Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors

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Purpose of Review: To synthesize the evidence regarding the effects of dietary sodium reduction and increased potassium intake on (and their associations with) blood pressure and risk for chronic cardiovascular diseases (CVD).

DRAFT Key Messages
• Interventions that decrease dietary sodium intake reduce blood pressure in both normotensive adults and those with hypertension. The effect of sodium reduction is greater in adults with hypertension than in those with normal blood pressure.
• Prospective cohort studies show that higher intakes of sodium are associated with greater risk for developing hypertension.
• Use of potassium-containing salt-substitutes to reduce sodium intake reduces blood pressure in adults.
• Increasing potassium intake decreases blood pressure in adults with hypertension.
• Interventions to reduce sodium intake decrease all-cause mortality slightly, but studies are inconsistent and small in number.
• Although there appears to be an association between all-cause mortality and 24-hour sodium excretion at higher sodium levels, the linearity of this relationship at lower sodium levels could not be determined.
This report is based on research conducted by an Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xxxx-xxxxx). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators has any affiliations or financial involvement related to the material presented in this report.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Suggested citation:
Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Acknowledgments

Will be acknowledged in the final report.

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts will be acknowledged in the final report.

Peer Reviewers

Prior to publication of the final evidence report, EPCs seek input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers will be acknowledged in the final report.
Effects of Dietary Sodium and Potassium Intake on Chronic Disease Outcomes and Related Risk Factors: A Systematic Review

Structured Abstract

Objectives. This systematic review synthesized the evidence regarding the effects of dietary sodium reduction and interventions to increase potassium intake on (and their associations with) blood pressure and risk for chronic cardiovascular diseases (CVD). The purpose of the review is to provide a future Dietary Reference Intakes (DRI) Committee with the evidence on chronic disease endpoints for consideration in reviewing the DRIs for sodium and potassium.

Data Sources. PubMed, EMBASE, the Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials, CINAHL, Web of Science, references of prior reviews, hand searches of gray literature, and expert recommendations.

Review Methods. Two reviewers independently screened citations and full-text publications. Eligible studies included randomized controlled trials (RCTs), nonrandomized controlled trials, and prospective observational studies published to 2017 that enrolled healthy populations or those with pre-existing hypertension, CVD, diabetes, or obesity and that assessed blood pressure, incident hypertension, achievement of prespecified blood pressure goals, all-cause mortality, CVD morbidity and mortality, CHD morbidity and mortality, stroke, myocardial infarction, renal morbidity and mortality, kidney stones, and adverse events. We extracted data, assessed risk of bias, summarized and synthesized results, and evaluated strength of evidence separately for randomized controlled trials and other study designs.

Results. We identified 12,054 unique citations, of which 241 publications reporting on 159 studies were deemed eligible for the review.

Moderate-strength evidence supports a blood-pressure lowering effect of dietary sodium reduction in adults. The blood-pressure lowering effect is greater in adults with hypertension than in normotensive adults. Sodium reduction also increases the proportion of study participants who achieved a prespecified blood pressure goal in small numbers of trials (moderate SoE) but does not significantly decrease the incidence of hypertension (based on a small number of trials). Observational studies show an association between lower urinary sodium excretion and reduced risk for hypertension (low SoE because of high RoB and lack of consistency).

Only a small number of RCTs assessed the effects of sodium reduction on longer-term chronic disease outcomes: Low-strength evidence supports a small effect of sodium reduction on reducing all-cause mortality (studies were few in number and did not consistently report all-cause mortality as a primary outcome). We found no effect of sodium reduction on CVD mortality, CVD morbidity, or combined CVD mortality/morbidity (low strength of evidence). Low-strength evidence from prospective cohort studies supports an association between sodium intake and all-cause mortality but evidence was inconsistent regarding an association with combined CVD morbidity/mortality and a lack of association with stroke risk.

Use of potassium salt substitutes in place of sodium chloride and increased potassium intake itself significantly decrease blood pressure (moderate SoE), but evidence is insufficient to assess
their effect on risk for hypertension or longer-term chronic conditions or the potential moderating effects of other factors. Evidence from prospective cohort studies is insufficient to assess associations of potassium status with outcomes of interest.

**Conclusions.** Dietary sodium reduction, increased potassium intake, and use of potassium-containing salt substitutes significantly decrease blood pressure, but their effects on longer term chronic disease outcomes, particularly CVD and CHD morbidity and mortality, need more research.
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Executive Summary

Background and Objectives

Cardiovascular and circulatory diseases, including coronary heart disease (such as myocardial infarction and heart failure), coronary artery disease (such as stroke), and kidney disease,¹ are responsible for the majority of deaths worldwide. A primary risk factor for CVD, stroke, and other circulatory diseases is hypertension (HTN).

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 Evidence has also suggested a protective role for dietary potassium, independently or through its influence on the body’s handling of sodium.³ The aim of the current review and numerous prior reviews has been to assess the evidence that lowering dietary sodium reduces the risk for HTN and in turn the risk for CVD and that maintaining or increasing dietary potassium provides benefit.⁴

The 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 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 Daily 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.
The Sodium Dietary Reference Intakes

The 2005 IOM report set the AI for sodium for the population aged 19-50 years at 1500 mg 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 firefighters. 6

The critical endpoint selected for determination of the Tolerable Upper Intake Level (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 Evidence8 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 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.8-10, 14 Since hypertension is strongly associated with a higher risk for CVD, stroke, congestive heart failure, and kidney disease and lowering blood pressure lowers these risks, an indirect relationship between sodium intake and CVD has been proposed.15-17 Assessing the relationship between sodium intake and chronic disease outcomes (i.e., CVD, Stroke, MI, 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, 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.
The Potassium DRIs

The 2005 IOM committee also set an AI level for potassium at 4,700 milligrams per day, based on levels that blunt the sodium-related increase in blood pressure as well as the reduction in risk of kidney stones. 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. 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.

The 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. 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 the Review

This report focuses on sodium and potassium intake, blood pressure, incident hypertension, and risk for 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 (through 2002) and updated evidence, regarding sodium and potassium intakes or exposures, 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 (hyponatremia or hypokalemia).
The protocol has been published on the AHRQ Effective Healthcare website (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

Sodium

KQ 1: 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 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.

KQ 4: 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

KQ 5: 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.

KQ 6: 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.

KQ 7: Among adults, what is the effect of interventions aimed at increasing potassium intake on CVD, and kidney disease morbidity and mortality, and 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.

KQ 8: 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 (EPC) conducted this review following established methods as outlined in the Agency for Healthcare Research and Quality (AHRQ)’s Methods Guide for Comparative Effectiveness Reviews. 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 relevant studies.
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 of eligible studies was assessed by two independent investigators using an instrument based on AHRQ guidance. The investigators consulted to reconcile any discrepancies in overall risk of bias assessments. Overall summary risk of bias 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. For both sodium and potassium, evidence is synthesized by study design (odd-numbered vs. even-numbered questions), outcome, types of intervention or exposure (and exposure 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 will be posted for peer review and for public comment and the report will be 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 risk of bias [low, moderate, or high]); (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). 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 12,054 unique titles, of which 241 publications (reporting on 159 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 exposure. The strength of evidence was high only for a very small number of comparisons, that is, the effects of sodium reduction on blood pressure. The strength of evidence of conclusions that would depend on associations was 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 key question 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.

KQ 1: 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 and diastolic blood pressure significantly in adults (moderate SoE).
• Sodium reduction in adults increases the likelihood of achieving a prespecified blood pressure goal (moderate SoE).
• Sodium reduction decreases BP in both those with hypertension and those with normal BP; the effect is greater in adults with HTN than in those with normal BP (moderate SoE).
• Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE).
• Sodium reduction lowers BP in both men and women (moderate SoE).

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 exposure status was not associated with systolic or diastolic BP in adults based on prospective observational studies (low SoE). All studies had high risk of bias for the methods used to assess sodium intake, and findings were inconsistent across studies.
• Sodium exposure status was positively associated with incident hypertension in adults (low SoE: All studies had high risk of bias 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 from a small number of RCTs suggest that sodium reduction decreases the risk for all-cause mortality (low SoE).
• In adults, evidence from a small number of RCTs suggests that sodium reduction does not affect risk for CVD mortality, stroke, or composite CVD outcomes (low SoE).

KQ 4: 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.

• A low level of evidence supports the association between higher sodium levels and higher risks for all-cause mortality (data are insufficient to determine the linearity of the association).
• A low level of evidence supports a lack of association of sodium intake levels and risk for stroke or combined CVD morbidity and mortality.
KQ 5: Among children and adults what is the effect of interventions to increase potassium intake on blood pressure and kidney stone formation?

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

- Increased potassium intake has a beneficial effect on blood pressure in adults (moderate SoE based on 11 parallel RCTs and 7 crossover RCTs).
- Increasing potassium intake via potassium supplementation or increased dietary potassium from food has a beneficial effect on blood pressure in populations with prehypertension or hypertension (moderate SoE based on 11 parallel RCTs and 7 crossover RCTs).

KQ 6: Among children and adults, what is the association between potassium intake and blood pressure and kidney stone formation?

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

- Higher potassium exposure status is associated with lower adjusted BP in adults. (Low SoE based on inconsistent findings and studies with high risk of bias).
- A low strength of evidence supports an association between higher potassium exposure and lower risk for kidney stones in adults (Low SoE, based on four cohorts with high risk of bias).

KQ 7: Among adults, what is the effect of interventions aimed at increasing potassium intake on CVD, and kidney disease morbidity and mortality, and total mortality?

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

- Evidence was insufficient, based on only one RCT, to address this question.
KQ 8: 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 status 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 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. Our report found similar effects of sodium reduction on BP in adults, but only statistically non-significant beneficial effects in children, possibly due to slight differences in analytic methods or studies that met inclusion criteria. The WHO report did not assess effects of sodium reduction on incident hypertension or achievement of specific BP goals. Our report limited inclusion of crossover RCTs to those with 2 weeks or more of washout or a process to ensure lack of carryover, whereas the WHO report did not exclude crossover studies on this basis. In addition, our review included sodium reduction RCTs regardless of achieved sodium excretion, whereas the WHO excluded RCTs with a mean difference in achieved sodium excretion of less than 40 mmol/d. More recently, Graudal and colleagues systematically reviewed the literature on sodium reduction and BP and reached similar conclusions to those of Aburto and our current review. The current review corroborates the findings of the Graudal review regarding a larger effect of sodium reduction on individuals with HTN than on normotensive individuals. The Graudal review also identified studies that enabled comparisons across racial/ethnic groups; however, they included studies with a minimum of one-week follow up and did not limit inclusion of crossover studies.

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; our report identified three studies that corroborated the lack of effect of sodium
reduction on blood lipids 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 much shorter follow-up of some included studies.24

Several recent systematic reviews also reviewed 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 and only weak effects on CVD mortality and morbidity; they largely attributed the latter effect to one study that was excluded from our review because the intervention did not control for other dietary changes (the remaining seven RCTs were included in our review).14 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 that increased sodium intake was linked to increased risk for stroke, stroke mortality, and CHD mortality.3 Graudal and colleagues conducted a subsequent meta-analysis of prospective cohort studies that assessed the association between sodium exposures and mortality: They reported an increased mortality risk at both low- and high intakes of sodium (referred to as a “U-shaped curve”).25 The review did not include RCTs, 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 current review adds to the evidence by demonstrating an effect of sodium reduction on reducing all-cause mortality, albeit with a small number of studies. Our review also corroborates the finding of the meta-analysis by Graudal regarding an association between lower intakes of sodium and risk for CVD mortality with a low level of evidence. However, the methods used to estimate sodium intake varied across the 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: the possibility that individuals who had elevated BP or other risk factors at baseline were already reducing their intake of sodium.

McMahon and colleagues reviewed the evidence on effects of sodium reduction on cardiovascular outcomes in persons with CKD.26 However like our review, they identified no studies with long enough followup to assess longterm chronic disease outcomes. Instead they reported on studies that assessed effects of sodium reduction on BP outcomes in persons with CKD, an outcome that was not included in our report. Of the eight studies they included, we included one in our assessment of effects of sodium reduction on BP in persons with DM, and the remaining seven would not have met inclusion criteria.

Aburto and colleagues subsequently reviewed the evidence for an association of potassium status with BP, HTN, and CVD for the WHO, concluding that higher potassium status was associated with reduced BP in individuals with HTN but not in normotensive persons.27 That report found insufficient evidence to draw conclusions regarding the association of potassium status with risk for CVD or CHD morbidity or mortality. Our current review confirmed the association of potassium with BP lowering, by identifying randomized controlled trials that assessed the effects of increased potassium intake and also extended this 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 status 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, as reflected in reduced 24-hour urinary sodium intake. We did not assess the evidence regarding the most effective intervention design(s).

Most recent studies (e.g., those published from 1995 to the present) demonstrated an overall low RoB. However, older studies tended to omit many details of study design and conflict of interest, so actual RoB was unclear for some items. Nearly all observational 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, and older cohort studies tended to rely on food frequency questionnaires. The implications of assessment of sodium and potassium status are discussed further below. Additional limitations are listed here, organized by a PICOTSS framework.

Populations
- Few to no studies conducted subgroup analyses by sex, age, race/ethnicity, or comorbidities.
- RCTs likely have highly selected populations, comprising highly motivated individuals.
- 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, some 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 antihypertensive medications could have masked the effects of a reduced sodium diet.
- Observational studies had limited ability to control for pre-existing health conditions at study baseline. As a result, the association of sodium intake with risk for CVD mortality only at higher sodium exposures, as observed in some studies, could be the result of reverse causality.
- Observational studies may have residual confounding, as they could not adjust for all factors that may increase risk for HTN, CVD, CHD outcomes.

Interventions/Exposures
- 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.
- Few studies assess effects of natural experiments, community- or government-level interventions, and of those that did, most did not meet inclusion criteria.
- 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 may be affected by factors that can’t be measured, such as intensity of counseling.
- Few observational studies used multiple 24-hour urinary excretion analyses, although increasing evidence demonstrates that multiple, non-consecutive 24-hour urinary sodium excretion need to be used as the indicator of compliance in RCTs and exposure in observational studies.\(^{19, 28}\) 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, FFQ, 24-h recalls, and food records) and random error (e.g., single 24-hour or spot urine collections or single-day food recalls).
- Impaired renal function could potentially affect urinary sodium excretion in response to changes in sodium and potassium intake, yet not all studies assessed baseline function.
- Both RCTs and observational studies varied widely in baseline and/or achieved/observed sodium intake. Differences in baseline status could affect the potential to achieve sodium reduction goals through dietary interventions and introduces a source of heterogeneity among prospective cohort studies. Wide variation in achieved status 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. Greater decreases in 24-hour excretion from baseline or greater differences between intervention and control groups (e.g., exceeding 40 mmol/d) did not always correlate with outcomes of interest.
- 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 AI for adults is 62 mmol/d), introducing a potential source of heterogeneity across studies.

Comparators
- Contamination 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.
- 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 academic 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, primarily because studies did not consistently report or adjust for such use. As a result, we could not eliminate the possibility that differences in sodium excretion or failure to see differences in sodium excretion might be due to use of drugs that affect Na excretion.

We did not conduct sensitivity analyses to determine the possible contribution of studies with high or moderate RoB to the findings.

Although we hoped to exclude prospective cohort studies that used methods other than multiple nonconsecutive measures of 24-hour urinary sodium excretion to assess status, doing so would have excluded most large cohort studies. Therefore, we included these studies but their risk of bias is higher.

Based on expert input, we excluded crossover studies that did not describe the use of washout or duration of washout and did not describe an attempt to assess the possible effects of carryover.

The duration of interventions or exposures 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 exposure 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
may have excluded a small number of studies that could have increased strength of evidence. However, evidence suggests potential carryover needs to be considered.29

Conclusions

A systematic review of the evidence regarding the effects of dietary sodium reduction and increased potassium intake on (and their associations with) blood pressure and risk for chronic cardiovascular diseases finds that interventions that reduce dietary sodium intake (including use of potassium-containing salt substitutes) reduce blood pressure in both normotensive adults and those with hypertension. Interventions to reduce sodium intake increase the likelihood of reaching a prespecified blood pressure goal and appear to modestly decrease the incidence of hypertension, in agreement with prospective cohort studies, which show that higher sodium intakes are associated with greater risk for hypertension.

Increasing potassium intake significantly decreases blood pressure.

Interventions to reduce sodium intake may decrease risk for all-cause mortality slightly but studies are inconsistent and small in number. The effects of sodium reduction and increased potassium intake on mortality and morbidity due to CVD, CHD, and renal disease need more research.

References


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Introduction

Background and Objectives

Cardiovascular and circulatory diseases, including coronary heart disease (such as myocardial infarction and heart failure), coronary artery disease (such as stroke), and kidney disease, are responsible for the majority of deaths worldwide. A primary risk factor for CVD, stroke, and other circulatory diseases is hypertension (HTN). Health organizations worldwide define 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. Evidence has also suggested a protective role for dietary potassium, independently or through its influence on the body’s handling of sodium. The aim of the current review and numerous prior reviews has been to assess the evidence that lowering dietary sodium reduces the risk for HTN and in turn the risk for CVD and that maintaining or increasing dietary potassium provides benefit.

The 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 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 Daily 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. 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. The report
established nutrient reference values for water, potassium, sodium, chloride and sulfate to maintain health and reduce chronic disease risk.

The Sodium Dietary Reference Intakes

The 2005 IOM report set the AI for sodium for the population aged 19-50 years at 1500 mg 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 Tolerable Upper Intake Level (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 additional 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 have shown that reducing sodium leads to reductions in blood pressure among people with and without high blood pressure. 5, 9-13

Additional evidence, largely from observational studies, has shown that higher dietary sodium intake is associated with greater risk for fatal and nonfatal stroke and cardiovascular disease. 8-10, 14 Since high blood pressure is strongly associated with a higher risk for CVD, stroke, congestive heart failure, and kidney disease and lowering blood pressure lowers these risks, an indirect relationship between sodium intake and CVD has been proposed. 15-17 Assessing the relationship between sodium intake and chronic disease outcomes (i.e., CVD, Stroke, MI, and kidney disease), and in particular 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 long-term 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 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, particularly decreases in sodium intake, is the repeated 24-hour urinary sodium excretion
Realization of the limitations of the existing observational studies requires reconsideration of the current state of knowledge.

**The Potassium DRIs**

The 2005 IOM committee also set an AI level for potassium at 4,700 milligrams per day, based on levels that blunt the sodium-related increase in blood pressure as well as the reduction in risk of kidney stones. 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. 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.

**The 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. 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 the Review**

This report focuses on sodium and potassium intake, chronic disease risk reduction, 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 or exposures, blood pressure and the risk for hypertension, and the risk for 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 (hyponatremia or hypokalemia).

**Key Questions**

**Sodium**

**Key Question 1.** 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.

**Key Question 2.** 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.

**Key Question 3.** 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.

**Key Question 4.** 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

Key Question 5. 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.

Key Question 6. 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.

Key Question 7. Among adults, what is the effect of interventions aimed at increasing potassium intake on CVD, and kidney disease morbidity and mortality, and 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.

Key Question 8. 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.

Analytic Frameworks
   The review was guided by the analytic frameworks shown in Figure 1 and 2.
CHD = Coronary Heart Disease; CVD = Cardiovascular Disease; KQ = Key Question

**Figure 1. Analytic framework for sodium and health outcomes**

**Figure 2. Analytic framework for potassium and health outcomes**

**Organization of This Report**

The remainder of this report presents the methods used to conduct the literature searches, data abstraction, and analysis for this review; the results of the literature searches, organized by KQ and intervention; the conclusions; and a discussion of the findings within the context of what is already known, the limitations of the review and the literature, and suggestions for future research.
Methods

The methods used to conduct this systematic review are based on the EPC Methods Guide.22 The key questions were developed by the federal sponsors prior to the start of the review and refined by the research team in collaboration with the TEP and the federal sponsors during development of the protocol.

Criteria for Inclusion/Exclusion of Studies in the Review

Inclusion and exclusion criteria are described below according to the PICOTSS (population, intervention/exposure, comparison group, outcome, time, setting, and study design) framework. The criteria are based on the 2005 IOM report and on discussions with and recommendations of federal sponsors and the TEP for the current review. Studies that were considered for addressing key questions intended to assess the effect of interventions on the outcomes of interest (KQ 1, 3, 5, and 7) were limited to RCTs and controlled clinical trials (CCTs). Both parallel and crossover trials were included; however, based on concerns about possible carryover effects, crossover trials that did not incorporate a minimum 2-week washout phase between treatment phases or did not explicitly describe the procedure used to ensure lack of carryover were excluded. If an article did not mention washout period duration, we searched for a separately published study protocol. If washout or a method to ensure lack of carryover were not mentioned in the protocol, the study was excluded.

Studies that were considered in addressing key questions pertaining to the association between sodium and/or potassium intake and health effects included both prospective observational studies and multivariate analyses of results of RCTs in which randomization was not maintained. Included observational studies were limited to those studies that measured and quantified intake of sodium and/or potassium with valid indicators. Valid assessment measures were selected together with input from the Technical Expert Panel (TEP) and content expert and are described below in the section on assessment of risk of bias.

The key questions pertaining to associations excluded studies that exclusively followed participants with preexisting disease specific to the clinical outcome of interest. In order to use valid samples to determine associations, the cohort would need to include participants with and without the condition of interest at follow-up. Because the pool of association studies included observational studies where the exposure to a specific dietary strategy was self-selected and compared groups might differ in more characteristics then simply dietary sodium or potassium intake, eligible studies were limited to those reporting baseline data for the outcomes of interest.

The intervention or exposure durations required for study inclusion (e.g., two years for studies on kidney disease) were determined by the federal sponsors, the TEP, and other clinical experts to ensure we included only studies with sufficient follow-up durations to detect the incident outcome of interest.

Other exclusions applying to all key questions

Only full-text peer-reviewed English-language publications were included. These decisions were made to ensure that sufficient study detail was provided and accessible to assess study quality fairly.
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<tr>
<td>KQ1</td>
<td>Studies in human participants will be eligible for inclusion in the review, with the exception of studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.</td>
<td>Studies evaluating interventions to reduce dietary sodium intake that specify the oral consumption from food or supplements of quantified amounts of sodium and sodium chloride (salt) or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/- 3% or more. Interventions simultaneously addressing sodium and potassium intake that document sodium/potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.</td>
<td>Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of sodium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.</td>
<td>Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, incident hypertension, percent participants at blood pressure goal, and change in blood pressure) will be eligible.</td>
<td>Studies reporting on an intervention period of at least four weeks will be eligible.</td>
<td>Studies in outpatient settings will be eligible.</td>
<td>Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.</td>
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<td>KQ2</td>
<td>Studies in community-dwelling (non-institutionalized) human participants will be eligible for inclusion in the review with the exception of studies exclusively reporting on</td>
<td>Studies that measure the intake (oral consumption from food or supplements of quantified amounts of sodium and sodium chloride [salt] or sodium-to-potassium ratio) with validated measures or that use biomarker values to assess sodium level (at least one 24-hour urinary analysis with or without reported quality control)</td>
<td>Studies comparing groups with different documented sodium intake or biomarker values for sodium will be eligible. Studies where differences in sodium intake or values are</td>
<td>Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, incident hypertension, percent participants at blood pressure goal, and change in blood pressure) will be eligible.</td>
<td>Studies reporting on an intervention period of at least four weeks will be eligible.</td>
<td>Studies in community-dwelling participants will be eligible.</td>
<td>Prospectiv e cohort studies and nested case-control studies, where at least two groups are compared based on</td>
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<td>KQ3</td>
<td>Studies in human adults will be eligible for inclusion in the review. Studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.</td>
<td>Studies evaluating interventions to reduce dietary sodium intake that specify the oral consumption from food or supplements of quantified amounts of sodium and sodium chloride (salt) or sodium-to-potassium ratio will be eligible. Studies with</td>
<td>Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet,</td>
<td>Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular disease morbidity, including acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment</td>
<td>Only interventions of two years or longer will be included for kidney disease outcomes; only interventions of three months or longer will be</td>
<td>Studies in outpatient settings will be eligible.</td>
<td>Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.</td>
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<td>failure, HIV, or cancer will be excluded.</td>
<td>trial arms in which participants demonstrate a weight change of +/- 3% or more will be excluded. Interventions simultaneously addressing sodium and potassium intake with documents sodium/potassium ratio are eligible. All other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.</td>
<td>studies comparing levels of sodium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.</td>
<td>elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI], requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, hospitalization for any cause of coronary heart disease or cardiovascular disease, chronic kidney disease (CKD), albuminuria or proteinuria (including urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), kidney stone incidence, or acute included for cardiovascular disease outcomes; all other studies need to report on an intervention period of at least four weeks to be eligible.</td>
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<td>KQ4</td>
<td>Studies in community-dwelling (non-institutionalized) adults will be eligible for inclusion in the review with the exception of studies exclusively reporting on patients with pre-existing conditions specific to the clinical outcomes of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.</td>
<td>Studies that measure the intake (oral consumption from food or supplements of quantified amounts of sodium and sodium chloride [salt] or sodium-to-potassium ratio) with validated measures or use biomarker values to assess sodium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of salt substitute with intervention/exposure adherence measure, and food diaries with reported validation [adherence check, electronic prompts]) will be eligible. Observational studies that report a weight change of +/- 3% or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies relying only on serum sodium levels, composition of salt substitute without intervention/exposure adherence measure, food diaries without reported validation, use of a published food frequency questionnaire, or partial or incomplete data. Studies comparing groups with different documented sodium intake or biomarker values for sodium will be eligible. Studies where differences in sodium intake or values are confounded with alteration of other nutrient levels will be excluded.</td>
<td>Studies reporting exclusively on kidney disease outcomes need to report follow up periods of at least two years, studies reporting exclusively on cardiovascular disease outcomes or stroke need to report on follow up periods of at least 12 months duration; studies reporting on other outcomes need to evaluate exposure lasting at least four weeks to be eligible.</td>
<td>Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular mortality; cardiovascular disease morbidity, including coronary heart disease (CHD), acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, or hospitalization for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (SCr),</td>
<td>Studies in community-dwelling participants will be eligible.</td>
<td>Studies reporting exclusively on kidney disease outcomes need to report follow up periods of at least two years, studies reporting exclusively on cardiovascular disease outcomes or stroke need to report on follow up periods of at least 12 months duration; studies reporting on other outcomes need to evaluate exposure lasting at least four weeks to be eligible.</td>
<td>Studies in community-dwelling participants will be eligible.</td>
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<td>KQ5</td>
<td>Studies in human participants will be eligible for inclusion in the review; studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer will be excluded.</td>
<td>Studies evaluating interventions to increase dietary potassium intake that specify the oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/- 3% or more among adults. Interventions simultaneously addressing sodium and potassium intake with documents sodium/potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other interventions.</td>
<td>Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of potassium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.</td>
<td>glomerular filtration rate (GFR), end stage renal disease, chronic kidney disease (CKD), albuminuria/proteinuria (including, urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), acute kidney injury will be eligible. Studies that do not report baseline data for the outcomes of interest will be excluded.</td>
<td>Studies reporting exclusively on kidney stone formation need to report on an intervention period of two years; all other studies need to report on an intervention period of at least four weeks to be eligible.</td>
<td>Studies in outpatient settings will be eligible.</td>
<td>Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.</td>
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<td>KQ6</td>
<td>Studies in community-dwelling (non-institutionalized) human participants will be eligible for inclusion in the review; studies reporting exclusively on patients with pre-existing conditions specific to the clinical outcomes of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer will be excluded.</td>
<td>Studies that measure intake (oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio) with validated measures or use biomarkers values to assess potassium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of potassium supplement with intervention/exposure adherence measure, use of a published food frequency questionnaire, and food diaries) will be eligible. Observational studies that report a weight change of +/- 3% or more (in any exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies measuring potassium intake by reporting chemical analysis of diet without intervention/exposure adherence measures, composition of potassium supplement without</td>
<td>Studies comparing groups with different documented potassium intake, serum potassium levels, or urinary potassium excretion will be eligible. Studies where differences in potassium intake or values are confounded with alteration of other nutrient levels will be excluded.</td>
<td>Studies reporting on blood pressure outcomes (e.g., systolic blood pressure, diastolic blood pressure, rate of hypertensive/non-hypertensive participants, hypertension incidence, percent participants at blood pressure goal, change in blood pressure), and kidney stone incident or kidney stone regrowth will be eligible. Studies that do not report baseline blood pressure status and the presence or absence of kidney stones will be excluded.</td>
<td>Studies exclusively reporting on kidney stone formation need to follow participants for at least five years; all other studies need to report on exposure of at least four weeks to be eligible.</td>
<td>Studies in community-dwelling participants will be eligible.</td>
<td>Prospectively cohort studies and nested case-control studies, where at least two groups are compared based on measured potassium intake or biomarker values will be eligible. Retrospective studies, case series, cross-sectional studies or surveys, and case reports will be excluded.</td>
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<td>KQ7</td>
<td>Studies in adults will be eligible for inclusion in the review; studies reporting exclusively on patients with heart failure, end stage renal disease, HIV, or cancer will be excluded.</td>
<td>Studies evaluating interventions to increase dietary potassium intake that specify the oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio will be eligible, with the exception of trial arms in which participants demonstrate a weight change of +/- 3% or more. Interventions simultaneously addressing sodium and potassium intake with documents sodium/potassium ratio are eligible; all other multicomponent interventions in which the effect of sodium reduction cannot be disaggregated from other intervention components will be excluded.</td>
<td>Studies comparing interventions to placebo or control diets will be eligible. Studies comparing an experimental diet to usual diet, studies comparing levels of potassium intake, or studies that alter sodium/potassium ratio in other ways will be included if they control for other nutrient levels.</td>
<td>Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular disease morbidity, including acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, or hospitalization for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (Scr), glomerular filtration rate</td>
<td>Studies reporting exclusively on kidney disease outcomes need to report on an intervention period of two years, studies reporting on cardiovascular disease or stroke need to report on an intervention period of three months; all other studies need to report on an intervention period of at least four weeks to be eligible.</td>
<td>Studies in outpatient settings will be eligible.</td>
<td>Parallel RCTs and cross-over RCTs with a washout period of two weeks or more will be eligible.</td>
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<td>KQ8</td>
<td>Studies in community-dwelling (non-institutionalized) adults will be eligible for inclusion in the review with the exception of studies exclusively reporting on patients with pre-existing conditions specific to the clinical outcomes of interest, as well as studies exclusively reporting on patients with end stage renal disease, heart failure, HIV, or cancer.</td>
<td>Studies that measure intake (oral consumption from food or supplements of quantified amounts of potassium, potassium supplements, salt substitutes such as potassium chloride, or sodium-to-potassium ratio) with validated measures or use biomarkers values to assess potassium level (at least one 24-hour urinary analysis with or without reported quality control measure, chemical analysis of diet with intervention/exposure adherence measure, composition of potassium supplement with intervention/exposure adherence measure, use of a published food frequency questionnaire, and food diaries) will be eligible. Observational studies that report a weight change of +/- 3% or more (in any</td>
<td>Studies comparing groups with different documented potassium intake, serum potassium levels, or urinary potassium excretion will be eligible. Studies where differences in potassium intake or values are confounded with alteration of other nutrient levels will be excluded.</td>
<td>Studies reporting on mortality (all-cause, CVD, CHD, or renal); cardiovascular disease morbidity, including coronary heart disease (CHD), acute coronary syndrome (unstable angina and myocardial infarction), stroke, myocardial infarction (ST-segment elevation myocardial infarction [STEMI] and non-ST elevation myocardial infarction [NSTEMI]), requiring coronary revascularization procedures (angioplasty, coronary stent placement, coronary artery bypass), other atherosclerotic revascularization procedures (carotid endarterectomy), left ventricular hypertrophy, hospitalization for heart failure, or hospitalization</td>
<td>Studies reporting exclusively on kidney stone formation need to follow participants for at least five years, studies reporting exclusively on kidney disease need to follow participants for at least two years, studies reporting exclusively on cardiovascular disease or stroke need to follow patients for at least 12 months; all other studies need to report on an exposure period of at least four weeks to be eligible.</td>
<td>Studies in community-dwelling participants will be eligible.</td>
<td>Prospectiv e cohort studies and nested case-control studies, where at least two groups are compared based on measured potassium intake or biomarker values will be eligible. Retrospective studies, case series, cross-sectional studies or surveys, and case</td>
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<td>exposure group) among adults; multicomponent studies that do not properly control for confounders; and studies measuring potassium intake by reporting chemical analysis of diet without intervention/exposure adherence measures, composition of potassium supplement without intervention/exposure measure, or serum potassium will be excluded.</td>
<td>for any cause of coronary heart disease or cardiovascular disease, or combined CVD morbidity and mortality; or reporting on renal function intermediary and clinical outcomes including creatinine clearance (CrCl), serum creatinine (Scr), glomerular filtration rate (GFR), end stage renal disease, chronic kidney disease (CKD), albuminuria/ proteinuria (including urine albumin-to-creatinine ratio, urine albumin dipstick level, urine protein-to-creatinine ratio, albumin excretion rate), kidney stone incidence, or acute kidney injury will be eligible. Studies that do not report baseline data on the outcomes of interest will be excluded.</td>
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Searching for the Evidence

This section describes the literature search strategies, and screening protocols used.

**Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions**

We first conducted a scoping review of the existing systematic reviews and evidence reports on sodium and potassium intake, including the 2005 DRI report to identify critical sources of collated research evidence relevant to this evidence report. We screened all studies of sodium and potassium cited in those reviews as well as the 2005 DRI report for inclusion based on our inclusion/exclusion criteria.

Additional searches were conducted for more recent literature in PubMed, CINAHL, EMBASE, the Cochrane Database of Systematic Reviews (CDSR), CENTRAL, and Web of Science for English-language publications. In addition, reference lists of the existing systematic reviews on the outcomes of interest were screened to identify relevant studies.

Searches were conducted for each key question and commenced in 2003, the year the original DRI report assembled study material. Search strategies were developed for each key question (see Appendix A), and searches were conducted in accordance with the latest edition of the Methods Guide for Effectiveness and Comparative Effectiveness Reviews.

Pairs of reviewers, including at least one senior, experienced reviewer, independently screened all citations found by the literature searches using Distiller online systematic review management software, after a training session. For all citations that were deemed potentially relevant by at least one reviewer, full-text publications were retrieved.

Full-text publications were independently screened by two reviewers, applying the inclusion and exclusion criteria. Reasons for exclusion were recorded. Disagreements about inclusion were resolved through discussion in the review team.

