Published in final edited form as:
Mayo Clin Proc. 2013 September ; 88(9): . doi:10.1016/j.mayocp.2013.06.005.

Role of Dietary Salt and Potassium Intake in Cardiovascular Health and Disease: A Review of the Evidence

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Abstract

The objective of this review is to provide a synthesis of the evidence on the effect of dietary salt and potassium intake on population blood pressure, cardiovascular disease, and mortality. Dietary guidelines and recommendations are outlined, current controversies regarding the evidence are discussed, and recommendations are made based on the evidence. Designed search strategies were used to search various databases for available studies. Randomized trials of the effect of dietary salt reduction and/or increased potassium intake on blood pressure, target organ damage, cardiovascular disease, and mortality were included. Fifty-two publications from January 1, 1990 to January 31, 2013 were identified for inclusion. Evidence from these studies demonstrate that a high salt intake not only increases blood pressure but also plays a role in endothelial dysfunction, cardiovascular structure and function, albuminuria and kidney disease progression, and cardiovascular morbidity and mortality in the general population. Conversely, dietary potassium attenuates these effects showing a linkage to reduction in stroke rates and cardiovascular disease risk. Various sub-populations, such as overweight and obese individuals and the aging adult, exhibit a greater sensitivity to the effects of reduced salt intake and may gain the most benefits. A diet that includes modest salt restriction while increasing potassium intake serves as a strategy to prevent and/or control hypertension and decrease cardiovascular morbidity and mortality. Thus, the body of evidence supports population-wide sodium reduction and recommended increases in dietary potassium as outlined by current guidelines as an essential public health effort to prevent kidney disease, stroke, and cardiovascular disease.

Introduction

Over the past century, medical research in the United States (US) has undergone a classical epidemiologic transition,[1] with the focus shifting from public health issues related to childhood infectious diseases, nutrient deficiencies and epidemics to noncommunicable diseases—including cardiovascular disease (CVD), hypertension, diabetes mellitus, and chronic kidney disease (CKD). While these diseases may have a genetic predisposition, there is a strong association with environmental influences, suggesting they are lifestyle-related. The problem is enormous: in 2009–2010, for example, 23.1% of adult Americans had prehypertension, while an additional 29.5% had hypertension.[2] Estimates projected by

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the American Heart Association (AHA) place the direct and indirect costs of hypertension at more than $93.5 billion per year.[3]

Population studies have demonstrated an association between dietary sodium chloride (termed salt in this review) as well as dietary potassium, and blood pressure (BP).[4–9] Along with the rising prevalence of hypertension and CVD, non-pharmacological dietary guidelines designed to promote the health of the public have therefore been instituted.[10] While these programs have an impact, most Americans consume well above the minimum daily requirement for dietary salt and further have inadequate potassium intake. To emphasize the excess salt in the American diet, the US Department of Health and Human Services/US Department of Agriculture (US DHHS/USDA) 2010 Dietary Guidelines advise Americans to reduce daily sodium intake to <2300 mg/d per person, with an even lower goal of 1500 mg/d for specific subpopulations; while the Institute of Medicine (IOM) has recommended an age-dependent targeted sodium intake of 1000–1500 mg/day and established a Tolerable Upper Level of Intake (UL) from 1500–2300 mg/day.[11] Between 2003–2008, the median daily sodium intake excluding table salt was 3371 mg (IQR: 2794, 4029) and median potassium consumption was 2631 mg (IQR: 2164 mg, 3161 mg) among US adults >20 years of age; 99.4% of US adults consumed >1500 mg of sodium daily and 90.7% consumed >2300 mg daily.[12] Recent high-profile publications, however, have challenged these guidelines. For this reason, this study considered the evidence that the level of dietary salt and potassium intake affects population BP, CVD, and mortality. Specifically, the authors examined the scientific rationale for population-wide recommendations to increase dietary potassium while reducing salt intake, the strength of available evidence, and offer recommendations for stakeholders to consider.

