP, SCR, SMK, NA^+
Ohta *et al.*[20]	HT (Japan)	133 (60)	60 (43–77)	72	162 (24-h [1])	eGFR[g]	None
Sharma *et al.*[12]	P (US)	13,917 (52)	45 (…[h])	88	153 [DR]	eGFR[g]; CKD	E, S, BMI, HT, DM, CVD
Han *et al.*[13]	P (Korea)	5,187 (55)	52 (19–97)	87	164 (SU[65])	eGFR[g]; UACR (<30 vs. ≥30 mg/g Cr)	S, BMI, HT, DM,
Engelen *et al.*[14]	T1DM (Netherlands)	1,212 (51)	40 (15–60)	102	172 (24-h [2])	eGFR[g]; AE (<20 vs. 20–200 μg/min)	S, BMI, SMK, ALC, NA^+, NUT, PA

AE, urinary albumin excretion; ALC, alcohol intake; ALDO, serum aldosterone; BMI, body mass index; BP, blood pressure; C, country; CCR, creatinine clearance; CVD, history of cardiovascular disease; DM, diabetes mellitus (determined by plasma glucose or hemoglobin A1c level); E, ethnicity; eGFR, estimated glomerular filtration rate; HT, hypertension; LIP, serum lipids; MED, medication to lower blood pressure, serum lipids, or plasma glucose; NA^+, urinary sodium; NUT, nutrients and/or energy intake; PA, physical activity; S, sex; SA, serum albumin; SCR, serum creatinine; SES, socioeconomic status; SMK, smoking; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio; UA, urinary albumin; UE, urinary excretion of potassium, calcium, and urea; US, United States; WHR, waist-to-hip ratio.
[a]P, HT, T1DM, and T2DM refer to a population sample, patients with hypertension, patients with type 1 diabetes mellitus, and patients with type 2 diabetes mellitus, respectively.
[b]Mean or median with (approximate) range.
[c]Estimated or measured glomerular filtration rate.
[d]Daily intake was obtained from 24-hour urine collection [number of samples], extrapolated from spot urine sample by validated formulas,[63–65] food frequency questionnaire (FFQ), or dietary recalls (DR).
[e]In the study by Sharma *et al.*,[12] chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min or an eGFR ≥ 60 with urinary albumin-to-creatinine ratio > 30 mg/g creatinine.
[f]All publications accounted for age with the exception of the study by Ohta *et al.*[20]
[g]Outcome assessed as a continuous variable.
[h]An ellipsis indicates missing information.

6 studies[13–18] and negative in 2 studies,[12,19] resulting in a nonsignificant pooled OR per 100 mmol sodium per day increment of 1.24 (CI, 0.92 to 1.68, $P = 0.16$) with substantial heterogeneity between studies ($I^2 = 88.5\%$, Q = 60.9, $P < 0.0001$). The results were similar after exclusion of the study by Sakabe *et al.*,[19] who reported a U-shaped association between albuminuria and daily salt intake (OR, 1.31; CI, 0.98 to 1.75, $P = 0.070$).

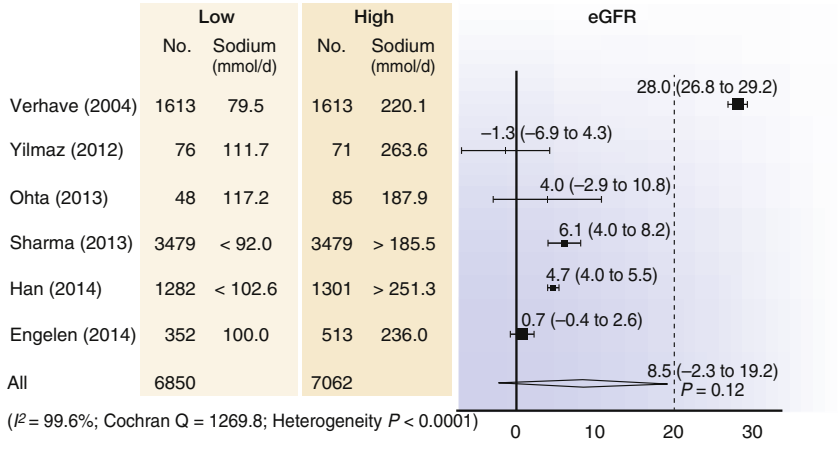

Figure 2 | Forest plot of mean difference (95% confidence intervals) of estimated glomerular filtration rate (eGFR) per 100 mmol/d increment in sodium intake derived from urinary or dietary measurements in 6 cross-sectional studies. Squares represent individual studies and have a size proportional to the inverse of the variance of the association size in each study. Number of participants (No.) and mean sodium intake in the low and high sodium exposure groups are given. If mean sodium intake was not reported, the upper and lower limits of the low and high sodium exposure groups were given instead. Detailed information on each study is available in Table 1.