**Data Abstraction and Data Management**

A detailed and standardized web-based data extraction form was used to record study-level information (see Protocol for list of study-level variables) and risk of bias assessments for all studies that met inclusion criteria (Appendix B). The form was pilot-tested and refined within the review team. Data were extracted by one reviewer and checked by a second, senior systematic reviewer to ensure accuracy.

A number of studies had study-level details and/or outcomes reported in more than one publication. For those articles, abstractors ensured that the records were linked so that the correct study level data (e.g., baseline conditions for subgroups) were matched with outcome data and so that data were not abstracted in duplicate.

Outcome data, including confounders and effect modifiers, were abstracted into Excel spreadsheets and prepared for analysis by two members of the research team (one member extracted data from trials and one extracted data from observational studies) and were reviewed for accuracy by one of the PIs and the biostatistician. Data from studies that met inclusion criteria that were included in the 2005 DRI report or other systematic reviews were re-extracted.

All included studies are described in evidence tables (Appendix C). At the end of the project, all data will be uploaded to customized forms in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) for full public access.
Assessment of Methodological Risk of Bias of Individual Studies

We assessed the methodological risk of bias of each original study included in the review, based on predefined criteria.

We implemented the Cochrane Risk of Bias tool to assess risk of bias of RCTs, with criteria modified to cover concerns in the types of nutrition trials considered for this review. These modifications included considering bias that could arise if participants in parallel randomized controlled trials (RCTs) were not matched for (or at least similar regarding) BMI, sodium excretion, age, gender, race/ethnicity, and hypertensive status; sodium exposure assessment; adherence/compliance; absence of the outcome of interest at baseline; and use of appropriate statistical methods for assessing crossover trial outcomes (see Appendix E).

To assess risk of bias among observational studies, we used questions from the Newcastle Ottawa tool that are relevant for prospective studies (see Appendix E). The risk of bias from the method used to assess sodium and potassium exposures was determined according to criteria described in Appendix E. Other items assessed included similarity at baseline across treatment groups or quantiles regarding age, BMI, ethnicity, hypertensive status, and urinary sodium excretion.

An overall risk of bias was determined for each RCT by tabulating the numbers of individual “low,” “high,” and “moderate” or “unclear” scores. RCTs earned a low overall risk-of-bias rating if their total “low” scores were 7 or higher (out of 11) and their “high” scores were 1 or fewer and did not include exposure assessment method; overall moderate/unclear ratings included 4 to 6 “low” scores and 2 or fewer “high” scores; overall high ratings included fewer than 4 “low” scores or more than 2 “high” scores.

An overall risk of bias was determined for each observational study by giving the risk of bias of the method used to assess sodium or potassium exposure the most weight and adjusting the grade down by tabulating the numbers of other individual “high,” “moderate” or “unclear” risk-of-bias domains. Observational studies earned a low overall risk-of-bias rating if the risk of bias of the method used to assess sodium or potassium exposure was rated “low” and all other individual risk-of-bias domains were rated “low.” Observational studies earned a high overall risk-of-bias rating if their risk of bias of the method used to assess sodium or potassium exposure was rated “high” or if the risk of bias of the method used to assess sodium or potassium exposure was rated “moderate” and more than 1 other individual risk-of-bias domains were rated “high” or unclear. The risk of bias of the method used to assess sodium or potassium exposure was rated separately. As such, an observational study could receive different overall ratings for sodium- and potassium-outcome pairs.

One reviewer assessed the methodological risk of bias for all included studies and one other reviewer confirmed or refuted the risk of bias assessments. Disagreements were reconciled among the systematic review team and resolved via group consensus. When determining the overall strength of evidence, we considered any quality issues pertinent to the specific outcomes of interest.

Original studies whose references were reference mined from existing systematic reviews were screened, assessed for risk-of-bias, and data abstracted along with studies identified in literature searches.
Data Synthesis/Analysis

All included studies are presented in evidence tables (Appendix C and D). Continuous outcomes are reported as mean differences (MD), dichotomous incidence outcomes are reported as relative risks (RR), together with the 95% confidence interval (CI). Random effects meta-analyses using the Hartung-Knapp-Sidik-Jonkman method were conducted on RCTs of similar populations or subpopulations\textsuperscript{26-29} (based on baseline comorbidities and nutrient status), implementation of similar interventions or use of similar exposure measures, and use of compatible outcome measures. Each study is weighted by the inverse of its variance. In a random effects model, the variance includes the within-study variance along with the between study variance. Studies including patients with pre-existing conditions specific to the clinical outcome of interest were excluded from analyses for the respective outcome of interest in this review, unless they report subgroup data where patients with pre-existing conditions were excluded.

When data from observational studies were sufficient (3 or more studies using 24-hour urinary excretion measures for each outcome), we performed both linear and non-linear dose-response meta-regressions to examine the associations between dietary intake levels and the risks of clinical outcomes using a two-stage hierarchical regression model.\textsuperscript{30, 31}

Meta-regressions were conducted to assess whether other minerals affected outcomes of interest, if sufficient numbers of studies assessed these effects (KQ1a, 3a, 5a, 7a) and to compare differences between subgroups (e.g., males and females).

Subgroup analyses were conducted when sufficient data were available to answer the subquestions on subpopulations of interest, i.e., sex, race/ethnicity, DRI age group(s) (1-3 y, 4-8y, 9-13y, 14-18y, 19-30y, 31-50y, 51-70y, and ≥71 y), reproductive status (pregnant and lactating women), as well as hypertensive status, diabetes, obesity (i.e., body mass index (BMI) ≥30), and renal health status for individual key questions.

The data for subgroups are reported in separate evidence tables (Appendix D).

Statistical heterogeneity was assessed and expressed as the $I^2$ statistic and considered in interpreting and weighing the results of meta-analyses.

Summary of findings tables organized by key question, interventions or exposures, and key outcomes, summarize the available evidence.

Grading the Strength of Evidence (SoE) for Major Comparisons and Outcomes

The project leaders assessed the strength of evidence (SoE) for the key outcomes listed in Table 2, based on guidance provided in the AHRQ EPC Methods Guide. These outcomes were also used to answer the subquestions.

<table>
<thead>
<tr>
<th>Key question</th>
<th>Key Outcomes</th>
</tr>
</thead>
</table>
| KQ1.         | Mean difference in systolic BP  
Mean difference in diastolic BP  
Percent participants at blood pressure goal  
Hypertension incidence  
Adverse events associated with sodium intake |
| KQ2.         | Mean difference in systolic BP  
Mean difference in diastolic BP  
Percent participants at blood pressure goal  
Hypertension incidence |
<p>| KQ3.         | All-cause mortality |</p>
<table>
<thead>
<tr>
<th>Key question</th>
<th>Key Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CVD mortality</td>
</tr>
<tr>
<td></td>
<td>CHD mortality</td>
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<tr>
<td></td>
<td>Renal disease mortality</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Number of patients with any CVD event as reported by the study authors</td>
</tr>
<tr>
<td></td>
<td>Combined CHD morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Combined CVD morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Mean difference between groups in eGFR</td>
</tr>
<tr>
<td></td>
<td>Number of patients with end stage renal disease</td>
</tr>
<tr>
<td></td>
<td>Adverse events associated with sodium intake</td>
</tr>
<tr>
<td>KQ4.</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>CVD mortality</td>
</tr>
<tr>
<td></td>
<td>CHD mortality</td>
</tr>
<tr>
<td></td>
<td>Renal disease mortality</td>
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<tr>
<td></td>
<td>Stroke</td>
</tr>
<tr>
<td></td>
<td>Coronary heart disease</td>
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<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Number of patients with any CVD event as reported by the study authors</td>
</tr>
<tr>
<td></td>
<td>Combined CHD morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Combined CVD morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Mean difference between groups in eGFR</td>
</tr>
<tr>
<td></td>
<td>Number of patients with end stage renal disease</td>
</tr>
<tr>
<td>KQ5.</td>
<td>Mean difference systolic BP</td>
</tr>
<tr>
<td></td>
<td>Mean difference in diastolic BP</td>
</tr>
<tr>
<td></td>
<td>Percent participants at blood pressure goal</td>
</tr>
<tr>
<td></td>
<td>Hypertension incidence</td>
</tr>
<tr>
<td></td>
<td>Number of patients with kidney stones (occurrence and recurrence, symptomatic and asymptomatic)</td>
</tr>
<tr>
<td></td>
<td>Kidney stone incidence</td>
</tr>
<tr>
<td></td>
<td>Number of kidney stones</td>
</tr>
<tr>
<td></td>
<td>Symptomatic kidney stone incidence</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>KQ6.</td>
<td>Mean difference systolic BP</td>
</tr>
<tr>
<td></td>
<td>Mean difference in diastolic BP</td>
</tr>
<tr>
<td></td>
<td>Percent participants at blood pressure goal</td>
</tr>
<tr>
<td></td>
<td>Hypertension incidence</td>
</tr>
<tr>
<td></td>
<td>Number of patients with kidney stones (occurrence and recurrence, symptomatic and asymptomatic)</td>
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<td></td>
<td>Kidney stone incidence</td>
</tr>
<tr>
<td></td>
<td>Number of kidney stones</td>
</tr>
<tr>
<td></td>
<td>Symptomatic kidney stone incidence</td>
</tr>
<tr>
<td>KQ7.</td>
<td>All-cause mortality</td>
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<tr>
<td></td>
<td>CVD mortality</td>
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<tr>
<td></td>
<td>CHD mortality</td>
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<tr>
<td></td>
<td>Renal disease mortality</td>
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<tr>
<td></td>
<td>Stroke</td>
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<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td></td>
<td>Number of patients with any CVD event as reported by the study authors</td>
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<tr>
<td></td>
<td>Combined CHD morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Combined CVD morbidity/mortality</td>
</tr>
<tr>
<td></td>
<td>Mean difference between groups in eGFR</td>
</tr>
<tr>
<td></td>
<td>Number of patients with end stage renal disease</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>KQ8.</td>
<td>All-cause mortality</td>
</tr>
<tr>
<td></td>
<td>CVD mortality</td>
</tr>
<tr>
<td></td>
<td>CHD mortality</td>
</tr>
<tr>
<td></td>
<td>Renal disease mortality</td>
</tr>
<tr>
<td>Key question</td>
<td>Key Outcomes</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
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<td>Myocardial infarction</td>
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</tr>
<tr>
<td>Mean difference between groups in eGFR</td>
<td></td>
</tr>
<tr>
<td>Number of patients with end stage renal disease</td>
<td></td>
</tr>
</tbody>
</table>

The SoE approach we used assesses the body of evidence for each conclusion based on five dimensions: study limitations (the risk of bias of the individual studies and the study designs), consistency (the degree to which included studies find the same direction or similar magnitude of effect, within study designs), directness (for this report, we used directness to mean two things: whether the outcome in question is intermediary or clinical, but mainly, whether the assessment of moderating factors was based on a direct or indirect comparison, for example men compared with women), precision (the degree of certainty surrounding an effect estimate), and reporting bias (the likelihood that some findings were omitted from publication).

Four strength-of-evidence ratings were used—high, moderate, low, or insufficient—as defined below. Bodies of evidence based entirely on pooled RCTs are considered to have a high strength of evidence, which can be down-graded for major concerns in each of the domains (study limitations, indirectness, inconsistency, imprecision, or suspected reporting bias). For example, a high strength of evidence conclusion would be based on a pooled analysis of (e.g.,) five or more RCTs sufficiently powered to assess the outcome of interest and with overall low risk of bias, with consistent findings across studies, relatively tight confidence intervals, and assessing a direct comparison. If overall risk of bias was high, if results were inconsistent, if confidence intervals were wide compared with the effect size (for mean differences), if the effect size was of borderline significance, or if the comparison of interest was indirect, we would downgrade one level for any one of those factors to moderate risk of bias or to low risk of bias for two or more of those factors. If the number of studies was insufficient to allow pooling or if only three or four small (particularly underpowered or inconsistent) studies could be included, we would downgrade to low strength of evidence. An insufficient strength of evidence was reserved for questions for which no more than two inconsistent RCTs were identified that addressed the question.

We used a similar approach for rating the strength of evidence based on observational studies (which were used to answer association questions), with several modifications detailed as follows. Bodies of evidence based on more than two large, population-based prospective cohort studies are considered to have a high strength of evidence, which can be down-graded for major concerns in each of the domains (study limitations, indirectness, inconsistency, imprecision, or suspected reporting bias). For each outcome, observational studies were first synthesized separately for each type of exposure measurement method (i.e., 24-hour urinary excretions, estimated 24-hour urinary excretions, and self-report dietary assessment methods), and then synthesized across different types of exposure measurement methods at the strength-of-evidence rating level. Almost all observational studies were synthesized qualitatively (within each type of exposure measurement method). When assessing consistency or inconsistency across studies, the ranges of exposure were taken into account, given that nutrient-outcome relationships may vary according to the ranges of exposure. Thus, the consistency or inconsistency across studies can be assessed only within the same ranges of exposures. Overlapping in study populations was carefully considered in the qualitative synthesis to avoid double counting data from the same
study cohort. Multiple publications from the same study cohort were retained in the review if they differed in study characteristics, outcome definitions, follow-up durations or statistical analyses.

For this review, we did not assess strengths of a body of evidence that included both RCTs and observational studies. However, if the RCT evidence is robust, observational studies may not contribute to strengthening the evidence unless they are high quality studies with large, precise effect sizes. Similarly, because of challenges in accounting for confounding, a body of evidence comprising only observational studies usually can provide only a low strength of evidence unless the studies demonstrate a very large effect, a strong dose-response association, or the observed effect cannot be accounted for by uncontrolled confounding.

Table 3. Definitions of the Levels of Strength of Evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains</td>
</tr>
<tr>
<td>Low</td>
<td>We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect</td>
</tr>
<tr>
<td>Insufficient</td>
<td>We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion</td>
</tr>
</tbody>
</table>

Assessing Applicability

Applicability was assessed at the level of the total body of evidence for each conclusion. We considered the similarity of the population to the North American population in terms of mean baseline intakes/status of sodium and potassium, weight status, and baseline comorbidities, as well as age.

Peer Review and Public Commentary

Experts in the fields of nutrition, epidemiology and statistics, and medicine and individuals representing stakeholder and user communities have been invited to provide external peer review of this draft systematic review; AHRQ and an associate editor will also provide comments. The draft report will be posted on the AHRQ website for 4 weeks to elicit public comment. We will address all reviewer comments, revise the text as appropriate, and document everything in a disposition of comments report that will be made available 3 months after the Agency posts the final systematic review on the EHC website.
Results

Introduction

This section first describes the results of the literature searches, followed by descriptions of the studies that met inclusion criteria for each of the KQs and the key points (conclusions).

Key questions 1 through 4 pertain to interventions and exposure that focus primarily on assessing effects of sodium or sodium to potassium ratios. Key questions 5 through 8 pertain to interventions and exposures that focus primarily on potassium. Studies that assess relationships of the sodium-to-potassium ratio with outcomes of interest are described in Key questions 1 through 4.

Results of Literature Searches

Our searches identified 11,610 references. An additional search via reference mining of systematic reviews resulted in 444 titles, which yielded 12,054 citations that underwent dual screening, of which 10,639 citations were rejected because they did not meet inclusion criteria. We identified 1,415 full text articles to be screened, of which 1,081 were excluded for the following reasons: population not of interest (42), interventions not of interest (399), comparators not of interest (5), outcomes not of interest (137), timing not of interest (165), setting not of interest (6), study design (275), language (4), protocol (4), duplicate data (24). We could not retrieve one article. We identified and reference-mined 88 systematic reviews and identified numerous research reports as well as seven citations that were helpful for the background on the topic.

We include 170 studies reported in 256 publications. A breakdown per key question is shown in Figure 3 below.
For each of the following questions, we describe first the key points, followed by detailed results for each of the subquestions. Results for healthy adults precede those for subpopulations of interest.

**Key Question 1. Sodium: Effect of interventions to reduce dietary sodium intake on blood pressure**

**Key Points**

- Sodium reduction decreases systolic and diastolic blood pressure significantly in adults (moderate SoE). Findings were inconsistent across studies.
- A low strength of evidence suggests that sodium reduction does not affect blood pressure in children. The number of studies that assessed effects in children was limited.
- Sodium reduction in adults increases the likelihood of achieving a prespecified blood pressure goal (moderate SoE).
- A low strength of evidence suggests that sodium reduction may have a small, statistically non-significant beneficial effect on the risk for incident HTN in adults.
- Sodium reduction lowers BP in both men and women (moderate SoE): However, a low strength of evidence suggests that sex does not moderate the effect of sodium reduction on BP in adults.
- Sodium reduction decreases systolic BP in both those with hypertension and those with normal BP; the effect is greater in adults with HTN than in those with normal BP (moderate SoE).
- Sodium reduction decreases diastolic BP in those with hypertension (moderate SoE) but not in those with normal BP (low SoE).
- Evidence is insufficient to support conclusions on potential moderating effects of race/ethnicity.
- Evidence is insufficient to support conclusions on potential moderating effects of diabetes, renal disease, or obesity.
- A low strength of evidence supports a lack of effect of sodium reduction on blood lipids (triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol); however, evidence is insufficient to draw a conclusion regarding the effects of sodium reduction on dizziness, headache, insulin sensitivity, and muscle cramping.
- Increasing potassium intake does not modify the effect of reducing dietary sodium on blood pressure compared with sodium reduction alone (low SoE).
- Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE).

Description of Included Studies

We identified 73 RCTs (reported in 76 publications) that met inclusion criteria to answer this question and related subquestions: 62 parallel RCTs and 11 crossover RCTs. Of the total, 56 address the question of whether sodium reduction lowers blood pressure (KQ1b and c), and 17 address the question of whether the effects of sodium reduction are moderated by other minerals (KQ1a). The study-level details are described below and in the evidence tables (Appendix C): The findings for KQ1a are described after the findings for KQ1b and 1c.

All studies that address this key question were designed to assess the effects of lower intakes of sodium relative to usual diet. Most studies randomized participants to a low sodium diet (via counseling and/or provision of food products) or to usual diet. Some imposed a low-sodium diet on all participants and then randomized them to receive sodium chloride tablets (to restore usual sodium intake) or placebo tablets (to maintain a low sodium intake). Studies designed to assess the added effects of other minerals, addressed in subquestion 1a, either combined a low-sodium diet with supplementation of other minerals or placebo, or they provided a potassium-containing salt substitute. For each study (or groups of studies), urinary sodium excretion is noted, if reported.

Outcomes addressed for this question include mean differences in blood pressure across intervention and control groups, incident hypertension, proportion of participants who meet a prespecified blood pressure goal, and adverse events associated with treatments.

Intervention durations ranged from 4 weeks (shorter duration studies were excluded) to three years. Followups were as long as 8 years: For most studies, we report only the longest followup for a specific outcome.

Parallel RCTs are described separately from crossover RCTs.
Key Question 1b. Among subpopulations defined by age (children, adolescents, young adults, older adults, elderly and reproductive status for women [pregnancy and lactation]), sex, and race/ethnicity

Description of Included Studies

No RCTs that met inclusion criteria compared outcomes among DRI age groups. Thirty-six parallel RCTs and twelve crossover RCTs reported on the effects of sodium reduction on systolic BP in adults only. Fourteen RCTs reported on the effects of sodium reduction on diastolic BP in adults only. Thirty-eight parallel RCTs, thirteen crossover RCTs, and one controlled clinical trial reported on the effects of sodium reduction on diastolic BP in adults only.

Eight RCTs reported on effects of sodium reduction on systolic BP in children. Seven RCTs reported on effects on diastolic BP in children. Two of the trials assessed effects in newborns. Two reported outcomes separately for boys and girls, and one included only adolescent girls. Five parallel RCTs reported on the effects of sodium reduction on systolic BP and five reported on diastolic BP, for adult males only. Four parallel RCTs reported on the effects of sodium reduction on systolic BP for adult females, and six parallel RCTs reported on the effects of diastolic BP. One crossover RCT compared the effects of dietary sodium reduction between adult males and females, and one reported the effects of three different dietary sodium levels on men and women. Three parallel RCTs reported on the effects of sodium reduction on systolic and diastolic BP separately in US whites and blacks. One crossover RCT compared the effects of three dietary sodium levels between whites and blacks.

Detailed Synthesis

Effects of Age on the Effects of Sodium Reduction on Blood Pressure: Adults vs. Children

Only one RCT that met inclusion criteria compared the effects of sodium reduction on BP, achievement of a prespecified goal blood pressure, or incident HTN across age groups. Therefore this section reports the results of studies of adults, followed by those for children for each outcome of interest.

Mean Difference in Systolic Blood Pressure

Adults

Thirty-six parallel RCTs and 12 crossover RCTs reported on the effects of sodium reduction on systolic BP in adult men and (nonpregnant) women (Figure 4a). Of those, 27 reported a MD in urinary sodium excretion of 40 mmol/d or more. Parallel RCTs were pooled separately from crossover RCTs as well as together. Random effects meta-analyses showed a significant
beneficial effect of sodium reduction on systolic BP for parallel RCTs (MD −2.83, 95% CI –3.75, −1.91; I² 61%), crossover RCTs (MD −3.77, 95% CI −5.45, −2.08; I² 89), and all RCTs combined (MD −3.23, 95% CI −4.06, −2.41; I² 78%) (low RoB overall: 31 RCTs with low RoB, 16 with moderate/unclear RoB, and one with high RoB). A moderate SoE supports a beneficial effect of sodium reduction on decreasing systolic BP (some inconsistency across study outcomes and high heterogeneity).

Three RCTs assessed the dose-response effects of decreasing levels of dietary sodium: one in adults with normal BP,258 one in adults with high-normal blood pressure,221 and one in adults with HTN. Two of the studies achieved decreasing sodium intakes via tomato juice with varying sodium contents, and the DASH diet modified the sodium content of a variety of foods.258,259 Only the DASH sodium study showed an increase in beneficial effect with decreasing sodium.221

Three RCTs enrolled only pregnant women;159,246,267 however, in one RCT, the women had HTN.159 A 6-month RCT conducted in the Netherlands randomized 42 pregnant normotensive women at 14 weeks gestation to a sodium restricted diet or usual care; urinary sodium excretion fell by two thirds in the sodium-restricted group compared with the control group, however term systolic blood pressure did not differ between groups.246 An 8-month RCT conducted in the Netherlands by the same group randomized 270 normotensive first trimester pregnant women (mean age 28) to dietary counseling aimed at restricting sodium or to usual care; urinary sodium excretion was expressed as sodium to creatinine ratio, and no inter-group differences were shown in systolic BP.267 A multisite RCT in the Netherlands randomized 361 first trimester pregnant women with high blood pressure readings in the first trimester to a low or normal sodium diet; the mean sodium excretion differed by 40 mmol/d across groups, however, no difference was seen in systolic BP at term.159 Thus across these three studies, sodium reduction did not decrease systolic BP in pregnant women at term (RoB moderate); however evidence is insufficient to draw a conclusion regarding the effect of sodium reduction on systolic BP.
**Figure 4a. Systolic blood pressure in sodium reduction trials: adults**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xie, 1999</td>
<td>90 (mmHg/24h)</td>
<td>258 (mmHg/24h)</td>
<td>-160</td>
<td>2.60</td>
<td>[1.89, 3.10]</td>
</tr>
<tr>
<td>Bead, 1992</td>
<td>57 (mmHg/24h)</td>
<td>161 (mmHg/24h)</td>
<td>-104</td>
<td>1.00</td>
<td>[0.85, 3.59]</td>
</tr>
<tr>
<td>Jula, 1992</td>
<td>70 (mmHg/24h)</td>
<td>186 (mmHg/24h)</td>
<td>-116</td>
<td>3.30</td>
<td>[1.65, 3.95]</td>
</tr>
<tr>
<td>Muhammad, 1996</td>
<td>92 (mmHg/24h)</td>
<td>199 (mmHg/24h)</td>
<td>-107</td>
<td>4.90</td>
<td>[1.95, 4.15]</td>
</tr>
<tr>
<td>Purka, 1993</td>
<td>77 (mmHg/24h)</td>
<td>167 (mmHg/24h)</td>
<td>-90</td>
<td>1.20</td>
<td>[0.50, 7.90]</td>
</tr>
<tr>
<td>Morgan, 1987</td>
<td>75 (mmHg/24h)</td>
<td>155 (mmHg/24h)</td>
<td>-80</td>
<td>-23.00</td>
<td>[-39.95, -6.14]</td>
</tr>
<tr>
<td>Scirone, 1992(normal salt)</td>
<td>56 (mmHg/24h)</td>
<td>136 (mmHg/24h)</td>
<td>-78</td>
<td>-4.80</td>
<td>[-9.95, 0.38]</td>
</tr>
<tr>
<td>Scirone, 1992(low salt)</td>
<td>53 (mmHg/24h)</td>
<td>129 (mmHg/24h)</td>
<td>-76</td>
<td>-8.00</td>
<td>[-13.54, -2.46]</td>
</tr>
<tr>
<td>How, 1994</td>
<td>75 (mmHg/24h)</td>
<td>150 (mmHg/24h)</td>
<td>-75</td>
<td>-5.00</td>
<td>[-19.95, 0.96]</td>
</tr>
<tr>
<td>Nestel, 1996(women)</td>
<td>77 (mmHg/24h)</td>
<td>150 (mmHg/24h)</td>
<td>-73</td>
<td>-7.00</td>
<td>[-16.73, 2.73]</td>
</tr>
<tr>
<td>Parker, 1990</td>
<td>68 (mmHg/24h)</td>
<td>141 (mmHg/24h)</td>
<td>-73</td>
<td>-9.10</td>
<td>[-5.35, 5.19]</td>
</tr>
<tr>
<td>Steegers, 1991</td>
<td>58 (mmHg/24h)</td>
<td>130 (mmHg/24h)</td>
<td>-72</td>
<td>1.10</td>
<td>[-7.93, 9.26]</td>
</tr>
<tr>
<td>Newson, 1993</td>
<td>90 (mmHg/24h)</td>
<td>156 (mmHg/24h)</td>
<td>-66</td>
<td>5.10</td>
<td>[-7.87, -2.33]</td>
</tr>
<tr>
<td>NHMRC-CEGAR, 1999</td>
<td>90 (mmHg/24h)</td>
<td>153 (mmHg/24h)</td>
<td>-63</td>
<td>5.50</td>
<td>[-8.41, -2.59]</td>
</tr>
<tr>
<td>Burt, 1990</td>
<td>102 (mmHg/24h)</td>
<td>190 (mmHg/24h)</td>
<td>-88</td>
<td>-8.10</td>
<td>[-17.47, 1.27]</td>
</tr>
<tr>
<td>Nestel, 1996(60+)</td>
<td>106 (mmHg/24h)</td>
<td>162 (mmHg/24h)</td>
<td>-56</td>
<td>3.00</td>
<td>[-6.54, 3.54]</td>
</tr>
<tr>
<td>van Brussel, 1997</td>
<td>75 (mmHg/24h)</td>
<td>130 (mmHg/24h)</td>
<td>-55</td>
<td>3.00</td>
<td>[-6.54, 3.54]</td>
</tr>
<tr>
<td>Dabbert, 1995</td>
<td>-50 (mmHg/24h)*</td>
<td>-5 (mmHg/24h)*</td>
<td>-45</td>
<td>-2.40</td>
<td>[-7.41, 2.61]</td>
</tr>
<tr>
<td>Dacor, 1999</td>
<td>136 (mmHg/24h)</td>
<td>190 (mmHg/24h)</td>
<td>-54</td>
<td>-7.10</td>
<td>[-16.19, 2.99]</td>
</tr>
<tr>
<td>Sihma, 1994</td>
<td>117 (mmHg/24h)</td>
<td>159 (mmHg/24h)</td>
<td>-42</td>
<td>-8.70</td>
<td>[-26.18, 11.76]</td>
</tr>
<tr>
<td>TOCH-Collaborative Research Group, 1997</td>
<td>135 (mmHg/24h)</td>
<td>177 (mmHg/24h)</td>
<td>-42</td>
<td>-1.00</td>
<td>[-2.02, 0.02]</td>
</tr>
<tr>
<td>Apoll, 2001</td>
<td>90 (mmHg/24h)</td>
<td>140 (mmHg/24h)</td>
<td>-50</td>
<td>4.20</td>
<td>[-5.93, -2.47]</td>
</tr>
<tr>
<td>Meland, 2002</td>
<td>-28 (mmHg/24h)*</td>
<td>10 (mmHg/24h)*</td>
<td>-38</td>
<td>5.00</td>
<td>[-18.95, 8.00]</td>
</tr>
<tr>
<td>Takahashi, 2006</td>
<td>169 (mmHg/24h)</td>
<td>237 (mmHg/24h)</td>
<td>-68</td>
<td>5.20</td>
<td>[-5.82, -0.58]</td>
</tr>
<tr>
<td>Getjes, 1994</td>
<td>116 (mmHg/24h)</td>
<td>146 (mmHg/24h)</td>
<td>-30</td>
<td>5.10</td>
<td>[-6.64, -4.56]</td>
</tr>
<tr>
<td>Nakano, 2016</td>
<td>116 (mmHg/24h)</td>
<td>147 (mmHg/24h)</td>
<td>-31</td>
<td>1.00</td>
<td>[-5.44, 3.44]</td>
</tr>
<tr>
<td>He, 2015(adults)</td>
<td>178 (mmHg/24h)</td>
<td>206 (mmHg/24h)</td>
<td>-28</td>
<td>1.00</td>
<td>[-3.83, 4.83]</td>
</tr>
<tr>
<td>Hwang, 2014</td>
<td>122 (mmHg/24h)</td>
<td>146 (mmHg/24h)</td>
<td>-24</td>
<td>1.00</td>
<td>[-18.5, 1.35]</td>
</tr>
<tr>
<td>Mercier, 1978</td>
<td>157 (mmHg/24h)</td>
<td>190 (mmHg/24h)</td>
<td>-33</td>
<td>-2.80</td>
<td>[-9.94, 3.34]</td>
</tr>
<tr>
<td>Araki, 1985</td>
<td>167 (mmHg/24h)</td>
<td>190 (mmHg/24h)</td>
<td>-23</td>
<td>-9.26</td>
<td>[-14.37, 3.95]</td>
</tr>
<tr>
<td>He, 2000</td>
<td>148 (mmHg/24h)</td>
<td>159 (mmHg/24h)</td>
<td>-11</td>
<td>0.26</td>
<td>[-3.47, 3.95]</td>
</tr>
<tr>
<td>All, 1982</td>
<td>169 (mmHg/24h)</td>
<td>177 (mmHg/24h)</td>
<td>-8</td>
<td>3.00</td>
<td>[-10.30, 2.70]</td>
</tr>
<tr>
<td>HPTRC1990, 1990</td>
<td>39 (mmHg/24h)</td>
<td>43 (mmHg/24h)</td>
<td>-4</td>
<td>0.10</td>
<td>[-1.94, 2.04]</td>
</tr>
<tr>
<td>Meissman, 1995</td>
<td>107 (mmHg/24h)</td>
<td>162 (mmHg/24h)</td>
<td>-54</td>
<td>-2.00</td>
<td>[-5.83, -1.23]</td>
</tr>
<tr>
<td>Appel, 1992</td>
<td>142 (mmHg/24h)</td>
<td>144 (mmHg/24h)</td>
<td>-2</td>
<td>-4.20</td>
<td>[-8.21, 0.81]</td>
</tr>
<tr>
<td>Copps, 1999</td>
<td>80 (mmHg/24h)</td>
<td>91 (mmHg/24h)</td>
<td>-11</td>
<td>0.50</td>
<td>[-3.22, 4.22]</td>
</tr>
<tr>
<td>Gillman, 1996</td>
<td>159 (mmHg/24h)</td>
<td>166 (mmHg/24h)</td>
<td>7</td>
<td>-21.50</td>
<td>[-39.39, -3.62]</td>
</tr>
<tr>
<td>Motokawa, 2011</td>
<td>183 (mmHg/24h)</td>
<td>NR</td>
<td>35</td>
<td>3.20</td>
<td>[-8.15, 1.75]</td>
</tr>
</tbody>
</table>

**Random effects model:**

**Heterogeneity: $I^2 = 61%$**

**Heterogeneity: $I^2 = 55%$**

**Random effects model:**

**Heterogeneity: $I^2 = 78%$**

* change from baseline

** difference between intervention and control

ANZHPC 0353CH: Australian National Health and Medical Research Council Dietary Salt Study Management Committee

HPTRC: Hypertension Prevention Trial Research Group
### Children

Eight parallel RCTs reported on effects on systolic BP in children (Figure 4b). Of the eight, 1 RCT showed a difference in 24-hour sodium excretion of 40 mmol/d or more. A random effects meta-analysis showed a non-significant decrease in systolic BP among children in sodium reduction interventions compared with those given usual diets (MD – 0.73, 95% CI –1.83, 0.36; I² 48%) (low RoB). The effects on systolic BP in adults and children differed significantly (p=0.006).

One RCT reported on the effects of a sodium reduction intervention on both children and their parents. This study, in northern China, enrolled 293 children and 553 family members in a 3 ½ month cluster-randomized trial. At followup, the difference between intervention and control 24-hour sodium excretion exceeded 40 mmol/d for adults but not for children. Both adults and children had a non-statistically significant decrease in systolic BP compared with controls (MD – 1.6, 95% CI –3.83, 0.63 for adults vs. MD –0.60, CI –2.83, 1.63 for children) (low RoB).

These findings suggest a lack of effect of sodium reduction on systolic BP in children and a difference in the effects of sodium reduction on systolic BP in adults and children (low SoE).

![Figure 4b. Systolic blood pressure in sodium reduction trials: children](image)

#### Mean Difference in Diastolic Blood Pressure

### Adults

Thirty eight parallel RCTs and 13 crossover RCTs reported on the effects of sodium reduction on diastolic BP in adult men and non-pregnant women (Figure 5a). Of those, 28 reported a MD in urinary sodium excretion of 40 mmol/d or more. Parallel RCTs were pooled separately from crossover RCTs as well as together. Random effects meta-analyses showed a significant beneficial effect of sodium reduction on diastolic BP for parallel RCTs (MD –2.09, 95% CI –2.76, –1.43; I² 72%), crossover RCTs (MD –2.51, 95% CI –4.07, –0.95; I² 86%), and all RCTs combined (MD –2.23, 95% CI –2.86, –1.60; I² 78%) (low RoB overall: 32 low, 17 moderate/unclear; 1 high). A moderate SoE supports a beneficial effect of sodium reduction on diastolic BP in adults.