Methods and Evidence Base

Studies in this review include randomized controlled trials (RCTs) linking dietary salt and potassium intakes to subsequent morbidity and mortality which determine the health outcomes of reducing salt intake and/or increasing potassium intakes by diet or supplementation. The following databases (from January 1, 1990 up to January 31, 2013) were examined: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (Pubmed and Quertle), EMBASE, Cumulative Index to Nursing & Allied Health Literature (CINAHL), Database of Abstracts of Reviews of Effects (DARE), the Turning Research into Practice (TRIP) database, EBSCOhost, Scopus, and ClinicalTrials.gov. Consideration was given to variations in terms used and spelling of terms so that studies were not overlooked and took the general form: (“dietary salt” or “dietary sodium” or (synonyms)) and (“dietary potassium” or (synonyms)) and (“blood pressure” or “hypertension” or “vascular disease” or “heart disease” or “chronic kidney disease” or “stroke” or “mortality” or (synonyms)). Studies were excluded if 1) the paper was an observational or ecological study, a review, or editorial/commentary; 2) the language was not English; 3) the participant total was <20; or 4) the outcome of the trial did not include systolic and diastolic BP, markers of renal damage, CKD, markers and indices of vascular function, CVD and CVD-related hospital admissions, or mortality. Studies that examined outcomes in the setting of heart failure were also excluded.

Studies were selected for inclusion based upon the following criteria:

- Study design: RCTs
- Types of participants: Children and adults, irrespective of gender or ethnicity. Studies of pregnant women were excluded.
- Studies must include an assessment of dietary salt and/or dietary potassium; and could involve participants receiving a dietary intervention that restricted salt, one in

which the intervention was advice to reduce salt intake, and/or one that increased dietary potassium and/or involved potassium supplementation. Dietary salt and/or potassium could be assessed either by dietary recall, measurement of dietary intake and/or supplement usage in an intervention, or by laboratory assessment of urinary sodium and potassium since both track closely with dietary intakes.

- Comparator: control, placebo, or no intervention.

The titles and abstracts of studies identified by the search strategy were independently screened by the authors (KJA and PWS) and clearly irrelevant studies discarded. For inclusion, abstracts had to identify the study design, an appropriate population and a relevant intervention/exposure, as described above. The full-text reports of all potentially relevant studies were obtained and assessed independently for eligibility, based on the defined inclusion criteria, by both authors. Standardized data extraction forms were used; and relevant data were extracted by a single reviewer (KJA) and checked by a second reviewer (PWS). Any disagreement was resolved by discussion. Extracted outcomes at the latest follow-up point within the trial and also at the latest follow-up after the trial, where this was available, were utilized in order to maximize the number of events reported. The methodological quality of evidence provided by the included studies was graded using published guidelines (Table 1).[13,14] While RCTs were initially graded “A”, the grade was reduced by inherent limitations of the trial, such as short study duration, small number of study participants that might limit the applicability of the findings to the population as a whole, or experimental bias.

While many of the studies included in this review were high quality, the combined data are difficult to group together for analysis, because of inherent variations in 1) the targeted level of dietary salt intake, 2) the choice of a control population, 3) the duration of the studies, 4) gender and race of the study population, 5) underlying organ injury, and 6) the selected end-points. Moreover, some studies had small numbers of participants, and while the study may have been well done, the ability to generalize the findings to an entire population may not be feasible. Finally, a majority of available studies focused specifically on BP changes and not other clinically important end-points such as target-organ damage and mortality. Nevertheless, the studies permit some recommendations to consider; and, these recommendations are graded in standard fashion (Table 2).[13,14]

Results

From the literature evaluated, fifty-two studies met the criteria for this review (Table 3 and eTable 1). Of these studies, twenty-eight publications involved modification of dietary salt intake,[15–42] twelve involved modification of dietary potassium intake, [43–54] and twelve involved modification of both dietary salt and potassium.[55–66] (Table 3 and eTable 1). Of the twenty-eight publications in which dietary salt was adjusted, twenty-four studies with 4019 participants receiving an intervention, 3714 participants serving as controls, and an approximate median follow-up of 3.5 months reported outcomes for SBP;[15–38] twenty-three studies with 3969 participants receiving an intervention, 3580 participants serving as controls, and an approximate median follow-up of 3.5 months reported outcomes for DBP; [15–22,24–38] three studies with 640 participants receiving an intervention, 715 participants serving as controls, and an approximate median follow-up of 2 months reported outcomes for MAP; [21,39,40] three studies with 273 participants receiving an intervention, 228 participants serving as controls, and an approximate median follow-up of 1.5 months reported outcomes for ABP.[26,28,37] Of the twelve publications in which dietary salt and potassium were adjusted, eleven studies with 2713 participants receiving an intervention, 2430 participants serving as controls, and an approximate median follow-up of 12 months reported outcomes for both SBP and DBP[55–65] (Table 3). The most compelling evidence on