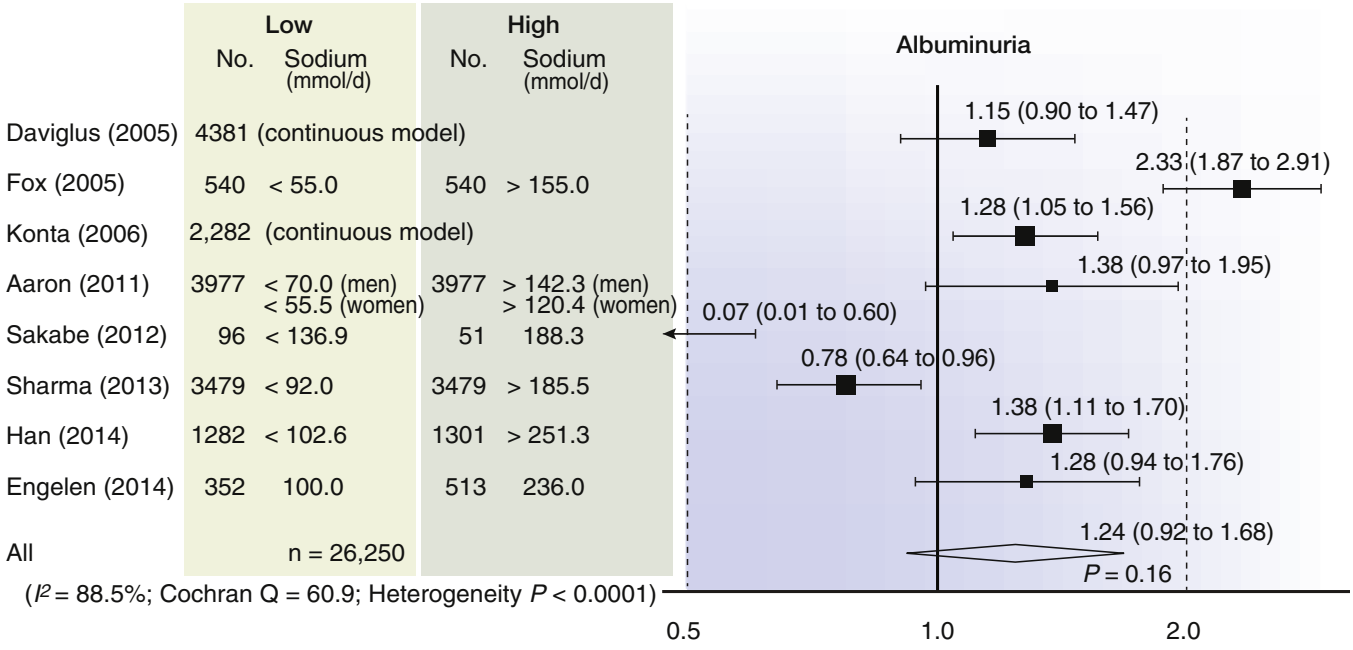

Figure 3 | Forest plot of odds ratios (95% confidence intervals) for albuminuria per 100 mmol/d increment in the estimated sodium intake in 8 cross-sectional studies. Squares represent individual studies and have a size proportional to the inverse of the variance of the effect size in each study. Number of participants (No.) and mean sodium intake in the low and high sodium exposure groups are given. If mean sodium intake was not reported, the upper and lower limits of the low and high sodium exposure groups were given instead. Detailed information, including outcome assessment and covariables adjusted, is available in Table 1.

Cohort studies

The characteristics of the 5 cohort studies are presented in Table 2. One study was population based,[21] 3 included patients with CKD,[22,24,25] and 1 was performed in a group of patients with type 2 diabetes.[23] Sodium intake was determined from 24-hour urine collections in 3 studies[22,24,25] and from a food frequency questionnaire in 2.[21,23] The follow-up period ranged from 32 months[22] to 11 years.[21] According to the Newcastle-Ottawa scale[48] for the assessment of the methodological quality of cohort studies, 2 studies were awarded 6 stars,[21,22] 2 were awarded 7 stars,[23,25] and 1 was awarded 8 stars,[24] as shown in Supplementary Table S2. Outcomes were defined as microalbuminuria,[21] end-stage renal disease (ESRD),[22,24,25] or CKD.[23] Effect size was reported either as an odds ratio (OR) or a hazard ratio. We combined all categorical outcomes in a single meta-analysis and labeled the effect size as relative risk. As shown in Figure 4, all cohort studies except the study by He *et al.*[40] showed a statistically significant association between the renal endpoint and sodium intake. Moreover, the direction of the association differed among studies, resulting in a pooled relative risk per 100 mmol/d increment in estimated sodium intake close to unity (1.08; CI, 0.92 to 1.29; $P = 0.35$). We detected substantial heterogeneity between studies ($I^2 = 67.7\%$; Q = 12.4; $P = 0.015$).

Intervention studies

The characteristics of the 20 intervention trials, which included 804 participants, are summarized in Table 3. Four studies had a nonrandomized design in which participants were sequentially maintained on a low-sodium and a high-sodium diet,[26–29] 15 were randomized cross-over trials,[30–44] and 1 had a randomized open-label parallel-group design.[45] The LowSALT CKD study (Universal Trial Number U1111-1125-2149)[42,43] was represented twice because investigators reported the results for eGFR[43] and proteinuria[42] in separate papers. Of 20 studies, 11 were conducted in untreated or treated hypertensive patients and/or normotensive individuals[26,29–31,34,38–41,44] or in offspring of hypertensive and normotensive parents,[33] 1 in patients with IgA nephropathy,[35] 4 in diabetic patients,[28,32,36,37] and 4 in patients with CKD.[27,42,43,45] The intervention lasted from 4 to 42 days in the cross-over and sequential trials and 182 days in the parallel-group trial. The within-study difference between high and low sodium intake ranged from 90 to 285 mmol/d. In all studies, the renal outcome was measured on a continuous scale, that is, eGFR or creatinine clearance in 17 studies[26–37,39,41,43–45] and albuminuria in 6 trials.[35,36,38,40,42,43] Quality assessment according to the Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials[49] and the Methodological Index for Non-randomized Studies[50] are shown in Supplementary Tables S3 and S4, respectively. Of the 16 randomized trials, none was free of bias. All 4 nonrandomized trials were at high risk of bias for 3 or more of the items on the methodological index for non-randomized studies checklist.[50]

Glomerular filtration rate and creatinine clearance. As shown in Figure 5, all 17 intervention trials revealed