Among the three RCTs that enrolled only pregnant women, none of the three showed inter-group differences in diastolic BP.
Children
Of the seven RCTs that reported on effects on diastolic BP in children (Figure 5b),\textsuperscript{4, 74, 113, 188, 212, 238, 264} one reported a mean difference in 24-hour urinary sodium excretion 40 mmol/d or greater.\textsuperscript{113} A random effects meta-analysis showed a non-significant decrease in diastolic BP with sodium reduction (MD $-2.10$, 95% CI $-4.75$, 0.55; $I^2$ 79%) (low overall RoB). Adults did not differ significantly from children in the effect of sodium reduction on diastolic BP ($p=0.845$).

In the one RCT that compared children with their families, sodium reduction had no significant effect on diastolic BP in either adults or children.\textsuperscript{4}

These findings suggest a lack of effect of sodium reduction on diastolic BP in children and a lack of significant difference in the effects of sodium reduction on diastolic BP in adults and children (low SoE).
Figure 5a. Diastolic blood pressure in sodium reduction trials: adults
Figure 5b. Diastolic blood pressure in sodium reduction trials: children

Percent participants at blood pressure goal

Five parallel and one crossover RCTs reported on the effect of sodium reduction on the likelihood of adult study participants reaching a prespecified blood pressure goal (Figure 6). Five of the trials reported a difference in 24-hour sodium excretion of 40 mmol/d or more. The goals varied, with three RCTs reporting on likelihood of reducing need for antihypertensive medications, one reporting on likelihood of not needing to resume medication after withdrawal, one reporting on the likelihood of achieving a significant BP decrease, and one on achieving a prespecified BP goal. The random effects pooled estimated relative risk (RR) favored reduced sodium (1.73, 95% CI 1.24, 2.40) but studies were highly heterogeneous (I² 87%) (three low RoB, 3 moderate RoB; moderate SoE for achieving a prespecified goal).

Figure 6. Likelihood of achieving prespecified blood pressure goal in trials of sodium reduction

Hypertension Incidence in Adults
Three RCTs reported on the effects of sodium reduction on incident HTN in adult men and nonpregnant women (Figure 7).\textsuperscript{139, 140, 256, 267} TOHP I defined incident HTN as attaining a systolic BP of 160 mm Hg or higher and/or a diastolic BP of 90 mm Hg or higher and/or treatment with an antihypertensive (follow up was 7 years).\textsuperscript{256} TOHP II defined incident HTN as systolic BP of 140 or higher or diastolic BP of 90 or higher, or use of antihypertensive drugs (at 4 years).\textsuperscript{139} The HPTRG defined incident HTN using the same criteria as TOHP II (at 3 years).

Two of the RCTs reported that differences in sodium excretion across intervention arms exceeded 40 mmol/d (however, in TOHP-II, the difference in sodium excretion exceeded 40 mmol/d or more only for men). The random effects estimate for RR of incident HTN showed a statistically non-significant decrease with sodium reduction (RR 0.83, 95% CI 0.67, 1.03; I\(^2\) 0%) (low RoB).

A fourth RCT assessed the effect of sodium reduction on the risk for gestational hypertension: This study found no difference between groups on the rate of incident hypertension.\textsuperscript{267}

Based on the inconsistency in direction of effects and imprecision, these findings suggest a lack of beneficial effect of sodium reduction on the risk for incident HTN in adults (low SoE). No studies reported on this outcome in children.

Adverse events associated with sodium intake

Mortality and CVD/CHD morbidity outcomes reported for sodium reduction interventions are described in the response to KQ3.

Eight RCTs described other adverse events reported in RCTs of sodium reduction. Two studies reported no significant between-group differences in the risk for dizziness or unsteadiness.\textsuperscript{72, 272} Across two studies that reported on headache, one reported no difference, and one reported a significantly higher rate in the usual sodium group.\textsuperscript{72, 138} Three studies reported no between-group differences in blood lipids (total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides).\textsuperscript{122, 183, 228} One study reported no difference in fasting or post-oral glucose challenge serum glucose or insulin,\textsuperscript{183} and one study reported no difference in insulin sensitivity across three levels of sodium intake.\textsuperscript{258} One study reported improvements in muscle cramps across both groups.\textsuperscript{62}

A low strength of evidence supports a lack of adverse effects of reduced sodium on blood lipids, but evidence is insufficient from studies that met inclusion criteria to assess other adverse effects of sodium reduction.

Figure 7. Risk for incident hypertension in trials of sodium reduction

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOHP Collaborative Research Group, 1997</td>
<td>125 (mmol/24h)</td>
<td>177 (mmol/24h)</td>
<td>-52</td>
<td>0.88</td>
<td>[0.75; 0.96]</td>
</tr>
<tr>
<td>HPTRG, 1999</td>
<td>148 (mmol/24h)</td>
<td>159 (mmol/24h)</td>
<td>-11</td>
<td>0.69</td>
<td>[0.53; 1.01]</td>
</tr>
<tr>
<td>HPTRG, 1999</td>
<td>35 (mmol/24h)</td>
<td>43 (mmol/24h)</td>
<td>-5</td>
<td>0.83</td>
<td>[0.67; 1.03]</td>
</tr>
</tbody>
</table>

Random effects model
Heterogeneity: I\(^2\) = 0%

Random effects model
Heterogeneity: I\(^2\) = 0%

Favors Intervention Favors Comparator

HPTRG = Hypertension Prevention Trial Research Group
Effects of Sex

Mean Difference in Systolic Blood Pressure

Five parallel RCTs reported on the effects of sodium reduction on systolic BP in adult males,\textsuperscript{139, 190, 200, 208, 238} and four parallel RCTs reported on the effects of sodium reduction on systolic BP for females.\textsuperscript{139, 200, 238, 267, 272} Two crossover RCTs reported on adult males and females;\textsuperscript{221, 271} one, the DASH-sodium Trial reported on the effects of three different dietary sodium levels on men and women.\textsuperscript{269} RoB was moderate for two RCTs,\textsuperscript{190, 267} and low for six RCTs.\textsuperscript{139, 190, 200, 208, 221, 267, 271, 272}

Seven RCTs reported differences in 24-hour sodium excretion of 40 mmol or more between the high and low sodium groups for at least some subgroups.\textsuperscript{139, 200, 208, 221, 267, 271, 272}

The random effects pooled estimate for the change in systolic BP for adult males showed a statistically significant improvement in favor of reduced sodium (MD $-2.67$ (95% CI $-5.05$, $-0.29$; $I^2$ 74%)). For adult females, the improvement was also statistically significant (MD $-4.04$ (95% CI $-6.30$, $-1.78$; $I^2$ 47%)) (Figure 8). Of note, the difference between males and females was not significant. The DASH-Sodium Trial\textsuperscript{221} reported significant decreases in SBP from the highest to the lowest concentration of dietary sodium for both men and women who consumed the control diet, with no significant differences between men and women (low RoB).

A low strength of evidence supports a lack of moderating effect of sex on the effects of sodium reduction on SBP (based on insufficient numbers of direct comparisons—only two studies made direct comparisons—and imprecision).

Figure 8. Systolic blood pressure in sodium reduction trials: sex effects

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender = 1: Male</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wen, 2013</td>
<td>648 (mmol/24h)</td>
<td>207.5 (mmol/24h)</td>
<td>$-123$</td>
<td>$-8.60$</td>
<td>$[-13.72, -3.48]$</td>
</tr>
<tr>
<td>Sacks, 2001 (control diet)</td>
<td>64 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>$-77$</td>
<td>$-5.70$</td>
<td>$[-10.62, -0.78]$</td>
</tr>
<tr>
<td>Sacks, 2000 (DASH diet)</td>
<td>67 (mmol/24h)</td>
<td>144 (mmol/24h)</td>
<td>$-77$</td>
<td>$-4.90$</td>
<td>$[-9.54, 0.54]$</td>
</tr>
<tr>
<td>Kumanjuya, 2005 (Black men)</td>
<td>145 (mmol/24h)</td>
<td>219 (mmol/24h)</td>
<td>$-74$</td>
<td>$0.50$</td>
<td>$[-0.95, 1.95]$</td>
</tr>
<tr>
<td>Parker, 1990</td>
<td>68 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>$-73$</td>
<td>$-0.10$</td>
<td>$[-5.55, 5.35]$</td>
</tr>
<tr>
<td>Nestel, 1993 (men)</td>
<td>103 (mmol/24h)</td>
<td>162 (mmol/24h)</td>
<td>$-59$</td>
<td>$-3.00$</td>
<td>$[-6.54, 0.54]$</td>
</tr>
<tr>
<td>Appel, 2018 (men)</td>
<td>103 (mmol/24h)</td>
<td>152 (mmol/24h)</td>
<td>$-49$</td>
<td>$-5.00$</td>
<td>$[-7.47, -2.53]$</td>
</tr>
<tr>
<td>Kumanjuya, 2005 (White men)</td>
<td>143 (mmol/24h)</td>
<td>191 (mmol/24h)</td>
<td>$-48$</td>
<td>$-1.00$</td>
<td>$[-2.23, 0.23]$</td>
</tr>
<tr>
<td>Morgan, 1978</td>
<td>157 (mmol/24h)</td>
<td>180 (mmol/24h)</td>
<td>$-23$</td>
<td>$-1.00$</td>
<td>$[-3.00, 1.10]$</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: $I^2 = 74%$</strong></td>
<td></td>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender = 2: Female</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wen, 2013</td>
<td>648 (mmol/24h)</td>
<td>207.5 (mmol/24h)</td>
<td>$-123$</td>
<td>$-10.20$</td>
<td>$[-15.12, -5.28]$</td>
</tr>
<tr>
<td>Sacks, 2001 (control diet)</td>
<td>64 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>$-77$</td>
<td>$-7.50$</td>
<td>$[-12.42, 1.93]$</td>
</tr>
<tr>
<td>Sacks, 2000 (DASH diet)</td>
<td>67 (mmol/24h)</td>
<td>144 (mmol/24h)</td>
<td>$-77$</td>
<td>$-4.00$</td>
<td>$[-9.49, 0.90]$</td>
</tr>
<tr>
<td>Nestel, 1993 (women)</td>
<td>77 (mmol/24h)</td>
<td>150 (mmol/24h)</td>
<td>$-73$</td>
<td>$-7.00$</td>
<td>$[-16.73, 2.73]$</td>
</tr>
<tr>
<td>van Baal, 1997</td>
<td>75 (mmol/24h)</td>
<td>130 (mmol/24h)</td>
<td>$-55$</td>
<td>$-3.00$</td>
<td>$[-4.54, 0.54]$</td>
</tr>
<tr>
<td>Appel, 2018 (women)</td>
<td>95 (mmol/24h)</td>
<td>125 (mmol/24h)</td>
<td>$-30$</td>
<td>$-3.30$</td>
<td>$[-5.97, -0.63]$</td>
</tr>
<tr>
<td>Kumanjuya, 2005 (Black women)</td>
<td>117 (mmol/24h)</td>
<td>130 (mmol/24h)</td>
<td>$-21$</td>
<td>$-3.00$</td>
<td>$[-5.40, -0.60]$</td>
</tr>
<tr>
<td>Kumanjuya, 2005 (White women)</td>
<td>123 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>$-18$</td>
<td>$-1.60$</td>
<td>$[-3.90, 0.70]$</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity: $I^2 = 47%$</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean Difference in Diastolic Blood Pressure

Seven RCTs reported on diastolic BP for males only,\textsuperscript{208, 221, 272, 139, 190, 193, 200, 238} and seven RCTs reported on the effects on diastolic BP in females.\textsuperscript{139, 159, 193, 200, 221, 238, 267, 272} One crossover
study reported the effects of three different dietary sodium levels on men and women.\textsuperscript{221, 269} RoB was low for six RCTs,\textsuperscript{139, 159, 200, 202, 208, 221, 272} and moderate for three RCTs,\textsuperscript{159, 190, 193, 200, 267, 269}. Eight RCTs had a difference in urinary excretion of 40 mmol/d or more.\textsuperscript{139, 159, 200, 208, 221, 267, 271, 272}

The random effects pooled estimate showed a non-statistically significant beneficial effect of sodium reduction on diastolic BP in men (MD \(-1.44 [95\% \text{ CI} -3.47, 0.59] ; I^2 75\%) and a significant effect among women (MD \(-1.70 [95\% \text{ CI} -2.47, -0.93] ; I^2 0\%). No significant difference was observed between males and females (Figure 9). The DASH-Sodium Trial\textsuperscript{39, 269} reported significant dose-dependent decreases in DBP for both men and women who consumed the control diet, with no significant differences between them (low RoB).

A low strength of evidence supports a lack of moderating effects of sex on the effects of sodium reduction on DBP (based on few direct comparisons and inconsistency).

**Figure 9. Diastolic blood pressure in sodium reduction trials: sex effects**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender = 1: Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgan, 180 (male, DEP=105 mmHg)</td>
<td>78 (mmol/24h)</td>
<td>110 (mmol/24h)</td>
<td>-32</td>
<td>-7.00 [-14.92, 0.92]</td>
<td></td>
</tr>
<tr>
<td>Sacks, 280 (cholesterol diet)</td>
<td>64 (mmol/24h)</td>
<td>114 (mmol/24h)</td>
<td>-50</td>
<td>-3.20 [-6.39, -0.01]</td>
<td></td>
</tr>
<tr>
<td>Sacks, 280 (DASH diet)</td>
<td>67 (mmol/24h)</td>
<td>114 (mmol/24h)</td>
<td>-47</td>
<td>-1.80 [-4.79, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Kumanovka, 2005 (Black men)</td>
<td>145 (mmol/24h)</td>
<td>219 (mmol/24h)</td>
<td>-75</td>
<td>-1.50 [0.18, 2.44]</td>
<td></td>
</tr>
<tr>
<td>Park, 2005</td>
<td>68 (mmol/24h)</td>
<td>114 (mmol/24h)</td>
<td>-46</td>
<td>-1.00 [-1.84, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Nestel, 1993 (women)</td>
<td>100 (mmol/24h)</td>
<td>162 (mmol/24h)</td>
<td>-62</td>
<td>-2.90 [-4.95, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Appel, 2001 (men)</td>
<td>103 (mmol/24h)</td>
<td>152 (mmol/24h)</td>
<td>-49</td>
<td>-1.50 [-2.47, 0.49]</td>
<td></td>
</tr>
<tr>
<td>Kumanovka, 2005 (White women)</td>
<td>143 (mmol/24h)</td>
<td>191 (mmol/24h)</td>
<td>-48</td>
<td>-1.50 [-3.00, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Morgan, 1978</td>
<td>157 (mmol/24h)</td>
<td>180 (mmol/24h)</td>
<td>-23</td>
<td>-7.00 [-11.18, -2.84]</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 75%$</td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender = 2: Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacks, 280 (cholesterol diet)</td>
<td>64 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>-77</td>
<td>-3.70 [-6.69, -0.51]</td>
<td></td>
</tr>
<tr>
<td>Sacks, 280 (DASH diet)</td>
<td>67 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>-74</td>
<td>-1.70 [-4.69, 1.29]</td>
<td></td>
</tr>
<tr>
<td>Nestel, 1993 (women)</td>
<td>77 (mmol/24h)</td>
<td>150 (mmol/24h)</td>
<td>-73</td>
<td>-3.00 [-9.44, 3.44]</td>
<td></td>
</tr>
<tr>
<td>Morgan, 180 (female, DEP=105 mmHg)</td>
<td>58 (mmol/24h)</td>
<td>125 (mmol/24h)</td>
<td>-67</td>
<td>-3.00 [-10.92, 4.92]</td>
<td></td>
</tr>
<tr>
<td>van Boxel, 1997</td>
<td>75 (mmol/24h)</td>
<td>130 (mmol/24h)</td>
<td>-55</td>
<td>-5.00 [-11.44, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Knut, 1999</td>
<td>84 (mmol/24h)</td>
<td>124 (mmol/24h)</td>
<td>-40</td>
<td>-2.00 [-4.63, 0.63]</td>
<td></td>
</tr>
<tr>
<td>Appel, 2001 (men)</td>
<td>95 (mmol/24h)</td>
<td>125 (mmol/24h)</td>
<td>-30</td>
<td>-2.90 [-5.89, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Kumanovka, 2005 (Black women)</td>
<td>117 (mmol/24h)</td>
<td>130 (mmol/24h)</td>
<td>-13</td>
<td>-2.90 [-5.89, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Kumanovka, 2005 (White women)</td>
<td>123 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>-18</td>
<td>-2.90 [-5.89, 0.00]</td>
<td></td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hypertension incidence**

One RCT assessed differences in the effects of sodium reduction on relative risk for incident hypertension by sex (criteria are described below in the description of findings for all adults) (low RoB).\textsuperscript{139} One RCT assessed incidence of gestational hypertension (shown in Figure 10 only for comparison) (moderate RoB).\textsuperscript{139, 267} The study that compared differences by sex also assessed white and black men and women separately.\textsuperscript{139} No significant difference was seen across sexes (Figure 10) but evidence is insufficient to draw a conclusion regarding moderating effects of sex on the effects of reducing sodium on this outcome.
Figure 10. Hypertension incidence in sodium reduction trials: sex effects

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender = 1: Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumanyika, 2005 (Black men)</td>
<td>145 (mmol/24h)</td>
<td>219 (mmol/24h)</td>
<td>0.92</td>
<td>[0.80; 1.42]</td>
</tr>
<tr>
<td>Kumanyika, 2005 (White men)</td>
<td>143 (mmol/24h)</td>
<td>191 (mmol/24h)</td>
<td>0.83</td>
<td>[0.66; 1.01]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td>0.94</td>
<td>[0.51; 1.39]</td>
</tr>
<tr>
<td>Heterogeneity: ( I^2 = 9% )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender = 2: Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumanyika, 2005 (Black women)</td>
<td>117 (mmol/24h)</td>
<td>136 (mmol/24h)</td>
<td>0.80</td>
<td>[0.68; 1.12]</td>
</tr>
<tr>
<td>Kumanyika, 2005 (White women)</td>
<td>123 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>0.95</td>
<td>[0.73; 1.25]</td>
</tr>
<tr>
<td>van Buur, 1997</td>
<td>75 (mmol/24h)</td>
<td>130 (mmol/24h)</td>
<td>1.05</td>
<td>[0.56; 2.01]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td>0.99</td>
<td>[0.68; 1.21]</td>
</tr>
<tr>
<td>Heterogeneity: ( I^2 = 9% )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effects of Race/Ethnicity**

**Mean Difference in Systolic Blood Pressure**

Three parallel RCTs and one crossover RCT reported on the effects of sodium reduction on systolic BP separately by race.\(^{139, 256, 269, 272}\) Mean differences in 24-hour sodium excretion reached 40 mmol/d or more among Blacks in three of four RCTs,\(^{139, 221, 256}\) and among whites or non-Blacks in the same studies; however the difference was smaller for white women in the TOHP II study.\(^{139}\) Sodium reduction had a statistically significant beneficial effect on systolic blood pressure among both black participants (MD \(-3.76, 95\%\) CI \(-6.22, -1.31; I^2 92\%) and non-Black participants (MD \(-2.69, 95\%\) CI \(-4.17, -1.02; I^2 73\%) (low RoB; high heterogeneity). Non-blacks and blacks did not differ significantly in MD in systolic BP (confidence intervals were wide) (Figure 11). Evidence was insufficient based on the small number of direct comparisons, inconsistency, and imprecision to draw a conclusion regarding the moderating effect of race/ethnicity on the effects of reducing sodium on systolic BP.
Figure 11. Systolic blood pressure in sodium reduction trials: effects of race and ethnicity

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race = 1: African American</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saad, 2001 (control diet)</td>
<td>64 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>-77</td>
<td>-8.00</td>
<td>[-9.45, -6.55]</td>
</tr>
<tr>
<td>Saad, 2001 (GLI diet)</td>
<td>67 (mmol/24h)</td>
<td>144 (mmol/24h)</td>
<td>-77</td>
<td>-9.00</td>
<td>[-10.65, -7.35]</td>
</tr>
<tr>
<td>Kumanya, 2005 (Black men)</td>
<td>145 (mmol/24h)</td>
<td>210 (mmol/24h)</td>
<td>-65</td>
<td>3.00</td>
<td>[-0.85, 6.85]</td>
</tr>
<tr>
<td>Kumanya, 1993 (Black men)</td>
<td>99 (mmol/24h)</td>
<td>196 (mmol/24h)</td>
<td>-97</td>
<td>-3.25</td>
<td>[-7.15, 0.65]</td>
</tr>
<tr>
<td>Kumanya, 1993 (Black women)</td>
<td>99 (mmol/24h)</td>
<td>196 (mmol/24h)</td>
<td>-97</td>
<td>-4.20</td>
<td>[-7.78, -0.62]</td>
</tr>
<tr>
<td>Appel, 2009 (African American)</td>
<td>183 (mmol/24h)</td>
<td>277 (mmol/24h)</td>
<td>-94</td>
<td>-4.00</td>
<td>[-8.34, -0.66]</td>
</tr>
<tr>
<td>Kumanya, 2005 (Black women)</td>
<td>117 (mmol/24h)</td>
<td>159 (mmol/24h)</td>
<td>-42</td>
<td>-3.00</td>
<td>[-5.48, -0.53]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td>-3.76</td>
<td>[-6.22, -1.31]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 92.2\%

**Race = 2: Non-African American**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saad, 2001 (control diet)</td>
<td>64 (mmol/24h)</td>
<td>141 (mmol/24h)</td>
<td>-77</td>
<td>-5.10</td>
<td>[-6.78, -3.43]</td>
</tr>
<tr>
<td>Saad, 2001 (GLI diet)</td>
<td>67 (mmol/24h)</td>
<td>144 (mmol/24h)</td>
<td>-77</td>
<td>-2.20</td>
<td>[-3.65, -0.76]</td>
</tr>
<tr>
<td>Kumanya, 2005 (White men)</td>
<td>145 (mmol/24h)</td>
<td>210 (mmol/24h)</td>
<td>-65</td>
<td>-1.00</td>
<td>[-2.23, 0.24]</td>
</tr>
<tr>
<td>Kumanya, 1993 (White men)</td>
<td>99 (mmol/24h)</td>
<td>196 (mmol/24h)</td>
<td>-97</td>
<td>-1.00</td>
<td>[-2.58, 0.58]</td>
</tr>
<tr>
<td>Kumanya, 1993 (White women)</td>
<td>99 (mmol/24h)</td>
<td>196 (mmol/24h)</td>
<td>-97</td>
<td>-4.20</td>
<td>[-7.78, -0.62]</td>
</tr>
<tr>
<td>Appel, 2009 (Non-African American)</td>
<td>183 (mmol/24h)</td>
<td>277 (mmol/24h)</td>
<td>-94</td>
<td>-4.00</td>
<td>[-8.34, -0.66]</td>
</tr>
<tr>
<td>Kumanya, 2005 (White women)</td>
<td>117 (mmol/24h)</td>
<td>159 (mmol/24h)</td>
<td>-42</td>
<td>-3.00</td>
<td>[-5.48, -0.53]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td></td>
<td>-3.76</td>
<td>[-6.22, -1.31]</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 73.8\%

Mean Difference in Diastolic Blood Pressure

Four RCTs reported on the effects of sodium reduction on diastolic BP separately by race.\textsuperscript{139}, \textsuperscript{221}, \textsuperscript{256}, \textsuperscript{272} Mean differences in 24-hour sodium excretion reached 40 mmol/d or more among Blacks in three of the four RCTs,\textsuperscript{139}, \textsuperscript{221}, \textsuperscript{256} and among whites or non-Blacks in the same studies; however the difference was smaller for white women in the TOHP II study.\textsuperscript{139} Sodium reduction had a small statistically significant beneficial effect on diastolic blood pressure among black participants (MD $-1.82$, 95% CI $-3.59$, $-0.04$, $I^2 0\%$) (low RoB). Among non-Black participants, sodium reduction decreased diastolic BP slightly but significantly (MD $-1.37$, 95% CI $-1.97$, $-0.76$, $I^2 15\%$). Non-blacks and blacks did not differ significantly in MD in diastolic BP (Figure 12). Evidence was insufficient based on the small number of direct comparisons, inconsistency, and imprecision to draw a conclusion regarding the moderating effect of race/ethnicity on the effects of reducing sodium on diastolic BP.
Hypertension Incidence

One RCT compared incident hypertension (see criteria below) rates between Whites and Blacks (both stratified by sex) (low RoB). This study found no significant effect of sodium reduction on incident hypertension and no difference between Blacks and Whites (Figure 13).

Key Question 1c. Among subpopulations defined by hypertension, diabetes, and obesity health status

Description of Included Studies and detailed synthesis

Forty-three RCTs enrolled participants with high-normal BP or HTN (see below). In categorizing studies regarding participants’ baseline blood pressure status, we relied on the terms
and definitions used by the authors, realizing that these terms and definitions have changed over time.

Three RCTs enrolled participants with DM,\textsuperscript{96, 112, 196} one also had nephropathy.\textsuperscript{196}

One RCT compared overweight and non-overweight participants.\textsuperscript{272} The remainder enrolled participants with mean BMIs in the slightly overweight range.

**Effects by Hypertensive Status**

Among the RCTs that compared sodium reduction to usual diet or usual sodium intake in adults, 11 parallel RCTs\textsuperscript{4, 44, 82, 139, 140, 160, 169, 188, 200, 246, 267} and five crossover RCTs\textsuperscript{105, 179, 222, 227, 259, 269} enrolled participants with normal BP. The remaining parallel,\textsuperscript{60, 95, 157, 229, 256} and six crossover RCTs in adults\textsuperscript{167, 218, 239, 258, 269, 271, 278} enrolled participants with high-normal BP, or mild, moderate or more severe HTN (one RCT compared responses in mild vs. more severe HTN and one compared responses in normotensive to those of adults with HTN) (Figures 14 and 15).\textsuperscript{193} In addition, one controlled clinical trial enrolled healthy normotensive adults,\textsuperscript{85} and two enrolled adults with hypertension.\textsuperscript{157, 160}

**Mean Difference in Systolic Blood Pressure**

One study directly compared effects of sodium reduction on systolic BP between normotensive and hypertensive groups of adults.\textsuperscript{221} The DASH-Sodium Trial found that sodium reduction had a greater effect on BP in hypertensive than in normotensive adults (p=0.01, typical diet and p=0.003, DASH diet).

Random effects meta-analyses showed that sodium reduction lowered systolic BP both in studies of normotensive individuals (8 RCTs; MD $-1.18$, 95\% CI $-2.28$, $-0.08$; I$^2$ 27\%; low RoB) as well as in studies of those with prehypertension, mild HTN, and more severe HTN (35 RCTs; MD $-4.41$, 95\% CI $-5.57$, $-3.25$; I$^2$ 27\%; low RoB). The effect in studies that enrolled participants with HTN was significantly greater than that in studies of normotensives (p<0.001) (Figure 14).

A moderate SoE supports a beneficial effect of sodium reduction on systolic BP in adults with HTN and a moderate SoE supports a beneficial effect in those with normal BP.
### Figure 14. Systolic blood pressure in sodium reduction trials: effects of hypertension

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 1982</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Beard, 1983</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Weir, 1990</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Richards, 1984</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>de Serio–Khan, 2010</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Jul, 1992</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Nall, 1994</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Singh, 1992</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
<tr>
<td>Morgan, 1987</td>
<td>50 (mmHg)</td>
<td>50 (mmHg)</td>
<td>0</td>
<td>0.0</td>
<td>[0.0, 0.0]</td>
</tr>
</tbody>
</table>

### Mean Difference in Diastolic Blood Pressure

Mean difference in diastolic blood pressure: -2.4 mmHg (95% CI: -3.0 to -1.8 mmHg).
One small RCT stratified their description of the effects of sodium reduction on diastolic BP between individuals with mild and those with more advanced HTN. The effects were comparable in both groups; however, they did not do a statistical comparison, and they did not account for the use of medication among those with more advanced HTN.

A random effects meta-analysis of studies that assessed the effects of sodium reduction among normotensives and those that assessed effects in those with HTN showed that sodium reduction did not significantly lower diastolic BP in studies of normotensive individuals (9 RCTs; MD –0.59, 95% CI –1.31, 0.13; I² 70%; low RoB) but significantly lowered diastolic BP in studies of those with prehypertension and HTN (37 RCTs; MD –2.56, 95% CI –3.26, –1.85; I² 70%; low RoB) (p<0.003 for the difference between those with HTN and those with normal BP) (Figure 15).

A moderate SoE supports a beneficial effect of sodium reduction on diastolic BP in adults with HTN and a low SoE suggests a lack of beneficial effect in those with normal BP.
Figure 15. Diastolic blood pressure in sodium reduction trials: effects of hypertension
Effects by Diabetic Status

Mean Difference in Systolic Blood Pressure

Four RCTs that met inclusion criteria enrolled participants with DM. Three were parallel RCTs,\(^9\),\(^1\),\(^2\),\(^3\),\(^4\),\(^5\), and one was a crossover RCT that enrolled adults with DM and nephropathy (all low RoB).\(^6\) No studies compared the effects of sodium reduction by diabetic status.

One small UK study randomized 34 participants with mild hypertension and Type 2 DM and without nephropathy to 3 months of moderately sodium restricted- or usual diabetic diet. Sodium reduction resulted in a significant difference in urinary sodium excretion across groups (60mM) but a non-statistically significant decrease in systolic BP.\(^6\)

A small study (n=16) in Germany imposed a sodium-restricted diet on 16 participants with mild hypertension and Type 1 DM with nephropathy. After a 2-week run-in period, participants were randomized to receive sodium tablets to normalize sodium intake or placebo tablets to maintain sodium reduction.\(^6\) After four weeks, 24-hour urinary sodium excretion differed across groups by over 100mM; systolic BP was not significantly different between groups.

A UK trial randomized 40 individuals with HTN and Type 2 DM to 9 months of a salt substitute or usual diet.\(^1\) At the end of the intervention period, urinary sodium excretion did not differ across treatment groups. Systolic BP was significantly reduced in the intervention group, compared with the control group (MD –21.50, 95% CI –39.38, –3.62).

A crossover trial in the Netherlands randomized individuals with diabetic nephropathy to sodium reduction via dietary counseling with or without hydrochlorothiazide (HCTZ).\(^6\) This study found that sodium reduction decreased systolic BP and that the effects were additive with those of HCTZ.

Mean Difference in Diastolic Blood Pressure

In the UK study of Type 2 DM patients, sodium reduction had a non-significant effect on diastolic BP.\(^6\)

In the German study of Type 1 DM patients, sodium reduction significantly decreased diastolic BP (MD –5.30, 95% CI –10.15, –0.45).\(^6\)

The UK study that randomized individuals with Type 2 DM and HTN to salt substitute or usual diet reported a non-significant decrease in diastolic BP.\(^1\)

The trial of individuals with diabetic nephropathy found that dietary sodium reduction also decreased diastolic BP.\(^6\)

Summary

Three of four RCTs found that sodium reduction decreased BP in individuals with HTN and DM compared with usual diet. However, evidence was insufficient, based on four heterogeneous trials, to draw a conclusion regarding the effects of sodium reduction on BP in adults with DM.

Obesity

Mean Difference in Systolic Blood Pressure

None of the included studies addressed the effect of obesity. As described above in the introduction to this section, one RCT compared the effects of sodium reduction between overweight or obese and non-overweight participants.\(^4\) The multisite US Trial of
Nonpharmacologic Interventions on the Elderly (TONE) randomized 681 individuals, 60-80 years, with HTN to 3.5 months of sodium and/or calorie reduction. Among non-overweight participants, mean differences in urinary sodium excretion between the sodium restricted and usual treatment groups exceeded 40 mmol/d, whereas among the overweight participants, mean differences in urinary sodium excretion were significant but did not reach 40 mmol/d. Sodium reduction significantly reduced systolic BP in both overweight (MD –4.9, 95% CI –7.2, –2.6) and non-overweight (MD –3.9, 95% CI –6.2, –1.5) participants.

**Mean Difference in Diastolic Blood Pressure**

The TONE study reported that diastolic BP decreased significantly among non-overweight participants (MD –2.2, 95% CI –3.7, –0.7) but non-significantly among overweight participants.48

**Key Question 1a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium [reduction]?**

The evidence we present in the response to this subquestion describes the modulatory effects of potassium on the effects of reduced dietary sodium (we do not define reduced dietary sodium or low sodium in this review, as definitions and target goals differed across studies, and some provided no definition or goal). Five studies (reported in seven publications) compare the effects of a low sodium diet with and without potassium enrichment (direct comparison).80, 82, 117, 118, 140, 169, 201 Four studies assessed the effects of modifying potassium intake via foods;80, 82, 140, 169 the remaining trial administered potassium supplements.117 Thirteen studies assess the effects of using potassium salt substitutes in place of sodium chloride table salt (indirect comparison).60, 82, 84, 110, 112, 175, 178, 195, 224, 249, 284, 286, 287 One of the studies reports on an intervention that included both low sodium foods and potassium salt substitute.82 These studies are analyzed separately from those that assessed the effects of sodium reduction with or without supplemental potassium.

We identified no RCTs that assessed the modifying effects of divalent cationic minerals (e.g., calcium or magnesium) alone on the effect of dietary interventions to lower sodium.

**Comparison of low sodium diet with or without increased potassium intake**

As described above in the introduction to this section, five RCTs compared the effects of a low-sodium diet alone with the effects of combining a low-sodium diet with a high potassium diet or potassium supplement (some containing divalent cations).80, 82, 117, 118, 140, 169, 201

The five RCTs enrolled 80-529 participants; three were conducted in the US, one was conducted in Australia, and the remaining study was conducted in South Africa. Mean ages ranged from 39 to 61. The proportion of males ranged from 15 percent to 100 percent. One study enrolled healthy adults,140 and the remaining studies enrolled individuals with mild-to-moderate or more advanced hypertension. Follow-up times ranged from 2 months to 36 months.
Mean difference in systolic blood pressure

Among the five RCTs, the difference in urinary sodium excretion between the intervention and control groups did not reach 40 mmol/day in any study (Figure 16). Only one study, the one trial that administered potassium supplements, showed a substantial increase in potassium excretion in the potassium-enriched group. Risk of bias was moderate for one trial and low for four trials for an overall low risk of bias across studies. Random effects meta-analysis of the five RCTs showed no significant effect of low sodium diet combined with increased potassium intake on systolic BP (MD –0.56 mm Hg, 95% CI –2.94, 1.81; I² 30%). The study that employed a potassium supplement did not achieve findings that differed from those of the food-based studies.

These findings suggest raising dietary potassium via food or supplements has no significant moderating effect on the SBP lowering effect of sodium reduction (low strength of evidence[SoE] based on inconsistency and imprecision).