the dose-response relationship between salt and blood pressure came from rigorously controlled trials in which more than two levels of salt diets were implemented, such as the seminal work by MacGregor and colleagues[67] and the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial.[27] In adults with prehypertension or stage 1 hypertension in the DASH-Sodium trial, a clear dose-response relationship was demonstrated in both the general American diet and the DASH diet when salt intake was reduced from 8 to 6 and to 4 g/d; and, the decrease in BP was greater at a lower level of salt intake (i.e. from 6 to 4 g/d compared with that from 8 to 6 g/d).[27] Other large well-designed RCTs including the Trials of Hypertension Prevention I and II (TOHP I and TOHP II) [56,59,65] and the Trial of Nonpharmacologic Interventions in the Elderly (TONE)[16,36] have reinforced the important role of salt intake in determining the levels of BP in the populations under study. Additional RCTs have also lent support to reduction of salt in specific populations.[19,22,30,32,38,55,58]

Eighteen studies involving 3470 participants receiving the intervention and 3171 serving as controls documented the effect of changes in dietary sodium on laboratory parameters, markers of CVD and/or CKD progression, CVD events and/or CVD mortality over a median follow-up time of 3.5 months.[15,16,19,20,22,25,29–34,36,37,39–42] Additionally, three studies with 803 participants receiving the intervention and 1248 participants serving as controls documented the effect of changes in dietary sodium and potassium on laboratory parameters, markers of CVD and/or CKD progression, CVD events and/or CVD mortality over a median follow-up time of 6 months. [57,61,66] (Table 3). Dietary salt contributed to vascular and target organ injury as established in those studies in which markers of renal injury, inflammation and oxidative stress, and vascular function measures and indices were the selected outcomes.[16,19,20,22,30,32,33,42,48,68] The evidence from RCTs associating dietary salt and/or potassium with CVD morbidity and both CVD and all-cause mortality (Table 3 and Supplementary Table) exhibited a direct effect of dietary salt intake on target organ damage and subsequent vascular disease events and death. Based upon the combined evidence, we assigned Level 1 to the recommendation that dietary salt intake should be limited.

Of the twelve publications in which dietary potassium was modified, all reported outcome data on both SBP and DBP. These studies involved 752 participants receiving an intervention, 785 participants serving as controls, and an approximate median follow-up of 2.5 months. Three studies with 139 participants receiving an intervention, 176 participants serving as controls, and an approximate median follow-up of 1.5 months reported outcomes for MAP; [45,49,54] two studies with 90 participants receiving an intervention, 90 participants serving as controls, and an approximate median follow-up of 6.5 months reported outcomes for ABP[43,48] (Table 3). Most published studies confirmed a BP-reducing effect by potassium intake either by consumption of more fruits and vegetables, salt-substitutes and enrichment, or supplementation; and these studies suggest that it also plays a cardioprotective role.[7,18,39,45,48,53,55,58,60–63] The BP-lowering benefit has been shown in both normotensive[44,45,49] and hypertensive individuals. [7,18,39,46–48,50,52–54,58,60–62] One conflicting trial in prehypertensive individuals in the UK found no effect of potassium from increased fruit and vegetable consumption;[43] however the study had some design flaws and was seemingly underpowered. In addition, the effect of potassium supplementation and salt restriction on BP may not be additive. High potassium intake, rather, may have the greatest effect when salt intake is high, since potassium supplementation did not reduce BP in hypertensive men also maintained on a low-salt diet.[46] This study contrasts with another study in which participants who were advised to increase potassium intake from natural foods required fewer antihypertensive medications.[51]

