Comparative Effectiveness Review
Number 206

Effective Health Care Program

Sodium and Potassium Intake: Effects on Chronic Disease Outcomes and Risks

Evidence Summary

Background and Objectives

Cardiovascular disease (CVD) and kidney disease[1] are responsible for the majority of deaths worldwide. A primary risk factor for CVD (cardiovascular disease), stroke, and other circulatory diseases is hypertension (HTN). In November 2017, the American Heart Association and the American College of Cardiology modified the definition of hypertension to a systolic blood pressure of 130 or higher and a diastolic blood pressure of 80 or higher. Before issue of the 2017 report on which these changes were based, health organizations worldwide defined hypertension as a systolic blood pressure (BP) of 140 or higher or a diastolic BP of 90 or higher; however, for the purpose of this review, the definition of HTN is that used by the individual included studies.

Sodium and potassium are vital for life. However, the role of excess dietary sodium as a major risk factor for HTN has been supported by large bodies of evidence.[2, 3] Evidence has also suggested a protective role for dietary potassium, independently or through its influence on the body's management of sodium.[4] The aim of the current report is to assess the evidence that interventions to decrease sodium intake or increase potassium intake on blood pressure, total mortality, and risk for CVD and kidney disease as well as evidence from prospective cohort studies on the

Purpose of Review

To synthesize the evidence regarding the effects of dietary sodium reduction and increased potassium intake on blood pressure and risk for cardiovascular diseases (CVD) and renal disease outcomes and related risk factors.

Key Messages

- Decreasing dietary sodium intake most likely reduces blood pressure in normotensive adults and more so in those with hypertension.
- Higher sodium intake may be associated with greater risk for developing hypertension.
- Use of potassium-containing salt substitutes in the diet to reduce sodium intake most likely reduces blood pressure in adults.
- Increasing potassium intake most likely decreases blood pressure in adults with hypertension.
- All-cause mortality may be associated with sodium intake.
- Reduced sodium intake may decrease the risk for combined CVD morbidity and mortality.

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associations between sodium, potassium, or sodium to potassium ratio and these outcomes.

Dietary Reference Intakes

The Governments of the United States and Canada have jointly undertaken the development of the Dietary Reference Intakes (DRIs) since the mid-1990s. Federal DRI committees from each country work collaboratively to identify DRI needs, prioritize nutrient reviews, and advance work to resolve any methodological issues that could impede new reviews. DRIs are a set of reference values that provide guidance on adequate and safe intakes of nutrients across the life span, by sex, and during pregnancy and lactation in apparently healthy individuals. They are based on an expert consensus process in which ad hoc committees convened by the Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine Health and Medicine Division (HMD) used scientific evidence, augmented by scientific judgment when dealing with uncertainties, to derive the reference values. The default reference values for adequate intakes are Estimated Average Requirements (EARs), from which a Recommended Dietary Allowance (RDA) is derived, "the average daily intake level sufficient to meet the nutrient requirement of nearly all healthy individuals" (97.5 percent) in a particular age and sex (life stage) group. If the available data are inadequate to identify an RDA requirement for nutrient sufficiency, an Adequate Intake (AI) reference value may be used in place of an EAR/RDA. The AI is a recommended intake level thought to meet or exceed the nutrient requirements of almost all individuals in a particular life stage and sex group.[5] The reference value that represents an intake above which the risk of potential adverse effects due to excessive intakes may increase is called the Tolerable Upper Intake Level (UL).

The DRIs are for dietary intakes only (i.e., foods and dietary supplements) and are intended to cover the needs of almost all healthy persons. These values serve multiple purposes, including guidance for (a) health professionals for use in dietary counseling and for developing educational materials for consumers and patients, (b) scientists in designing and interpreting research, (c) users of national nutrition monitoring, and (d) policy for a number of applications such as the Dietary Guidelines for Americans, nutrition labeling, and federal nutrition programs.

In 2005, the Dietary Reference Intakes: Water, Potassium, Sodium, Chloride, and Sulfate report was released by the Institute of Medicine Food and Nutrition Board.[6] The report established nutrient reference values for water, potassium, sodium, chloride and sulfate to maintain health and reduce chronic disease risk.

Sodium Dietary Reference Intakes

The 2005 IOM report set the AI for sodium for the population aged 19-50 years at 1500 mg (65 mmol) per day based on three criteria: (1) the amount of sodium that would likely need to be ingested in order to meet the needs of all other essential nutrients through food (2) the amount of sodium that would need to be replenished due to sweat losses in un-acclimatized individuals who are exposed to high temperatures or who are moderately physically active (as recommended in other DRI reports) and (3) the level of sodium intake that had shown an association in some studies with adverse effects on blood lipids and insulin resistance. The AI does not apply to highly active populations such as competitive athletes and workers exposed to extreme heat stress, such as fire fighters.[6]

The critical endpoint selected for determination of the UL was blood pressure.[5] The IOM concluded that the relationship between sodium intake and blood pressure was continuous without an apparent threshold; thus it was difficult to precisely set a UL, especially because other factors (weight, exercise, potassium intake, dietary pattern, alcohol intake, and genetic factors) also affect blood pressure. The IOM set the UL for sodium at 2,300 mg per day for people aged 14 years and over, with lower values for those 1-13 years of age. The ULs for children were extrapolated from the adult UL based on median energy intakes.