Figure 16. Systolic blood pressure in combination interventions to restrict sodium

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlton, 2008</td>
<td>154 (mmol/24h)</td>
<td>169 (mmol/24h)</td>
<td>-4.53</td>
<td>[-9.05, -0.01]</td>
</tr>
<tr>
<td>Grimm, 1988</td>
<td>115 (mmol/24h)</td>
<td>113 (mmol/24h)</td>
<td>-0.20</td>
<td>[-2.94, 2.54]</td>
</tr>
<tr>
<td>HPTRG, 1990</td>
<td>36 (mmol/8h)</td>
<td>38 (mmol/8h)</td>
<td>-1.30</td>
<td>[-3.24, 0.64]</td>
</tr>
<tr>
<td>Langford, 1991</td>
<td>95 (mmol/24h)</td>
<td>128 (mmol/24h)</td>
<td>1.88</td>
<td>[-3.14, 6.80]</td>
</tr>
<tr>
<td>Nawson, 1988</td>
<td>73 (mmol/24h)</td>
<td>86 (mmol/24h)</td>
<td>1.00</td>
<td>[-1.64, 3.64]</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>Heterogeneity: I² = 30%</strong></td>
<td><strong>Favors intervention</strong></td>
<td><strong>Favors Comparator</strong></td>
<td><strong>MD</strong></td>
</tr>
</tbody>
</table>

HPTRG = Hypertension Prevention Trial Research Group

Mean difference in diastolic blood pressure

Random effects meta-analysis of the five RCTs showed no significant effect of low sodium diet combined with increased potassium intake on diastolic BP (MD –0.09 mm hg, 95% CI –1.92, 1.74; I² 53%) (Figure 17).

These findings suggest raising dietary potassium via food or supplements has no significant moderating effect on the DBP lowering effect of sodium reduction (low SoE based on inconsistency and imprecision).

Figure 17. Diastolic blood pressure in combination interventions to restrict sodium

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charlton, 2008</td>
<td>154 (mmol/24h)</td>
<td>169 (mmol/24h)</td>
<td>-2.49</td>
<td>[-5.16, 0.17]</td>
</tr>
<tr>
<td>Grimm, 1988</td>
<td>115 (mmol/24h)</td>
<td>113 (mmol/24h)</td>
<td>0.60</td>
<td>[-0.96, 2.15]</td>
</tr>
<tr>
<td>HPTRG, 1990</td>
<td>36 (mmol/8h)</td>
<td>38 (mmol/8h)</td>
<td>-0.60</td>
<td>[-2.29, 0.49]</td>
</tr>
<tr>
<td>Langford, 1991</td>
<td>95 (mmol/24h)</td>
<td>129 (mmol/24h)</td>
<td>0.05</td>
<td>[-2.81, 2.91]</td>
</tr>
<tr>
<td>Nawson, 1988</td>
<td>73 (mmol/24h)</td>
<td>86 (mmol/24h)</td>
<td>1.60</td>
<td>[-0.21, 3.41]</td>
</tr>
<tr>
<td><strong>Random effects model</strong></td>
<td><strong>Heterogeneity: I² = 53%</strong></td>
<td><strong>Favors intervention</strong></td>
<td><strong>Favors Comparator</strong></td>
<td><strong>MD</strong></td>
</tr>
</tbody>
</table>

HPTRG = Hypertension Prevention Trial Research Group
Percent Participants at Blood Pressure Goal

No studies that met inclusion criteria for this intervention reported directly on this outcome. Two RCTs reported on the effects of increasing potassium intake on the need to increase or resume use of HTN medication.

The Trial of Antihypertensive Interventions and Management (TAIM) randomized individuals with HTN to a low sodium, high potassium diet or the usual diet. No effect was seen on the primary outcome, change in diastolic BP (see above). At the end of 6 months, 16.5 percent of those in the low sodium plus potassium group required additional HTN medication, compared with 20 percent of those in the usual diet group (no significant difference) (low RoB).169

The Minnesota Mount Sinai Hypertension Trial (MMSHT), in which men were withdrawn from their antihypertensive medication at baseline and randomized to a low sodium diet with or without potassium chloride supplements, found that at 6 months, 55 percent of each group—those in the low sodium, potassium supplement group as well as those in the low sodium only group—had to resume their antihypertensive medication (low RoB).117,118

The findings of these two RCTs provide insufficient evidence on which to base a conclusion regarding the effects of increasing potassium intake on the likelihood of meeting a blood pressure goal (or, in this case, better BP control).

Incidence of Hypertension

The Hypertension Prevention Trial, the only study that met inclusion criteria for this intervention and enrolled healthy participants, reported no differences between the effect of low-sodium diet with and without increased potassium intake on incident hypertension, as indicated by initiation of anti-hypertensive drugs (low RoB).140

Evidence is insufficient to draw a conclusion on the moderating effect of potassium on sodium reduction.

Adverse Events Associated with Use of Potassium Supplements in a Low Sodium Diet

One RCT that met inclusion criteria for this intervention reported on adverse events.118 The MSHT reported no statistically significant differences between the potassium-supplemented and placebo-treated groups over two years’ followup in six indicators of gastrointestinal function or in need to change medication because of side effects (low RoB).

Conclusions regarding adverse events associated with increasing potassium intake are presented in the response to KQ5.

Potassium-containing salt substitutes

Thirteen RCTs compared the effects of a salt substitute containing some combination of potassium and sodium vs. a regular diet including sodium chloride (indirect comparison).60, 82, 84, 110, 112, 175, 178, 195, 224, 249, 284, 286, 287 One of the studies reported on an intervention that included both low sodium foods and potassium salt substitute.82

The thirteen RCTs enrolled 35 to 2566 participants; five were conducted in China, two were conducted in the UK, and one each was conducted in Finland, Tibet, the Netherlands, Italy, South Africa, and Brazil. Mean ages ranged from 21 to 67. The proportion of males ranged from 15 percent to 62 percent. Nine studies enrolled only individuals with mild-to-moderate or more advanced hypertension, and four enrolled mostly participants with hypertension. Follow-up times
ranged from 1 month to 36 months. Nine trials had a low RoB and the remaining four had moderate RoB.

**Mean difference in systolic blood pressure**

Of the 13 RCTs that met inclusion criteria for this question, only three showed a difference in urinary sodium excretion of 40 mmol or more. Random effects meta-analysis showed a statistically significant effect of the salt substitute on systolic BP (MD –5.34, 95% CI –7.26, –3.42; $I^2$ 72%) (Figure 18).

**Figure 18. Systolic blood pressure in trials of salt substitutes**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>MD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barros, 2015</td>
<td>127 (mmol/24h)</td>
<td>162 (mmol/24h)</td>
<td>–10.08</td>
<td>[–22.23, 2.07]</td>
</tr>
<tr>
<td>Chantong, 2008</td>
<td>154 (mmol/24h)</td>
<td>169 (mmol/24h)</td>
<td>–4.53</td>
<td>[–9.65, –0.01]</td>
</tr>
<tr>
<td>Geleijnse, 1994</td>
<td>116 (mmol/24h)</td>
<td>148 (mmol/24h)</td>
<td>0.80</td>
<td>[–4.45, 6.05]</td>
</tr>
<tr>
<td>Gillman, 1996</td>
<td>166 (mmol/24h)</td>
<td>159 (mmol/24h)</td>
<td>–21.50</td>
<td>[–39.38, –3.62]</td>
</tr>
<tr>
<td>Li, 2016</td>
<td>237 (mmol/24h)</td>
<td>261 (mmol/24h)</td>
<td>–1.10</td>
<td>[–3.30, 1.10]</td>
</tr>
<tr>
<td>Little, 2004</td>
<td>NR</td>
<td>NR</td>
<td>1.42</td>
<td>[–11.18, 14.02]</td>
</tr>
<tr>
<td>Mu, 2009</td>
<td>45 (mmol/8h)</td>
<td>65 (mmol/8h)</td>
<td>–7.10</td>
<td>[–9.62, –4.58]</td>
</tr>
<tr>
<td>Sarkkinen, 2011</td>
<td>160 (mmol/24h)</td>
<td>160 (mmol/24h)</td>
<td>–8.00</td>
<td>[–10.70, –5.30]</td>
</tr>
<tr>
<td>Suppa, 1998</td>
<td>193 (mmol/24h)</td>
<td>190 (mmol/24h)</td>
<td>–4.20</td>
<td>[–9.48, 0.08]</td>
</tr>
<tr>
<td>TCSSSCG, 2007</td>
<td>8 (mmol/l spot)*</td>
<td>NR</td>
<td>–5.40</td>
<td>[–8.50, –2.30]</td>
</tr>
<tr>
<td>Zhao, 2014</td>
<td>20 (grams/day)**</td>
<td>26 (grams/day)**</td>
<td>–7.70</td>
<td>[–12.78, –2.62]</td>
</tr>
<tr>
<td>Zhou, 2009(Hypertensives)</td>
<td>162 (mmol/24h)</td>
<td>233 (mmol/24h)</td>
<td>–9.80</td>
<td>[–13.75, –5.86]</td>
</tr>
<tr>
<td>Zhou, 2009(Normotensives)</td>
<td>162 (mmol/24h)</td>
<td>231 (mmol/24h)</td>
<td>–5.80</td>
<td>[–8.66, –2.94]</td>
</tr>
<tr>
<td>Zhou, 2016</td>
<td>NR</td>
<td>NR</td>
<td>–5.72</td>
<td>[–8.65, –2.79]</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
<td></td>
<td>–5.34</td>
<td>[–7.26, –3.42]</td>
</tr>
</tbody>
</table>

* difference between intervention and control
** estimated intake
TCSSSCG = The China Salt Substitute Study Collaborative Group

Subgroup analyses by sex in the 3-year RCT found that the beneficial effect of the salt substitute was similar for both men and women.

Subgroup analyses by age group in the 3-year RCT found that the beneficial effect of the salt substitute was limited to those between 40 and 70 years of age, compared with those younger than 40 or over 70.

One RCT analyzed the effect of the intervention separately for participants with hypertension and those with normal blood pressure. At 6 months, urinary sodium excretion was identical in hypertensives and normotensives in the same intervention groups. The mean difference in SBP at 6 months was significant for both hypertensives and normotensives but greater for hypertensives than for normotensives.

These findings suggest use of potassium-containing salt substitutes has a significant beneficial effect on SBP (moderate SoE due to imprecision of estimate and slight inconsistency). Evidence is insufficient to draw conclusions regarding the moderating effects of sex or age on the effects of salt substitutes on SBP.

**Mean difference in diastolic blood pressure**

Random effects meta-analysis of 13 studies showed a significant effect of the salt substitute on diastolic BP (MD –2.62, 95% CI –3.71, –1.53; $I^2$ 69%) (Figure 19).

These findings suggest use of potassium-containing salt substitutes has a significant beneficial effect on DBP (moderate SoE based on imprecision).
Percent Participants at Blood Pressure Goal

One study assessed the effects of potassium-containing salt substitutes on blood pressure control. After 3 months, Zhao (2014) reported a non-statistically significant increase in the proportion of participants with good blood pressure control (SBP/DBP <140/90) with the use of the salt substitutes (RR 0.57, 95% CI 0.28, 1.17) (low RoB).\textsuperscript{284}

The findings of this RCT provide insufficient evidence on which to base a conclusion regarding the effects of salt substitutes on the likelihood of meeting a blood pressure goal (in this case, better BP control).

Incidence of Hypertension

Although no studies that met inclusion criteria for this intervention assessed hypertension incidence, two studies reported on the effects of potassium-containing salt substitutes on use of antihypertensive medications.\textsuperscript{284, 286} Both studies used the 25% potassium chloride salt substitute, and neither study withdrew participants from antihypertensive medications at baseline. Participants in one study were all hypertensive; after 3 months, salt substitutes resulted in a small, non-significant reduction in use of antihypertensive medications (low RoB).\textsuperscript{284} At 3 years, the study by Zhou, in which half of participants had HTN at baseline, showed that use of the salt substitute resulted in a significant decrease in use of antihypertensive medications (low RoB).\textsuperscript{286}

The findings of these two RCTs provide insufficient evidence on which to base a conclusion regarding the effects of salt substitutes on incident hypertension.
Adverse Events Associated with Use of Salt Substitutes

Three studies of salt substitutes assessed the risk for adverse events.\textsuperscript{84, 224, 284} Deaths and cardiovascular events are described in the response to KQ3a.

The China Salt Substitute Study Collaborative Group\textsuperscript{84} compared the risk for hyperkalemia between the salt substitute group and the control group. No incidents of hyperkalemia were reported (low RoB).

Zhao reported that two intervention group participants discontinued because of gastrointestinal complaints, and one control group participant discontinued due to poor taste of the salt (low RoB).\textsuperscript{284}

Sarkkinen reported 7 instances of respiratory symptoms (five in the intervention group and two in the control group); 17 reports of GI symptoms (12 in the intervention group); and three reports of CV symptoms (one in the intervention group) (low RoB).\textsuperscript{224}

The findings of these studies suggest that use of potassium-containing salt substitutes may be associated with a small increase in the risk for minor respiratory and GI adverse events (low SoE, based on number of studies and lack of ability to pool findings across studies).

Key Question 2. Among adults and children, what is the association between dietary sodium intake and blood pressure?

Key Points

- A low strength of evidence supports a lack of association of sodium exposure with systolic or diastolic BP in adults based on observational studies. All studies had high risk of bias based on the methods used to assess sodium intake (typically single 24-hour urine excretion with or without validation).
- A low strength of evidence supports an association of sodium exposure with incident hypertension in adults. All studies had high risk of bias based on the methods used to assess sodium intake.
- Evidence is insufficient to draw conclusions about the association between sodium exposure and BP in children. Three studies had high risk of bias, based on methods used to assess sodium intake.
- Evidence is insufficient based on lack of direct comparisons to draw conclusions regarding a moderating effect of sex on the effects of lower sodium exposure on blood pressure incident hypertension, or achievement or a prespecified goal.
- Evidence is insufficient based on lack of direct comparisons to draw conclusions regarding a moderating effect of race/ethnicity on the effects of lower sodium exposure on blood pressure, incident hypertension, or achievement or a prespecified goal.
Evidence is insufficient to draw conclusions about the moderating effects of age on blood pressure.

Evidence is insufficient to draw conclusions regarding the moderating effect of hypertension on the association between sodium exposure and BP.

Evidence is insufficient to draw conclusions regarding the moderating effect of renal health status on the association between sodium exposure and BP.

Evidence is insufficient to draw conclusions regarding the moderating effect of weight status on the association between sodium exposure and BP.

Overview

To address the question of the association between sodium exposures and blood pressure outcomes, we examined prospective cohort studies as well as post hoc observational assessments of the association between dietary sodium excretion and outcomes of interest from a small number of studies. Key question 2a reviews the associations between sodium exposure and blood pressure and hypertension outcomes and the moderating effects of sex, race/ethnicity, and age (adults vs. children). Key question 2b reviews the moderating effects of hypertension, diabetes, obesity, and renal disease on these associations.

Key Question 2a. Among subpopulations defined by sex, race/ethnicity and age (children, adolescents, young adults, older adults, elderly).

Description of Included Studies and Detailed Synthesis

Effect of Sex

Associations were reported by sex only for BP outcomes. No associations were reported for incident HTN or achievement of prespecified goals.

Adult Studies  
24-hour Urinary Excretion

The Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study followed a cohort of healthy children in Germany from infancy to young adulthood. Krupp et al followed a sub-cohort of adolescents from the DONALD study, from the age of 12 until they reached adult age (18-25). The multivariate analysis, adjusted for adult age, adult BMI, adolescent BP, adolescent height, maternal BP, maternal education, energy intake, intake of saturated fat, as well as fruit and vegetables (including 100% juice), indicated a significantly positive association between 24-hour salt (sodium chloride) excretion and SBP in males but not in females. SBP was on average 7.5 mmHg higher in males in the highest quartile compared to those in the lowest quartile of salt excretion. No association was found for DBP in either males or females (high RoB: single 24-hour urinary excretion with validation and 3-day food records).
One study that met inclusion criteria assessed the association of sodium excretion with risk for gestational hypertension. Inoue and colleagues followed a cohort of 184 pregnant women in Japan from their 20th to 30th gestational week. After adjusting for age, parity, multiple pregnancy, family history of hypertension, BMI, serum uric acid, eGFR, and hematocrit, they found no association between urinary salt (sodium chloride) excretion and BP (high ROB: single 24-hour urinary excretion with validation).

**Assessment of Dietary Sodium**

The NHLBI Growth and Health Study followed a cohort of 10-year old girls in the U.S. over 10 years (to the age of 20). Adjusting for race, height, activity levels, screen time, energy intake (and percentage of calories from solid fats and added sugar), and dietary fiber, they found no association between sodium intake (from multiple 3-day diet records) and SBP or DBP (high ROB: dietary assessment method).

**Child Studies**

**24-hour Urinary Excretion**

In their assessments of the association between sodium exposure and BP in the DONALD cohort during childhood, the researchers found no differences between boys and girls in the association of sodium intake and BP (in both prepubertal and pubertal age groups).

**Summary**

Evidence is insufficient based on lack of direct comparisons to draw conclusions regarding a moderating effect of sex on the effects of lower sodium exposure on blood pressure, incident hypertension, or achievement or a prespecified goal.

**Effects of Race/ethnicity**

Only one cohort study assessed associations by race. In race-stratified analyses, the NHLBI study, which relied on 3-day diet records to assess sodium exposure) reported no association between sodium intake and BP either among black or among white women.

**Summary**

Evidence is insufficient based on lack of direct comparisons to draw conclusions regarding a moderating effect of race/ethnicity on the effects of lower sodium exposure on blood pressure, incident hypertension, or achievement or a prespecified goal.

**Effects of Age**

No studies directly compared adults with children.
Adult Studies

Mean Systolic and Diastolic Blood Pressure

24-hour Urinary Excretion

Singer and colleagues followed a cohort of 3,505 hypertensive adults, mean age 52, who participated in a worksite hypertension program in the US, over an average of 18.6 years. After 6.5 years' in-program time, they found a small but statistically significant inverse association between 24-hour urinary sodium excretion and SBP by quartile, where the mean SBP was the highest in Q1 (lowest sodium excretion) and lowest in Q4 (Adjustment factors unclear). No association was seen for DBP. (high ROB: single 24-hour urinary sodium with validation).

Phase 1 of the Trials of Hypertension Prevention (TOHP-1), randomly assigned 327 healthy adults with a DBP 80-89 mmHg to receive counseling for dietary sodium reduction and 417 healthy adults to maintain their usual diet over 18 months. After adjustment for age, sex, race, baseline BP, and baseline sodium excretion, the pooled dose-response analysis indicated a significant association between 24-hour urinary sodium excretion and SBP, where a 100 mmol decrease in urinary sodium corresponds to a 1.4 mmHg decrease in SBP (high ROB: single 24-hour urinary excretion with validation).

Estimation of 24-hour Urinary Sodium Excretion from Spot or Overnight Urine

The Circulatory Risk in the Community Study (CIRCS) conducted in a rural Japanese city followed a cohort of 889 normotensive adults (mean age 57.3) for a mean follow-up period of 6 years. After adjusting for age, sex, BMI, drinking status, current smoking and eGFR, they found no association between sodium concentrations in spot urine and SBP or DBP (high ROB based on assessment method).

Chien and colleagues followed a cohort of 1,520 healthy men and women (mean age 52) in a Taiwan village over a median of 8 years (the Chin-Shan Community Cardiovascular Cohort Study [CCCC]). They found that after adjusting for age and sex, higher 24-hour urinary sodium excretion was significantly correlated with higher SBP and DBP (high ROB). The main outcome for this study was incident hypertension, reported below.

The Renal Risk in Derby (RRID) study followed a cohort of 1607 adults with stage-3 chronic kidney disease (mean age 72.6) in the UK over 1 year. At followup, they found a significant association between reduced sodium intake, measured by estimating 24-hour urinary excretion, and reduced SBP and DBP (Adjustment factors unclear; high ROB).

Hypertension incidence

Urinary sodium excretion

The Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study has followed 8,592 men and women since the late 1990s. At a median followup of 6.4 years, they assessed incident hypertension in a subgroup of 5,556 normotensive adults (mean age 43). They found that the association between urinary sodium excretion and incident hypertension was significantly modified by serum uric acid and urine albumin excretion. Among individuals in the highest tertiles of serum uric acid and urine albumin, higher sodium intake was significantly associated with higher incidence of hypertension (HR=1.09 and 1.18 respectively; p<0.05).
adjusting for age, BMI, sex, alcohol intake, smoking status, family history of hypertension, eGFR, plasma glucose and cholesterol, and urinary potassium, calcium, and creatinine (moderate ROB).

At a median followup of 7.6 years, the PREVEND researchers assessed the association between urinary sodium-to-potassium ratio and risk for HTN. After adjustment for age, sex, BMI, smoking status, alcohol consumption, parental history of HTN, education, and urinary magnesium and calcium excretion, multivariate analysis found no association between sodium-potassium excretion ratio and the risk of hypertension (low ROB).

The CCCC described above found a significant J-shape relationship between urinary sodium excretion and the risk of hypertension across quartiles. Controlling for BMI, lifestyle, socioeconomic status, baseline diabetes status, and systolic BP, the multivariate analysis showed that, compared with individuals in the second quartile, those in the highest quartile had a significantly higher risk of developing hypertension (RR=1.26; p=0.043) while those in the first quartile had a non-significantly higher risk of hypertension (RR=1.24; P=0.07) (high ROB).

Inoue and colleagues found no association between urinary salt (sodium chloride) excretion and the incidence of pregnancy-induced hypertension in the multivariate analysis, further controlling for pregnancy >40 years, chronic hypertension, BUN, creatinine, and baseline blood pressure (high ROB).

The Trial Of Nonpharmacological interventions in the Elderly (TONE), which randomly assigned 681 elderly US men and women (mean age 65.8) with hypertension to a reduced sodium intervention (dietary counseling with the goal of achieving 80 mmol/d urinary sodium excretion) or control group, assessed the association between urinary sodium excretion and need to resume use of antihypertensives across intervention groups. At an average of 27.8 months’ followup, dose-response analyses found that greater reduction in urinary sodium excretion was significantly associated with reduced risk of an end point defined by the occurrence of systolic BP≥150 mmHg, diastolic BP ≥90mmHg, resumption of anti-hypertensives, or a CVD event (low overall RoB but high ROB for assessment of sodium intake).

Dietary sodium intake

The China Health and Nutrition Survey (CHNS) followed a cohort of 16,869 Chinese adults, aged 20 to 60, over 10 years. After adjusting for energy intake, age, sex, education, income, region, BMI, physical activity, smoking status, and alcohol consumption, flexible parametric models showed a significant dose-response association between sodium intake (from multiple 24-hour dietary recalls) in the third to fifth quintiles and incident hypertension (HR=1.20, 1.37, and 1.84, respectively [95% CI not reported]; p<0.05) (High ROB based on dietary assessment method).

Child Studies

Mean Systolic and Diastolic Blood Pressure

Three prospective cohort studies followed children 17 and younger. A prospective cohort study that followed infants from birth reported a significant association between sodium intake and high systolic BP at 3-4 years. The others found no association between sodium intake and SBP or DBP.
24-hour Urinary Sodium Excretion

Shi and colleagues followed a sub-cohort of 6-year old healthy children from the DONALD study, described above, for 10 years. Using two adjustment models, they found no statistically significant association between 24-hour urinary sodium excretion and SBP or DBP either in the pre-pubertal or in the pubertal stage (high ROB: single 24-hour sample with validation).

Estimated Urinary Sodium Excretion from Spot Urine

Geleijnse and colleagues followed a cohort of 233 healthy children, aged 5 to 17, who resided in a small Netherlands town. At a median of 7 years’ followup, no significant association was observed between estimated 24-hour urinary sodium excretion (from overnight collection) and systolic or diastolic BP (adjustment factors unclear; high RoB).

Dietary Assessment of Sodium Intake

Vitolo and colleagues followed a cohort of 331 full-term healthy infants from low-income families in Brazil for 3 to 4 years. The multivariate analysis showed that children consuming more than 1,200 mg of sodium per day presented a significantly greater risk for having high SBP, adjusting for exclusively breastfeeding for at least 4 months, child overweight, waist-to-height ratio greater than 0.5 and change in body mass index z score greater than 0.67 (high ROB based on dietary assessment method).

Summary

A low strength of evidence supports a lack of association of sodium exposure with systolic or diastolic BP in adults based on observational studies. All studies had high risk of bias based on the methods used to assess sodium intake (typically single 24-hour urine excretion with or without validation).

A low strength of evidence supports an association of sodium exposure with incident hypertension in adults. All studies had high risk of bias based on the methods used to assess sodium intake.

Evidence is insufficient to draw conclusions about the association between sodium exposure and BP in children. Three studies had high risk of bias, based on methods used to assess sodium intake.

Evidence is insufficient to draw conclusions about the moderating effects of age on blood pressure.

Key Question 2b. Among subpopulations defined by hypertension, diabetes, and obesity health status.

Description of Included Studies

One prospective cohort study that met inclusion criteria enrolled men and women with hypertension. One study included only people with stage 3 chronic kidney disease. The remaining studies enrolled entirely or mostly healthy people.
One study compared the association between sodium concentrations in spot urine and BP in overweight (BMI>25) with that in non-overweight (BMI≤25) individuals. No studies that met inclusion criteria assessed the moderating role of diabetes.

**Detailed Synthesis**

**Hypertension**

No studies compared outcomes between normotensive and hypertensive individuals.

In a study described above that followed a cohort of adults with hypertension in a worksite-based program, Singer and colleagues reported that at 6.5 years, a higher quartile of sodium intake was slightly but significantly associated with lower SBP among hypertensive men and women, while no association was found with DBP (high RoB for assessment of sodium exposure).

TONE, which assessed the effect of a sodium reduction intervention among hypertensive older adults, found that greater reduction in sodium intake was associated with lower risk of having elevated BP, resumption of anti-hypertensive medication, or a CVD event in dose-response analyses (high RoB for assessment of sodium exposure).

**Summary**

Evidence is insufficient to draw conclusions regarding the moderating effect of hypertension on the association between sodium exposure and BP.

**Renal Health Status**

No studies directly compared groups with kidney disease and those with healthy individuals.

One study assessed associations between sodium excretion and BP among those with impaired renal health (high RoB: estimated urinary sodium). The RRID study, which followed men and women with stage 3 chronic kidney disease, reported that decreased sodium intake was significantly associated with reduced SBP and DBP (RoB).

**Summary**

Evidence is insufficient to draw conclusions regarding the moderating effect of renal health status on the association between sodium exposure and BP.

**Obesity**

Only one study assessed the potential moderating effect of overweight or obesity on the association between sodium exposure and outcomes of interest.

Among non-overweight individuals (BMI<25), the CIRCS found a significant association between multivariable-adjusted sodium concentration in spot urine and SBP, where a 53mmol/l increase in sodium concentration increases SBP by 1.1 mmHg. Nonetheless, the relationship slightly attenuated when further adjusting for baseline SBP (p=0.078). Among overweight individuals, no significant association was observed between sodium concentration and SBP. For both overweight and non-overweight people, no association was found between sodium concentration and DBP (high RoB for assessment of sodium exposure).
Summary

Evidence is insufficient to draw conclusions regarding the moderating effect of weight status on the association between sodium exposure and BP.
Key Question 3. 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?

Key Points

- In adults, a low strength of evidence suggests that sodium reduction decreases the risk for all-cause mortality (three RCTs; low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not affect risk for CVD mortality (three RCTs; low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not affect risk for stroke (three RCTs; low RoB overall).
- In adults, evidence is insufficient to assess the effect of sodium reduction on the risk for myocardial infarction (one RCT; low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not affect risk for a composite measure of any CVD outcomes as reported by study authors (five RCTs; low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not significantly decrease risk for combined CVD morbidity and mortality (seven RCTs; low RoB).
- Evidence was insufficient to reach conclusions about the effects of sex, race/ethnicity, age, or reproductive status on the effects of sodium reduction on CVD or CHD outcomes.
- Evidence is insufficient to draw conclusions on the moderating effects of hypertension, diabetes, or renal disease on the effects of sodium reduction interventions on all-cause, CVD, or CHD mortality, CVD- or CHD morbidity, or other longer term CVD outcomes.
- Conflicting evidence from two RCTs is insufficient to draw conclusions regarding the moderating impact of overweight or obesity on the effect of sodium reduction on composite CVD outcomes (low RoB).
- Evidence was insufficient, based on one RCT, to draw conclusions on whether the effects of sodium reduction on clinical CVD, CHD, and renal outcomes as well as all-cause mortality are affected by higher dietary potassium.
- Evidence was insufficient, based on two RCTs, to draw conclusions on the moderating effects of potassium-containing salt substitutes on the effects of sodium reduction on clinical CVD, CHD, and renal outcomes and all-cause mortality.

This question addresses three subquestions: a) the moderating effects of other minerals on the effects of reduced sodium on all-cause mortality and CVD/CHD mortality and morbidity; b) the effects of reduced sodium on those outcomes in adults, and moderating effects of sex and race/ethnicity; and c) moderating effects of comorbidities on those outcomes. We begin by addressing subquestion b.
Key Question 3b. Among subpopulations defined by sex, race/ethnicity, age (adults, older adults, elderly), and for women (pregnancy and lactation).

Description of Included Studies

A total of nine RCTs (reported in 13 publications) that met inclusion criteria reported on the effects of reduced sodium intake on all-cause mortality or CVD, CHD, or renal morbidity or mortality in adults.48, 82, 84, 89, 90, 93, 95, 133, 140, 190, 192, 272, 280

All studies randomized participants to receive counseling/education about reducing dietary sodium or no counseling; two studies also used a potassium-containing salt substitute.82, 84

One study enrolled healthy adults;140 one study enrolled individuals with prehypertension;89, 90, 93 and six studies enrolled only participants with hypertension.82, 84, 95, 192, 272, 280

Follow-up times ranged from 3 months to 240 months. Three studies occurred in the US, one in Australia, one in Taiwan, one in China, two in the UK, and one in South Africa.

Nine studies had a low RoB and one had a moderate RoB.

Three RCTs stratified analyses of the effects of interventions to decrease sodium by one of the demographic subgroups of interest. Outcomes for which stratified analyses were reported included all-cause mortality192 and composite CVD outcomes.48, 90 Two RCTs reported outcomes by sex,48, 90 two reported outcomes by race/ethnicity; and three reported outcomes by age.48, 90, 192

No studies stratified outcomes exactly by the DRI age categories, and no studies stratified outcomes by reproductive status (pregnant or breastfeeding).

Detailed Synthesis

Effects of Age

Of nine RCTs that reported on all-cause mortality or CVD outcomes,48, 82, 84, 89, 90, 93, 95, 133, 140, 190, 192, 272, 280 none stratified by DRI age categories. Two RCTs stratified CVD outcomes by age group.48, 90

The TONE study reported that individuals in the 60-69 age group had a significant beneficial effect of reduced sodium (HR 0.66, 95% CI 0.54, 0.82), whereas individuals in the 70-80 age group had a non-significant benefit (HR 0.75, 95% CI 0.50, 1.14).48

The combined TOHP I and TOHP II followup study showed similar non-significant benefits of sodium reduction for age groups 30-44 and 45-54.90

The remainder of this section describes studies in adults by outcomes of interest.

All-cause Mortality

Six studies (described in five publications) reported deaths from any cause.84, 89, 95, 133, 140, 192

Three of the studies reported the deaths as reasons for withdrawal or as serious adverse events, rather than as prespecified outcomes.84, 95, 133, 140

Two studies, described in one publication, reported an intervention-related decrease in all-cause mortality.89 In a study designated the Trials of Hypertension Prevention Follow-up Study,
Cook and colleagues (2016) followed up participants from the TOHP I and TOHP II trials to assess the effects of dietary sodium reduction on all-cause mortality (a secondary outcome to CVD) over 20 years using ITT analysis. Net 24-hour urinary sodium decreased in the intervention groups by 44 mmol and 33 mmol, respectively (absolute levels achieved were not reported). Within each study and in the combined studies, adjusted all-cause mortality was slightly but not significantly lower in the reduced sodium group (HR 0.85, CI 0.66, 1.09).

A random-effects meta-analysis of the studies that assessed the effects of interventions to reduce sodium found a borderline significant beneficial effect of sodium reduction on the risk for all-cause mortality (RR 0.92, 95% CI 0.84, 1.00, I² 0%; n=4,328; low RoB) (Figure 20). Thus the findings suggest sodium reduction may decrease the risk for all-cause mortality in adults (low strength of evidence).

**Figure 20. Relative risk for all-cause mortality in sodium reduction trials**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ware, 2010(67)**</td>
<td>84 mmol (24h)</td>
<td>207 mmol (24h)</td>
<td>-123</td>
<td>0.96</td>
<td>[0.82, 1.14]</td>
</tr>
<tr>
<td>de Boker-Achard, 2013(166)**</td>
<td>136 mmol (24h)</td>
<td>149 mmol (24h)</td>
<td>-13</td>
<td>0.89</td>
<td>[0.76, 1.05]</td>
</tr>
<tr>
<td>Cook, 2016(65)(TOHP-1)</td>
<td>99 mmol (24h)</td>
<td>149 mmol (24h)</td>
<td>-50</td>
<td>1.20</td>
<td>[0.98, 1.49]</td>
</tr>
<tr>
<td>Cook, 2016(67)(TOHP-2)</td>
<td>136 mmol (24h)</td>
<td>177 mmol (24h)</td>
<td>-41</td>
<td>0.99</td>
<td>[0.95, 1.03]</td>
</tr>
<tr>
<td>Morgan, 1996(171)**</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.92</td>
<td>[0.84, 1.00]</td>
</tr>
</tbody>
</table>

CVD Mortality

Three RCTs (reported in two publications) reported on the effects of reduced dietary sodium on CVD mortality in adults. Two of the RCTs enrolled adults with high-normal or borderline high BP, and the third enrolled adults with HTN. None of the studies found a statistically significant beneficial effect.

Morgan reported no difference in rates of mortality due to CVD between the low sodium and usual care groups (moderate RoB). Cook reported in the TOHP Followup Study that across the TOHP I and TOHP trials (low RoB for both), CVD accounted for 10 deaths in the reduced sodium groups compared with 15 deaths in the comparison groups; the difference was not statistically significant. A random-effects meta-analysis of the three found no significant effect. Thus the findings suggest sodium reduction may not affect the risk for CVD mortality in adults (low strength of evidence).