Table 2 | Characteristics of cohort studies

Study	Recruitment (country)[a]	Number	Age, yr (range)[b]	GFR (ml/min)[c]	Sodium (mmol/d)[d]	Outcomes[e]	RR (FU, y)[f]	Covariables[g]
Lin *et al.*[21]	P (US)	205/3,348 (100)	67 (54–79)	85	88 [FFQ]	UACR (25–355 mg/g Cr)	OR (∼11)	BMI, HT, DM, SMK, PA, CVD, GFR
Vegter *et al.*[22]	CKD (Netherlands)	92/500 (24)	52 (18–70)	43	178 (24-h [1])	ESRD or doubling of serum creatinine	HR (∼2.7)	S, BP, CCR, UUE, UP
Dunkler *et al.*[23]	T2DM (40 countries)	1,971/6,213 (32)	66 (55–81)	72	213 [FFQ]	CKD (new micro- or macro-albuminuria in spot urine, GFR decline of >5% per year, or ESRD)	OR (5.5)	S, R, DM, UA, GFR, ΔUACR, BMI, BP, SMK, PA, SES
Fan *et al.*[24]	CKD (US)	617/840 (40)	52 (18–70)	33	150 (24-h [4])	ESRD	HR (6.0)	E, S, BMI, BP, DM, LIP, GFR, UP, CVD, CKD, SMK, R
He *et al.*[25]	CKD (US)	939/3,737 (44)	58 (21-74)	45	161 (24-h [3])	ESRD or halving of eGFR	HR (∼8)	E, S, CS, CCR, EDU, WC, BMI, LBM, SMK, ALC, PA, LIP, DM, CVD, UK

ALC, alcohol intake; BMI, body mass index; BP, blood pressure; CKD, chronic kidney disease; CCR, creatinine clearance; Cr, creatinine; CS, clinical site; CVD, cardiovascular disease; E, ethnicity; EDU, education; ESRD, end-stage renal disease; DM, diabetes mellitus or plasma glucose; FFQ, food frequency questionnaire; FU, follow-up; GFR, glomerular filtration rate; HR, hazard ratio; HT, hypertension; LBM, lean body mass; LIP, dyslipidemia or total cholesterol; OR, odds ratio; PA, physical activity; R, randomization group; RR, relative risk; S, sex; SES, socioeconomic status; SMK, smoking; T2DM, type 2 diabetes mellitus; UA, albuminuria; UACR, urinary albumin-to-creatinine ratio; ΔUACR, difference of urinary albumin-to-creatinine ratio; UK, urinary potassium excretion; UP, proteinuria; US, United States; UUE, urinary urea excretion; WC, waist circumference.
[a]P, CKD, and T2DM refer to a population sample, patients with chronic kidney disease, and patients with type 2 diabetes mellitus, respectively.
[b]Mean or median with (approximate) range.
[c]Estimated or measured glomerular filtration rate.
[d]Daily intake was obtained from 24-hour urine collection [number of samples] or food frequency questionnaire.
[e]End-stage renal disease is defined as initiation of dialysis or kidney transplantation. Participants with urinary albumin-to-creatinine ratio > 355 mg/g creatinine were initially excluded from the study by Lin *et al.*[21]
[f]Relative risk is expressed as odds ratio (OR) or hazard ratio (HR) with follow-up (FU) duration in years given in parentheses.
[g]All publications accounted for age and use of antihypertensive drugs.

higher values for eGFR or creatinine clearance in patients on the high sodium diet as compared with those on the low sodium diet. Both the Cochran Q (10.2; $P = 0.86$) and the I^2 statistics (0%) showed no heterogeneity between trials. The pooled effect size per 100 mmol/d increment in the estimated sodium intake amounted to 4.6 ml/min (CI, 3.4 to 5.8 ml/min; $P < 0.0001$). The result of Egger's test indicated a trend toward asymmetry of the funnel plot (Supplementary Figure S1), with smaller studies tending to show a larger effect size ($P = 0.060$).

Albuminuria and related renal dysfunction. Because reported renal outcomes differed between trials, we calculated effect size as the percentage difference in the renal endpoint between the high- and low-sodium diets. As illustrated in Figure 6, in all 6 trials, albuminuria,[36] proteinuria,[35,38,42] or the urinary albumin-to-creatinine[40] or protein-to-creatinine[43] ratio tended to increase in response to high sodium intake. The pooled effect size showed a significant 53% (CI, 21% to 84%; $P = 0.0010$) higher renal dysfunction on the high- versus the low-sodium diet. An assessment of the between-study variability yielded an I^2 of 56.3% and

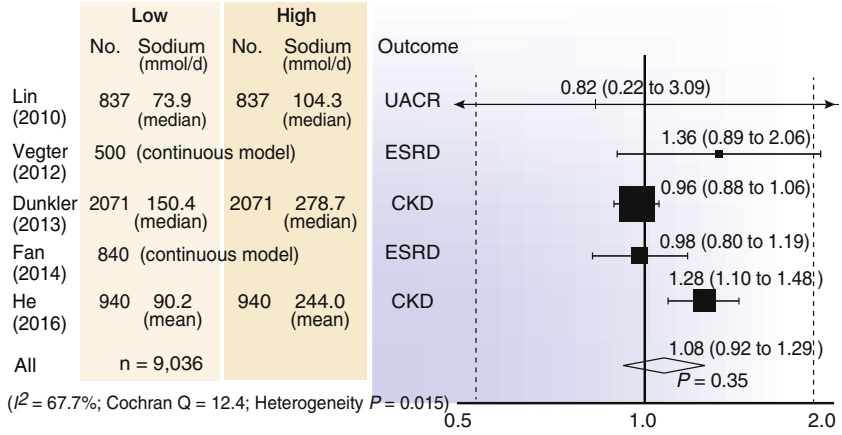

Figure 4 | Forest plot of relative risks (95% confidence intervals) for renal endpoints per 100 mmol/d increment in the estimated sodium intake in 5 cohort studies. Squares represent individual studies and have a size proportional to the inverse of the variance of the effect size in each study. Outcomes: CKD, chronic kidney disease; ESRD, end-stage renal disease; UACR, urinary albumin-to-creatinine ratio. Detailed information on each study is available in Table 2.