Five studies with 325 participants receiving an intervention, 403 participants serving as controls, and an approximate median follow-up of 10 months documented an effect of

dietary potassium on laboratory parameters, markers of CVD and/or CKD progression, CVD events and/or CVD mortality[43,46,48,51,54] (Table 3). In addition to BP reduction, dietary potassium supplementation improved measures of endothelial function, vascular compliance, and cardiovascular structure and functional parameters.[48] In a large trial involving Taiwanese veterans, participants randomized to receive potassium-enriched salt lived significantly longer than their control counterparts.[66] The evidence supported roles for dietary potassium intake in BP regulation and as a vascular protectant, producing a small effect on BP and a significant health benefit (Level 1 recommendation).

Discussion

This analysis focused specifically on randomized controlled trials (RCT). The quality of the evidence of the included studies was then graded using published guidelines. While many of these RCTs received a grade less than “A”, a sufficient number of studies were graded “A” (Table 1), resulting in a level 1 recommendation for salt restriction and potassium supplementation. For some investigators, the relationship between dietary salt intake and health has been considered strong enough to make predictions regarding reduction in cardiovascular events and mortality should a population-wide reduction in dietary salt occur.[69] However, controversy regarding salt restriction continues. While there now appears to be relative agreement regarding a relationship between dietary salt intake and blood pressure, a cause-and-effect relationship between salt intake and cardiovascular event rates and mortality is more contentious. It is worth noting that a definitive pre-clinical study of the effect of dietary salt and potassium intake on lifespan of mammals was published over a half century ago by Meneely and Ball.[70] These investigators found that dietary salt intake in rats promoted a dose-dependent decrease in survival related to cardiovascular and renal disease. In addition, supplementing dietary potassium mitigated the effects of high salt intake.[70] Studies in humans are significantly more difficult since control of potential variables is more challenging and years to decades are generally required to determine benefit particularly in lower risk populations. Nevertheless, the trials reviewed in this study provided high quality evidence supporting a health benefit from restricting dietary sodium and increasing potassium.

Most professional scientific organizations therefore have agreed that the US/Western-style diet contains excessive amounts of salt; and, high levels of salt consumption in any population leads to higher rates of hypertension, CVD, and CVD-mortality. The debate was rekindled when a high-profile prospective study showing an association between low baseline UNa excretion and higher CVD mortality.[71] The limitations in the strength of evidence included the observational nature of the study as well as inherent flaws in design and methods as articulated in subsequent correspondence.[72–74] One issue of particular concern was the under-collection of 24-h urine among individuals in the lowest tertile of UNa excretion, as indicated by lower creatinine excretion, potassium, and 24-h urine volume.[75]

The conclusion of the present study also differs from a recent meta-analysis that evaluated whether BP reduction was an explanatory factor in any effect of dietary salt interventions on mortality and CVD outcomes identified.[76] In that report, criteria for inclusion included (1) randomization with follow up of at least six-months, (2) intervention was reduced dietary salt (restricted salt dietary intervention or advice to reduce salt intake), (3) adults, (4) and mortality or cardiovascular morbidity data was available.[76] Of seven trials identified, they concluded that the combined experimental evidence was insufficient to determine the health effect of reducing salt.[76] A weakness in that meta-analysis was the inclusion of a trial on heart failure in which sick participants were on intensive drug regimens. Participants in that trial were treated with doses of furosemide between 250–500 mg twice daily, as well as

spironolactone, angiotensin converting enzyme inhibitors, beta-blockers, and digitalis. In this heavily medicated population, a reduction in dietary salt intake promoted an increase in mortality.[77] While the validity of that particular study was not doubted, it was not included in the present analysis because of the severity of illness of the population in the study.