Since 2005, two related IOM reports, Strategies to Reduce Sodium Intake in the United States,[7] and Sodium Intake in Populations: Assessment of Evidence[8] have been published. The literature summarized in these reports as well as a number of subsequent evidence reviews, which include both observational studies and randomized controlled trials, support the relationship between sodium intake and blood pressure. In addition, some recent reviews of randomized controlled trials and observational studies have shown that reducing sodium leads to reductions in blood pressure among people with and without high blood pressure.[9-13]

Additional evidence, largely from observational studies, has shown that higher dietary sodium intake is associated with greater risk for hypertension, fatal and nonfatal stroke, and cardiovascular disease.[8, 13-15] Hypertension is strongly associated with a higher risk for CVD, stroke, congestive heart failure, and kidney disease.[16] Lowering blood pressure lowers these risks, and some evidence

supports an indirect relationship between sodium intake and CVD has been proposed.[17] Assessing the relationship between sodium intake and chronic disease outcomes (i.e., CVD, Stroke, myocardial infarction (MI), coronary heart disease (CHD), and kidney disease), and more importantly, whether reducing dietary intakes of sodium lowers the risk of these diseases, requires that the findings from observational studies be subjected to greater scrutiny and that they be supported by the findings of randomized controlled trials.

The limitations of the observational studies assessing the relationship between sodium intake and CVD outcomes have been carefully reviewed and critiqued.[18] Limitations may include methods used for sodium intake assessment, residual confounding, and possible reverse causality. Assessment of sodium intake in observational studies as well as in older randomized controlled trials has typically relied on the use of food frequency questionnaires or spot urine assays of urinary sodium excretion. However, these methods have repeatedly been shown to be highly prone to both random and systematic error. More accurate but still error prone methods include 24- to 72-hour food diaries or recall assessment or 8-hour (overnight) urine assays. The most accurate method of assessing sodium intake in observational studies, particularly decreases in sodium intake, is the repeated 24-hour urinary sodium excretion with validation.[19, 20] In light of the limitations of the existing observational studies, the current state of knowledge needs to be reconsidered.

Potassium DRIs

The 2005 IOM committee also set an AI level for potassium at 4,700 milligrams (120 mmol) per day, based on levels that blunt the sodium-related increase in blood pressure as well as the reduction in risk of kidney stones.[6] The DRI report noted the need for dose-response studies on potassium related to cardiovascular disease and blood pressure. The IOM Sodium Intake in Populations report listed "analyses examining the effects of dietary sodium in combination with other electrolytes, particularly potassium" on health outcomes as a research gap.[8] Understanding the health effects of potassium added to the diet and the interaction of potassium with sodium are essential. The latter is particularly important in monitoring the health impact of the use of potassium chloride (KCl) as a salt substitute in reformulating foods to reduce the amount of sodium, as KCl is already in use as a salt substitute in foods, including selected restaurant and packaged foods.

Use of Chronic Disease Endpoints in Setting DRIs

The DRI steering committees jointly decided that prior to undertaking a nutrient review, whether—and how—data on chronic disease risk reduction could be used in setting future DRI values need to be determined. Thus, a scientific expert panel was convened to review and critically evaluate evidentiary, dose response, and process issues related to the use of chronic disease endpoints and develop options for their incorporation into future DRI reviews.[21] The panel report identified the challenges that would need to be overcome in using chronic disease endpoints, namely systematically identifying and evaluating the strength of the evidence underlying proposed relationships. Because chronic disease endpoints were essential to development of the current UL for sodium, 2,300 milligrams per day, and may be used to set other DRI values, the US and Canadian steering committees commissioned the HMD to develop an authoritative report on the feasibility and practicality of using chronic disease endpoints in setting DRI values, and to develop an appropriate framework for use by future DRI panels. The commission of a systematic review for nutrients under review is now an integral part of the DRI process. The current review was undertaken at the recommendation of the DRI Working Group and its federal partners to inform the update of the sodium and potassium DRIs by the Institute of Medicine (Health and Medicine Division [HMD] of the National Academies of Sciences, Engineering, and Medicine).

Scope and Key Questions

Scope of Review

This report focuses on sodium and potassium intake, blood pressure, incident hypertension, and risk for all-cause mortality, chronic diseases, and related outcomes in all populations, including those with hypertension, Type 2 Diabetes, renal disease, CVD, and obesity.

The goal of this review is to provide a future DRI sodium and potassium panel with a systematic review of the evidence, including the general body of evidence reviewed by the 2005 DRI panel[6] (through 2002) and updated evidence, regarding sodium and potassium intakes, blood pressure, and the risks for hypertension, CVD, coronary heart disease, stroke, renal disease, and kidney stones.

This report does not include a review of studies that assess the levels of dietary sodium and potassium required to prevent deficiencies.