Table 3 | Characteristics of intervention trials

Study	Recruitment (country)	Study design (blinding)	No. of participants (% female)	Age, yr (range)[a]	GFR (ml/min)[b]	Low vs. high sodium (g/d)[c]	Outcomes	Days of intervention
Bruun *et al.*[30]	UHT, NT (Denmark)	CO (O)	22 (36)	47 (29–67)	88 (NT), 81 (UHT)	2.9–22.2	GFR	4
Campese *et al.*[26]	UHT (US)	SQ (O)	26 (27)	50 (26–74)	101	1.2–11.7	GFR	23
Cianciaruso *et al.*[27]	NT, CKD (US)	SQ (O)	21 (0)	39 (…[e])	109 (NT), 76 (CKD)	2.0–13.7	GFR	14
Mallamaci *et al.*[31]	UHT, NT (Italy)	CO (O)	21 (0)	43 (30–65)	112 (UHT), 117 (NT)	2.4[d]–12.4[d]	eGFR	7
Yoshioka *et al.*[32]	T2DM (Japan)	CO (O)	19 (42)	60 (40–74)	108	5.0–14.9	eGFR	7
Campese *et al.*[28]	T2DM, UHT (US)	SQ (O)	19 (32)	52 (37–67)	105	1.2–14.6	GFR	23
Bruun *et al.*[33]	OS (Denmark)	CO (O)	42 (19)	26 (19–32)	101	2.9–17.6	GFR	4
Chiolero *et al.*[34]	UHT, NT (Switzerland)	CO (O)	65 (35)	38 (20–64)	111 (UHT), 114 (NT)	3.4–14.2[d]	GFR	7
Konishi *et al.*[35]	IgAN (Japan)	CO (O)	38 (74)	40 (20–59)	113	2.0–4.7	CCR, P	7
Imanishi *et al.*[36]	T2DM (Japan)	CO (O)	16 (44)	60 (39–81)	111	4.7–11.7	CCR, A	7
Luik *et al.*[37]	T1DM, NT (Netherland)	CO (O)	48 (38)	27 (37–57)	121 (T1DM), 115 (NT)	2.9–11.7	GFR	7
van Berge-Landry and James[44]	UHT (US)	CO (O)	48 (21)	51 (36–66)	109	1.4–18.1	eGFR	28
Swift *et al.*[38]	UHT (UK)	CO (D)	40 (58)	50 (30–70)	91	2.0–12.0	P	28
Visser *et al.*[29]	NT (Netherland)	SQ (O)	78 (0)	23 (17–29)	133	2.9–11.7	GFR	14
Pimenta *et al.*[39]	HT (US)	CO (O)	12 (67)	55 (37–74)	133	2.9–14.6	eGFR	7
He *et al.*[40]	UHT (UK)	CO (D)	169 (33)	50 (30–75)	118	2.0–10.2	AR	42
Mallamaci *et al.*[41]	UHT (Italy)	CO (S)	32 (28)	48 (30–66)	99	0.9–11.7	CCR	14
de Brito-Ashurst *et al.*[45]	CKD+HT (UK)	PG (O)	48 (42)	58 (31–85)	42	8.2[d]–14.4[d]	eGFR	182
McMahon *et al.*[42]	CKD (Australia)	CO (D)	20 (25)	69 (47–91)	32	4.1–11.1	P	14
Campbell *et al.*[43]	CKD (Australia)	CO (D)	20 (25)	69 (47–91)	32	4.1–11.1	eGFR, PR	14

The articles by McMahon *et al.*[42] and Campbell *et al.*[43] are reports of the same trial (Universal Trial Number U1111-1125-2149), but focused on different outcomes.
A, albuminuria; AR, urinary albumin-to-creatinine ratio; CCR, creatinine clearance; CKD, chronic kidney disease; CO, randomized cross-over; D, double blind; HT, hypertensive patients; IgAN, patients with IgA nephropathy; NT, normotensive or healthy volunteers; O, open-label; OS, offspring of hypertensive versus normotensive parents; P, proteinuria; PG, randomized parallel-group trial; PR, urinary protein-to-creatinine ratio; S, single blind; SQ, sequential non-randomized intervention on sodium intake; T1DM, patients with type 1 diabetes mellitus; T2DM, patients with type 2 diabetes mellitus; UHT, untreated hypertensive patients; UK, United Kingdom; US, Untied States.
[a]Mean or median with (approximate) range.
[b]Estimated or measured glomerular filtration rate.
[c]Targeted sodium intake.
[d]Target levels were undefined and the urinary sodium excretion was given instead.
[e]An ellipsis indicates missing information.

a Cochran Q of 11.4 ($P = 0.043$). The meta-regression analysis demonstrated that as the trial duration became longer, the effect sizes became significantly smaller (Figure 7; $P = 0.018$).

DISCUSSION

The key findings can be summarized as follows: (i) in observational studies, renal function as assessed by eGFR, albuminuria, urinary albumin-to-creatinine ratio, CKD, or ESRD yielded insufficient direct evidence for association with sodium intake; (ii) there was substantial heterogeneity among the results of both cross-sectional studies and intervention trials with proteinuria or albuminuria as the outcome; (iii) 5 longitudinal studies did not generate robust evidence that reduction of salt intake would prevent CKD or its progression; (iv) the majority of the reviewed intervention studies failed to provide sufficient information on design, results, and potential sources of bias, resulting in low quality scores, as assessed by the Cochrane Collaboration's tool[49] or the Methodological Index for Non-randomized Studies[50] when applied to nonrandomized intervention studies; and (v) intervention studies demonstrated that eGFR and albuminuria or proteinuria increased with higher salt intake.