**Stroke**

Three RCTs reported on incidence of stroke in adults; only one study reported it as a prespecified outcome (Figure 21). No significant difference was seen in the incidence of stroke in any study (all RoB) or in a pooled analysis of the studies. We also assessed the association between mean differences in 24-hour urinary sodium excretion and relative risk for stroke; of the three studies, only one reported a mean difference of 40 mmol/d or more, and only this RCT reported a (non-significant) decrease in the RR for stroke with sodium reduction.
Thus the findings suggest sodium reduction may not affect the risk for stroke in adults (low strength of evidence).

Figure 21. Relative risk for stroke in sodium reduction trials

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>RRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appel, 2001 #722</td>
<td>59 (mmol/L24h)</td>
<td>140 (mmol/L24h)</td>
<td>−81</td>
<td>0.50</td>
<td>[0.65; 5.50]</td>
</tr>
<tr>
<td>Charron, 2000 #11469</td>
<td>154 (mmol/L24h)</td>
<td>169 (mmol/L24h)</td>
<td>15</td>
<td>2.92</td>
<td>[0.12; 69.52]</td>
</tr>
<tr>
<td>Gheorhan, 1999 #12321</td>
<td>159 (mmol/L24h)</td>
<td>165 (mmol/L24h)</td>
<td>6</td>
<td>3.80</td>
<td>[0.13; 69.52]</td>
</tr>
</tbody>
</table>

Random effects model
Heterogeneity: $I^2 = 0\%$

Myocardial Infarction

The TONE study reported on the incidence of MI as an adverse event in older adults. During the 30-month period following medication withdrawal, no significant difference was found in the incidence of MI: Two instances of MI were reported in the reduced sodium group, compared with four such events in the control group.

Number of Patients with any CVD Event as Reported by the Study Authors

The TONE study, as described above, reported a composite outcome of blood pressure control (need to begin or resume medication) or CVD/CHD measures over a follow up of 30 months. They also reported any cardiovascular event as an adverse event outcome: In the reduced sodium group, 36 participants were diagnosed with 44 CV events, compared with 57 events among 46 participants in the control group, a non-significant difference. Reduced sodium resulted in a non-significantly lower risk for experiencing an endpoint (RR 0.81, CI 0.54, 1.21).

The primary outcome for the TOHP I and II followup was a composite of CVD outcomes that included MI, stroke, coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or CVD mortality. Followup information was obtained for 77 percent of participants. The sodium reduction intervention significantly decreased adjusted relative risk for CVD by 25 percent (RR 0.75, 95% CI 0.57, 0.99, p=0.04). A random effects pooled analysis that included the TOHP-I and TOHP-II composite outcomes and CVD morbidity outcomes from three other trials showed a non-statistically significant beneficial effect of sodium reduction on this outcome (RR 0.85, 95% CI 0.69, 1.05, $I^2 0\%$; n=4,328; low RoB)(Figure 22). These findings suggest sodium reduction does not affect risk for the composite outcome of any CVD event (low strength of evidence).
Figure 22. Relative risk for any cardiovascular disease event in sodium reduction trials (as reported by the study authors)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>Difference in Achieved Sodium</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook, 2007</td>
<td>99 (mmol/24h)</td>
<td>146 (mmol/24h)</td>
<td>−47</td>
<td>0.72</td>
<td>[0.47, 1.12]</td>
</tr>
<tr>
<td>Cook, 2007</td>
<td>135 (mmol/24h)</td>
<td>177 (mmol/24h)</td>
<td>−42</td>
<td>0.68</td>
<td>[0.45, 1.03]</td>
</tr>
<tr>
<td>Appel, 2001</td>
<td>99 (mmol/24h)</td>
<td>140 (mmol/24h)</td>
<td>−41</td>
<td>0.78</td>
<td>[0.52, 1.18]</td>
</tr>
<tr>
<td>Morgan, 2000</td>
<td>NR</td>
<td>NR</td>
<td></td>
<td>1.20</td>
<td>[0.78, 1.88]</td>
</tr>
<tr>
<td>TCSSSGC, 2007</td>
<td>0 (mmol/spot)*</td>
<td>NR</td>
<td></td>
<td>1.58</td>
<td>[1.22, 1.97]</td>
</tr>
</tbody>
</table>

* difference between intervention and control
TCSSSGC = The China Salt Substitute Study Collaborative Group

Combined CVD Morbidity and Mortality

Seven RCTs that met inclusion criteria reported on the effects in adults of altered sodium on outcomes that contributed to an outcome of combined morbidity and mortality due to CVD. Sodium reduction non-significantly decreased the relative risk for this outcome (Figure 23). Among three RCTs that reported differences of 40 mmol/d or more in achieved 24-hour sodium excretion, none reported a statistically significant decrease in the RR for combined CVD morbidity and mortality with sodium reduction. These findings do not support an effect of reduced sodium on this composite outcome (low strength of evidence).

Figure 23. Relative risk for combined CVD morbidity and mortality

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Sodium Control</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appel, 2001</td>
<td>99 (mmol/24h)</td>
<td>140 (mmol/24h)</td>
<td>0.79</td>
<td>[0.52; 1.18]</td>
</tr>
<tr>
<td>Charlton, 2008</td>
<td>154 (mmol/24h)</td>
<td>168 (mmol/24h)</td>
<td>2.93</td>
<td>[1.12; 6.92]</td>
</tr>
<tr>
<td>Cook, 2007</td>
<td>135 (mmol/24h)</td>
<td>177 (mmol/24h)</td>
<td>0.88</td>
<td>[0.65; 1.12]</td>
</tr>
<tr>
<td>Gilligan, 1996</td>
<td>159 (mmol/24h)</td>
<td>166 (mmol/24h)</td>
<td>3.00</td>
<td>[1.13; 6.92]</td>
</tr>
<tr>
<td>Morgan, 1980</td>
<td>NR</td>
<td>NR</td>
<td>1.20</td>
<td>[0.98; 1.49]</td>
</tr>
<tr>
<td>TCSSSGC, 2007</td>
<td>8 (mmol/spot)*</td>
<td>NR</td>
<td>1.58</td>
<td>[1.22; 1.97]</td>
</tr>
</tbody>
</table>

* difference between intervention and control
TCSSSGC = The China Salt Substitute Study Collaborative Group

Other CVD Outcomes

The Hypertension Prevention Trial (HPT) assessed differences in gross morbidity (hypertension) between intervention groups (all adults) and reported no differences. A study conducted in China assessed the effects of sodium reduction on left ventricular mass (hypertrophy). Xie (the Chinese PEP investigators) cluster-randomized seven hypertension clinics (169 adults patients) to a manualized educational intervention or to routine care for up to 3 years. The intervention included counseling on non-pharmacologic approaches to lower
blood pressure. Because randomization was at the clinic level, results were reported as changes from baseline for each group. No significant differences were seen in 24-hour urinary sodium excretion at the end of years 1 or 2. Likewise, left ventricular hypertrophy did not differ significantly between groups.

**Effect of Sex**

Two RCTs stratified reports of any CVD outcomes by sex.\(^43,85\)

The TONE study reported that men experienced a greater decrease in urinary sodium excretion than did women in response to the intervention (\(-27\) [95% CI 16, -39] vs. \(-53\) [95% CI -41, -64] mmol, \(p<0.001\)). Both men and women showed a decreased incidence in the composite CVD outcome measure compared with the control group, similar to that of the overall intervention population (men: HR 0.72, 95% CI 0.56, 0.94, \(p=0.01\); women: HR 0.64, 95% CI 0.49, 0.83, \(p=0.001\)).\(^48\)

Likewise, the combined 12-17-year followup of TOHP I and TOHP II showed similar findings for men and women and for the overall study population, although the effect size for women was not statistically significant (men: HR 0.71, 95% CI 0.51, 0.97, \(p=0.032\); women: HR 0.71, 95% CI 0.35, 1.43, \(p=0.33\)).\(^90\)

Evidence was insufficient to draw a conclusion regarding a moderating effect of sex on the effect of sodium reduction on CVD outcomes.

**Effects of Race/ethnicity**

Two RCTs stratified CVD outcomes by race/ethnicity.\(^48,90\)

The TONE study reported that urinary sodium excretion was similar between blacks and whites although within racial groups, sex differences persisted. The relative HR for the composite CVD outcome for blacks associated with the reduced dietary sodium intervention showed a significant beneficial effect, similar to that of non-blacks (HR 0.56, 95% CI 0.37, 0.84, \(p=0.005\) vs. HR 0.72, 95% CI 0.58, 0.98 [as reported]).\(^48\)

The combined TOHP I and TOHP II followup study reported that only white participants had a statistically significant composite CVD response to the sodium reduction intervention (HR 0.71, 95% CI 0.52, 0.98; \(p=0.034\)), whereas the responses of blacks and individuals of “other” racial/ethnic groups were not significant (blacks: HR 0.86, 95% CI 0.33, 2.26; other: HR 0.08, 95% CI 0.00, 22.90).\(^90\)

Evidence was insufficient to draw a conclusion regarding a moderating effect of race/ethnicity on the effect of sodium reduction on CVD outcomes.

**Key Question 3c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.**

**Description of Included Studies**

Two RCTs stratified analyses of the effects of interventions to decrease sodium by comorbidity subgroups: the two RCTs reported composite CVD outcomes (combined MI, stroke, CABG, PTCA, and CVD mortality events) by BMI status.\(^48,90\) No studies stratified analyses by hypertensive status, diabetes status, or renal health status.
Detailed Synthesis

Obesity

The TONE trial reported no significant difference in the beneficial impact of the low sodium intervention on overweight participants compared with those who were not overweight, where overweight was defined as BMI 27.8 or higher for men and 27.3 or higher for women.\textsuperscript{48}

The combined analysis of TOHP I and TOHP II reported that for individuals with BMI of 25 or more, the sodium reduction intervention significantly decreased the risk for the composite CVD outcome (HR 0.72, 95\% CI 0.53, 0.96), whereas for those with BMI less than 25, the decrease in risk was not statistically significant (HR 0.24, 95\% CI 0.05, 1.16).\textsuperscript{90}

Summary

Evidence is insufficient to draw conclusions on the moderating effects of hypertension, diabetes, or renal disease on the effects of sodium reduction interventions on all-cause, CVD, or CHD mortality, CVD- or CHD morbidity, or other longer term CVD outcomes.

Conflicting evidence from two RCTs is insufficient to draw conclusions regarding the impact of overweight or obesity on the effect of sodium reduction on composite CVD outcomes. The two RCTs had overall low RoB but high RoB for assessment of sodium exposure.

Key Question 3a. Do other minerals (e.g., potassium, calcium, magnesium) modify the effect of sodium?

Description of Included Studies

One RCT, the HPT, compared the effect of counseling to achieve a low sodium/high potassium diet to that of a low sodium diet alone on gross morbidity (defined as hospitalization) and death.\textsuperscript{140} This study was described above in the response to KQ1a.

Two RCTs assessed the effects of salt substitutes on all-cause mortality and one assessed the effects on CVD outcomes.\textsuperscript{84, 284}

Detailed Synthesis

All-cause Mortality

The HPT reported one death each in both the low dietary sodium and low dietary sodium plus high dietary potassium groups (low RoB).\textsuperscript{140}

Zhao\textsuperscript{284} reported three deaths during the three-month study period, one in the group that received salt substitutes and two in the usual diet group (low RoB). The China Salt Substitute Study Collaborative Group\textsuperscript{84} reported that the relative risk for deaths was the same across groups (absolute risk 4 per group) (low RoB).

Number of Patients with any CVD Event as Reported by the Study Authors

The China Salt Substitute Study Collaborative Group reported that the risk for cardiovascular events was slightly but not significantly increased in the salt substitute group compared with the
usual diet group (RR 1.58, CI 0.52, 4.79).\textsuperscript{84} Sarkkinen reported three instances of CV symptoms, one in the intervention group and two in the control groups, in a study of salt substitutes described in the response to KQ1a.\textsuperscript{224}

**Other CVD Outcomes**

The HPT reported no difference between groups on the outcome of gross morbidity, that is, hospitalization for any reason.\textsuperscript{140}

**Summary**

Evidence was insufficient, based on one RCT, to draw conclusions on whether the effects of sodium reduction on clinical CVD, CHD, and renal outcomes as well as all-cause mortality are affected by higher dietary potassium.

Evidence was insufficient, based on two RCTs, to draw conclusions on the moderating effects of potassium-containing salt substitutes on the effects of sodium reduction on clinical CVD, CHD, and renal outcomes and all-cause mortality. None of the studies that addressed this subquestion had these outcomes as their primary outcomes, and none were adequately powered to assess long-term mortality and morbidity outcomes.
Key Question 4. 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?

Key Points

- Although there appears to be an association between all-cause mortality and 24-hour sodium excretion at higher sodium levels (low SOE), the linearity of this relationship at lower sodium levels could not be determined (insufficient SOE).
- Data are insufficient to determine the linearity of the association of sodium intake levels with CVD mortality.
- A low level of evidence supports a lack of association of sodium intake levels with stroke or combined CVD morbidity and mortality.
- Evidence is insufficient to assess effects of sex, race/ethnicity, age, or comorbidities on associations between sodium intake status and outcomes of interest.

Overview

In this section, for each outcome of interest, we first describe the studies that assess associations for sodium intake of generally healthy populations. Findings are described separately for sodium intake assessed by urinary sodium excretion (24-hour excretion and estimated excretion, separately) and sodium intake assessed by dietary sodium intake. We then describe the studies that assess associations between sodium to potassium ratios: urinary sodium to potassium followed by dietary sodium to potassium.

Detailed Synthesis

Total mortality

Sodium Intake and Total Mortality

A total of 20 publications that reported analyses examining the associations between sodium intake levels and total mortality outcome met inclusion criteria. These publications analyzed data from 14 studies among generally healthy adult populations, and seven studies among people with existing diseases such as hypertension, type 2 diabetes, type 1 diabetes, CVD, and CKD.

Thirteen prospective cohort studies and one case-cohort study examined the associations between sodium intake levels and total mortality outcomes among generally healthy adult populations. These studies included 13 cohorts, which are the combined FLEMENHO and EPOGH cohort, the TOHP (I and II) cohort, the Scottish Heart Health study, PREVEND, a population-based cohort in south-western Finland, a pooled analysis of four cohorts (PURE, EPIDREAM, ONTARGET and...
TRANSCEND),\textsuperscript{184} PURE cohort,\textsuperscript{204} PURE South America cohort,\textsuperscript{168} the Rotterdam study,\textsuperscript{111} NHANES I,\textsuperscript{41,127} NHANES II Mortality study,\textsuperscript{87} NHANES III,\textsuperscript{282} and MONICA.\textsuperscript{67} The pooled analysis of four cohorts\textsuperscript{184} had overlapping study populations with the PURE cohort\textsuperscript{204} and PURE South America cohort.\textsuperscript{168} The other 10 studies analyzed data from nine non-overlapping cohorts (two studies analyzed data from NHANES I)\textsuperscript{31,127} across European countries and the U.S. All studies included both adult men and women at baseline (mean ages ranged from 40.9 to 69.2 years). Mean or median follow-up time ranged from 3.7 to 19 years.

Sodium intake levels were assessed by 24-hour urinary sodium excretion in five studies,\textsuperscript{89,155,247,262,263} by spot-urine samples in four studies,\textsuperscript{184,111,168,204} by 24-hour dietary recall in four studies,\textsuperscript{41,87,127,282} and by 3-day dietary records in one study.\textsuperscript{67} The sodium intake ranged from 68 mmol/d (1564 mg/d) to 365 mmol/d (8395 mg/d); the wide range might be attributable to the variety of methods used to assess exposure. Individual study results are shown in Figures 24 and 25, and Table 4.

**Overall Results**

The relationships between sodium intake levels and total mortality outcomes are inconsistent among the nine studies that examined urinary sodium levels and total mortality.\textsuperscript{89,111,155,168,184,204,247,262,263} Five studies examined the relationships between baseline 24-hour urinary sodium excretion levels and risk of total mortality and showed inconsistent results,\textsuperscript{89,155,247,262,263} although random-effects meta-analysis of three studies\textsuperscript{89,155,263} showed that a 50 mmol increase in 24-hour urinary excretion level was associated with an average 9 percent increase in the risk of total mortality (pooled RR = 1.09; 95% CI 1.00, 1.19; $I^2 = 22.6\%$). However, the meta-analysis pooled estimate would have been smaller with wider confidence intervals if all five studies were included. Of the nine studies, three multi-country studies had overlapping study populations and results consistently showed a U-shaped association between 24-hour urinary sodium excretion estimated by Kawasaki equation and total mortality outcome.\textsuperscript{168,184,204} Cohorts with overlaps were grouped together, as they had consistent findings. Finally, five studies also showed inconsistent results for the linear relationship between dietary sodium intake and total mortality outcome.\textsuperscript{41,67,87,127,282} All studies, except for the Scottish Heart Health study, controlled for various demographics, lifestyle factors, and medical history or medications. Among these, PREVEND,\textsuperscript{155} FLEMENGO, the EPOGH cohort study,\textsuperscript{247} and the Rotterdam study\textsuperscript{111} also adjusted for urinary potassium excretion in their analyses. The Scottish Heart Health study adjusted only for age in their analyses, so the results may be at increased risk for confounding.

The strength of evidence was rated low for the linear association between higher sodium levels and higher risks for all-cause mortality primarily because the overall risk of bias was rated moderate and findings were consistent at the higher ranges of sodium intake levels across studies.
Figure 24. Categorical analysis of the association between urinary sodium levels and total mortality outcome in generally healthy populations.
Figure 25. Categorical analysis of the association between dietary sodium levels and total mortality outcome in generally healthy populations.

Yang, 2011 NHANES III

Mortality: 2270/12267

Bongard, 2016 MONICA

Mortality: 150/960
<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook, 2016&lt;sup&gt;49&lt;/sup&gt; TOHP I &amp; II</td>
<td>Overweight and pre-HTN</td>
<td>Both</td>
<td>median 25.7 y (TOHP I); 22.4 y (TOHP II)</td>
<td>44/417 (TOHP I); 92/1191 (TOHP II)</td>
<td>0.106 (TOHP I); 0.077 (TOHP II)</td>
<td>24-hour urinary sodium excretion</td>
<td>TOHP I: 3839 mg/d in men &amp; 2948 mg/d in women; TOHP II: 4576 mg/d in men &amp; 3541 mg/d in women</td>
<td>per 1 mg/d increase</td>
<td>HR</td>
<td>1.12</td>
<td>1</td>
<td>1.26</td>
</tr>
<tr>
<td>Kieneker, 2016&lt;sup&gt;155&lt;/sup&gt; PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>493/7795</td>
<td>0.063</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 155 mmol/24 hr in men &amp; 122 mmol/24 hr in women</td>
<td>per 50 mmol/d increase</td>
<td>HR</td>
<td>1.02</td>
<td>0.9</td>
<td>1.16</td>
</tr>
<tr>
<td>Tuomilehto, 2001&lt;sup&gt;263&lt;/sup&gt;</td>
<td>All</td>
<td>Both</td>
<td>up to 13 years</td>
<td>180/2436</td>
<td>0.074</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83) in men &amp; 162 (SD 62) mmol/d in women</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.22</td>
<td>1.02</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Male</td>
<td>up to 13 years</td>
<td>136/1173</td>
<td>0.116</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.3</td>
<td>1.06</td>
<td>1.59</td>
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<tr>
<td></td>
<td>Female</td>
<td>Female</td>
<td>up to 13 years</td>
<td>44/1263</td>
<td>0.035</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 162 (SD 62)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>0.91</td>
<td>0.56</td>
<td>1.47</td>
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<tr>
<td>Normal weight</td>
<td>Male</td>
<td>Male</td>
<td>up to 13 years</td>
<td>60/659</td>
<td>0.091</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>0.98</td>
<td>0.7</td>
<td>1.36</td>
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<td>Author, Year Cohort name</td>
<td>Subgroup</td>
<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric</td>
<td>Estimate</td>
<td>Lower 95% CI</td>
<td>upper 95% CI</td>
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<tr>
<td>Overweight</td>
<td>Male</td>
<td>up to 13 years</td>
<td>76/514</td>
<td>0.148</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.56</td>
<td>1.21</td>
<td>2.00</td>
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</tr>
<tr>
<td>Geleijnse, 2007 Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Estimated 24-hour urinary sodium excretion (spot urine)</td>
<td>NR</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.95</td>
<td>0.81</td>
<td>1.12</td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary sodium excretion (spot urine)</td>
<td>NR</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.12</td>
<td>0.86</td>
<td>1.46</td>
<td></td>
</tr>
<tr>
<td>He, 1999 NHANES I</td>
<td>Non-overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/6797</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100 mmol increase</td>
<td>RR</td>
<td>0.98</td>
<td>0.88</td>
<td>1.09</td>
</tr>
<tr>
<td>Overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/2688</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100 mmol increase</td>
<td>RR</td>
<td>1.32</td>
<td>1.16</td>
<td>1.50</td>
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<td>Alderman, 1998 NHANES I</td>
<td>All</td>
<td>Both</td>
<td>ND</td>
<td>ND/11346</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>Mean 2515 mg/d in men and 1701 mg/d in women</td>
<td>per SD (1313 mg) increase</td>
<td>HR</td>
<td>0.88</td>
<td>0.80</td>
<td>0.96</td>
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<tr>
<td>Cohen, 2006 NHANES II</td>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>1343/7154</td>
<td>0.188</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 (SD 231) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.93</td>
<td>0.87</td>
<td>1.00</td>
</tr>
<tr>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>1343/7154</td>
<td>0.188</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 mg/d</td>
<td>&lt;2300 mg/d vs. ≥2300 mg/d</td>
<td>HR</td>
<td>1.20</td>
<td>1.10</td>
<td>1.40</td>
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<tr>
<td>Yang, 2011 NHANES III</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>2270/12267</td>
<td>0.185</td>
<td>Dietary sodium intake</td>
<td>Median 3434 (IQR 2641-4384) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.20</td>
<td>1.03</td>
<td>1.41</td>
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<td>Author, Year Cohort name</td>
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<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric</td>
<td>Estimate</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
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</tr>
<tr>
<td>Male</td>
<td>Male</td>
<td>median 14.8 y</td>
<td>1267/5899</td>
<td>0.215</td>
<td>Dietary sodium intake</td>
<td>Median 4165 (IQR 3390-5043) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.34</td>
<td>1.12</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>Female</td>
<td>median 14.8 y</td>
<td>1003/6368</td>
<td>0.158</td>
<td>Dietary sodium intake</td>
<td>Median 2838 (IQR 2252-3521) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.07</td>
<td>0.75</td>
<td>1.53</td>
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<tr>
<td>Non-Hispanic White</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1253/2269</td>
<td>0.552</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.23</td>
<td>1.01</td>
<td>1.49</td>
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<tr>
<td>Non-Hispanic Black</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>527/1540</td>
<td>0.342</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.16</td>
<td>0.93</td>
<td>1.45</td>
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<tr>
<td>Mexican American</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>449/1859</td>
<td>0.241</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.20</td>
<td>0.91</td>
<td>1.58</td>
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<tr>
<td>Hypertensive</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1155/NR</td>
<td>--</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.18</td>
<td>0.88</td>
<td>1.57</td>
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<tr>
<td>Non-hypertensive</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1115/NR</td>
<td>--</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.22</td>
<td>1.02</td>
<td>1.46</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Urinary Sodium Excretion and Total Mortality

24-hour urinary sodium

Five studies examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of total mortality and showed inconsistent results. Specifically, the FLEMENGHO and EPOGH cohort study, PREVEND study, and the Scottish Heart Health study found that baseline 24-hour urinary sodium excretion levels were not associated with risks of total mortality, while the TOHP cohort of overweight and pre-hypertensive adults and a Finnish cohort study by Tuomilehto and colleagues (2001) showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of total mortality at the follow-ups. All studies, except for the Scottish Heart Health study, controlled for various demographics, lifestyle factors, and cardiovascular disease risk factors. The FLEMENGHO and EPOGH cohort and PREVEND studies further controlled for urinary potassium excretion in their analyses. The Scottish Heart Health study adjusted only for age in their analyses so the results may be at higher risk for confounding.

Random-effects model meta-analysis of three prospective cohort studies showed that a 50 mmol increase in 24-hour urinary excretion level was associated with an average 9 percent increase in the risk of total mortality (pooled RR = 1.09; 95% CI 1.00, 1.19; I² = 22.6%). Figure 26. However, the meta-analysis pooled estimate would have been smaller with wider confidence intervals if all five studies were included, because the two studies that could not be included in this meta-analysis (one because it reported only population means, which could not be converted to effect sizes, and one because it did not report confidence intervals) both reported non-significant relationships between levels of 24-hour urinary sodium excretion and total mortality outcomes. Specifically, the FLEMENGHO and EPOGH cohort study showed that low (median = 95 mmol/d in women; 120 mmol/d in men), medium (median = 150 mmol/d in women; 189 mmol/d in men), and high (median = 291 mmol/d in women; 232 mmol/d in men) tertiles of 24-hour urinary sodium excretion were not significantly associated with the risks for total mortality (adjusted HR = 1.14, 95% CI 0.87, 1.50; 0.94, 95% CI 0.75, 1.18; and 1.06, 95% CI 0.84, 1.33, respectively; n=3681). These analyses compared the risk in each tertile with the overall risk in the whole study population using multiple Cox regression and deviation from mean coding. This approach allows computation of CIs for the hazard ratio (HR) in each tertile without definition of an arbitrary reference group. The Scottish Heart Health study showed a borderline significant inverse relationship between quintiles of 24-hour urinary sodium excretion levels (range from 46.8 to 416.7 mmol/d) and total mortality outcome in men (age-adjusted HR = 0.99, 0.65, 0.86, 0.71 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754), and no significant association in women (age-adjusted HR = 0.61, 0.82, 0.67, 0.85 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875). Again, because the Scottish Heart Health study adjusted only for age in their analyses, these results are at higher risk for confounding.
Figure 26. Random-effects model meta-analysis of adjusted relative risks of total mortality per 50 mmol/d increase in urinary sodium excretion in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>n/N</th>
<th>adj. RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook, 2016</td>
<td>44/117 for TOHP I; TOHP II</td>
<td>1.28 (0.99, 1.65)</td>
</tr>
<tr>
<td>Kieneker, 2016 PREVEND</td>
<td>493/7796</td>
<td>1.02 (0.90, 1.16)</td>
</tr>
<tr>
<td>Tuomilehto, 2001</td>
<td>186/2436</td>
<td>1.10 (1.01, 1.21)</td>
</tr>
<tr>
<td>Overall (I-squared = 22.6%, p = 0.275)</td>
<td></td>
<td>1.09 (1.00, 1.19)</td>
</tr>
</tbody>
</table>

**Estimated 24-hour urinary sodium excretion**

The association between *estimated* 24-hour urinary sodium excretion and total mortality was examined in four studies. Among these four studies, three studies had overlapping study populations. The pooled analysis of four cohorts (PURE, EPIDREAM, ONTARGET and TRANSCEND) from 49 countries showed a U-shaped relationship between baseline levels of 24-hour urinary sodium excretion (estimated by Kawasaki equation) and risks of total mortality (n=133118), using the median quintile of urinary excretion (195 mmol/d) as the reference group. That is, compared with urinary sodium excretion of 4 (172 mmol) to 5 (215 mmol) g/day (median = 195 mmol/d), urinary sodium excretion of 7 (300 mmol) g/day or more (adjusted HR 1.31, 95% CI 1.17, 1.47) and less than 3 g/day (adjusted HR 1.41, 95% CI 1.28, 1.54) were both associated with increased risk of total mortality. Similar U-shape relationships were found in subgroup analyses by hypertension status (n=63559 with hypertension and n=69559 without hypertension). Not surprisingly, the analyses using the PURE cohort (n=101945) and PURE South America cohort (n=16549) also showed U-shaped associations, but the level of urinary sodium excretion used as the reference group was different in the PURE cohort (4 to 5.99 g/day; median = 217 mmol/d), and some comparisons were not statistically significant due to smaller sample sizes. The fourth study is the Rotterdam study, which showed no significant linear relationship between estimated 24-hour urinary excretion based on an overnight urine sample and total mortality (adjusted RR 0.95 per SD increase; 95% CI 0.81, 1.12; n=5531).
Dietary Sodium Intake and Total Mortality

Five studies analyzed data from four cohorts (NHANES I,\textsuperscript{41,127} NHANES II,\textsuperscript{87} NHANES III,\textsuperscript{282} and MONICA\textsuperscript{67}) to examine the relationship between dietary sodium intake and total mortality outcome. Results were inconsistent across studies, each of which used different analytic methods. The studies that analyzed data from NHANES I and II follow-up cohorts, which enrolled a representative US sample from 1971 to 1975 and from 1976 to 1980 respectively, showed an inverse relationship between dietary sodium intake and total mortality.\textsuperscript{41,87,127} In contrast, the studies that analyzed data from the NHANES III follow-up cohort and MONICA, which enrolled a representative US sample from 1988 to 1994 and adults living in France between 1995 and 1997, respectively, found a positive relationship between dietary sodium intake and total mortality.\textsuperscript{67,282}

The ranges of dietary sodium intake levels differed across studies. In the NHANES I follow-up study, the mean dietary sodium intake was 2515 mg/day (109 mmol/d) in men and 1701 mg/day (74 mmol/d) in women, and higher dietary sodium intake levels were associated with lower risks of total mortality (adjusted HR 0.88 per SD [1313 mg or 57 mmol] increase; 95% CI 0.80, 0.96; n=11346).\textsuperscript{41} However, subgroup analyses by overweight status (albeit using different methods) showed a significant positive association among overweight adults. The interaction between sodium intake and body weight (non-overweight vs. overweight) was significant (p for interaction =0.002). In the NHANES II follow-up study, the mean dietary sodium intake was 2719 mg/day (118 mmol/d), and higher dietary sodium intake levels were associated with lower risks of total mortality (adjusted HR = 0.93 per 1000 mg increase; 95% CI 0.87, 1.00; n=7154).\textsuperscript{87} Furthermore, when compared to dietary sodium intake levels of 2300 mg/day or more, sodium intakes less than 2300 mg/d were significantly associated with an increased risk of total mortality (adjusted HR = 1.20; 95% CI 1.10, 1.40).

In contrast, in the NHANES III follow-up study, the median dietary sodium intake was 3434 mg/day (149 mmol/d), and higher dietary sodium intake levels were associated with an increased risk of total mortality for both categorical and continuous analyses (adjusted HR = 1.20 per 1000 mg increase; 95% CI 1.03, 1.41; n=12267).\textsuperscript{282} There were no significant interactions by sex, race/ethnicity, or presence of hypertension. Finally, in the MONICA cohort, the median dietary sodium intake was 3434 mg/day (149 mmol/d), and higher dietary sodium intake levels were associated with an increased risk of total mortality (adjusted HR 1.00, 95% CI 1.00, 2.68 comparing quartiles 2, 3, and 4 to the lowest quartile, respectively; p=0.023 for trend; n=960).\textsuperscript{67}
Sodium/Potassium ratio

A total of six studies\(^89,111,155,207,247,282\) that reported analyses examining the associations between sodium-to-potassium ratio (Na-K ratio) and total mortality outcome were included. These studies analyzed data from six non-overlapping cohorts among generally healthy adult populations.

Five prospective cohort studies\(^89,155,207,247,282\) and one case-cohort study\(^111\) examined the associations between levels of Na-K ratio and total mortality outcome among generally healthy adult populations. The cohorts included in these studies are the combined FLEMENGHO and EPOGH cohort\(^247\), NHANES III\(^282\), PREVEND\(^155\), NIPPON DATA80\(^207\), TOHP\(^89\), and the Rotterdam Study.\(^111\) All studies included both adult men and women. Mean age was reported to be in the 40s for most studies, except for one study that had a mean age of 76.9 years (the Rotterdam Study), and one study that did not report mean age but included participants over 20 years of age (NHANES III). Mean or median follow-up times ranged from 5 years to 24 years.

Na-K ratios were assessed by 24-hour urinary excretion in three studies\(^89,155,247\), by spot urine (estimated 24-hour urinary excretion) in one study\(^111\), by 24-hour dietary recall in one study\(^282\), and by 3-day weighed food records in one study\(^207\). Individual study results are shown in Figure 27 and Table 5.

Overall Results

The relationships between levels of Na-K ratio and total mortality outcome are inconsistent among the four studies that examined urinary Na-K ratios and total mortality.\(^89,111,155,247\) However, both studies that assessed dietary Na-K intake showed significant and positive linear associations with total mortality.\(^207,282\) All studies controlled for various demographic, clinical, and lifestyle factors. The overall risk of bias was rated as low to moderate.

Urinary Sodium/Potassium Ratio and Total Mortality

Four studies that examined urinary Na-K ratios and total mortality outcome reported inconsistent results. The TOHP studies showed a significant linear association between continuous Na-K ratio and total mortality (adjusted HR = 1.13; 95% CI 1.01, 1.27; n=1608). However, using categories of Na-K ratio, no significant linear trend was detected.\(^89\) In the FLEMENGHO and EPOGH study, a slight but nonsignificant inverse linear trend (p=.063; n=3681) was detected using tertiles of Na-K ratio, with higher risk of total mortality occurring in the lower tertiles of Na-K ratio.\(^247\) The Rotterdam study found no relationship between Na-K ratio and total mortality in the full case-cohort or in participants free of CVD and hypertension at baseline.\(^111\) The PREVEND study found no linear association between Na-K ratio and total mortality (adjusted HR = 1.00; 95% CI 0.90, 1.12; n=7795).\(^155\)

Dietary Sodium/Potassium Ratio and Total Mortality

The two studies that assessed dietary Na-K ratio reported consistent significant associations with total mortality.\(^207,282\) In NHANES, the risk of total mortality increased with increasing quartile of Na-K ratio (p for trend <.001; n=12267).\(^282\) In addition, significant linear associations between continuous Na-K ratio and total mortality were reported among the entire cohort and in all the subgroups examined (sex, race/ethnicity, and hypertension). In the NIPPON DATA80 cohort, significant linear (age-adjusted model: p=.005; n=8283) and quadratic nonlinear (fully adjusted model: p=.001) trends were found between quintiles of Na-K ratio and total mortality.
Those in the highest quintile of Na-K ratio had a significantly increased risk of total mortality compared to those in the lowest quintile (adjusted HR = 1.16; 95% CI 1.06, 1.27).