The protocol has been published on the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Web site (http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=2428). In addition, the protocol was registered in PROSPERO (CRD42017056126).

Key Questions

The Key Questions (KQs) for sodium and potassium are as follows.

Sodium

KQ1. Among adults and children of all age groups (including both sexes and pregnant and lactating women), what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on blood pressure at the time of the study and in later life?

- **a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?**
- **b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).**
- **c. Among subpopulations defined by hypertension, diabetes, and obesity health status.**

KQ2. Among adults and children, what is the association between dietary sodium intake and blood pressure?

- **a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).**
- **b. Among subpopulations defined by hypertension, diabetes, and obesity health status.**

KQ3. Among adults, what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on CVD and kidney disease morbidity and mortality and on total mortality?

- **a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?**
- **b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).**
- **c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.**

KQ4. Among adults, what is the association between dietary sodium intake and CVD, CHD, stroke, and kidney disease morbidity and mortality, and between dietary sodium intake and total mortality?

- **a. Do other minerals (e.g., potassium, calcium, magnesium) modify the association with sodium?**
- **b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).**
- **c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.**

Potassium

KQ5. Among children and adults what is the effect of interventions to increase potassium intake on blood pressure and kidney stone formation?

- **a. Do other minerals (e.g., sodium, calcium, magnesium) modify the effect of potassium?**
- **b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).**
- **c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.**

KQ6. Among children and adults, what is the association between potassium intake and blood pressure and kidney stone formation?

- **a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).**
- **b. Among subpopulations defined by hypertension, diabetes, and obesity health status.**

KQ7. Among adults, what is the effect of interventions aimed at increasing potassium intake on CVD and kidney disease morbidity and mortality, and on total mortality?

- **a. Do other minerals modify the effect of potassium (e.g., sodium, calcium, magnesium)?**
- **b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).**
- **c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.**

KQ8.Among adults, what is the association between dietary potassium intake and CVD, CHD, stroke, and kidney disease morbidity and mortality, and between dietary potassium and total mortality?

a. **Do other minerals (e.g., sodium, calcium, magnesium) modify the association with potassium?**
b. **Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).**
c. **Among subpopulations defined by hypertension, diabetes, and obesity health status.**

Methods

The Evidence-based Practice Center conducted this review following established methods as outlined in the AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews.[22] A complete description of the methods appears in the full report.

Literature Search Strategy

We searched PubMed®, CINAHL®, Embase®, the Cochrane Database of Systematic Reviews (CDSR), CENTRAL, and Web of Science for English-language publications, commencing with 2003. In addition, reference lists of existing systematic reviews on the outcomes of interest as well as the 2005 DRI report were screened to identify all relevant studies from inception.

Criteria for Inclusion/Exclusion of Studies in the Review

We included randomized and nonrandomized controlled trials and observational studies published in English that examined interventions to restrict sodium intake or increase potassium intake, used a comparator group, and reported outcomes of interest in participants at least 4 weeks or more after the initiation of the intervention (longer minimum followup times were established for some outcomes, as described in the full report). Observational studies were included if they were prospective cohort studies with followup times and baseline participant conditions that met prespecified criteria.

Pairs of investigators independently determined study eligibility and resolved disagreements through discussions; if needed, the project leader was consulted until consensus was achieved.

Quality (Risk of Bias) Assessment of Individual Studies

Risk of bias (RoB) of eligible studies was assessed by two independent investigators using an instrument based on AHRQ guidance.[22] The investigators consulted to reconcile any discrepancies in overall RoB assessments. Overall summary RoB assessments for each study were classified as low, moderate, or high based on a composite of the individual items.

Data Synthesis

The results for each study are described in evidence tables as well as in figures and summary tables in the full report. For both sodium and potassium, evidence is synthesized by study design (odd-numbered vs. even-numbered questions), outcome, types of intervention or intake assessment), and, where possible, separately by subgroups of interest.

Where possible, we pooled results of studies with similar study designs and interventions and report these summary findings. We also conducted meta-regressions on the findings of trials that assessed the effects of sodium reduction, to compare the outcomes relative to mean differences in 24-hour urinary sodium excretion.

A draft version of the report was posted for peer review and for public comment and the report was revised in response to comments. However, the findings and conclusions are those of the authors, who are responsible for the contents of the report.

Strength of the Body of Evidence

We evaluated the overall strength of evidence for each outcome and subgroup based on five domains: (1) study limitations (study design, number of studies, study size, and overall RoB [low, moderate, high, or unclear]); (2) directness (the degree to which the assessed outcome represented the true outcome of interest, the findings were based on randomized controlled trials, or, in the case of subgroup analyses, whether subgroups were compared within the same intervention); (3) consistency (similarity of effect direction and size); (4) precision (degree of certainty around an estimate); and (5) reporting bias (evidence that reported outcomes were prespecified by the study protocol).[22] Four strength of evidence grades were possible:

- High: High confidence that the evidence reflects the true effect. Further research is unlikely to change the estimates.