Recent guidelines recommend dietary sodium intake restriction to prevent CKD or its progression. However, the proposed daily target intakes vary widely, including less than 2.4 g[5] for adults with CKD and hypertension, less than 2.0 g[6] for patients with CKD, less than 2.3 g for the general population,[7] and less than 1.5 g for individuals at high risk for CKD.[7] Guidelines cautioning that an excessive restriction of sodium intake, for instance to less than 1.5 g/d,[8] might be harmful are a notable exception, especially considering the lack of evidence for a beneficial effect against CKD, as exemplified by our quantitative review of the literature. The recent literature likewise reflects the uncertainty of whether reducing dietary sodium intake would promote renal health. By pooling the ONTARGET and TRANSCEND data, Smyth *et al.*[51] built further on the article by Dunkler *et al.*[23] (see Figure 6). The primary outcome was a decline in eGFR of 30% or more or long-term dialysis.[51] There was no significant association between sodium and any renal outcome (primary outcome OR, 0.99; 95% CI, 0.89–1.09 for highest [median 6.2 g/d] vs. lowest third [median 3.3 g/d]).[51] On the other hand, in a cross-over trial of 45 patients with nondiabetic CKD (stages 1–3) and 24-hour albuminuria in excess of 300 mg, Keyzer *et al.*[52] found that moderate dietary sodium restriction substantially reduced the residual albuminuria during fixed-dose angiotensin–converting enzyme inhibition.

	Low		High	
	No.	Sodium (mmol/d)	No.	Sodium (mmol/d)
Bruun (1990)	22	50	22	330
Campese (1991)	26	20	26	200
Cianciaruso (1996)	21	35	21	235
Mallamaci (1996)	21	41	21	213
Yoshioka (1998)	19	85	19	255
Campese (1998)	19	20	19	250
Bruun (2000)	42	50	42	300
Chiolero (2000)	65	57	65	237
Konishi (2001)	38	86	38	207
Imanishi (2001)	16	80	16	200
Luik (2002)	48	50	48	200
van Berge-Landry (2004)	48	24	48	309
Visser (2009)	78	50	78	200
Pimenta (2009)	12	50	12	250
Mallamaci (2013)	32	15	32	200
de Brito-Ashurst (2013)	23	141	25	246
Campbell (2014)	20	70	20	190
All	550		552	

(I^2 = 0%; Cochran Q = 10.2; Heterogeneity P = 0.86)

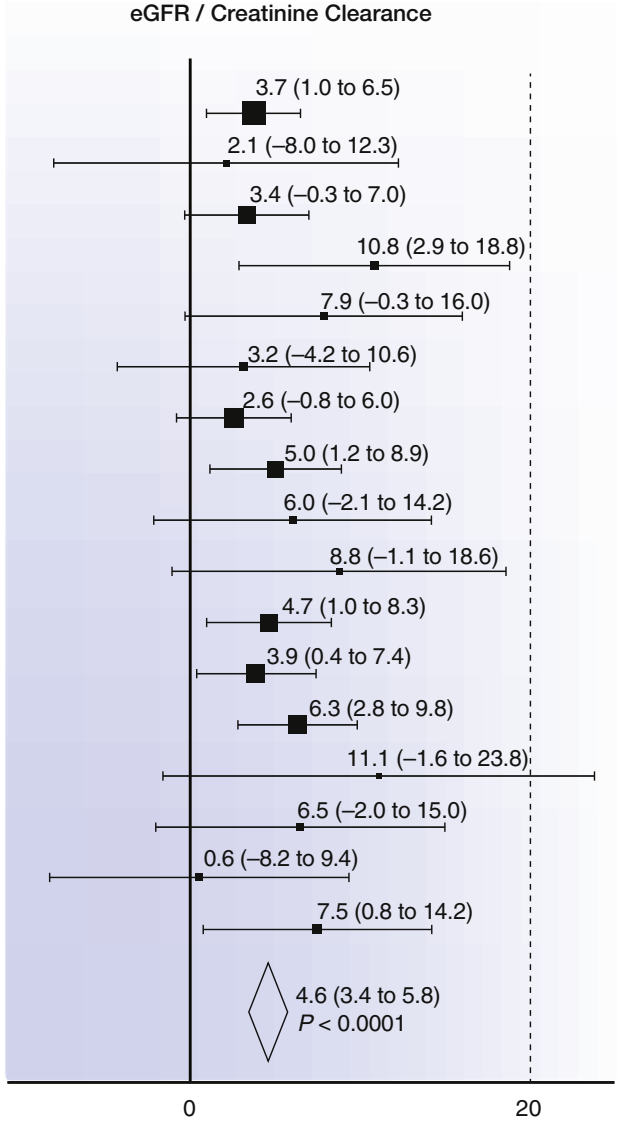

Figure 5 | Forest plot of the percentage difference (95% confidence intervals) in estimated glomerular filtration rate (eGFR) or creatinine clearance between the high and low sodium intake groups rescaled to a 100 mmol/d difference in estimated sodium intake. Squares represent individual studies and have a size proportional to the inverse of the variance of the effect size in each trial. Detailed information on each study is available in Table 3.