Figure 27. Categorical analysis of the association between levels of sodium to potassium ratio and total mortality outcome in generally healthy populations.
Table 5. Continuous analyses of the association between sodium to potassium ratio and total mortality outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
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<tbody>
<tr>
<td>Kieneker, 2016\textsuperscript{155} PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5 y (IQR 9.9 - 10.8y)</td>
<td>493/7795</td>
<td>0.063</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>HR</td>
<td>1.00</td>
<td>0.90</td>
<td>1.12</td>
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<tr>
<td>Cook, 2016\textsuperscript{199} TOHP I &amp; II</td>
<td>Overweight and pre-HTN</td>
<td>Both</td>
<td>median 25.7 y (TOHP I); 22.4 y (TOHP II)</td>
<td>44/417 (TOHP I); 92/1191 (TOHP II)</td>
<td>0.106</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>HR</td>
<td>1.13</td>
<td>1.01</td>
<td>1.27</td>
</tr>
<tr>
<td>Geleijnse, 2007\textsuperscript{111} Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Estimated 24-Hour Urinary Excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>RR</td>
<td>1.01</td>
<td>0.91</td>
<td>1.12</td>
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<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>RR</td>
<td>1.13</td>
<td>0.93</td>
<td>1.36</td>
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<td>CVD free and BMI ≥25 kg/m²</td>
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<td>median 5.5 y</td>
<td>NR/NR</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>RR</td>
<td>1.19</td>
<td>1.02</td>
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<td>Yang, 2011\textsuperscript{282} NHANES III</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>2270/12267</td>
<td>0.185</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.89</td>
<td>1.5</td>
<td>2.37</td>
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<tr>
<td>Male</td>
<td>Male</td>
<td>median 14.8 y</td>
<td>1267/5899</td>
<td>0.215</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.84</td>
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<td>Female</td>
<td>Female</td>
<td>median 14.8 y</td>
<td>1003/6368</td>
<td>0.158</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>2.24</td>
<td>1.28</td>
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<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
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<td>Exposure ranges</td>
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<td>Non-Hispanic White</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1253/2269</td>
<td>0.552</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.91</td>
<td>1.45</td>
<td>2.52</td>
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<td>Non-Hispanic Black</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>527/1540</td>
<td>0.342</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.74</td>
<td>1.08</td>
<td>2.8</td>
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<tr>
<td>Mexican American</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>449/1859</td>
<td>0.241</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>2.28</td>
<td>1.05</td>
<td>4.97</td>
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<tr>
<td>Hypertensive</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1155/NR</td>
<td>--</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>2.09</td>
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<tr>
<td>Non-hypertensive</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1115/NR</td>
<td>--</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>2.00</td>
<td>1.37</td>
<td>2.91</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
CVD mortality

Sodium intake and CVD mortality

A total of 12 studies\textsuperscript{41, 87, 100, 111, 127, 168, 204, 205, 240, 247, 263, 282} that reported analyses examining the associations between sodium intake levels and CVD mortality outcome were included. These studies analyzed data from nine studies among generally healthy adult populations,\textsuperscript{41, 87, 111, 127, 168, 204, 247, 263, 282} and three studies among people with existing diseases such as hypertension,\textsuperscript{240} Type 2 DM,\textsuperscript{100} and CVD.\textsuperscript{205}

Eight prospective cohort studies,\textsuperscript{41, 87, 127, 168, 204, 247, 263, 282} and one case-cohort study\textsuperscript{111} examined the associations between sodium intake levels and CVD mortality among generally healthy adult populations. These studies included eight cohorts, which are the combined FLEMENGO and EPOGH cohort,\textsuperscript{247} a population-based cohort in south-western Finland,\textsuperscript{263} PURE cohort,\textsuperscript{204} PURE South America cohort,\textsuperscript{168} the Rotterdam study,\textsuperscript{111} NHANES I,\textsuperscript{41, 127} NHANES II Mortality study,\textsuperscript{87} and NHANES III.\textsuperscript{282} Study populations overlap between the PURE and PURE South America cohorts.\textsuperscript{168, 204} The other 10 studies analyzed data from nine non-overlapping cohorts (two studies analyzed data from NHANES I\textsuperscript{41, 127}) across European countries and the U.S. All studies included adult men and women at baseline (mean ages ranged from 40.9 to 69.2 years). Mean or median follow-up time ranged from 3.7 to 19 years.

Sodium intake levels were assessed by 24-hour urinary sodium excretion in two studies,\textsuperscript{247, 263} by spot-urine samples in three studies,\textsuperscript{111, 168, 204} by 24-hour dietary recalls in four studies.\textsuperscript{41, 87, 127, 282} The sodium intake ranged from 95 mmol/d (2176 mg/d) to 365 mmol/d (8395 mg/day). Individual study results are shown in Figure 28 and Table 6.

Overall Results

The relationships between sodium intake levels and CVD mortality are inconsistent among the five studies that examined urinary sodium levels and CVD mortality outcomes.\textsuperscript{111, 168, 204, 247, 263} Of these, two studies examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of CVD mortality and showed conflicting results.\textsuperscript{247, 263} Two multi-country studies had overlapping study populations and both showed a U- or J-shaped association between 24-hour urinary sodium excretion estimated by Kawasaki equation and CVD mortality.\textsuperscript{168, 204} but the third study showed no significant linear relationship.\textsuperscript{111} Four studies that analyzed NHANES I, II, and III also showed inconsistent results for the relationship between dietary sodium intake and CVD mortality outcome.\textsuperscript{41, 87, 127, 282} All studies controlled for various demographics, lifestyle factors, and medical history or medications. Among these, the FLEMENGO and EPOGH cohort study,\textsuperscript{247} and the Rotterdam study\textsuperscript{111} also adjusted for urinary potassium excretion in their analyses. The strength of evidence was rated insufficient for both linear and non-linear associations between sodium intake levels and CVD mortality outcome primarily because the findings are inconsistent and the overall risk of bias was rated high. Indirect comparisons across studies with wide ranges of sodium intake levels (as opposed to analyses within single studies with wide ranges of intake) suggest a non-linear association between sodium intake levels and CVD mortality outcome; however, data are insufficient to determine an optimal intake level or exact shape of the non-linear association due to limitations and heterogeneity in the sodium exposure assessment methods across studies.
Urinary Sodium Excretion and CVD Mortality

Twenty four-hour Urinary Excretion
Two studies examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of CVD mortality and showed conflicting results.\textsuperscript{247,263} Specifically, the FLEMENGHO and EPOGH cohort study\textsuperscript{247} found a significant inverse association between CVD mortality and tertiles of baseline 24-hour urinary sodium excretion levels (p=0.02; n=3681), and the low tertile (median = 95 mmol/d in women; 120 mmol/d in men) was associated with a significantly increased risk of CVD mortality (adjusted HR = 1.56; 95% CI 1.02, 2.36). The medium (median = 150 mmol/d in women; 189 mmol/d in men) and high (median = 291 mmol/d in women; 232 mmol/d in men) tertiles of 24-hour urinary sodium excretion were not significantly associated with the risks for CVD mortality (adjusted HR [95% CI] = 1.05 [0.72, 1.53] and 0.95 [0.66, 1.38], respectively). These analyses compared the risk in each tertile with the overall risk in the whole study population using multiple Cox regression and deviation from mean coding. This approach allows computation of CIs for the hazard ratio (HR) in each tertile without definition of an arbitrary reference group. On the contrary, a Finnish cohort study by Tuomilehto et al. (2001)\textsuperscript{263} showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of CVD mortality at followup (adjusted HR per 100 mmol/d increase = 1.36; 95% CI 1.05, 1.76; n=2436). The results were similar in subgroup analyses (by sex or by overweight status [normal vs. overweight] status although not statistically significant in women and in normal weight subgroups.

Estimated 24-hour urinary sodium excretion
The association between estimated 24-hour urinary sodium excretion and CVD mortality was examined in three studies.\textsuperscript{111,168,204} Among these, two studies had overlapping study populations.\textsuperscript{168,204} The analyses using PURE cohort (n=101945)\textsuperscript{204} and PURE South America cohort (n=16549)\textsuperscript{168} both showed that highest quintile of urinary sodium excretion (>365 mmol/d) was associated with a significantly increased risk of CVD mortality (adjusted HR [95% CI] = 1.54 [1.21, 1.95] and 1.72 [1.24, 2.4], respectively), but the level of urinary sodium excretion used as the reference group was 4 to 5.99 g/day (median = 217 mmol/d) in PURE cohort and was 5 to 5.99 g/day (median = 239 mmol/d) in PURE South America cohort. The lowest quintile of urinary sodium excretion (<104 mmol/d) was also associated with a significantly increased risk of CVD mortality in the PURE cohort (adjusted HR = 1.77; 95% CI 1.36, 2.13) but not statistically significant in the PURE South America cohort (adjusted HR = 1.2; 95% CI 0.86, 1.65) possibly due to smaller sample sizes. The third study is the Rotterdam study, which showed a non-significant relationship between estimated 24-hour urinary excretion based on an overnight urine sample and CVD mortality outcome (adjusted RR = 0.77 per SD increase; 95% CI 0.60, 1.01; n=5531).\textsuperscript{111}

Dietary Sodium Intake and CVD Mortality
Four studies analyzed data from three cohorts (NHANES I,\textsuperscript{41,127} NHANES II,\textsuperscript{87} and NHANES III\textsuperscript{282}) to examine the relationship between dietary sodium intake and CVD mortality outcome. Results were inconsistent across studies. The studies that analyzed data from NHANES I and II follow-up cohorts, which enrolled U.S. representative sample from 1971 to 1975 and from 1976 to 1980 respectively, showed an inverse relationship between dietary sodium intake and CVD mortality.\textsuperscript{41,87,127} In contrast, the studies that analyzed data from the NHANES III
follow-up cohort, which enrolled a US representative sample from 1988 to 1994, did not find a significant relationship between dietary sodium intake and CVD mortality.\textsuperscript{282}

In the NHANES I follow-up study, the mean dietary sodium intake was 2515 mg/day (109 mmol/d) in men and 1701 mg/day (74 mmol/d) in women, and higher dietary sodium intake levels were associated with lower risks of CVD mortality (adjusted HR = 0.89 per SD [1313 mg or 57 mM] increase; 95% CI 0.77, 1.02; n=11346).\textsuperscript{41} However, subgroup analyses by overweight status showed a significant positive association among overweight adults (adjusted RR 1.32 per 100mM increase; 95% CI 1.16, 1.50; n=2688), but not among normal weight adults (adjusted RR 0.98 per 100mM increase; 95% CI 0.88, 1.09; n=6797).\textsuperscript{127} In the NHANES II follow-up study, the mean dietary sodium intake was 2719 mg/day (118 mmol/d), and higher dietary sodium intake levels were associated with lower risks of CVD mortality (adjusted HR = 0.89 per 1000 mg increase; 95% CI 0.80, 0.99; n=7154).\textsuperscript{87} Furthermore, when compared to dietary sodium intake level ≥2300 mg/day, sodium intake <2300 mg/d was significantly associated with an increased risk of CVD mortality (adjusted HR = 1.40; 95% CI 1.10, 1.70). In the NHANES III follow-up study, the median dietary sodium intake was 3434 mg/day (149 mmol/d), and dietary sodium intake levels were not significantly associated with risks of CVD mortality for both categorical and continuous analyses (adjusted HR = 0.94 per 1000 mg increase; 95% CI 0.67, 1.32; n=12267).\textsuperscript{282} There were no significant interactions by sex, race/ethnicity, or presence of hypertension.
Figure 28. Categorical analysis of the association between urinary and dietary sodium levels and CVD mortality outcome in generally healthy populations.
Table 6. Continuous analyses of the association between sodium levels and CVD mortality outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
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<tbody>
<tr>
<td>Tuomilehto, 2001</td>
<td>All</td>
<td>Both</td>
<td>up to 13 years</td>
<td>180/2436</td>
<td>0.034</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83) in men &amp; 162 (SD 62) mmol/d in women</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.36</td>
<td>1.05</td>
<td>1.76</td>
</tr>
<tr>
<td>Geleijnse, 2007</td>
<td>Male</td>
<td>Male</td>
<td>up to 13 years</td>
<td>136/1173</td>
<td>0.061</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.38</td>
<td>1.04</td>
<td>1.82</td>
</tr>
<tr>
<td>Female</td>
<td>Female</td>
<td>Female</td>
<td>up to 13 years</td>
<td>44/1263</td>
<td>0.012</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 162 (SD 62)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.43</td>
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<td>Normal weight</td>
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<td>Male</td>
<td>up to 13 years</td>
<td>60/659</td>
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<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.23</td>
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<td>Male</td>
<td>up to 13 years</td>
<td>76/514</td>
<td>0.0837</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.44</td>
<td>1.02</td>
<td>2.04</td>
</tr>
<tr>
<td>Geleijnse, 2007</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.039</td>
<td>Estimated 24-hour urinary sodium excretion (spot urine)</td>
<td>117 (SD 69) mmol/d in a random sample</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.77</td>
<td>0.60</td>
<td>1.01</td>
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<td>He, 1999</td>
<td>Both</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary sodium excretion (spot urine)</td>
<td>NR</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.83</td>
<td>0.47</td>
<td>1.44</td>
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<td>He, 1999</td>
<td>Non-overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/6797</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100-mM increase</td>
<td>RR</td>
<td>1.00</td>
<td>0.84</td>
<td>1.19</td>
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<td>Author, Year Cohort name</td>
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<td>Overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/2688</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100-mM increase</td>
<td>RR</td>
<td>1.45</td>
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<td>1.75</td>
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<td>All</td>
<td>Both</td>
<td>ND</td>
<td>ND/11346</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>Mean 2515 mg/d in men and 1701 mg/d in women</td>
<td>per SD (1313 mg) increase</td>
<td>HR</td>
<td>0.89</td>
<td>0.77</td>
<td>1.02</td>
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<td>Cohen, 2006 NHANES II</td>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>1343/7154</td>
<td>0.188</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 (SD 23) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.89</td>
<td>0.80</td>
<td>0.99</td>
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<td>Yang, 2011 NHANES III</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>2270/12267</td>
<td>0.185</td>
<td>Dietary sodium intake</td>
<td>Median 3434 (IQR 2641-4384) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.94</td>
<td>0.67</td>
<td>1.32</td>
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<td>Male</td>
<td>Male</td>
<td>median 14.8 y</td>
<td>1267/5899</td>
<td>0.215</td>
<td>Dietary sodium intake</td>
<td>Median 4165 (IQR 3390-5043) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.17</td>
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</tr>
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<td>Female</td>
<td>Female</td>
<td>median 14.8 y</td>
<td>1003/6368</td>
<td>0.158</td>
<td>Dietary sodium intake</td>
<td>Median 2838 (IQR 2252-3521) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.69</td>
<td>0.38</td>
<td>1.25</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1253/2269</td>
<td>0.552</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.89</td>
<td>0.58</td>
<td>1.37</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>527/1540</td>
<td>0.342</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.81</td>
<td>0.51</td>
<td>1.28</td>
<td></td>
</tr>
<tr>
<td>Mexican American</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>449/1859</td>
<td>0.241</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.33</td>
<td>0.75</td>
<td>2.35</td>
<td></td>
</tr>
<tr>
<td>Author, Year Cohort name</td>
<td>Subgroup</td>
<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric</td>
<td>Estimate</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
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</tr>
<tr>
<td>Hypertensive Both median 14.8 y 1155/NR -- Dietary sodium intake NR per 1000 mg/d increase HR 0.86 0.56 1.31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-hypertensive Both median 14.8 y 1115/NR -- Dietary sodium intake NR per 1000 mg/d increase HR 1.05 0.69 1.59</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile rage; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Sodium/Potassium Ratio and CVD Mortality

A total of four studies\textsuperscript{111, 207, 247, 282} that reported analyses examining the associations between sodium to potassium ratio (Na-K ratio) and cardiovascular disease (CVD) mortality outcome were included. These studies analyzed data from 4 non-overlapping cohorts among generally healthy adult populations.

Three prospective cohort studies\textsuperscript{207, 247, 282} and one case-cohort study\textsuperscript{111} examined the associations between levels of Na-K ratio and CVD mortality among generally healthy adult populations. The cohorts included in these studies are the combined FLEMENGHO and EPOGH cohort,\textsuperscript{247} NHANES III,\textsuperscript{282} NIPPON DATA80,\textsuperscript{207} and the Rotterdam Study.\textsuperscript{111} All studies included both adult men and women. Mean age was reported to be in the 40s for two of the studies (FLEMENGHO/EPOGH and NIPPON DATA80), and 76.8 years for the cases in the Rotterdam Study; the NHANES III study did not report mean age but included participants \(>20\) years of age. Mean or median follow-up time ranged from 5 years to 24 years.

Na-K ratios were assessed by 24-hour urinary excretion in one study,\textsuperscript{247} by spot urine (estimated 24-hour urinary excretion) in one study,\textsuperscript{111} by 24-hour dietary recall in one study,\textsuperscript{282} and by 3-day weighed food records in one study.\textsuperscript{207} Individual study results are shown in Figure 29 and Table 7.

Overall Results

The relationships between levels of Na-K ratio and CVD mortality outcome are inconsistent among the two studies that examined urinary Na-K ratios and CVD mortality outcome.\textsuperscript{111, 247} However, both studies that assessed dietary Na-K intake showed significant and positive linear associations with CVD mortality.\textsuperscript{207, 282} All studies controlled for various demographic, clinical, and lifestyle factors. The overall risk of bias was rated as low to moderate.

Urinary Sodium/Potassium Ratio and CVD mortality

Two studies that examined urinary Na-K ratios and CVD mortality outcome reported inconsistent results. The FLEMENGHO/EPOGH study reported a significant inverse linear trend \((p=.0069; n=3681)\) using tertiles of Na-K ratio, with higher risk of CVD mortality occurring in the lower tertiles of Na-K ratio when each tertile was compared to the overall risk in the whole cohort.\textsuperscript{247} In the Rotterdam study, however, no relationship was observed between Na-K ratio and CVD mortality in the full case-cohort, in subjects free of CVD and hypertension at baseline, or in CVD-free subjects with a BMI \(\geq25\text{ kg/m}^2\).\textsuperscript{111}

Dietary Sodium/Potassium Ratio and CVD mortality

The two studies that assessed dietary Na-K ratio reported consistent significant associations with CVD mortality.\textsuperscript{207, 282} In NHANES, the risk of CVD mortality increased with increasing quartile of Na-K ratio among the whole cohort \((p\text{ for trend }=.01; n=12267)\).\textsuperscript{282} In addition, a significant linear association between continuous Na-K ratio and CVD mortality was reported among the whole cohort \((HR = 1.90; 95\% \text{ CI 1.20, 3.03})\). In subgroup analyses, significant linear associations were found in men, but not in women; in non-Hispanic Blacks and Mexican-Americans, but not in non-Hispanic Whites; and in both hypertensives and non-hypertensives. In the NIPPON DATA80 cohort, significant linear \((\text{age-adjusted model: } p=.032; n=8283)\) and quadratic non-linear \((\text{fully adjusted model: } p=.005)\) trends were found between...
quintiles of Na-K ratio and CVD mortality.\textsuperscript{207} Those in the highest quintile of Na-K ratio had a significantly increased risk of CVD mortality compared to those in the lowest quintile (adjusted HR = 1.39; 95% CI 1.20, 1.61).

Figure 29. Categorical analysis of the association between sodium levels and CVD mortality outcome in generally healthy populations.
<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geleijnse, 2007\textsuperscript{11} Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>217/5531</td>
<td>0.039</td>
<td>Estimated 24-Hour Urinary Excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>RR</td>
<td>0.92</td>
<td>0.80</td>
<td>1.07</td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>RR</td>
<td>0.91</td>
<td>0.65</td>
<td>1.27</td>
</tr>
<tr>
<td>CVD free and BMI ≥25 kg/m\textsuperscript{2}</td>
<td>Both</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/NR</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mmol)</td>
<td>RR</td>
<td>0.86</td>
<td>0.60</td>
<td>1.25</td>
</tr>
<tr>
<td>Yang, 2011\textsuperscript{12} NHANES III</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>825/12267</td>
<td>0.067</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.90</td>
<td>1.20</td>
<td>3.03</td>
</tr>
<tr>
<td>Male</td>
<td>Male</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>437/5899</td>
<td>0.074</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>2.24</td>
<td>1.11</td>
<td>4.52</td>
</tr>
<tr>
<td>Female</td>
<td>Female</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>388/6368</td>
<td>0.061</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.74</td>
<td>0.73</td>
<td>4.14</td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>498/2269</td>
<td>0.219</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.66</td>
<td>0.93</td>
<td>2.95</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>163/1540</td>
<td>0.106</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.93</td>
<td>1.05</td>
<td>3.57</td>
</tr>
<tr>
<td>Author, Year Cohort name</td>
<td>Subgroup</td>
<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric Estimate</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
<td></td>
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</tr>
<tr>
<td>Mexican American</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>147/1859</td>
<td>0.079</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>5.88</td>
<td>1.67</td>
<td>20.68</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>490/NR</td>
<td>--</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>2.40</td>
<td>1.09</td>
<td>5.31</td>
<td></td>
</tr>
<tr>
<td>Non-hypertensive</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>335/NR</td>
<td>--</td>
<td>Dietary sodium/potassium intake</td>
<td>NR</td>
<td>per 1-unit increase (mg/mg)</td>
<td>HR</td>
<td>1.95</td>
<td>1.00</td>
<td>3.80</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Other CVD outcomes

Sodium intake
Two publications\textsuperscript{126, 210} reported analyses examining the associations between sodium intake levels and other CVD outcomes among generally healthy adult populations. The two studies are the EPIC-Norfolk prospective cohort study\textsuperscript{210} and the NHANES I follow-up study.\textsuperscript{126} Both studies included both adult men and women at baseline and reported heart failure outcomes. Mean or median follow-up times were 12.9 and 19 years. Sodium intake levels were assessed by spot-urine samples in one study,\textsuperscript{210} and by 24-hour dietary recall in another.\textsuperscript{126} The sodium intake ranged from 33.7 mmol/d (775 mg/d) to 229 mmol/d (5272 mg/d). Individual study results are shown in Figure 30.

Urinary Sodium Excretion and Other CVD Outcomes

Estimated 24-hour urinary sodium excretion
The EPIC-Norfolk prospective cohort study (n=19857)\textsuperscript{210} showed a U-shaped relationship between 24-hour urinary sodium excretion levels (estimated by Tanaka equation) and risks of heart failure, using the second quintile level of urinary sodium excretion as the reference group (128 to 148 mmol/d). Specifically, both lowest (≤127 mmol/d) and highest (≥191 mmol/d) quintiles of estimated urinary sodium excretion levels were associated with a significant increased risk of heart failure (adjusted HR [95% CI] = 1.30 [1.08, 1.55] and 1.22 [1.06, 1.46] in the multivariable model including blood pressure as covariates. Similar U-shaped relationships were shown in men and in women. The overall risk of bias was rated moderate.

Dietary Sodium Intake and Other CVD Outcome
NHANES I follow-up study showed no associations between dietary sodium intake levels and risks of congestive heart failure (CHF) among non-overweight adults (n=5233), but showed that highest quartile of dietary sodium intake level (mean = 167.6 mmol/d) was significantly associated with an increased risk of CHF (adjusted HR = 1.43; 95% CI 1.01, 1.91) compared to the lowest intake level (mean = 33.7 mmol/d) among overweight adults (n=5129).\textsuperscript{6138} In continuous analyses, relative risk of CHF for a 100-mmol/d higher intake of sodium was 0.90 (95% CI, 0.67, 1.20) among non-overweight adults, and 1.26 (95% CI, 1.03, 1.53) among overweight adults.
Figure 30. Categorical analysis of the association between urinary or dietary sodium levels and heart failure outcome in generally healthy populations.
Coronary Heart Disease Mortality

Sodium Intake and Coronary Heart Disease Mortality

A total of five publications that analyzed the associations between sodium intake levels and coronary heart disease (CHD) or ischemic heart disease (IHD) mortality outcome met inclusion criteria. These publications analyzed data from five non-overlapping studies among generally healthy adult populations.

Five prospective cohort studies examined the associations between sodium intake levels and CHD or IHD mortality outcomes among generally healthy adult populations. These cohorts are the Scottish Heart Health study, a population-based cohort study set in south-western Finland, the NHANES I Mortality study, and NHANES III. All studies included both adult men and women at baseline (mean ages ranged from 43 to 48 years). Mean or median follow-up times ranged from 7.6 to 19 years.

Sodium intake levels were assessed by 24-hour urinary sodium excretion in two studies, and by 24-hour dietary recall in three studies. The sodium intake ranged from 68 mmol/d (1564 mg/d) to 253 mmol/d (5826 mg/d). Individual study results are shown in Figure 31 and Table 8.

Overall Results

The relationships between sodium intake levels and CHD or IHD mortality outcomes are inconsistent between the two studies that examined urinary sodium levels and CHD mortality. The other three studies mostly showed non-significant results for relationship between dietary sodium intake and CHD or IHD mortality outcome. Except for the Scottish Heart Health study, all studies controlled for various demographics, lifestyle factors, and medical history or medications. The Scottish Heart Health study adjusted only for age in their analyses, so the results may be at increased risk for confounding. The overall risk of bias was rated moderate. The strength of evidence was rated insufficient, primarily because of imprecision and inconsistent findings across studies.

Urinary Sodium Excretion and CHD Mortality

24-hour urinary sodium

Two studies that examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of CHD mortality showed inconsistent results. The Scottish Heart Health study adjusted only for age in their analyses so the results may be at higher risk for confounding. Specifically, the Scottish Heart Health study reported that baseline 24-hour urinary sodium excretion levels were positively associated with risks of CHD mortality in women (age-adjusted HR 0.36, 0.41, 0.85, 2.05 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875), but not in men (age-adjusted HR 0.96, 0.62, 0.97, 10.92, comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754), whereas a Finnish cohort study by Tuomilehto and colleagues (2001) showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of CHD mortality at the followups (adjusted HR 1.56; 95% CI 1.15, 2.12; n=2436). The positive association between 24-hour urinary sodium excretion and CHD mortality was significant only in men (adjusted HR = 1.55; 95% 1.12, 2.13; n=1263), but not in women (adjusted HR 2.07; 95% 0.80, 5.36; n=1263).
Dietary Sodium Intake and CHD Mortality

Three studies analyzed data from the NHANES I,\textsuperscript{127} NHANES II,\textsuperscript{87} and NHANES III.\textsuperscript{282} cohorts to examine the relationship between dietary sodium intake and CHD or IHD mortality. Results were mostly not statistically significant, except for a subgroup analysis of the NHANES I cohort that found that higher dietary sodium intake levels were significantly associated with higher risks of CHD mortality (see response to Key Question 4c).\textsuperscript{127}

In the NHANES I follow-up study, subgroup analyses by overweight status showed that the association between dietary sodium intake levels and CHD mortality was significant among overweight adults (adjusted RR 1.29 per 100 mM increase; 95% CI 1.01, 1.64; n=2688), but not among non-overweight adults (adjusted RR 1.07 per 100 mM increase; 95% CI 0.89, 1.28; n=6797).\textsuperscript{127} The interaction between sodium intake and body weight (non-overweight vs. overweight) was not statistically significant (p for interaction = 0.22). In the NHANES II follow-up study, the mean dietary sodium intake was 2719 mg/day (118 mmol/d), and higher dietary sodium intake levels were not significantly associated with risks of CHD mortality (adjusted HR 0.91 per 1000 mg increase; 95% CI 0.79, 1.05; n=7154).\textsuperscript{87} Additionally, when compared to dietary sodium intake levels of 2300 mg/day or more, sodium intakes less than 2300 mg/d were not significantly associated with CHD mortality (adjusted HR 1.21; 95% CI 0.87, 1.68). In the NHANES III follow-up study, the median dietary sodium intake was 3434 mg/day (149 mmol/d), and dietary sodium intake levels were not significantly associated with risk of IHD mortality for either categorical or continuous analyses (adjusted HR 1.20 per 1000 mg increase; 95% CI 0.80, 1.77; n=12267).\textsuperscript{282}

Figure 31. Categorical analysis of the association between urinary or dietary sodium levels and CHD mortality outcome in generally healthy populations.
Table 8. Continuous analyses of the association between sodium levels and CHD mortality outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuomilehto, 2001[^263]</td>
<td>All</td>
<td>Both</td>
<td>up to 13 years</td>
<td>61/2436</td>
<td>0.025</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83) in men &amp; 162 (SD 62) mmol/d in women</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.56</td>
<td>1.15</td>
<td>2.12</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Male</td>
<td>up to 13 years</td>
<td>54/1173</td>
<td>0.046</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.55</td>
<td>1.12</td>
<td>2.13</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Female</td>
<td>up to 13 years</td>
<td>7/1263</td>
<td>0.006</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 162 (SD 62)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>2.07</td>
<td>0.8</td>
<td>5.36</td>
</tr>
<tr>
<td>He, 1999[^27] NHANES I</td>
<td>Non-overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/6797</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100-mmol increase</td>
<td>RR</td>
<td>1.07</td>
<td>0.89</td>
<td>1.28</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/2688</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100-mmol increase</td>
<td>RR</td>
<td>1.29</td>
<td>1.01</td>
<td>1.64</td>
</tr>
<tr>
<td>Cohen, 2006[^87] NHANES II</td>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>282/7154</td>
<td>0.039</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 (SD 23) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.91</td>
<td>0.79</td>
<td>1.05</td>
</tr>
<tr>
<td></td>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>282/7154</td>
<td>0.039</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 mg/d</td>
<td>&lt;2300 mg/d vs. ≥2300 mg/d</td>
<td>HR</td>
<td>1.21</td>
<td>.87</td>
<td>1.68</td>
</tr>
<tr>
<td>Yang, 2011[^282] NHANES III</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>2270/12267</td>
<td>0.185</td>
<td>Dietary sodium intake</td>
<td>Median 3434 (IQR 2641-4384) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.20</td>
<td>0.81</td>
<td>1.77</td>
</tr>
</tbody>
</table>
Sodium/Potassium Ratio and CHD Mortality

One study[^282] that examined the association between Na-K ratio and IHD mortality was identified. This study analyzed data from the NHANES III cohort, a generally healthy adult population.

The NHANES III cohort included both adult men and women. Mean age was not reported, but the cohort included participants over 20 years of age. Median followup time was 14.8 years in this study. Na-K ratios were assessed by 24-hour dietary recall. The study results are shown in Figure 32.

Findings for Dietary Sodium/Potassium Ratio and CHD/IHD Mortality

The risk of IHD mortality increased with increasing quartile of Na-K ratio among the whole cohort (p for trend <.001; n=12267). In addition, a significant linear association between continuous Na-K ratio and IHD mortality was reported among the whole cohort (HR = 3.66; 95% CI 1.94, 6.90).

Figure 32. Categorical analysis of the association between sodium to potassium ratio and IHD mortality outcome in generally healthy populations.

Sodium and Stroke

Sodium intake and Stroke

A total of 10 studies[^40,87,111,127,151,189,204,205,247,263] that analyzed associations between sodium intake levels and stroke outcome were included. These studies analyzed data from seven studies among generally healthy adult populations[^87,111,127,151,204,247,263] and three studies among people with pre-existing diseases such as hypertension[^40], CKD, and CVD[^205].

Six prospective cohort studies[^87,127,151,204,247,263] and one case-cohort study[^111] examined the associations between sodium intake levels and stroke among generally healthy adult populations. These studies included seven non-overlapping cohorts, which are the combined FLEMENGHO and EPOGH cohort[^247], a population-based cohort in south-western Finland[^263], the PURE cohort[^204], the Rotterdam study[^111], the Hawaiian study cohort[^151], NHANES I[^127] and the
NHANES I Mortality study. Except for the Hawaiian study cohort, all studies included both adult men and women at baseline (mean ages ranged from 40.9 to 69.2 years). The Hawaiian study cohort enrolled men of Japanese ancestry (mean age = 54.3 years). Mean or median follow-up times ranged from 3.7 to 19 years.

Sodium intake levels were assessed by 24-hour urinary sodium excretion in two studies, by spot-urine samples in two studies, and by 24-hour dietary recalls in three studies. The sodium intake ranged from 62 mmol/d (1424 mg/d) to 365 mmol/d (8395 mg/day). Individual study results are shown in Figure 33 and Table 9.

Overall Results

The relationships between sodium intake levels and stroke were mostly not significant among the four studies that examined urinary sodium levels and stroke, except for one large multi-country study that showed that the lowest quintile (<2 g/d) of 24-hour urinary sodium excretion (estimated by Kawasaki equation) was associated with an increased risk of stroke, but the second quintile of urinary sodium excretion (3.0-3.99 g/d or median = 152 mmol/d) was associated with a reduced risk of stroke. However, this study was rated high risk of bias for sodium exposure assessment method. The associations between dietary sodium intake and stroke were also non-significant in two studies; a third study showed that higher sodium intake levels were significantly associated with higher risks of stroke among overweight adults, but not among non-overweight adults. Except for the Hawaiian study, all studies controlled for various demographics, lifestyle factors, and medical history or medications. Among these, the FLEMEGHO and EPOGH cohort studies did not find significant associations between risks of fatal and nonfatal stroke and tertiles of baseline 24-hour urinary sodium excretion levels (adjusted HR 1.07, 95% CI 0.58, 2.0, 1.29 [0.74, 2.2], and 0.78 [0.45, 1.33] in the low, median, and high sodium excretion tertiles; n=3681). These analyses compared the risk in each tertile with the overall risk in the whole study population using multiple Cox regression and deviation from mean coding. This approach allows computation of CIs for the HR in each tertile without definition of an arbitrary reference group. Furthermore, a Finnish cohort study by Tuomilehto et al. (2001) also did not find a significant relationship between baseline 24-hour urinary sodium excretion and stroke at followup (adjusted HR per 100 mmol/d increase = 1.13; 95% CI 0.84, 1.51; n=2436). The results were similar in subgroup analyses by sex.

Urinary Sodium Excretion and Stroke

Two studies examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of stroke: Both showed non-significant results. Specifically, the FLEMEGHO and EPOGH cohort studies did not find significant associations between risks of fatal and nonfatal stroke and tertiles of baseline 24-hour urinary sodium excretion levels (adjusted HR 1.07, 95% CI 0.58, 2.0, 1.29 [0.74, 2.2], and 0.78 [0.45, 1.33] in the low, median, and high sodium excretion tertiles; n=3681). These analyses compared the risk in each tertile with the overall risk in the whole study population using multiple Cox regression and deviation from mean coding. This approach allows computation of CIs for the HR in each tertile without definition of an arbitrary reference group. Furthermore, a Finnish cohort study by Tuomilehto et al. (2001) also did not find a significant relationship between baseline 24-hour urinary sodium excretion and stroke at followup (adjusted HR per 100 mmol/d increase = 1.13; 95% CI 0.84, 1.51; n=2436). The results were similar in subgroup analyses by sex.