- Moderate: Moderate confidence that the estimate reflects the true effect. Further research may change estimates and our confidence in the estimates.
- Low: Limited confidence that the estimate of effect lies close to true effect. Further research is likely to change confidence in the estimate of effect, and may change the estimate.
- Insufficient: Evidence is either unavailable or does not permit a conclusion to be drawn.

Results

We identified 15,912 unique titles, of which 257 publications (reporting on 171 studies) were deemed eligible for review. A flow diagram appears in the main text of the report.

The bodies of evidence varied greatly in size by outcome and sodium or potassium intake. No conclusions were deemed to have a high strength of evidence. The strength of evidence of conclusions that depended on associations (observational studies) were assessed separately from those based on interventions.

The key findings (primarily those for which the strength of evidence was high or moderate) are summarized by KQ below, along with the strength of evidence. The findings for healthy adults are presented first, followed by the findings for subpopulations of interest. Additional findings are provided in the main report.

Odd-numbered KQs are addressed with randomized controlled trials (RCTs) and controlled clinical trials, whereas even-numbered questions are addressed with prospective cohort studies. The conclusions are based primarily on data from controlled trials.

KQ1. Among adults and children of all age groups (including both sexes and pregnant and lactating women), what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on blood pressure at the time of the study and in later life?

a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?

b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, and obesity health status.

- Sodium reduction decreases systolic (mean difference [MD] –3.23 millimeters [mm] mercury [Hg], 95% confidence intervals [CI] –4.07, –2.38; I^2 77%; 47 RCTs) and diastolic (MD -2.24 mm Hg, 95% CI –2.96, –1.61; I^2 75%; 48 RCTs) blood pressure significantly in adults (weighted mean difference in sodium intake 42 mmol/d) (moderate strength of evidence [SoE]).
- Sodium reduction in adults may increase the likelihood of achieving a prespecified blood pressure goal (low SoE; 6 RCTs).
- Sodium reduction lowers BP in both men and women (moderate SoE); the evidence does not support a moderating effect of sex on BP in adults (low SoE).
- Short term sodium reduction interventions do not appear to show statistically significant effects on BP in children (low SoE based on eight RCTs); however, a sensitivity analysis that excluded high or unclear RoB studies resulted in a small difference in systolic blood pressure and a statistically significant decrease in diastolic BP with sodium reduction for children (MD –1.54, 95% CI –2.57, –0.51; I^2 0%; 4 RCTs)
- Sodium reduction decreases systolic BP in both those with hypertension (MD –4.14, 95% CI –5.21, –3.07; I^2 75%) and those with normal BP (MD –1.51, 95% CI –2.76, –0.26; I^2 42%); the effect is greater in adults with HTN than in those with normal BP ($p<0.001$, moderate SoE; 45 RCTs). Sodium reduction decreases diastolic BP in those with hypertension (moderate SoE; 37 RCTs).
- Evidence may not support a moderating effect of increasing dietary potassium via food or supplements on the blood pressure-lowering effect of sodium reduction (low SoE; 5 RCTs).
- Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE; 13 RCTs).

KQ2. Among adults and children, what is the association between dietary sodium intake and blood pressure?

a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).

b. Among subpopulations defined by hypertension, diabetes, and obesity health status.

- Sodium intake may be associated with systolic BP in adults based on prospective observational studies (low SoE, 5 studies). Most studies had high RoB for the

methods used to assess sodium intake, and findings were inconsistent across studies.

- Sodium intake may be associated with risk of incident hypertension in prospective cohort studies of adults (low SoE, 5 studies). Most studies had high RoB for the methods used to assess sodium intake, and the number of studies was small).

KQ3. Among adults, what is the effect (benefits and harms) of interventions to reduce dietary sodium intake on CVD and kidney disease morbidity and mortality and on total mortality?

a. Do other minerals (e.g., potassium, calcium, magnesium) modify the association with sodium?

b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

- In adults, evidence was insufficient to draw a conclusion regarding the effect of sodium reduction on the risk for all-cause mortality or CVD mortality, alone.
- Sodium reduction may significantly decrease the risk for combined CVD morbidity and mortality (8 RCTs; low SoE).
- Evidence from a small number of RCTs does not support an effect of sodium reduction on the risk for stroke. (3 RCTs; low SoE)
- Sodium reduction may significantly decrease the risk for a composite measure of any CVD outcomes as reported by study authors (7 RCTs; low SoE).

KQ4. Among adults, what is the association between dietary sodium intake and CVD, CHD, stroke, and kidney disease morbidity and mortality, and between dietary sodium intake and total mortality?

a. Do other minerals (e.g., potassium, calcium, magnesium) modify the association with sodium?

b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

- Although sodium levels appear to be associated with risk for all-cause mortality (low SoE, based on 11 studies), the shape of the relationship could not be determined (insufficient SoE).
- Evidence is insufficient to assess the possible association of sodium intake level and risk for CVD, CHD, or stroke morbidity or mortality.