The wide gap between available evidence and the guidelines to prevent CKD and its progression by reducing sodium intake also mirrors the controversy about the hypothesized but unproven benefit that a population-wide reduction of sodium intake would reduce blood pressure and thereby decrease cardiovascular mortality and morbidity rates. We reported previously, in a large prospective European cohort involving 3681 participants, that lower 24-hour urinary sodium excretion predicted higher cardiovascular mortality with multivariable adjustments applied.[53] Patients with diabetes mellitus are at high risk for CKD. Nevertheless, cohort studies with a median follow-up of 10 years[54,55] demonstrated that a 24-hour urinary sodium excretion of less than 2.3 g at baseline was paradoxically associated with higher all-cause[54,55] and cardiovascular[55] mortality and a higher risk of ESRD[55] in patients with type 1[54] and type 2[55] diabetes, thereby replicating the findings on cardiovascular mortality in the European population study.[53] Unfortunately, we could not include the study by Thomas *et al.*[54] in our meta-analysis, because the association between the incidence of ESRD and 24-hour urinary sodium excretion was modeled by cubic splines and because the authors could no longer provide corresponding data based on a linear model.

In the PURE study,[56] morning fasting urine samples from 101,945 persons in 17 countries were investigated. In the PURE cohort, daily sodium intakes of more than 5 g and less than 3 g predicted a higher incidence of cardiovascular disease, resulting in a J-shaped association curve. Similarly, a meta-analysis[57] of 23 cohort studies and 2 follow-up studies of randomized controlled trials with 274,683 individuals

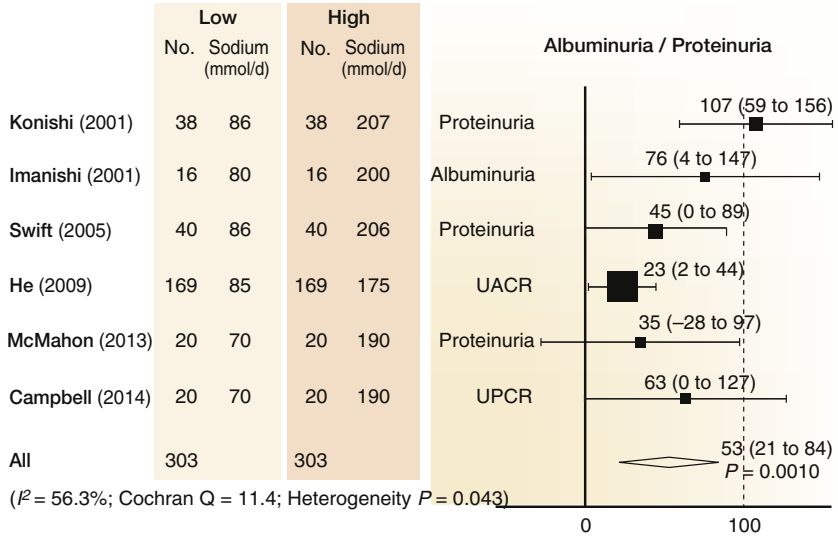

Figure 6 | Forest plot of the percentage difference (95% confidence intervals) in albuminuria between the high and low sodium intake groups rescaled to a 100 mmol/d difference in estimated sodium intake. Squares represent individual studies and have a size proportional to the inverse of the variance of the effect size in each trial. Detailed information on each study is available in Table 3. Outcomes: UACR, urinary albumin-to-creatinine ratio; UPCR, urinary protein-to-creatinine ratio.

demonstrated a U-shaped association of cardiovascular disease event and mortality with urinary sodium excretion. More recently, Mente *et al.*[58] conducted a pooled analysis of 4 large prospective studies from 49 countries, including 133,118 individuals, and stratified participants by presence versus absence of hypertension. Among participants with hypertension, an estimated daily sodium excretion of 7 g or more (hazard ratio, 1.23; CI, 1.11 to 1.37; $P < 0.0001$) and less than 3 g (hazard ratio, 1.34; CI, 1.23 to 1.47; $P < 0.0001$) were both associated with increased risk of the composite outcome consisting of death and major cardiovascular disease events compared with the reference sodium excretion of 4 to 5 g/d. Furthermore, in normotensive individuals, an estimated daily sodium excretion of 7 g or more was not associated with risk of a composite endpoint (hazard ratio, 0.90; CI, 0.76 to 1.08; $P = 0.25$), whereas an excretion of less than 3 g remained associated with a significantly increased risk (hazard ratio, 1.26; CI, 1.10 to 1.45; $P = 0.0009$).[58] Nevertheless, as O'Brien comments,[59] any population approach for lowering sodium should be targeted at a minority of patients with hypertension who consume large amounts of sodium. A public health strategy targeting the population at large might be confusing

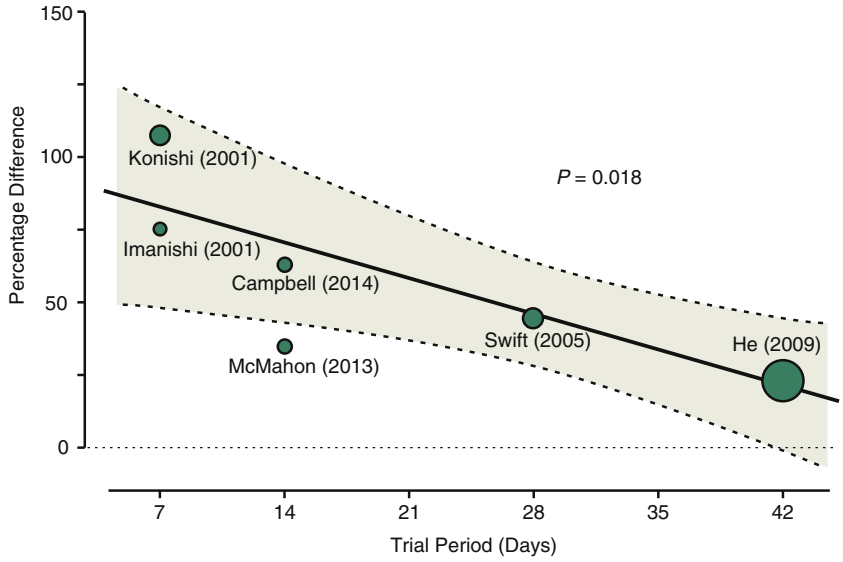

Figure 7 | Meta-regression analysis of the percentage difference in the renal outcome plotted versus the duration of the intervention in 6 trials. The regression line was drawn with 95% confidence intervals and weighted for the inverse of the variance of the effect sizes in individual studies. Circles have a size proportional to the number of participants. *P* denotes significance of the regression slope.