The association between estimated 24-hour urinary sodium excretion and stroke outcome was examined in two studies. The PURE cohort(n=101945) found that the lowest quintile of urinary sodium excretion (<3 g/d) was associated with an increased risk of stroke but the second quintile of urinary sodium excretion (3.0-3.99 g/d or median = 152 mmol/d) was associated with a reduced risk of stroke (adjusted HR 1.39, 95% CI 1.21, 1.95 and 1.72, 1.24, 2.4, respectively), compared to the third quintile level (4 to 5.99 g/day or median 217
mmol/d).\textsuperscript{204} No significant associations were observed between the fourth and the highest quintiles of urinary sodium excretion (6-6.99 g/d and >7 g/d) and risks of stroke compared to the third quintile level as the reference group. The Rotterdam study showed no significant linear relationship between levels of estimated 24-hour urinary excretion (based on an overnight urine sample) and risks of stroke (adjusted RR 1.08 per SD increase; 95% CI 0.80, 1.46; n=5531).\textsuperscript{111}

**Dietary Sodium Intake and Stroke**

Three studies analyzed data from three cohorts (NHANES I,\textsuperscript{127} NHANES II,\textsuperscript{87} and the Hawaiian study cohort of men of Japanese ancestry\textsuperscript{151}) to examine the relationship between dietary sodium intake and stroke, and mostly showed non-significant results except for a subgroup analysis by overweight status.

In NHANES I (n=6797), a subgroup analysis by overweight status showed that higher sodium intake levels were significantly associated with higher risks of stroke among overweight adults (adjusted RR 1.39 per 100 mM increase; 95% CI 1.09, 1.77; n=2688), but not among non-overweight adults (adjusted RR 0.99 per 100 mM increase; 95% CI 0.81, 1.21).\textsuperscript{127} The interaction between sodium intake and body weight (non-overweight vs. overweight) was significant (p for interaction =0.03) In the NHANES II follow-up study, the mean dietary sodium intake was 2719 mg/day (118 mM/day). This study showed no significant associations between dietary sodium intake levels and risks of stroke (adjusted HR 0.95 per 1000 mg increase; 95% CI 0.75, 1.21; n=7154).\textsuperscript{87} Compared to dietary sodium intake levels ≥2300 mg/day, sodium intake <2300 mg/d was associated with a non-significant increased risk of stroke (adjusted HR 1.78, 95% CI 0.89, 3.66). In the Hawaiian study cohort of men of Japanese ancestry (n=8006), the age-adjusted stroke incidences were similar across quartiles of dietary sodium intake levels (median = 2.39-3.01 g/d).\textsuperscript{151}

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**Figure 33. Categorical analysis of the association between urinary sodium levels and stroke outcome in generally healthy populations.**

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Table 9. Continuous analyses of the association between sodium levels and stroke outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuomilehto, 2001</td>
<td>All</td>
<td>Both</td>
<td>up to 13 years</td>
<td>84/2420</td>
<td>0.035</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83) in men &amp; 162 (SD 62) mmol/d in women</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.13</td>
<td>0.84</td>
<td>1.51</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Male</td>
<td>up to 13 years</td>
<td>43/1161</td>
<td>0.038</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.00</td>
<td>0.68</td>
<td>1.47</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Female</td>
<td>up to 13 years</td>
<td>41/1259</td>
<td>0.033</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 162 (SD 62)</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.34</td>
<td>0.87</td>
<td>2.07</td>
</tr>
<tr>
<td>Geleijnse, 2007 Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.039</td>
<td>Estimated 24-hour urinary sodium excretion (spot urine)</td>
<td>117 (SD 69) mmol/d in a random sample</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.08</td>
<td>0.80</td>
<td>1.46</td>
</tr>
<tr>
<td></td>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary sodium excretion (spot urine)</td>
<td>NR</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.02</td>
<td>0.66</td>
<td>1.58</td>
</tr>
<tr>
<td>Kagan,1985 Hawaiian study cohort</td>
<td>Japanese ancestry</td>
<td>Male</td>
<td>10 y</td>
<td>238/8006</td>
<td>0.030</td>
<td>Dietary sodium intake</td>
<td>2.39-3.01 g</td>
<td>Chi-squared for trend across quintiles of sodium intake levels</td>
<td>RR</td>
<td>0.99</td>
<td>0.81</td>
<td>1.21</td>
</tr>
<tr>
<td>He, 1999 NHANES I</td>
<td>Non-overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>NR/6797</td>
<td>NR</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100 mmol increase</td>
<td>RR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Author, Year, Cohort name</td>
<td>Subgroup</td>
<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric</td>
<td>Estimate</td>
<td>Lower 95% CI</td>
<td>upper 95% CI</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>NR/2688</td>
<td>NR</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100-mmol increase</td>
<td>RR</td>
<td>1.39</td>
<td>1.09</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td>Cohen, 2006, NHANES II</td>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>1343/7154</td>
<td>0.188</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 (SD 23) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.95</td>
<td>0.75</td>
<td>1.21</td>
</tr>
<tr>
<td>All</td>
<td>Both</td>
<td>mean 13.7 y</td>
<td>1343/7154</td>
<td>0.188</td>
<td>Dietary sodium intake</td>
<td>Mean 2719 mg/d</td>
<td>&lt;2300 mg/d vs. ≥2300 mg/d</td>
<td>HR</td>
<td>1.78</td>
<td>0.89</td>
<td>3.55</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Sodium/Potassium Ratio and Stroke

A total of four studies that reported analyses examining the association between Na-K ratio and fatal or nonfatal stroke events were included. These studies analyzed data from four non-overlapping cohorts among generally healthy adult populations.

Three prospective cohort studies and one case-cohort study examined the associations between levels of Na-K ratio and stroke among generally healthy adult populations. The cohorts included in these studies are the combined FLEMENGHO and EPOGH cohort, PREVEND, NIPPON DATA80, and the Rotterdam Study. All studies included both adult men and women. Mean age was reported to be in the 40s for all studies, except for the Rotterdam Study, which reported a mean age of 74 years for cases and 69.2 years for controls who were randomly sampled from the cohort. Mean or median follow-up times ranged from 5 years to 24 years.

Na-K ratios were assessed by 24-hour urinary excretion in two studies, by spot urine (estimated 24-hour urinary excretion) in one study, and by 3-day weighed food records in one study. Individual study results are shown in Figure 34 and Table 10.

Overall Results
The three studies that examined urinary Na-K ratios and stroke events found no association. However, these results were not consistent with the results from the study that examined dietary Na-K intake. All studies controlled for various demographic, clinical, and lifestyle factors. The overall risk of bias was rated as low to moderate.

Urinary Sodium/Potassium Ratio and Stroke events (fatal and non-fatal)

Three studies that examined urinary Na-K ratios and stroke outcomes reported consistent lack of association between Na-K ratios and stroke events. In the combined FLEMENGHO and EPOGH cohort, no association was detected between tertiles of Na-K ratio and risk of fatal and non-fatal events due to stroke. In the Rotterdam study, no relationship was observed between Na-K ratio and incidence of fatal or non-fatal stroke events, either in the full case-cohort or in participants who were free of CVD and hypertension at baseline. Finally, in the PREVEND study, no association was observed between continuous or quintiles of Na-K ratio and fatal and non-fatal stroke events.

Dietary Sodium/Potassium Ratio and Stroke Mortality

One study, the NIPPON DATA80 cohort study, assessed the association between quintiles of dietary Na-K ratio and risk of mortality from stroke and found significant linear (age-adjusted model: p=.009; n=8283) and quadratic non-linear (fully adjusted model: p=.002) trends. Those in the highest quintile of Na-K ratio had a significantly increased risk of total stroke mortality compared to those in the lowest quintile (adjusted HR = 1.43; 95% CI 1.17, 1.76).
Figure 34. Categorical analysis of the association between levels of sodium to potassium ratio and stroke outcome in generally healthy populations.
<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kieneker, 2016** PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>1172/7795</td>
<td>0.022</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/m mol)</td>
<td>HR</td>
<td>0.81</td>
<td>0.64</td>
<td>1.02</td>
</tr>
<tr>
<td>Geleijnse, 2007** Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>181/5531</td>
<td>0.033</td>
<td>Estimated 24-Hour Urinary Excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/m mol)</td>
<td>RR</td>
<td>0.99</td>
<td>0.83</td>
<td>1.18</td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>NR</td>
<td>per 1-unit increase (mmol/m mol)</td>
<td>RR</td>
<td>0.90</td>
<td>0.66</td>
<td>1.22</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Myocardial infarction

Sodium intake

A total of two publications\textsuperscript{111, 204} reported analyses examining the associations between sodium intake levels and myocardial infarction (MI) outcome among generally healthy adult populations.

The two studies are the PURE prospective cohort study\textsuperscript{204} and the Rotterdam case-cohort study.\textsuperscript{111} Both studies included both adult men and women at baseline (mean ages were 51 and 69.2 years, respectively). Mean or median follow-up time were 3.7 and 5.5 years. Sodium intake levels were assessed by spot-urine samples in both studies, ranging from 104 mmol/d (2392 mg/d) to 365 mmol/d (8395 mg/d). Individual study results are shown in Figure 35.

Overall Results

The two studies both showed non-significant results for the relationship between estimated 24-hour urinary sodium excretion and MI.\textsuperscript{111, 204} Both studies controlled for various demographics, lifestyle factors, and medical history or medications. One study\textsuperscript{111} also adjusted for urinary potassium excretion in their analyses. The strength of evidence was rated insufficient, primarily because the overall risk of bias was rated high due to the limitations for exposure assessment.

Urinary Sodium Excretion and Myocardial Infarction

Estimated 24-hour urinary sodium excretion

The analyses using the PURE cohort (n=101945)\textsuperscript{204} showed no significant associations between 24-hour urinary sodium excretion levels (estimated by Kawasaki equation) and risks of MI, using the third quintile level of urinary sodium excretion as the reference group (4 to 5.99 g/day; median = 217 mmol/d. The Rotterdam study also showed no significant linear relationship between estimated 24-hour urinary excretion based on an overnight urine sample and MI (adjusted RR = 1.19 per SD increase; 95% CI 0.97, 1.46; n=5531).\textsuperscript{111} Both studies were rated high risk-of-bias due to the limitations for exposure assessment.
Figure 35. Categorical analysis of the association between urinary sodium levels and MI outcome in generally healthy populations.

Sodium to Potassium ratio

One study\textsuperscript{111} that examined the association between Na-K ratio and fatal and non-fatal MI was included. This was a case-cohort analysis from the Rotterdam Study, a population-based study including men and women aged 55 years of age or older. The mean age was 71 years for the cases of incident MI and 69.2 years for the controls who were randomly sampled from the entire cohort. The median follow-up time was 5.5 years. Na-K ratios were assessed by spot urine. No significant linear association was found between estimated 24-hour urinary excretion and incidence of fatal and non-fatal MI among all the subjects (RR = 1.04; 95% CI = 0.93, 1.17) or among subjects free of CVD and hypertension at baseline (RR = 0.91; 95% CI = 0.72, 1.16). The overall risk of bias for this study was rated as moderate.

Combined CVD morbidity and mortality

Sodium intake

A total of seven publications\textsuperscript{88, 93, 155, 168, 184, 204, 247} reported analyses examining the associations between sodium intake levels and combined CVD morbidity and mortality outcome among generally healthy adult populations. These studies included six cohorts: the combined FLEMENGO and EPOGH cohort,\textsuperscript{247} the TOHP (I and II) cohort,\textsuperscript{88, 93} PREVEND,\textsuperscript{155} a pooled analysis of four cohorts (PURE, EPI-DREAM, ONTARGET and TRANSCEND),\textsuperscript{184} the PURE cohort,\textsuperscript{204} and the PURE South America cohort.\textsuperscript{168} The pooled analysis of four cohorts\textsuperscript{184} had overlapping study populations with the PURE cohort\textsuperscript{204} and PURE South America cohort.\textsuperscript{168} All studies included both adult men and women at baseline (mean ages ranged from 40.9 to 58 years). Mean or median follow-up time ranged from 3.7 to 10.5 years.

Sodium intake levels were assessed by 24-hour urinary sodium excretion in four studies,\textsuperscript{88, 93, 155, 247} and by spot-urine samples in three studies.\textsuperscript{168, 184, 204} The sodium intake ranged from 80 mmol/d (1840 mg/d) to 365 mmol/d (8395 mg/d). Individual study results are shown in Figure 36 and Table 11.
**Overall Results**

The relationships between urinary sodium levels and combined CVD morbidity and mortality outcomes are inconsistent. The definitions of CVD morbidity and mortality outcomes are heterogeneous. Of the seven publications, two publications analyzed data from the same studies. (TOHP I and II follow-up study, PREVEND, and the FLEMEN-GHO and EPOGH cohort study) also adjusted for urinary potassium excretion in their analyses. The overall risk of bias was rated moderate. The strength of evidence was rated insufficient primarily due to the limitations in the sodium exposure assessment methods and heterogeneity in outcome definitions.

**Urinary Sodium Excretion and Combined CVD Morbidity and Mortality**

**24-hour urinary sodium**

Three studies (in 4 publications) examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of combined CVD morbidity and mortality outcomes. The results were inconsistent across studies. Specifically, the TOHP (I and II) follow-up study, which enrolled the control groups from the original sodium reduction trials, showed a trend in increasing 24-hour urinary sodium excretion levels with higher risks of total cardiovascular events in categorical analyses or in continuous analyses (adjusted RR per 100 mmol/d increase = 1.42; 95% CI 0.99, 2.04). Although no significant interactions were observed between sex (men vs. women), race (White vs. Black), or obesity (BMI ≥ 30 vs. BMI < 30) and 24-hour sodium excretion levels, the subgroup results showed statistically significantly increased risks of total cardiovascular events in men (adjusted RR per 100 mmol/d increase = 1.26; 95% CI 1.04, 1.53), in Whites (adjusted RR per 100 mmol/d increase = 1.21; 95% CI 1.04, 1.49), and in obese individuals (adjusted RR per 100 mmol/d increase = 1.33; 95% CI 1.05, 1.63). On the contrary, both the FLEMEN-GHO and EPOGH cohort study and PREVEND study showed no significant associations between the baseline 24-hour urinary sodium excretion levels and risks of total cardiovascular events. Specifically, the FLEMEN-GHO and EPOGH cohort study showed that low (median = 95 mmol/d in women; 120 mmol/d in men), medium (median = 150 mmol/d in women; 189 mmol/d in men), and high (median = 291 mmol/d in women; 232 mmol/d in men) tertiles of 24-hour urinary sodium excretion were not significantly associated with the risks for total fatal and nonfatal cardiovascular events (adjusted HR [95% CI] = 1.13 [0.90, 1.42], 1.11 [0.90, 1.42], and 0.90 [0.73, 1.11], respectively; n=3681). These analyses compared the risk in each tertile with the overall risk in the whole study population using multiple Cox regression and deviation from mean coding. This approach allows computation of CIs for the hazard ratio (HR) in each tertile without definition of an arbitrary reference group. The PREVEND study did not find a significant linear relationship between 24-hour urinary sodium excretion levels and risks of composite cardiovascular outcome (adjusted RR per 50 mmol/d increase = 0.97; 95% CI 0.87, 1.08).
Estimated 24-hour urinary sodium excretion

The association between estimated 24-hour urinary sodium excretion and combined CVD morbidity and mortality outcome was examined in three studies.\textsuperscript{168, 184, 204} However, these three studies had overlapping study populations, and showed consistent results. The pooled analysis of four cohorts (PURE, EPIDREAM, ONTARGET and TRANSCEND) from 49 countries showed a U-shaped relationship between baseline levels of 24-hour urinary sodium excretion (estimated by Kawasaki equation) and risks of major CVD events (n=133118), using the median quintile of urinary excretion (195 mmol/d) as the reference group.\textsuperscript{184} That is, compared with urinary sodium excretion of 4 (172 mM) to 5 (215 mM) g/day (median = 195 mmol/d), urinary sodium excretion of 7 (300mM) g/day or more (adjusted HR = 1.21; 95% CI 1.10, 1.34]) and less than 3 g/day (adjusted HR = 1.34; 95% CI 1.23, 1.47) were both associated with increased risk of major CVD events. Similar U-shape relationships were found in subgroup analyses by hypertension status (n=63559 with hypertension and n=69559 without hypertension) although higher urinary sodium excretion levels (5 to 5.99 g/day, 6 to 6.99 g/day, or ≥7 g/day) were not significantly associated with risks of major CVD events among non-hypertensive individuals.\textsuperscript{184} Not surprisingly, the analyses using the PURE cohort (n=101945)\textsuperscript{204} and PURE South America cohort (n=16549)\textsuperscript{168} also showed U-shaped associations, but the level of urinary sodium excretion used as the reference group was different in the PURE cohort (4 to 5.99 g/day; median = 217 mmol/d), and some comparisons were not statically significant due to smaller sample sizes.
Figure 36. Categorical analysis of the association between urinary sodium levels and combined CVD morbidity and mortality outcome in generally healthy populations.
Table 11. Continuous analyses of the association between sodium levels and combined morbidity and mortality outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgrou p</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estim ate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook, 2009&lt;sup&gt;93&lt;/sup&gt; TOHP I &amp; II control groups</td>
<td>All</td>
<td>Both</td>
<td>median 5 y (TOHP I) 4 y (TOHP II)</td>
<td>166/2084</td>
<td>0.080</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 158 (IQR 127-194) mmol/24 hr</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.42</td>
<td>0.99</td>
<td>2.04</td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Male</td>
<td>Median 4-5 y</td>
<td>141/1459</td>
<td>0.097</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 171 mmol/24 hr</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.26</td>
<td>1.04</td>
<td>1.53</td>
</tr>
<tr>
<td></td>
<td>Women</td>
<td>Female</td>
<td>Median 4-5 y</td>
<td>25/625</td>
<td>0.040</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 134 mmol/24 hr</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.21</td>
<td>0.79</td>
<td>1.85</td>
</tr>
<tr>
<td></td>
<td>White</td>
<td>Both</td>
<td>Median 4-5 y</td>
<td>141/1743</td>
<td>0.081</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.21</td>
<td>1.04</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>Black</td>
<td>Both</td>
<td>Median 4-5 y</td>
<td>19/284</td>
<td>0.067</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.86</td>
<td>0.94</td>
<td>3.63</td>
</tr>
<tr>
<td></td>
<td>BMI&lt;30</td>
<td>Both</td>
<td>Median 4-5 y</td>
<td>100/1284</td>
<td>0.078</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.16</td>
<td>0.9</td>
<td>1.49</td>
</tr>
<tr>
<td></td>
<td>BMI≥30</td>
<td>Both</td>
<td>Median 4-5 y</td>
<td>66/798</td>
<td>0.083</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 100 mmol/d increase</td>
<td>RR</td>
<td>1.33</td>
<td>1.05</td>
<td>1.68</td>
</tr>
<tr>
<td>Kieneker, 2016&lt;sup&gt;155&lt;/sup&gt; PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>785/7795</td>
<td>0.101</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 155 mmol/24 hr in men &amp; 122 mmol/24 hr in women</td>
<td>per 50-mmol/d increase</td>
<td>HR</td>
<td>0.97</td>
<td>0.87</td>
<td>1.08</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Sodium to potassium ratio

Three studies\textsuperscript{93, 155, 247} examined the association between sodium-to-potassium ratio (cohorts included in these studies are the FLEMENGHO and EPOGH cohort,\textsuperscript{247} the PREVEND study,\textsuperscript{155} and the combined TOHP I/II cohort study.\textsuperscript{93} All studies included generally healthy adult men and women. Median follow-up time ranged from 4 to 10.5 years. Sodium-to-potassium ratios were assessed by 24-hour urinary excretion in all three studies. Individual study results are shown in Figure 37 and Table 12.

Overall Results

The relationships between urinary sodium-to-potassium ratios and combined CVD morbidity and mortality outcomes are inconsistent across studies.\textsuperscript{93, 155, 247} All studies controlled for various demographics, lifestyle factors, and medical history or medications. The overall risk of bias was rated as low to moderate.

Urinary Sodium Excretion and Combined CVD Morbidity and Mortality

24-hour urinary sodium-to-potassium ratio

In the combined FLEMENGHO and EPOGH cohort, an elevated risk of CVD fatal and nonfatal events was detected in the lowest tertile of sodium-to-potassium ratio when compared with the overall risk in the whole outcome cohort (adjusted HR = 1.26; 95% CI 1.00, 1.52).\textsuperscript{247} No associations were observed in the middle or highest tertiles of Sodium-to-potassium ratio. In the PREVEND study, there was no association between either continuous or quintiles of sodium-to-potassium ratio and risk of combined CVD morbidity and mortality (adjusted HR = 0.98; 95% CI 0.89, 1.08).\textsuperscript{155} In the TOHP I/II cohorts, no association was found between quartiles of sodium-to-potassium ratio and cardiovascular events, although a significant and positive linear trend was detected (p for trend = 0.04). When sodium-to-potassium ratio was analyzed as a continuous variable, a significant association was found after adjusting for several sociodemographic and lifestyle factors (adjusted HR = 1.24; 95% CI 1.05, 1.46). In subgroup analyses, significant linear associations were found in men (adjusted HR = 1.26; 95% CI 1.04, 1.53), but not in women (adjusted HR = 1.21; 95% CI 0.79, 1.85); in Whites (adjusted HR = 1.24; 95% CI 1.04, 1.49), but not in Blacks (adjusted HR = 1.85; 95% CI 0.94, 3.63); and in those with BMI\textgeq30 (adjusted HR = 1.33; 95% CI 1.05, 1.68), but not in those with BMI<30 (adjusted HR = 1.16; 95% CI 0.90, 1.49).
Figure 37. Categorical analysis of the association between levels of sodium to potassium ratio and combined morbidity and mortality outcome in generally healthy populations.
Table 12. Continuous analyses of the association between sodium to potassium ratio and combined CVD morbidity and mortality outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kieneker, 2016&lt;sup&gt;155&lt;/sup&gt; PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>785/7795</td>
<td>0.101</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>0.98</td>
<td>0.89</td>
<td>1.08</td>
</tr>
<tr>
<td>Cook, 2009&lt;sup&gt;93&lt;/sup&gt; TOHP I/II control groups</td>
<td>All</td>
<td>Both</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>166/2084</td>
<td>0.080</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.24</td>
<td>1.05</td>
<td>1.46</td>
</tr>
<tr>
<td>Men</td>
<td>Male</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>141/1459</td>
<td>.112</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.26</td>
<td>1.04</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>Female</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>25/625</td>
<td>.04</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.21</td>
<td>0.79</td>
<td>1.85</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Both</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>141/1743</td>
<td>.081</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.24</td>
<td>1.04</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>Both</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>19/284</td>
<td>.067</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.85</td>
<td>0.94</td>
<td>3.63</td>
<td></td>
</tr>
<tr>
<td>BMI &lt;30</td>
<td>Both</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>100/1286</td>
<td>.078</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.16</td>
<td>0.90</td>
<td>1.49</td>
<td></td>
</tr>
<tr>
<td>BMI ≥30</td>
<td>Both</td>
<td>median 5y (TOHP I) 4y (TOHP II)</td>
<td>66/798</td>
<td>.083</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 1-unit increase (mmol/mm mol)</td>
<td>HR</td>
<td>1.33</td>
<td>1.05</td>
<td>1.68</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile rage; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Combined CHD Morbidity and Mortality

Sodium intake

A total of five publications\textsuperscript{127, 147, 247, 262, 263} that reported analyses examining the associations between sodium intake levels and combined CHD morbidity and mortality outcome met inclusion criteria. These publications analyzed data from five non-overlapping prospective cohort studies among generally healthy adult populations. These cohorts are the combined FLEMENGHO and EPOGH cohort\textsuperscript{247} the Scottish Heart Health study\textsuperscript{262} PREVEND\textsuperscript{147} a population-based cohort in south-western Finland\textsuperscript{263} NHANES I.\textsuperscript{127} All studies included both adult men and women at baseline (mean ages ranged from 40.9 to 50 years). Mean or median follow-up time ranged from 7.6 to 19 years.

Sodium intake levels were assessed by 24-hour urinary sodium excretion in four studies,\textsuperscript{147, 247, 262, 263} and by 24-hour dietary recall in one study.\textsuperscript{127} The sodium intake ranged from 68 mmol/d (1564 mg/d) to 334 mmol/d (7682 mg/d). Individual study results are shown in Figure 38 and Table 13.

Overall Results

The relationships between sodium intake levels and combined CHD morbidity and mortality outcomes are inconsistent among the four studies that examined urinary sodium levels and combined CHD morbidity and mortality outcome.\textsuperscript{147, 247, 262, 263} The definitions of CVD morbidity and mortality outcomes are heterogeneous. Only one study assessed the associations between dietary sodium intake levels and risks of CHD among overweight vs. non-overweight adults, and the results showed no significant associations.\textsuperscript{127} All studies, except for the Scottish Heart Health study, controlled for various demographics, lifestyle factors, and medical history or medications. Among these, PREVEND\textsuperscript{147} and FLEMENGHO, the EPOGH cohort study\textsuperscript{247} also adjusted for urinary potassium excretion in their analyses. The Scottish Heart Health study adjusted only for age in their analyses, so the results may be at increased risk for confounding. The overall risk of bias was rated moderate. The strength of evidence was rated insufficient primarily due to the limitations in the sodium exposure assessment methods and heterogeneity in outcome definitions.

Urinary Sodium Excretion and Combined CHD Morbidity and Mortality

24-hour urinary sodium

Four studies examined the relationships between baseline 24-hour urinary sodium excretion levels and risks of CHD morbidity and mortality and showed inconsistent results.\textsuperscript{147, 247, 262, 263} Specifically, the FLEMENGHO and EPOGH cohort study showed that low (median = 95 mmol/d in women; 120 mmol/d in men), medium (median = 150 mmol/d in women; 189 mmol/d in men), and high (median = 291 mmol/d in women; 232 mmol/d in men) tertiles of 24-hour urinary sodium excretion were not significantly associated with the risks for fatal and coronary events (adjusted HR [95% CI] = 1.42 [0.99, 2.04], 1.17 [0.89, 1.54], and 0.86 [0.65, 1.13], respectively; n=3681) although there was a trend in decreasing risks with higher tertiles of 24-hour urinary sodium excretion (p=0.10).\textsuperscript{247} These analyses compared the risk in each tertile with the overall risk in the whole study population. This approach allows computation of CIs for
the hazard ratio (HR) in each tertile without definition of an arbitrary reference group. On the contrary, a Finnish cohort study by Tuomilehto and colleagues (2001)\textsuperscript{263} showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of CHD at the follow-ups (adjusted HR = 1.34; 1.08, 1.67). The PREVEND study\textsuperscript{147} did not find a significant linear association between baseline 24-hour urinary sodium excretion and CHD events (adjusted HR = 1.07; 95% CI 0.98, 1.18; n=7543). Subgroup analyses by hypertension status showed that a significant positive linear relationship between levels of 24-hour urinary sodium excretion and risks of CHD in hypertensive individuals (adjusted HR = 1.14; 95% CI 1.01, 1.28), but no significant relationship in normotensive individuals (adjusted HR = 0.97; 95% CI 0.82, 1.15).\textsuperscript{147} The Scottish Heart Health study showed a positive relationship between quintiles of 24-hour urinary sodium excretion levels and all CHD outcome in women (age-adjusted HR = 0.93, 1.97, 1.09, 1.76 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875], but no significant association in men (age-adjusted HR = 1.18, 1.11, 1.26, 1.23 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754).\textsuperscript{262} Again, because the Scottish Heart Health study adjusted only for age in their analyses, these results are at higher risk for confounding.

**Dietary Sodium Intake and Combined CHD Morbidity and Mortality**

One study performed subgroup analyses by overweight status using data from NHANES I\textsuperscript{127} to examine the relationship between dietary sodium intake and CHD outcome. Results showed no significant associations among overweight adults (adjusted RR = 1.06 per 100 mmol increase; 95% CI 0.88, 1.29; n=2688), or among non-overweight adults (adjusted RR = 0.95 per 100 mmol increase; 95% CI 0.83, 1.10; n=6797).\textsuperscript{127} The interaction between sodium intake and body weight (non-overweight vs. overweight) was not significant (p for interaction =0.39).

**Figure 38. Categorical analysis of the association between urinary sodium levels and combined CHD morbidity and mortality outcome in generally healthy populations.**

![Graphs showing categorical analysis of the association between urinary sodium levels and combined CHD morbidity and mortality outcome in generally healthy populations.](image-url)
Table 13. Continuous analyses of the association between sodium levels and combined CHD morbidity and mortality outcome in generally healthy populations.

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joosten, 2014 [147] PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>452/7543</td>
<td>.060</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 137 mmol/24 hr</td>
<td>per 1 g/d increase</td>
<td>HR</td>
<td>1.07</td>
<td>0.98</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Normotensive</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>162/NR</td>
<td>.021</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 137 mmol/24 hr</td>
<td>per 1 g/d increase</td>
<td>HR</td>
<td>0.97</td>
<td>0.82</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>290/NR</td>
<td>.038</td>
<td>24-hour urinary sodium excretion</td>
<td>Median 137 mmol/24 hr</td>
<td>per 1 g/d increase</td>
<td>HR</td>
<td>1.14</td>
<td>1.01</td>
<td>1.28</td>
</tr>
<tr>
<td>Tuomilehto, 2001 [263]</td>
<td>All</td>
<td>Both</td>
<td>up to 13 years</td>
<td>180/2436</td>
<td>0.074</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 216 (SD 83) in men &amp; 162 (SD 62) mmol/d in women</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>1.34</td>
<td>1.08</td>
<td>1.67</td>
</tr>
<tr>
<td>He, 1999 [127] NHANES I</td>
<td>Non-overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/6797</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100 mmol increase</td>
<td>RR</td>
<td>0.96</td>
<td>.86</td>
<td>1.08</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>Both</td>
<td>mean 19 y</td>
<td>ND/2688</td>
<td>ND</td>
<td>Dietary sodium intake</td>
<td>NR</td>
<td>per 100 mmol increase</td>
<td>RR</td>
<td>0.94</td>
<td>.76</td>
<td>1.17</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Sodium/Potassium ratio

Two studies that examined the association between sodium-to-potassium ratio (Na-K ratio) and risk of morbidity and mortality from coronary heart disease (CHD) were included.\textsuperscript{155, 247} Na-K ratios were assessed by 24-hour urinary excretion among generally healthy populations in both studies.

Overall Results
The two studies that examined urinary Na-K ratios and risk of morbidity and mortality from CHD reported consistent lack of associations. Both studies controlled for various demographic, clinical, and lifestyle factors. The overall risk of bias was rated as low.

Urinary Sodium/Potassium Ratio and Risk of Morbidity and Mortality from CHD
The analysis from the PREVEND cohort included subjects free of cardiovascular events at baseline. The cohort included both men and women, with an average age of 49.1 years. The median follow-up time was 10.5 years. No significant association was found with risk of ischemic heart disease when Na-K ratio was analyzed either as a continuous variable (HR = 1.05; 95% CI = 0.95, 1.15) or in quintiles.\textsuperscript{155} The analysis from the combined FLEMENGHO and EPOGH cohort was a population-based cohort that included both men and women, with an average age of 40.9 years. The median follow-up time was 7.9 years. No significant associations to risks of coronary fatal and nonfatal events were found when tertiles of Na-K ratio were compared with the overall risk in the whole outcome cohort. (HR (95% CI) = 1.31 (0.94, 1.84); 0.97 (0.73, 1.3); and 1.03 (0.77, 1.37) for the low, medium and high tertiles of Na-K ratio, respectively).

Mean difference between groups in estimated Glomerular Filtration Rate
The PREVEND study followed 5315 Dutch adults free of CKD, aged 28 to 75 years, for a median of 10.3 years. Using a multi-variable adjusted model, this study found no association between 24-hour urinary sodium excretion and risk of developing CKD, defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min per 173 m\(^2\), or urinary albumin excretion of >30 mg/24 h, or both (adjusted HR per 50 mmol/d increase = 0.97; 95% CI 0.89, 1.07).\textsuperscript{154} The overall risk of bias was rated low.

Number of patients with end stage renal disease
No studies were identified that assessed this outcome.
Key Question 4a. Do other minerals (e.g., sodium, calcium, magnesium) modify the association with sodium?

Description of Included Studies

No studies were identified that addressed this question.

Key Question 4b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).

Description of Included Studies

Effect of Sex

Among the studies described in the overview for this question, five reported subgroup analyses by sex.

All-cause mortality

The Scottish Heart Health study showed a borderline significant inverse relationship between quintiles of 24-hour urinary sodium excretion levels (range from 46.8 to 416.7 mmol/day) and total mortality outcome in men (age-adjusted HR = 0.99, 0.65, 0.86, 0.71 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754), and no significant association in women (age-adjusted HR = 0.61, 0.82, 0.67, 0.85 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875).262

The differences in the ranges of dietary sodium intake levels across studies might partly explain inconsistent findings across and within studies. In the NHANES I follow-up study, the mean dietary sodium intake was 2515 mg/day (109 mmol/day) in men and 1701 mg/day (74 mmol/day) in women, and higher dietary sodium intake levels were associated with lower risks of total mortality (adjusted HR 0.88 per SD [1313 mg or 57 mmol] increase; 95% CI 0.80, 0.96; n=11346).41

In the NHANES III follow-up study, where higher dietary sodium intake levels were associated with an increased risk of total mortality, no significant interactions were seen by sex. In addition, significant linear associations between continuous Na-K ratio and total mortality were reported for both men and women.282

CVD mortality

In the 2001 Finnish cohort study,263 higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of CVD mortality for both men and women, although the association was not statistically significant in women.

In the NHANES I follow-up study, where the mean dietary sodium intake was 50 percent higher in men than in women, higher dietary sodium intake levels were associated with lower risks of CVD mortality.41

In the NHANES III follow-up study, no significant interactions by sex were seen for CVD mortality. The risk of CVD mortality increased with increasing quartile of Na-K ratio among the whole cohort (p for trend =.01; n=12267).282 In addition, a significant linear association between
continuous Na-K ratio and CVD mortality was reported among the whole cohort (HR = 1.90; 95% CI 1.20, 3.03). In subgroup analyses assessing the moderating effect of sex on the association of Na-K ratio to CVD mortality, significant linear associations were found in men, but not in women.

**CHD Mortality**

the Scottish Heart Health study\textsuperscript{262} reported that baseline 24-hour urinary sodium excretion levels were positively associated with risks of CHD mortality in women (age-adjusted HR 0.36, 0.41, 0.85, 2.05 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875), but not in men (age-adjusted HR 0.96, 0.62, 0.97, 10.92, comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754).