KQ5. Among children and adults, what is the effect of interventions to increase potassium intake on blood pressure and kidney stone formation?

a. Do other minerals (e.g., sodium, calcium, magnesium) modify the effect of potassium?

b. Among subpopulations defined by sex, race/ethnicity, age (children, adolescents, young adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

- Increased potassium intake from dietary supplements reduces blood pressure in adults (moderate SoE based on 10 parallel RCTs and 8 crossover RCTs). However the effect is limited to studies of adults with prehypertension or hypertension (moderate SoE). Studies of adults with normal BP did not show evidence that increased potassium intake decreases blood pressure in this group (3 RCTs; low SoE)
- Evidence does not support an effect of increasing potassium intake through changes in food intake alone on BP in adults (low SoE based on four RCTs).
- Evidence is insufficient to support a conclusion regarding the effect of increasing potassium intake on kidney stone formation (1 RCT).

KQ6. Among children and adults, what is the association between potassium intake and blood pressure and kidney stone formation?

a. Among subpopulations defined by sex, race/ethnicity, and age (children adolescents, young adults, older adults, elderly).

b. Among subpopulations defined by hypertension, diabetes, and obesity health status.

- Evidence from prospective cohort studies does not support a consistent association of higher potassium intake with lower adjusted BP in cohort studies of adults (6 prospective cohort studies; low SoE based on inconsistent findings and studies with high RoB).
- Higher potassium intake appears to be associated with a lower risk for kidney stones in cohort studies of adults (low SoE, based on 4 prospective cohorts [reported in 2 publications] with high RoB).

KQ7. Among adults, what is the effect of interventions aimed at increasing potassium intake on CVD and kidney disease morbidity and mortality, and on total mortality?

a. Do other minerals modify the effect of potassium (e.g., sodium, calcium, magnesium)?

b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, obesity, and renal health status.

- Evidence was insufficient, based on only one RCT, to address this question.

KQ8. Among adults, what is the association between dietary potassium intake and CVD, CHD, stroke, and kidney disease morbidity and mortality, and between dietary potassium and total mortality?

a. Do other minerals (e.g., sodium, calcium, magnesium) modify the association with potassium?

b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).

c. Among subpopulations defined by hypertension, diabetes, and obesity health status.

- Evidence is insufficient to identify associations of potassium intake with long-term chronic disease outcomes of interest, primarily due to the limitations in the potassium intake assessments.

Discussion

Summary of Findings in Relation to What Is Already Known

Since the Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate was published in 2005, a number of systematic reviews have been conducted on the effects of sodium intake and sodium reduction on BP, as well as CVD and CHD outcomes. We briefly review our findings in light of the findings of the most recent reviews. Aburto and colleagues conducted reviews on the relationship between sodium and potassium intake and BP, CVD, CHD, and stroke from observational studies and the effects of sodium reduction and increased potassium intake as reported in RCTs; these reviews were sponsored by the World Health Organization (WHO) in support of their current guidelines. The WHO review on sodium and BP, which included 37 RCTs, found significant beneficial effects of interventions to reduce sodium on blood pressure in adults and children but no difference between very low- (defined as a target of 50mmol/d) and low-sodium (defined as a target of 100mmol/d) interventions.[4, 23] Our report found similar effects of sodium reduction on BP in adults, but only statistically non-significant beneficial effects in children. A sensitivity analysis that omitted high- and unclear RoB studies showed that when only low- and moderate-RoB studies were pooled, sodium reduction resulted in a statistically significant decrease in diastolic BP in children (the decrease in systolic BP remained non-significant). The WHO report did not assess effects of sodium reduction on incident hypertension or achievement of specific BP goals. The inclusion criteria for our report and those of the WHO report differed in several ways. Our review included sodium reduction RCTs regardless of achieved sodium excretion, whereas the WHO review excluded RCTs with a mean difference in achieved sodium excretion of less than 40 mmol/d.

More recently, Graudal and colleagues systematically reviewed the trial literature on sodium reduction and BP and reached similar conclusions to those of Aburto and our current review; the Graudal review excluded only trials with a duration of less than 4 days, resulting in a larger number of included trials.[24] Our review also corroborates the findings of the Graudal review regarding a larger effect of sodium reduction on individuals with HTN than on normotensive individuals.

The WHO report found no effect of sodium reduction on plasma epinephrine, norepinephrine, blood lipids, or kidney function, as measured by serum creatinine and creatinine clearance; four studies that met our inclusion criteria corroborated the apparent absence of effect of sodium reduction on blood lipids (reported as adverse effects or primary outcomes), but no studies met our inclusion criteria for assessing changes in kidney function or catecholamines. In contrast, the Graudal review reported significant increases in cholesterol and triglycerides, possibly due to the shorter followup of some included studies and the larger number of studies that met inclusion criteria.[24]

Several recent systematic reviews also appraised the evidence linking sodium with all-cause mortality, CVD, CHD, or stroke. A 2014 systematic review by Adler and colleagues that reviewed eight RCTs assessing effects of sodium reduction on these longer-term outcomes reported no effect on all-cause mortality.[15]

Graudal and colleagues (2014) conducted a meta-analysis of prospective cohort studies that assessed the association between sodium intakes and mortality: They reported an

increased mortality risk at both low- and high intakes of sodium (which they referred to as a "U-shaped curve").[25] The review include only observational studies, and the findings could be explained by errors in estimation of sodium intake at the lower or the upper end as well as reverse causality.