for those with a low sodium intake and harmful for those with low blood pressure. The overriding adage in medicine, certainly for measures that affect the whole population is "*primim non nocere*" (do not cause harm). At variance with the overoptimistic and unproven guidelines,[5–7] our current meta-analysis extends the cautionary approach proposed by O'Brien[59] and others[53–58] to the application of a population-wide restriction of sodium intake to prevent CKD and its progression to ESRD.

To our knowledge, our meta-analysis is the first quantitative review of the potential repercussion of dietary sodium intake on renal function. Our study must be interpreted within the context of its potential limitations. First, across studies, sodium intake was quantified by using different approaches, including spot and 24-hour urine samples, food-frequency questionnaires, and dietary records. Evaluation of dietary sodium intake based on food questionnaires and dietary records is the least reliable method. Although acceptable for large groups in cohorts or populations, estimation of usual sodium intake from a spot urine sample is not a state-of-the-art practice.[59] Even the measurement of 24-hour urinary sodium excretion is insufficient to characterize an individual's sodium intake,[60] although it is adequate to quantify sodium intake in a group of people.[53] Second, we aggregated heterogeneous outcomes in longitudinal studies, encompassing CKD, urinary albumin-to-creatinine ratio, and ESRD. Similarly, the sodium intervention studies applied various measurement scales for albuminuria or proteinuria, which included urinary protein excretion, the urinary albumin-to-creatinine ratio, and urinary albumin excretion. We addressed heterogeneity among studies in endpoint definitions by using percentage differences in outcomes between high and low sodium intake and by rescaling our outcomes measures to a 100 mmol/d increment in sodium intake. In spite of these precautions, our pooled results require careful interpretation. Third, because of varying study designs, causal inference is a bridge too far, in particular for longitudinal studies. In some studies included in our meta-analysis, sodium intake was estimated on a single occasion, so that changes in sodium intake during follow-up were not accounted for.[22,23] Fourth, despite modest heterogeneity observed among intervention studies with eGFR as the outcome, the majority of these studies, in particular those published before 2009, had relatively low quality scores according to 2 checklists.[49,50] Fifth, the intervention studies of eGFR and albuminuria or proteinuria in relation to changes in sodium intake had a short duration with a median of only 2 weeks. The longest intervention lasted half a year.[45] Sixth, because we did not have access to participant-level data, we were unable to explore whether the association of renal outcomes with sodium intake might be J-shaped or U-shaped. However, the results on glomerular filtration rate (GFR) (Figure 5), although based on summary statistics, seem to exclude a nonlinear association. Finally, several drugs, especially antihypertensive agents, influence renal function. However, information on drug use or special diets was seldom reported and did not allow us to account for these potential confounders in a systematic way.

In keeping with our findings, 2 recently published studies[54,55] indicated that a daily sodium intake below ~2.3 g/d is associated with adverse cardiovascular health outcomes[54,55] or ESRD.[54] Chang *et al.*[61] reported that urinary sodium did not predict changes in urinary albumin excretion over 6 months in 481 participants with normal kidney function ($P = 0.1$). In 2807 FinnDiane study participants, urinary sodium excretion at baseline was inversely associated with the cumulative incidence of ESRD ($P < 0.001$).[54] In contrast, multivariable-adjusted analysis of the Chronic Renal Insufficiency Cohort Study ($n = 3939$)[25] showed that relative to the lowest quartile of 24-hour urinary sodium excretion (116.8 mmol/d), the hazard ratio for the highest quartile (194.6 mmol/d) was 1.54 (CI, 1.23 to 1.92) for the risk of having ESRD or decreasing eGFR by 50%. However, findings in patients with CKD cannot be extrapolated to the general population. Only long-term intervention trials, such as that piloted in the Sodium Intake in Chronic Kidney Disease initiative,[62] might break the impasse, but only on the condition that their results can be replicated in different settings, in the population at large as well as in patients with a wide range of risk for progression to ESRD.

In summary, our quantitative review demonstrated that there is no robust evidence indicating that long-term reduction of salt intake would prevent CKD or delay its progression. However, our current findings, which were mainly obtained from individuals with slight renal impairment, cannot be extrapolated to patients with moderate or severe CKD.

METHODS

Literature search

We searched the PubMed database for peer-reviewed articles published between 1 January 1980 and 31 May 2016. We used the following key terms and operators: ((“sodium” AND (“dietary” OR “chloride”)) OR “salt”) combined with (“renal function” OR “CKD” OR “chronic kidney disease” OR “glomerular filtration rate” OR “GFR” OR “microalbuminuria” OR “macro-albuminuria” OR “proteinuria”). We restricted our search to human studies published in English.