In an observational analysis of the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (TRANSEND), O'Donnell et al. noted a J-shaped relationship between UNa and risk of a composite outcome of CVD events and mortality.[78] The J-shape is a result of a contradictory inverse relationship in 12% of participants with an estimated UNa excretion of <3000 mg/d. ONTARGET and TRANSCEND consisted of participants over 55 years of age with a high risk of stroke and CVD during follow-up.[78] At baseline, 70% had hypertension, almost 40% had diabetes, almost half had a history of MI, and more than one in five had a history of stroke.[78] The potential for an error in assessment of salt intake is likely since a single morning spot urine collection was used to determine the 24-hour UNa excretion estimate. Values obtained from spot urine specimens are not a suitable alternative for 24-hour collections, especially among sick patients such as those included in the study. Medications such as diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers can greatly affect sodium levels in spot urine collections; and, the use of these drugs is more likely in those at greatest risk for CVD and is thus subsequently linked to a greater potential for measurement error. Another study in patients with type 2 diabetes mellitus found that lower 24-h UNa excretion was associated with increased all-cause and cardiovascular mortality.[79] At baseline, participants that had the lowest tertile of salt intake in that study were significantly older, had a longer disease duration, and a reduced eGFR when compared to the intermediate and highest salt intake tertiles.[79] Additionally, the methods employed to ensure adequacy of urine collections were not detailed. Paradoxical findings such as those described by O'Donnell et al.[78] and Ekinci et al.[79] can result when illness is the cause rather than the consequence of the level of salt intake. Sick individuals have a higher risk of disease progression and associated outcomes; and, as one becomes more ill, caloric intake along with salt intake can fall dramatically. Although severe restrictions in dietary sodium intake might contribute to adverse outcomes in these patients with multiple co-morbidities, this classical framework, as noted by Whelton and colleagues, is potentially one of reverse causality.[80]

Protocol-based investigations of dietary salt and/or potassium relationships in studies such as the INTERSALT, TOHP phases I and II, TONE, and the DASH-Sodium trial all conducted careful measurement of 24-h urinary estimation of electrolytes. In contrast, some of the newer publications utilized data previously collected in studies that had a different purpose. Although availability and access of observational data sets are more convenient and less expensive, one must take caution with interpretation of results as they are not specifically designed to explore the dietary salt risk or dietary potassium benefit in regard to CVD prevention. Therefore, only meticulous protocol-based studies of sufficient quality should guide stakeholders' decisions in contributing to public policy.

Conclusions and Implications for Clinicians and the General Public

In the US, current recommendations and guidelines[81,82] emphasize a reduction in dietary salt and a simultaneous increase in dietary potassium consumption. The IOM, AHA, and the US DHHS/USDA recommend limiting salt intake. For potassium, the data suggest that supplementation is best achieved through alterations in the diet. The analyses provided in the present study support the application of these recommendations to the population as a whole, with some caveats. The first potential limitation is that the clinician should be aware

that patients with severe heart failure requiring high-dose diuretic and medication therapy will not benefit from salt restriction.[77] The unusual patients with salt-wasting tubulopathies should not be salt-restricted without close supervision. Patients with advanced CKD may be at risk of developing hyperkalemia should the daily intake of potassium increase to 4700 mg (120 mmol). Additional potentially vulnerable populations that require individualized dietary recommendations might include patients with multiple co-morbid conditions. Another limitation is that the evidence base is insufficient to provide a definitive lower limit for dietary salt and upper limit for potassium. Unfortunately, it seems unlikely that additional RCTs to guide population-based therapy will follow, since trials that examine clinical end-points such as mortality are expensive requiring large numbers of participants and taking years to achieve an adequate number of study outcomes. It therefore seems prudent to recommend more stringent reductions particularly in higher-risk potentially salt-sensitive individuals, such as blacks, individuals >51 years of age, and patients who have hypertension or pre-hypertension, *before* the onset of significant end-organ damage. Finally, unless there is a contraindication in select patients or conflicting clinical data begin to emerge, the evidence in pre-clinical studies of the detrimental effect of dietary salt on the vasculature independent of BP suggests that a practical choice for clinicians may be to encourage all patients to adhere to these guidelines in order to promote health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Dr. Sanders is supported by the Nephrology Research and Training Center at UAB; the Office of Research and Development, Medical Research Service, Department of Veterans Affairs; a George M. O'Brien Kidney and Urological Research Centers Program (P30 DK079337); and NIH R01 DK04699.