Our review of RCTs that reported on the effects of sodium reduction on all-cause mortality found a non-statistically significant decrease in the risk for all-cause mortality but evidence was insufficient on which to base a conclusion. Our review of prospective cohort studies found that sodium intake may be associated with increased risk but evidence was insufficient to draw any conclusions regarding the shape of the curve. The methods used to estimate sodium intake varied across the observational studies, and only a small number used multiple 24-hour sodium excretion measures with validation to ensure complete collection; in addition, these studies could not rule out reverse causation: In sodium studies, reverse causality arises when study participants with medical morbidity have reduced their sodium intake on medical advice or because their illness has resulted in decreased food consumption.

Our current review also adds to the evidence by identifying an effect of sodium reduction on reducing combined CVD morbidity and mortality across RCTs. The review by Adler found similar effects on CVD mortality and morbidity; they largely attributed the observed effect on mortality to one study that implemented use of a potassium salt substitute to reduce sodium intake.[26] We also reported statistically significant effects of sodium reduction on a composite of any CVD outcomes. The Adler review included one RCT[27] that we excluded, as it was a multicomponent intervention that did not control for other dietary changes (the remaining RCTs were included in our review).[15] The WHO also reviewed the evidence linking sodium with CVD, CHD, and stroke; that report, which included 14 prospective cohort studies and five RCTs, found sufficient evidence only to conclude (based on the evidence from cohort studies) that increased sodium intake was linked to increased risk for stroke, stroke mortality, and CHD mortality.[4]

We identified few studies on individuals with chronic kidney disease, and no studies that met our inclusion criteria addressed renal endpoints. A Cochrane review by McMahon and colleagues appraised the evidence on effects of sodium reduction on cardiovascular outcomes in persons with kidney disease.[28] However like our review, they identified no studies with long enough follow up to assess long term chronic disease outcomes. Instead they reported only on studies that assessed effects of sodium reduction on BP outcomes in persons with kidney disease, reporting that sodium reduction decreased systolic BP and diastolic BP in these studies. Across the studies that met our inclusion criteria, we also noted that sodium reduction generally decreased BP; however, we determined that the populations were too dissimilar (based on comorbidities) to permit studies to be pooled.

Aburto and colleagues subsequently reviewed the evidence for an association of potassium intake with BP, HTN, and CVD for the WHO, concluding that higher potassium intake was associated with reduced BP in individuals with HTN but not in normotensive persons.[29] That report found insufficient evidence to draw conclusions regarding the association of potassium intake with risk for CVD or CHD morbidity or mortality. Our current review confirmed the association of potassium with BP lowering, by identifying RCTs that assessed the effects of increased potassium intake and also extended their finding to healthy populations. We found insufficient evidence to draw any conclusions on the effects of increased potassium intake on incident HTN, and like the WHO review, we identified insufficient evidence to draw conclusions regarding the effects of increased potassium intake on CVD/CHD morbidity or mortality. In addition, the beneficial effects of increased potassium intake on BP were not reflected in any association between (urinary or dietary) potassium intake and BP.

Limitations of the Evidence Base

The purpose of this review was to assess the evidence for the intermediate and clinical health effects of reduced sodium intake, mainly as reflected in reduced 24-hour urinary sodium excretion. We did not assess the evidence regarding the most effective intervention design(s).

Most RCTs demonstrated an overall low or moderate RoB. However, a number of studies omitted many details of study design and conflict of interest, so actual RoB was unclear for some items. Nearly all observational (prospective cohort) studies that met inclusion criteria relied on single 24-hour urinary excretion measures, single or 2-day dietary recall without 24-hour urinary excretion, estimated sodium excretion to assess status, or food frequency questionnaires. The implications of assessment of sodium and potassium intake are discussed further below. Additional limitations are listed here, organized by a PICOTSS (populations, interventions, comparators, outcomes, timings, settings, study design) framework (see Table 1 in full report report).

Populations

- Few to no studies conducted subgroup analyses by sex, age, race/ethnicity, or comorbidities.
- RCTs may enroll individuals who are more motivated than average, although compliance across studies (usually based on 24-hour sodium excretion) does not necessarily support this possibility.
- Studies defined prehypertension and mild-to-moderate HTN differently or not at all, and some studies included individuals with pre- or mild HTN along with individuals with more advanced HTN.
- Although most RCTs either prohibited or required use of antihypertensive medications or withdrew participants from medications at baseline and assessed need to resume their use, at least 25 percent of studies did not consider use of these medications, or allowed participants to remain on medications but did not account for their use. Studies that enrolled only participants taking antihypertensive medications usually did not control for the class of medication, thus potentially introducing a confounding factor. Concurrent use of some antihypertensive medications could have masked the potential effects of a reduced sodium diet.
- Few studies of individuals with chronic kidney disease met the inclusion criteria for the review, and no studies that assessed renal outcomes met inclusion criteria.
- Observational studies had limited ability to control for pre-existing health conditions at study baseline, that might have resulted in decreased sodium intake, contributing to potentially spurious associations of lower sodium intakes with morbidity or mortality outcomes of interest.
- Observational studies may have residual confounding, as they could not adjust for all factors that may increase risk for HTN, CVD, CHD outcomes.