Selection criteria

Cross-sectional, cohort, and intervention studies meeting the following criteria qualified for inclusion in our meta-analysis: (i) the study was published as original research; (ii) study participants were at least 20 years old; (iii) study endpoints included glomerular filtration rate, albuminuria, or proteinuria reported on a continuous or categorical scale; (iv) information on sodium intake was available from spot or 24-hour urine collections, food-frequency questionnaires, or dietary records; and (v) both the central tendency and spread of the renal responses to sodium intake were either reported or could be computed from the reported statistics. Observational studies had to have a sample size of at least 100 participants.

Data extraction

In a first step, titles and abstracts of retrieved papers were reviewed. Potentially eligible articles were ordered by the last name of the first

author and year of publication, given a unique identification number, and entered into a dedicated literature database, using Reference Manager, version 12.0.3 (Thomson Reuters: http://www.refman.com). Next, 2 investigators (KN and KA) read all papers that passed the first stage of selection, independently assessed eligibility, extracted and computerized relevant information, and provided copies of eligible manuscripts to the senior co-authors (LT and JAS), who checked data extraction and summary statistics and resolved any disagreements. We rated the methodological quality of the studies according to a modified version of the criteria provided by the Agency for Healthcare Research and Quality[46,47] for cross-sectional studies, the Newcastle-Ottawa scale[48] for cohort studies, the Cochran Collaboration's risk of bias assessment tool[49] for randomized intervention trials, and the methodological index for nonrandomized studies[50] for nonrandomized intervention trials. The Newcastle-Ottawa Scale[48] uses a star system (with a maximum of 9 stars) to evaluate a study in 3 domains: selection of participants, comparability of study groups, and ascertainment of outcomes of interest. We judged studies that received a score of 9 stars to be at low risk of bias, studies that received 7 or 8 stars to be at medium risk, and those that received 6 or fewer stars to be at high risk of bias.

Exposure

As exposure measure, we used sodium intake as assessed by spot or 24-hour urine samples, food-frequency questionnaires, or dietary records. We estimated sodium intake from sodium excretion in spot urine samples according to the equations provided by INTERSALT,[63] Kawasaki *et al.*,[64] or Tanaka *et al.*[65] according to whatever method was used in the original publications. We computed weighted arithmetic means of sodium intake across cross-sectional and longitudinal observational studies, stratifying by the methods by which sodium intake was assessed.

Statistical analysis

We conducted meta-analyses separately for cross-sectional, cohort, and intervention studies and for eGFR and other renal endpoints (albuminuria or proteinuria) as outcome variables. For the cross-sectional and cohort studies, effect sizes were either differences in eGFR between categories of sodium intake or ORs estimating the effect of increasing sodium intake, either measured on a continuous or categorical scale, on a dichotomous renal endpoint. If renal endpoints in multiple groups of increasing sodium intake were reported in a study, we always contrasted the highest with the lowest level of sodium intake. For eGFR, we expressed the effect size in milliliters per minute, regardless of whether the estimate was standardized to body surface area. In most studies, albuminuria or proteinuria was reported on a dichotomized scale, and the effect size was reported as an OR. Therefore for 1 study[16] in which mean albuminuria was reported in groups of increasing sodium intake, we converted the effect size to a log OR by multiplying the standardized between-group difference[66] by 1.81.[67] For cohort studies, we considered ORs and HRs sufficiently equivalent to be pooled in 1 meta-analysis and labeled the outcome variable as relative risk. In the intervention trials, participants were randomized or allocated to a high or low sodium intake. All reported endpoints in these trials were continuous. For eGFR, we calculated the effect size as for the cross-sectional studies. We pooled all other endpoints reported in the intervention trials in 1 meta-analysis and computed the effect size as the percentage difference in the renal endpoint between high and low sodium intake. For all study designs, we rescaled the effect size to a difference in sodium intake of 100 mmol/d, corresponding to 2.3 g of sodium or 5.8 g of NaCl. If sodium intake was reported on a categorical scale, this was done by dividing the log ORs and the continuous effect sizes by the difference in sodium intake between the high and low exposure categories and multiplying by 100. In cases in which the difference in sodium intake between the 2 sodium intake groups was not reported and could not be calculated from the published statistics, we used the difference between the cutoff points of the high and low sodium intake groups as an estimate of the between-group difference in sodium intake. Except for glomerular filtration rate, we used maximally adjusted effect sizes, as reported in individual studies.

We assumed that the true association size between renal endpoints and sodium intake differed among studies. We therefore estimated the pooled effect size and its CI from random-effects models as implemented in the PROC MIXED procedure of the SAS package (SAS Institute, Cary, NC). Each study was weighted by the inverse of the within-study variance. We estimated heterogeneity across individual studies by Cochran's Q and I^2 statistics. For Cochran's Q test, the P value indicating significant heterogeneity was set at less than 0.10. For I^2, values less than 25%, from 25% to 50%, and more than 50% indicated modest, moderate, and substantial heterogeneity, respectively. We constructed funnel plots and tested the asymmetry using Egger's test to assess publication bias. We assessed publication bias only for analyses including at least 10 studies, because when there are fewer studies, the power of the test is too low to distinguish chance from asymmetry.[68]

DISCLOSURE

All the authors declared no competing interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table S1. Methodological quality of cross-sectional studies according to the Agency for Healthcare Research and Quality (ARHQ) checklist

Supplementary Table S2. Newcastle-Ottawa Scale for the assessment of the methodological quality of cohort studies

Supplementary Table S3. The Cochrane Collaboration's tool for assessing risk of bias in randomized controlled trials

Supplementary Table S4. Methodological Index for Non-Randomized Studies (MINORS)

Supplementary Figure 1. Funnel plot of mean difference (95% confidence intervals) in estimated glomerular filtration rate (eGFR) for a 100 mmol/d increment in the estimated sodium intake. Trial size was plotted against the difference in eGFR. Table 3 and Figure 5 provide detailed information on each study.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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