Abbreviations used in this paper

AHA	American Heart Association
ABP	Ambulatory Blood Pressure
BP	Blood Pressure
CFR	Coronary Flow Reserve
CKD	Chronic Kidney Disease
CVD	Cardiovascular Disease
DASH	Dietary Approaches to Stop Hypertension
DBP	Diastolic Blood Pressure
eGFR	Estimated Glomerular Filtration Rate
FMD	Flow-mediated Dilation
INTERSALT	International Study of Salt and Blood Pressure
IOM	Institute of Medicine
LV	Left ventricle
LVH	Left ventricular Hypertrophy
LVM	Left-ventricular Mass

MI	myocardial infarction
Na/K ratio	Sodium to Potassium Ratio
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial
PWV	Pulse Wave Velocity
RCT	Randomized Controlled Trial
SBP	Systolic Blood Pressure
TOHP	Trials of Hypertension Prevention
TONE	Trial of Nonpharmacologic Interventions in the Elderly
TRANSCEND	Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease
UAE	Urinary Albumin Excretion
UNa	Urinary Sodium
US	United States
US DHHS	United States Department of Health and Human Services
USDA	United States Department of Agriculture

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Article Highlights

- Evidence from multiple randomized trials reinforces a role for increased dietary salt intake in the elevation of blood pressure as well as endothelial dysfunction, vascular remodeling and dysregulation, albuminuria and kidney disease progression, and cardiovascular morbidity and mortality in the general population.
- Dietary potassium supplementation attenuates the effects of a high dietary salt intake showing a linkage to reduction in blood pressure, stroke rates, and cardiovascular disease risk.
- Modest dietary salt restriction accompanied with increasing potassium intake serves as a broad-spectrum strategy to prevent and/or control hypertension and decrease cardiovascular morbidity and mortality.
- As outlined by current guidelines in the US, population-wide sodium reduction and recommended increases in dietary potassium intake provide an essential public health effort to reduce rates of hypertension, prevent kidney disease, stroke, and cardiovascular disease.
- Presently, the evidence base is insufficient to determine a lower limit for dietary salt and an upper limit for dietary potassium intake.

Table 1

Definitions of the grades assigned to the evidence presented in this review

Grade	Quality of the Evidence	Meaning
A	High	Further research is unlikely to change the confidence in the estimate of the effect
B	Moderate	Further research is likely to have an impact on the confidence in the estimate of the effect and may change the estimate
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
D	Very low	The estimate of the effect is very uncertain

Table 2

Grades of the strength of the recommendations provided in this review

Grade	Implications for Patients	Implications for Clinicians
Level 1	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.
Level 2	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision that is consistent with the individual patient's characteristics.

Table 3

Randomized Clinical Trial Characteristics by Intervention and Outcome

Intervention	Studies (N)	Participants Receiving an Intervention (N)	Participants Serving as Controls (N)	Median Follow-up Time (months)
Assessed Systolic Blood Pressure				
Dietary Salt Adjustment [15–38]	24	4019	3714	3.5
Dietary Potassium Adjustment [43–54]	12	752	785	2.5
Adjustments to both Salt and Potassium Intake [55–65]	11	2713	2430	12
Assessed Diastolic Blood Pressure				
Dietary Salt Adjustment [15–22,24–38]	23	3969	3580	3.5
Dietary Potassium Adjustment [43–54]	12	752	785	2.5
Adjustments to both Salt and Potassium Intake [55]	11	2713	2430	12
Assessed Mean Arterial Pressure				
Dietary Salt Adjustment [21,39,40]	3	640	715	2
Dietary Potassium Adjustment [45,49,54]	3	139	176	1.5
Adjustments to both Salt and Potassium Intake	-	-	-	-
Assessed Ambulatory Blood Pressure				
Dietary Salt Adjustment [26,28,37]	3	273	228	1.5
Dietary Potassium Adjustment [43,48]	2	90	90	6.5
Adjustments to both Salt and Potassium Intake	-	-	-	-
Assessed Biomarkers, CVD and CKD Progression and/or Events, and CVD Mortality				
Dietary Salt Adjustment [15,16,19,20,22,25,29–34,36,37,39–42]	18	3470	3171	3.5
Dietary Potassium Adjustment [43,46,48,51,54]	5	325	403	10
Adjustments to both Salt and Potassium Intake [57,61,66]	3	803	1248	6