Interventions/Intakes

- RCTs use widely varying methods to achieve different sodium intake levels, and most RCTs actually employ multicomponent lifestyle interventions or at least multicomponent dietary interventions; thus not all changes in outcomes of interest might be attributable to reduced sodium or increased potassium intake. The potential implication of this variation in background diet for study findings is highlighted by the findings of the Dietary Approaches to Stop Hypertension (DASH) Sodium trial, which showed that at each dietary sodium level, mean BP was higher (2.2 to 5.9 mm Hg) among control diet participants than among the DASH diet groups, that the decreases in BP achieved with decreasing sodium intake were greater for those on the control diet than for those on the DASH diet, but that nevertheless, the low-sodium DASH participants achieved the greatest reduction in BP overall.[30] Thus a diet that includes more fruits and vegetables (and, as a result, more vitamins, minerals, and fiber, and less saturated fat), as well as whole grains and low-fat dairy, has effects on BP that are independent of sodium intake.
- Only a small number of studies assessed effects of natural experiments, community- or government-level interventions.
- Many RCTs failed to report intended goals of the intervention (e.g., achieving 70 mmol/d urinary sodium excretion or a difference between the intervention group and the control group of 40 mmol/d or more).
- Effectiveness of behavioral/lifestyle interventions in reducing sodium intake may be affected by unmeasured or unreported factors, such as intensity of counseling.
- Few prospective cohort studies used multiple 24-hour urinary excretion analyses, although increasing evidence demonstrates that multiple, non-consecutive 24-hour urinary sodium excretion measurements need to be used as the indicator of intake in observational studies.[19, 31, 32] Thus nearly all included prospective cohort studies had high risk for both systematic (24-h urine collections without evidence of quality control measures, spot or overnight urine collections, food frequency questionnaire (FFQ), 24-hour recalls, and food records) and random error (e.g., single 24-hour or spot urine collections or single-day food recalls).
- Both RCTs and prospective cohort studies varied widely in baseline sodium intake. Most RCTs employed 24-hour urinary sodium excretion as a measure of compliance with the intervention. However, differences in baseline intake could affect the potential to achieve sodium reduction goals through dietary interventions and introduces a source of heterogeneity among prospective cohort studies. Evidence in support of this idea is presented by a recent post hoc assessment of data from the DASH Sodium trial found that reducing sodium intakes in the context of the control or the DASH diet were associated with progressively greater reductions in BP with higher baseline BP (through baseline systolic BP of 150 mm Hg or higher).[33]

- Wide variation in achieved intake across RCTs introduces another potential source of heterogeneity and calls into question whether differences in achieved sodium intake can accurately predict changes in outcomes of interest.
- Few RCTs reported sodium/potassium ratios. Potentially related to this observation, studies that employed potassium-containing salt substitutes to reduce sodium intake or tested the effects of potassium supplements tended to find no consistent effects on sodium excretion.
- Few studies employ food-based interventions to assess the effects of increasing potassium intake. Those that do use dietary interventions do not consistently control for differences in other micronutrients, carbohydrates, and fiber.
- Potassium supplementation studies range from about 15 to 120 mmol/d in the amounts provided (average intakes from food range from 50 to 150 mmol/d and the current AI for adults is 120 mmol/d), introducing a potential source of heterogeneity across studies.

Comparators

- Confounding in dietary intervention studies (for example, adoption of use of salt substitutes or other salt reduction practices by control groups) was difficult to control or measure, and blinding had limited effectiveness when the comparison group consumed their usual diet (most dietary intervention studies that relied on counseling reported that participants were not blinded).
- Studies with usual diet as the control may not be comparable with studies that impose a low-sodium diet on all participants and then achieve differences in sodium intake using sodium tablets to mimic usual sodium intake.

Outcomes

- Studies defined HTN, CVD, and CHD outcomes differently.
- Few RCTs assessed the effect of sodium reduction or increased potassium intake on the risk for incident HTN as an outcome.
- Of the small number of studies that assessed long term CVD outcomes, few assessed these as primary or even prespecified outcomes, were not powered to assess them as prespecified outcomes, and reported them instead as adverse events.
- Little research assesses effects of sodium reduction on CHD outcomes.

Timing/Duration

- Few to no RCTs were identified that assessed longer-term clinical outcomes of most interest: RCTs seldom had adequate duration of interventions or followup to assess longer-term outcomes.
- Renal outcomes, including kidney stones, require longer followups to observe potential effects of interventions than were employed in any of the studies identified.
- Long-term outcomes resulting from brief interventions may not show effects.

Setting

- RCTs in clinical research settings are resource intensive and may have limited practical application. RCTs in populations confined to residential settings such as long-term care facilities, schools, or prisons may provide more useful results in terms of assessing outcomes but still fail to address the potential effects of voluntary efforts (individual or community) to reduce dietary sodium intake.

Study Design

- Observational studies predominated for long term chronic disease outcomes.
- As described, RCTs with parallel arm designs present challenges that are difficult to overcome regarding blinding, allocation concealment, and contamination.
- RCTs with crossover designs may provide some advantages, but existing crossover trials seldom describe washout periods or assess potential carryover effects of short (or no) washouts.

Limitations of This Review

Since the inclusion of participants with pre-existing conditions could confound attempts to link the outcomes of interest with changes in sodium intake, studies that enrolled sick participants were excluded from the affected analyses. For example, studies of patients with CVD were excluded from analysis of risk for CVD morbidity, but not analysis of CVD mortality, and studies of patients with cancer, HIV/AIDS, and end stage renal disease were excluded from all analyses.

We did not take use of antihypertensive medications into account in our analyses of RCT data, primarily because studies did not consistently report or adjust for such use.

As a result, we could not eliminate the possibility that potential effects of reduced sodium might be masked by the effects of such medications.

Similarly, we did not conduct sensitivity analyses to assess the effects of the methods used to measure blood pressure, which may strongly affect outcomes.

Because of the small number of studies that assessed moderating effects of demographic factors or comorbidities (and were powered to do so), we conducted meta-regressions to try to shed light on potential moderators, realizing these are indirect comparisons.

The duration of interventions or followup is likely critical. For that reason, we set strict lower limits on the durations of studies we included, especially for long term clinical outcomes. However, we did not attempt to assess the effects of intervention or followup duration on outcomes, mainly because we identified too few studies to enable realistic comparisons.

We excluded crossover studies that did not describe the use of washout or duration of washout and did not describe a process to assess the possible effects of carryover. As a result, we excluded one dose-response study, the findings of which supported the conclusion that decreasing sodium intake decreases blood pressure.[34] However, some evidence suggests potential carryover may need to be considered.[35]

Research Gaps Identified by This Review

In light of the large body of evidence on the effects of sodium reduction on blood pressure in healthy adults and those with hypertension, the determination that the effect of reducing sodium intake on blood pressure is supported by moderate but not high strength evidence is attributable to inconsistency in the direction of study findings and to study heterogeneity. Sensitivity analyses that omitted high- and unclear RoB studies did not appreciably alter consistency, heterogeneity, or effect sizes; thus, other factors—such as differing participant comorbidities, intervention design, or blood pressure measurement methods—may contribute to the variation.

Studies to assess whether those with HTN may benefit more or less from reduced dietary sodium than those with normal blood pressure showed greater benefits for those with HTN, but at least one fourth of studies that enroll adults with HTN do not report controlling for use of antihypertensive medication.

Among studies that met inclusion criteria, only a small number directly compared effects of sodium reduction on participants with normal blood pressure with those on participants with HTN. Studies to assess the benefits of reducing dietary sodium for those with normal blood pressure were fewer in number than studies of populations with HTN, and some studies of normotensive populations included individuals with high normal blood pressure.

Few studies that met inclusion criteria directly compared the effects of sodium reduction on men with those on women, the effects on one racial/ethnic group with those on other racial/ethnic groups, and the effects among different age groups. Few studies designed to determine whether dietary interventions reduce blood pressure among younger individuals—both children, adolescents, and young adult—met inclusion criteria.

Most dietary intervention studies to reduce sodium (or increase potassium) from food sources involved counseling, making it difficult to isolate the effects of sodium reduction, either because of poor adherence or because of the challenge of ruling out alterations in intake of other nutrients.

Few trials that met inclusion criteria assessed the effects of sodium reduction or increased potassium intake on CVD, CHD, stroke, or renal outcomes, including the effect of increasing potassium intake on the incidence of kidney stones.

Conclusions

We undertook this systematic review to appraise the evidence from trials regarding the effects of dietary sodium reduction and/or increased potassium intake on blood pressure and risk for cardiovascular diseases—as well as the evidence on associations of dietary sodium and potassium with blood pressure and cardiovascular diseases. This review finds that interventions that reduce sodium intake (including those that use potassium-containing salt substitutes in the diet) reduce blood pressure in both normotensive adults and to a greater extent in those with hypertension. Interventions to reduce sodium intake increase the likelihood of reaching a prespecified blood pressure goal and may decrease the incidence of hypertension in adults, in agreement with prospective cohort studies, which show that higher sodium intakes may be associated with greater risk for hypertension.

Increasing potassium intake via potassium supplements significantly decreases blood pressure, but the effects of increasing potassium intake through food alone remain unclear.

Interventions to assess the effects of reducing sodium intake on the risk for all-cause mortality are small in number and provide an insufficient basis on which to draw a conclusion. Prospective cohort studies suggest

sodium intake may be associated with all-cause mortality. Findings from randomized controlled trials also suggest that interventions to reduce sodium intake may decrease the risk for composite measures of cardiovascular disease outcomes.

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Full Report

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