The Finnish cohort study showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of CHD mortality at followup. However, the association was significant only in men (adjusted HR = 1.55; 95% 1.12, 2.13; n=1263), but not in women (adjusted HR 2.07; 95% 0.80, 5.36; n=1263). \textsuperscript{263}

**Stroke**

The Finnish cohort study\textsuperscript{263} found no significant relationship between baseline 24-hour urinary sodium excretion and stroke at followup and no differences by sex.

**Combined CVD Morbidity and Mortality**

In the TOHP (I and II) follow-up study, which enrolled the control groups from the original sodium reduction trials, no significant interactions were observed by sex, for the association between 24-hour sodium excretion levels and total cardiovascular events. But the subgroup results showed statistically significantly increased risks of total cardiovascular events in men (adjusted RR per 100 mmol/d increase = 1.26; 95% CI 1.04, 1.53) compared with women.\textsuperscript{93}

No studies reported analyses stratified by sex for other outcomes of interest.

**Effects of Race/Ethnicity**

**Total mortality**

In the NHANES III follow-up study, where higher dietary sodium intake levels were associated with an increased risk of total mortality, no significant interactions were seen by race/ethnicity.\textsuperscript{282}

**CVD Mortality**

In the NHANES III follow-up study, subgroup analyses assessing the moderating effect of race/ethnicity on the association of sodium to CVD mortality found no significant linear associations.

In NHANES, the risk of CVD mortality increased with increasing quartile of Na-K ratio among the whole cohort.\textsuperscript{282} In addition, a significant linear association between continuous Na-K ratio and CVD mortality was reported in non-Hispanic Blacks and Mexican-Americans, but not in non-Hispanic Whites;
Total CVD events
The TOHP (I and II) follow-up study found no significant interactions between race (White vs. Black) and 24-hour sodium excretion levels. However, the subgroup results showed statistically significantly increased risks of total cardiovascular events in Whites (adjusted RR per 100 mmol/d increase = 1.21; 95% CI 1.04, 1.49). 93

Effects of Age
No studies that met inclusion criteria for this question conducted subgroup analysis by age.

Key Question 4c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.

Description of Included Studies
Twelve publications examined the associations between sodium intake and total mortality, CVD, CHD, stroke, or kidney disease morbidity and mortality exclusively among people with existing diseases such as hypertension, primary aldosteronism, history of CVD, Type 2 DM, Type 1 DM, and CKD. The individual study results are shown in Figures 39 and 40 and in Table 14.

The results from these studies are described together with subgroup analyses of generally healthy population defined by hypertension and by weight status below. The sections are categorized according to comorbidity, rather than outcome.

Hypertension

All-cause Mortality
In a subgroup analysis of the pooled analysis of four cohorts (PURE, EPIDREAM, ONTARGET and TRANSCEND) from 49 countries, a U-shape relationship between baseline levels of 24-hour urinary sodium excretion (estimated by Kawasaki equation) and risk of total mortality was found among individuals with hypertension (n=63559) at baseline. However, no significant linear relationship was observed between baseline dietary sodium intake levels and risks of total mortality or CVD mortality (adjusted HR [95% CI] = 1.18 [0.8, 1.57] and 0.86 [0.56, 1.31], respectively) among adults with HTN in a subgroup analysis of NHANES III. Two publications analyzed data from the same prospective cohort study of adult hypertensive patients in a worksite HTN program in New York City. The later publication reported all-cause mortality outcomes after an average of 6.5 years of followup. This study found that lower baseline 24-hour urinary sodium excretion levels were associated with borderline lower risks of total mortality (adjusted HR [95% CI] = 0.81 [0.66, 1.00], 0.90 [0.73, 1.10], 0.88 [0.71, 1.09], comparing the first, second, and third quartiles to the highest quartile; n=3505).

CVD, CHD, and Stroke
Five publications examined the associations between sodium intake and CVD, CHD, or stroke outcomes among hypertensive adults. Of these, two publications analyzed data from the same prospective cohort study, and three publications reported subgroup analyses of three non-overlapping prospective cohort studies among generally healthy populations by hypertension status. The sodium intake levels were measured by 24-hour
urinary excretion in two studies (in three publications\textsuperscript{40, 147, 240}), by estimated urinary excretion in one study\textsuperscript{184} and by 24-hour dietary recall in one study.\textsuperscript{282} Results are not consistent across studies. Overall risk of bias was rated moderate.

Two publications analyzed data from the same prospective cohort study of adult hypertensive patients in a worksite HTN program in New York City.\textsuperscript{40, 240} The earlier publication reported CVD incidence, MI incidence, and stroke incidence after an average of 3.8 years of followup, and no significant associations were observed between quartiles of baseline 24-hour urinary sodium excretion levels and risks of CVD, MI, and stroke.\textsuperscript{40} However, only unadjusted analyses were performed in the earlier publication. A later publication reported CVD mortality and all-cause mortality outcomes after an average of 6.5 years of followup. This study found no significant associations between baseline 24-hour urinary sodium excretion levels and risks of CVD mortality (adjusted HR [95% CI] = 1.00 [0.71, 1.42], 0.96 [0.68, 1.36], 1.06 [0.75, 1.49] comparing the 1st, 2nd, and 3rd quartile to the highest quartile; n=3505)\textsuperscript{240} On the contrary, a subgroup analysis of the PREVEND study showed a significant positive linear relationship between levels of 24-hour urinary sodium excretion and risks of CHD in hypertensive individuals (adjusted HR = 1.14; 95% CI 1.01, 1.28).\textsuperscript{147}

**Kidney disease morbidity and mortality outcomes**

A study in Fukuoka, Japan, followed 133 hypertensive outpatients for an average of 10.5 years.\textsuperscript{206} This study reported on outcomes including eGFR and change in eGFR. Both males and females showed a significantly slower decline in renal function (as measured by change in eGFR) among those with lower average urinary sodium excretion (<9.5 g/day for men and <8 g/day for women) compared to those with higher average urinary sodium excretion.\textsuperscript{206} The association was independent of blood pressure change or an increased number of antihypertensive drugs. The overall risk of bias was rated moderate.

**Cardiovascular Disease**

One study examined the associations between estimated urinary sodium excretion levels and total mortality, CVD, CHD, or stroke outcomes among adults with a history of CVD (including HTN).\textsuperscript{205} ONTARGET and TRANSCEND were two large, multi-center, multi-country cohorts of people at high risk of CVD; and analyses of the combined cohorts reported on all-cause mortality, CVD mortality, MI incidence, and stroke incidence.\textsuperscript{205} This study found a U-shaped relationship between baseline levels of 24-hour urinary sodium excretion (estimated by Kawasaki equation) and risk of total mortality (n=26880), using the median quintile of urinary excretion (4-5.99 g/day or median 217 mmol/d) as the reference group. Both the lowest quintile (<2 g/day) and highest quintile (>8 g/day) of the urinary sodium excretion levels were associated with an increased risk of total mortality (adjusted HR [95% CI] = 1.19 [0.99, 1.45] and 1.56 [1.30, 1.89]). Similar U-shaped relationships were found between baseline levels of 24-hour urinary sodium excretion and risks of CVD mortality. Both lowest quintile (<2 g/day) and highest quintile (>8 g/day) of the urinary sodium excretion levels were associated with an increased risk of CVD mortality (adjusted HR [95% CI] = 1.37 [1.09, 1.73] and 1.66 [1.31, 2.1]). This study also found that the highest quintile (>8 g/day) of the urinary sodium excretion (estimated by Kawasaki equation) was significantly associated with an increased risk of stroke (adjusted HR = 1.48; 95% CI 1.09, 2.01) and MI (adjusted HR = 1.48; 95% CI 1.11, 1.98) compared to the reference quintile level (4-5.99 g/day or median 217 mmol/d) but the
comparisons between other quintiles to the median quintile of urinary sodium excretion were not statistically significant.

**Other CVD outcomes**

Another study followed 65 patients with primary hyperaldosteronism who were referred to a hypertension clinic in Italy. This study found that the percentage decrease in LV mass index was significantly greater in patients who had more than 10 percent reduction in urinary sodium excretion (15 ± 12.5 [SD] %) than in the remaining patients (5.5 ± 9.3 [SD] %) after 1 year followup. The overall risk of bias was rated high.

**Diabetes**

Four publications examined the associations between 24-hour urinary sodium excretion levels and total mortality, CVD, CHD, stroke, or kidney disease morbidity and mortality outcomes among patients with type 2 diabetes or type 1 diabetes. Among these, two studies had overlapping study populations. The overall risk of bias was rated moderate.

A subsample of ONTARGET participants who were diagnosed with vascular disease or type 2 diabetes with end-organ damage reported on CKD incidence and total mortality. No significant relationship was seen between urinary sodium excretion levels and total mortality (adjusted OR [95% CI] = 1.03 [0.93, 1.15] and 1.07 [0.86, 1.13] comparing the second and third tertiles to the lowest tertile; n=3088). This study did not find a significant association between estimated sodium excretion and risk of CKD in type 2 diabetes patients. Another observational study followed a subsample of ONTARGET participants, who were diagnosed with type 2 DM but without macroalbuminuria, for 5.5 years. This study found no association between sodium intake and CKD, defined as new microalbuminuria or macroalbuminuria or more than 5% decline in glomerular filtration rate per year.

A cohort study followed adult patients with type 2 diabetes attending a single diabetes clinic in Australia, and found an inverse association between baseline 24-hour urinary sodium excretion levels and total mortality outcome (adjusted HR = 0.72 per 100 mmol increase; 95% CI 0.55, 0.94; n=620). It also found an inverse association between baseline 24-hour urinary sodium excretion levels and CVD mortality (adjusted HR = 0.65 per 100 mmol increase; 95% CI 0.44, 0.95; n=620). The FinnDiane study prospectively followed Finnish adult patients with Type 1 diabetes without end-stage renal disease for a median of 10 years. This study found a U-shaped relationship between baseline levels of 24-hour urinary sodium excretion and risks of total mortality and ESRD (n=2807), setting 150 mmol/d (3450 mg/day) urinary excretion as the reference level (data reported in the figures only).

**Chronic Kidney Disease**

Three publications examined the associations between 24-hour urinary sodium excretion levels and total mortality, CVD, CHD, stroke, or kidney disease morbidity and mortality outcomes among patients with CKD. Of these, two publications analyzed data from the CRIC study and reported on all-cause mortality, composite CVD incidence, MI incidence, and stroke incidence. The third publication was an analysis of the MDRD study on risk of kidney failure and risk of a composite outcome defined as kidney failure or all-cause mortality.
In the CRIC study of patients with CKD in the U.S. (n=3757), the highest quartile of 24-hour urinary sodium excretion (≥194.6 mmol/24 hours or ≥4476 mg/day) was significantly associated with an increased risk of total mortality (adjusted HR = 1.42; 95% CI 1.05, 1.91), compared to the lowest quartile (<116.8 mmol/24 hours or <2686 mg/day).125 The second and third quartiles of 24-hour urinary sodium excretion were not significantly associated with the risks of total mortality compared to the lowest quartile (adjusted HR [95% CI] = 1.14 [0.89, 1.46] and 1.13 [0.86, 1.49], respectively).125 Another publication from the CRIC cohort study reported a significantly increased risk of stroke (adjusted HR = 1.81; 95% CI 1.08, 3.02), comparing the highest quartile of 24-hour urinary sodium excretion (≥4548 mg/d) to the lowest quartile (<2894 mg/d).189 There was also a significant continuous linear association between baseline 24-hour urinary sodium excretion levels and stroke outcome (adjusted HR per 1000 mg increase; 95% CI 1.05, 1.28; n=3542)189 No significant interactions were observed between 24-hour urinary sodium excretion and sex, race (black vs. nonblack), older age (≥60 vs. <60 years), or diabetes (diabetes vs. no diabetes) among CKD patients.

An analysis of 840 CKD patients enrolled in the MDRD study reported on risk of kidney failure and risk of a composite outcome defined as kidney failure or all-cause mortality.102 This study found no association between 24 hour urinary sodium excretion and kidney failure (HR = 0.99; 95% CI=0.91-1.08).

Obesity

Three subgroup analyses of a generally healthy population defined by obesity status were included.93,127,263 All three studies reported a positive relationship between sodium intake levels and risks of total and CVD mortality among overweight adults. The overall risk of bias was rated moderate.

Specifically, a 2001 Finnish cohort study showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of total mortality (adjusted HR per 100 mmol/d increase = 1.56; 95% CI 1.21, 2.00; n=514) and CVD mortality (adjusted HR per 100 mmol/d increase = 1.44; 95% CI 1.02, 2.04; n=514) among overweight adults. Furthermore, a subgroup analysis of the TOHP (I & II) study participants who were obese (BMI≥30) at baseline showed that higher levels of baseline 24-hour urinary sodium excretion were significantly associated with higher risks of total cardiovascular events (adjusted HR 1.33 per 100 mmol/d increase; 95% CI 1.05, 1.68; n=798).263

In subgroup analyses of the NHANES I follow-up study, higher dietary sodium intake levels were associated with higher risks of total mortality (adjusted RR = 1.32 per 100 mmol increase; 95% CI 1.16, 1.50; n=2688) CVD mortality (adjusted RR = 1.45 per 100 mmol increase; 95% CI 1.20, 1.75), CHD mortality (adjusted RR = 1.29 per 100 mmol increase; 95% CI 1.01, 1.64), and stroke (adjusted RR 1.39 per 100 mmol increase; 95% CI 1.09, 1.77) among overweight adults.127 This study showed no associations between dietary sodium intake levels and risks of congestive heart failure (CHF) among non-overweight adults, but showed that the highest quartile of dietary sodium intake level (mean = 167.6 mmol/d) was significantly associated with an increased risk of CHF (adjusted HR = 1.43; 95% CI 1.01, 1.91) compared to the lowest intake level (mean = 33.7 mmol/d).126 In continuous analyses, relative risk of CHF for a 100-mmol/d higher intake of sodium was 0.90 (95% CI, 0.67, 1.20) among non-overweight adults, and 1.26 (95% CI, 1.03, 1.53) among overweight adults.
Figure 39. Categorical analyses of the association between sodium levels and total mortality, CVD outcomes in non-healthy populations.

- Singer, 2015 [Hypertensive]
  - Mortality: 1013/3505
  - CVD mortality: 399/3505

- He, 2016 CRIC [CKD]
  - Mortality: 540/3757

- O’Donnell, 2011 ONTARGET & TRANSCEND [CVD]
  - Mortality: 3430/28880
  - CVD mortality: 399/3505

- Dunkler, 2015 ONTARGET [Type 2 DM subgroup]
  - Mortality: 450/3088

- O’Donnell, 2011 ONTARGET and TRANSCEND [CVD]
  - CVD mortality: 2057/28880

- Singer, 2015 [Hypertensive]
  - Mortality: 1013/3505
  - CVD mortality: 399/3505
Figure 40. Categorical analyses of the association between sodium levels and stroke outcome in non-healthy populations

Mills, 2016 CRIC [CKD]

Stroke: 148/3757

Relative Risk

0 50 100 150 200 250 300 350 400 450
mmol/24 hr

O’Donnell, 2011 ONTARGET and TRANSCEND [CVD]

Stroke: 1213/28880

Relative Risk

0 50 100 150 200 250 300 350 400 450
mmol/24 hr
Table 14. Continuous analyses of the association between sodium levels and total mortality outcome in non-healthy populations.
<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Populati on</th>
<th>Sex</th>
<th>Follow-up duratio n</th>
<th>Number of events / Total N</th>
<th>Cumulat ed Incidenc e</th>
<th>Exposure assessme nt</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estima te</th>
<th>Lowerr 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total mortality outcome</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ekinci, 2011&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Type 2 diabetes</td>
<td>Both</td>
<td>median 9.9 y</td>
<td>175/620</td>
<td>0.282</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 184 mmol/d</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>0.72</td>
<td>0.55</td>
<td>0.94</td>
</tr>
<tr>
<td>Thomas, 2011&lt;sup&gt;237&lt;/sup&gt; FinnDiane Study</td>
<td>Type 1 diabetes</td>
<td>Both</td>
<td>Median 10 y</td>
<td>217/2807</td>
<td>0.077</td>
<td>24-hour urinary sodium excretion</td>
<td>Median</td>
<td>non-linear relationship established by fractional polynomials</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>CVD mortality outcome</td>
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<tr>
<td>Ekinci, 2011&lt;sup&gt;100&lt;/sup&gt;</td>
<td>Type 2 diabetes</td>
<td>Both</td>
<td>median 9.9 y</td>
<td>175/620</td>
<td>0.282</td>
<td>24-hour urinary sodium excretion</td>
<td>Mean 184 mmol/d</td>
<td>per 100 mmol/d increase</td>
<td>HR</td>
<td>0.65</td>
<td>0.44</td>
<td>0.95</td>
</tr>
<tr>
<td>Stroke outcome</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Alderman, 1997&lt;sup&gt;240&lt;/sup&gt;</td>
<td>HTN</td>
<td>Both</td>
<td>median 3.8 y</td>
<td>23/2937</td>
<td>0.008</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>&lt;89 vs. ≥175 mmol/d</td>
<td>RR</td>
<td>1.2</td>
<td>0.30</td>
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<td></td>
<td>HTN: Male</td>
<td>Male</td>
<td>median 3.8 y</td>
<td>17/1900</td>
<td>0.009</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>&lt;89 vs. ≥175 mmol/d</td>
<td>RR</td>
<td>1.6</td>
<td>0.40</td>
<td>6.5</td>
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<tr>
<td>HTN: Female</td>
<td></td>
<td>median 3.8 y</td>
<td>6/1037</td>
<td>0.006</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>&lt;89 vs. ≥175 mmol/d</td>
<td>RR</td>
<td>0.5</td>
<td>0.05</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Mills, 2016</td>
<td>CKD Both</td>
<td>median 6.8 y</td>
<td>148/3542</td>
<td>0.042</td>
<td>24-hour urinary sodium excretion</td>
<td>mean 3701 (SD 1443) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.16</td>
<td>1.05</td>
<td>1.28</td>
<td></td>
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<tr>
<td>CKD: Male</td>
<td></td>
<td>median 6.8 y</td>
<td>NR/1950</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.15</td>
<td>1.02</td>
<td>1.3</td>
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<tr>
<td>CKD: Female</td>
<td></td>
<td>median 6.8 y</td>
<td>NR/1592</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.2</td>
<td>0.98</td>
<td>1.47</td>
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<tr>
<td>CKD: Black</td>
<td>Both</td>
<td>median 6.8 y</td>
<td>NR/1472</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.22</td>
<td>1.05</td>
<td>1.42</td>
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<tr>
<td>CKD: Non-black</td>
<td>Both</td>
<td>median 6.8 y</td>
<td>NR/2070</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.1</td>
<td>0.94</td>
<td>1.29</td>
<td></td>
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<tr>
<td>CKD: Age &lt;60</td>
<td>Both</td>
<td>median 6.8 y</td>
<td>NR/1767</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.17</td>
<td>1.02</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>CKD: Age ≥60</td>
<td>Both</td>
<td>median 6.8 y</td>
<td>NR/1775</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.15</td>
<td>0.98</td>
<td>1.34</td>
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<tr>
<td>CKD: DM</td>
<td>Both</td>
<td>median 6.8 y</td>
<td>NR/1684</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.17</td>
<td>1.05</td>
<td>1.32</td>
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<tr>
<td>CKD: No DM</td>
<td>Both</td>
<td>median 6.8 y</td>
<td>NR/1858</td>
<td>NR</td>
<td>24-hour urinary sodium excretion</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>1.13</td>
<td>0.93</td>
<td>1.36</td>
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</tr>
</tbody>
</table>

CKD = chronic kidney disease; CI = confidence interval; HR = hazard ratio; IQR = interquartile rage; MDRD = Modification of Diet in Renal Disease; NR = not reported; SD = standard deviation; y = years
Potassium

Key Question 5. Among children and adults what is the effect of interventions to increase potassium intake on blood pressure and kidney stone formation?

Key Points

- A moderate strength of evidence supports a beneficial effect of increased potassium intake on blood pressure in adults, based on 11 parallel RCTs and 7 crossover RCTs.
- Evidence is insufficient to draw a conclusion regarding the effects of increasing potassium through dietary changes on BP in adults, based on two RCTs.
- Evidence is insufficient to draw any conclusions regarding superiority of one form of potassium supplement over another for lowering BP in adults, based on single studies.
- Evidence is insufficient to draw a conclusion regarding a beneficial effect of increased potassium intake on BP in children, based on two conflicting studies.
- Evidence from three studies is insufficient to draw conclusions regarding the modifying effect of other minerals (one study each on calcium, magnesium, and reduced sodium) on the effects of dietary or supplemental potassium.
- Evidence is insufficient (based on one RCT) to draw a conclusion regarding the moderating effect of sex on the effects of increased potassium intake on BP in adults.
- Evidence is insufficient to draw a conclusion regarding a moderating effect of race/ethnicity on the effect of dietary or supplemental potassium on BP (four RCTs, only one of which directly compared blacks with the total population).
- Evidence is insufficient to draw a conclusion regarding moderating effects of age on the effects of increased potassium intake or increased dietary potassium on blood pressure. No studies directly compared individuals of different ages.
- Evidence is insufficient based on one study to draw conclusions regarding effects of increased potassium intake on achievement of a prespecified blood pressure goal or risk for HTN.
- Evidence is insufficient based on one study to draw conclusions regarding effects of increased potassium intake on risk for kidney stones.
- A low strength of evidence based on six RCTs suggests potassium supplements may be associated with minor gastrointestinal discomfort.
- A low strength of evidence suggests increased potassium intake or increased dietary potassium does not affect blood pressure in healthy populations (based on pooling of two parallel RCTs and one crossover RCT).
- A moderate strength of evidence supports a beneficial effect of potassium supplementation or increased dietary potassium from food on blood pressure in populations with prehypertension or hypertension (based on 11 parallel RCTs and 6 crossover RCTs with low RoB, some with inconsistent findings).
- Evidence is insufficient to draw conclusions regarding the moderating effects of diabetes, kidney disease, or obesity on the effects of potassium supplementation or increased dietary potassium from food on blood pressure.
Overview and Description of Included Studies

This question addresses three subquestions: a) the moderating effects of other minerals on the effects of increasing potassium intake on blood pressure related outcomes and kidney stone formation; b) the effects of increasing potassium on those outcomes in adults, and moderating effects of sex and race/ethnicity; and c) moderating effects of comorbidities on those outcomes. We begin by addressing subquestion b.

We identified 26 trials, described in 28 publications, that assessed the effects of potassium supplementation on blood pressure and related outcomes and kidney stone formation (described in detail in the Evidence Table in Appendix C). 65, 69, 73, 115, 186, 197, 235, 236, 238, 251, 256, 274, 59, 63, 80, 201, 209, 248, 180, 119, 123, 187, 202, 203, 216, 218, 270

Among the 26 studies, one enrolled adolescents in the upper 15th percentile of blood pressure for their age group, 238 one controlled non-randomized trial enrolled both adults and children, 237 and the remaining 24 enrolled adults only (the results for these studies are described in the response to key question 5b).

Two parallel RCTs and one crossover RCT assessed the effects of potassium on blood pressure in healthy adult participants. 69, 180, 197 Eleven parallel RCTs 235, 80, 119, 186, 203, 216, 256, 248, and seven crossover RCTs 236, 65, 115, 123, 209, 218, 270 reported on the effects of increased potassium intake or increased dietary potassium on BP in participants with prehypertension, or mild-, moderate-, or more advanced hypertension (findings reported in the response to key question 5c). 73, 115, 180, 186, 235, 248

Three studies reported the moderating effect of other minerals on the effect of increased dietary or supplemental potassium, described in the response to key question 5a. 202, 209, 216 Five additional studies that compared the effect of increased potassium intake and low sodium diet with that of low sodium diet alone 80, 82, 117, 118, 140, 169, 201 and thirteen additional studies that assessed the effects of potassium-containing salt substitutes 60, 82, 84, 110, 112, 175, 178, 195, 224, 249, 284, 286, 287 are described and analyzed in KQ1a.

Six studies were conducted in the UK, 65, 69, 73, 115, 123, 197 four were conducted in Italy, 108, 235, 236, 238 five in the US, 186, 187, 251, 256, 270, 274 two each were conducted in Spain, 59, 63 India, 209, 248 and Australia, 80, 201 and one each was conducted in Denmark, 180 Iran, 216 Kenya, 203 China, 119 and New Zealand. 218

Most studies administered potassium in the form of potassium chloride, in amounts ranging from 20 to 120mmol/d. However, three studies assessed a diet intervention to increase potassium intake, 65, 186, 202 one study administered potassium citrate (480mg/d) in the form of a low sodium bread, 63 several studies administered potassium citrate as a supplement, 59, 65, 69 one study administered potassium gluconate and citrate, 187 one compared potassium bicarbonate and chloride, 123 one administered potassium aspartate, 108 one administered potassium magnesium citrate, 270 and three studies did not specify the form of potassium. 203, 216, 218 Durations of supplementation ranged from 1 month (4 weeks) to 36 months.
Comparators in most studies were placebo; however, comparators also included other salts of potassium or a diet high in fruits and vegetables. Many but not all studies assessed urinary potassium excretion to monitor status and compliance. Of the studies that reported actual levels or comparisons between interventions and controls, most showed significantly higher levels for the intervention groups compared with the controls.

All but one study assessed the effects of increased potassium intake on changes in blood pressure and related outcomes; that remaining study assessed the effects of potassium citrate on the risk for kidney stones in individuals with idiopathic hypercitraturia. Fifteen RCTs had a parallel design, nine RCTs had a crossover design, and two were controlled clinical trials. The results of these three study designs are described separately.

Key Question 5b. Among subpopulations defined by age (children, adolescents, young adults, older adults, elderly) and reproductive status (pregnancy and lactation), sex, and race/ethnicity.

Detailed Synthesis

Effects of Age

Only two trials reported results of studies of increasing potassium intake for children: one RCT and one CCT. The remainder report results in adults. Descriptions of the included studies and pooled effect sizes for parallel and crossover RCTs of adults are described below and shown in the figures, separately from those for children. Parallel RCTs were pooled separately from crossover RCTs that reported on adults. Results are also described separately by type of intervention for adults.

Mean difference in systolic blood pressure

Adults

Potassium supplements vs. placebo

Parallel RCTs

Eleven parallel RCTs (results reported in 12 publications) that met inclusion criteria reported on the effects of potassium supplements, typically potassium chloride, to increase potassium status compared with placebo controls in adults. Of the eight RCTs that reported urinary potassium excretion, all reported increases in the intervention groups compared with controls. Two RCTs did not report the levels but reported that they were increased and correlated with supplementation. The random effects pooled estimate for the
The effects of increased potassium on systolic BP showed a significant beneficial effect (MD $-7.71$ (95% CI $-14.81, -0.61$; $I^2 97\%$; low RoB). The studies were highly heterogeneous with respect to intervention type (Figure 41a).

**Crossover RCTs**

Eight crossover RCTs that met inclusion criteria reported on the effects of potassium supplements vs. placebo on systolic blood pressure. Six RCTs reported increased urinary potassium excretion compared with the control groups, one RCT reported no significant difference, and one trial did not report on urinary potassium (high risk of bias for assessment of potassium exposure). The random effects pooled estimate of the mean difference in systolic BP showed a non-significant beneficial effect of increased potassium intake on systolic BP (MD $-2.91$, 95% CI $-6.18, 0.37$; $I^2 55\%$; low RoB) (Figure 41a).

**Pooled Parallel and Crossover RCTs**

Nineteen RCTs could be pooled. The random effects pooled effect estimate for both parallel and crossover RCTs showed a significant beneficial effect of increased potassium intake but very high heterogeneity (MD $-6.04$, 95% CI $-10.48, -1.60$; $I^2 95\%$).

**Controlled Clinical Trials**

Two non-randomized placebo controlled trials assessed the effects of increased potassium intake on systolic blood pressure.

A UK study that provided daily potassium gluconate/potassium citrate supplements to half of a group of healthy adults and placebo to the remainder reported increases in urinary potassium excretion but no significant change in systolic blood pressure (moderate RoB based on study design).

A study conducted in Italy administered 30mmol potassium aspartate daily to half of a group of adults with mild HTN and placebo to the remainder. At 4 weeks, systolic BP was significantly decreased in the potassium supplemented group (154.4 ± 8.2 vs. 142.2 ± 7.6 mmHg, p<0.001) (high RoB based on study design).

**Potassium from foods vs. usual diet**

**Parallel RCTs**

A 2-month RCT that used coaching about dietary choices and food vouchers to increase potassium intake among urban blacks in Baltimore with controlled hypertension found increases in urinary potassium excretion in the intervention group (compared with baseline and the control group) but no change in systolic BP (moderate RoB).

**Crossover RCTs**

A 1.5 month crossover RCT conducted in the UK compared the use of a diet enriched with fruits and vegetables to raise potassium levels to that of potassium citrate supplements and placebo controls among individuals with mild (early) hypertension (low RoB). This study reported no effects of increased potassium on systolic BP.
Potassium salts compared

Parallel RCTs
A 1.5-month parallel RCT conducted in the UK randomized 85 healthy participants to 30mmol potassium chloride, 30mmol potassium citrate, or placebo.\textsuperscript{69} Both potassium chloride and citrate significantly reduced systolic BP compared with placebo (MD $-5.24$, CI $-7.43$, $-3.06$ and $-6.69$, CI $-8.85$, $-4.43$, respectively) urinary potassium excretion was significantly increased in both intervention groups compared with the placebo group (low RoB).

Crossover RCTs
He and colleagues reported no difference in the effects of potassium bicarbonate, potassium chloride, and placebo on systolic BP (low RoB for urinary potassium excretion assessment).\textsuperscript{123} Vongpatanasin reported that 4 weeks of KCl supplementation decreased systolic BP but potassium magnesium citrate and potassium citrate did not (moderate RoB).\textsuperscript{270}

Children
Sinaiko and colleagues assessed the feasibility of reducing dietary sodium or supplementing with potassium in 5\textsuperscript{th} to 8\textsuperscript{th} grade youth in the US, mean age 13.\textsuperscript{238} The findings for sodium reduction were reported in the response to KQ1. They randomized 140 boys and girls in the upper 15\textsuperscript{th} percentile of blood pressure distribution for their age group to 3 years of increased potassium intake (1mmol per kg body weight per day) or placebo while maintaining usual diet. They reported a small, statistically insignificant mean difference in systolic BP (MD $-0.30$, 95\% CI $-7.92$, 7.32; $I^2$ 56\%; low RoB) (Figure 41b).

A CCT supplemented one member each of 38 pairs of normotensive twin children with a mixture of potassium gluconate and potassium citrate (approximately 40 mmol; daily doses were based on caloric needs calculated by weight and sex); the other members of the twin pairs received placebo.\textsuperscript{187} After 4 weeks, 24-hour urinary excretion increased significantly, but systolic BP did not change (low RoB).

Summary
Evidence is insufficient to draw a conclusion regarding moderating effects of age on the effects of increased potassium intake or increased dietary potassium on systolic blood pressure. No studies directly compared individuals of different ages.

A moderate strength of evidence supports a beneficial effect of increased potassium intake on systolic blood pressure in adults, based on 11 parallel RCTs and 8 crossover RCTs.

Evidence is insufficient to draw a conclusion regarding the effects of increasing potassium through dietary changes on systolic BP in adults, based on two RCTs with high risk of bias.

Evidence is insufficient to draw any conclusions regarding superiority of one form of potassium supplement over another for lowering systolic BP in adults, based on single studies with high risk of bias.

Evidence is insufficient to draw a conclusion regarding a beneficial effect of increased potassium intake on systolic BP in children, based on two conflicting studies, one with high risk of bias.
Figure 41a. Effect of increased potassium intake on mean difference in systolic BP for adults

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Pot Intervention</th>
<th>Achieved Sodium Control</th>
<th>Achieved Pot Control</th>
<th>MD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breshch, 2009[157]</td>
<td>122 (mmol/24h)</td>
<td>89 (mmol/24h)</td>
<td>123 (mmol/24h)</td>
<td>66 (mmol/24h)</td>
<td>-5.24 [-7.42, -3.06]</td>
</tr>
<tr>
<td>Buettik, 1994[158]</td>
<td>149 (mmol/24h)</td>
<td>95 (mmol/24h)</td>
<td>133 (mmol/24h)</td>
<td>55 (mmol/24h)</td>
<td>-2.30 [-15.15, 19.78]</td>
</tr>
<tr>
<td>Gu, 2007[159]</td>
<td>185 (mmol/24h)</td>
<td>64 (mmol/24h)</td>
<td>163 (mmol/24h)</td>
<td>54 (mmol/24h)</td>
<td>-3.70 [-7.81, -0.59]</td>
</tr>
<tr>
<td>Naslundh, 2005[160]</td>
<td>169 (mmol/24h)</td>
<td>NR</td>
<td>151 (mmol/24h)</td>
<td>NR</td>
<td>-7.60 [-10.43, -4.83]</td>
</tr>
<tr>
<td>Newton, 1998[161]</td>
<td>145 (mmol/24h)</td>
<td>90 (mmol/24h)</td>
<td>155 (mmol/24h)</td>
<td>72 (mmol/24h)</td>
<td>-9.90 [-6.81, -9.99]</td>
</tr>
<tr>
<td>O'Brien, 1996[162]</td>
<td>NR</td>
<td>193 (mmol/24h)</td>
<td>NR</td>
<td>56 (mmol/24h)</td>
<td>-36.00 [-43.06, -33.31]</td>
</tr>
<tr>
<td>Rose, 2001[163]</td>
<td>-382 (NR)*</td>
<td>305 (NR)*</td>
<td>-79 (NR)*</td>
<td>9 (NR)*</td>
<td>-8.40 [-11.58, -5.22]</td>
</tr>
<tr>
<td>Sani, 1997[164]</td>
<td>180 (mmol/24h)</td>
<td>87 (mmol/24h)</td>
<td>184 (mmol/24h)</td>
<td>57 (mmol/24h)</td>
<td>-14.00 [-21.78, -5.32]</td>
</tr>
<tr>
<td>Sani, 1996[165]</td>
<td>165 (mmol/24h)</td>
<td>75 (mmol/24h)</td>
<td>165 (mmol/24h)</td>
<td>52 (mmol/24h)</td>
<td>3.40 [1.21, 6.59]</td>
</tr>
<tr>
<td>Sundar, 1996[166]</td>
<td>98 (mmol/24h)</td>
<td>67 (mmol/24h)</td>
<td>98 (mmol/24h)</td>
<td>56 (mmol/24h)</td>
<td>-11.30 [-22.95, 0.35]</td>
</tr>
<tr>
<td>Welsh, 1997[167]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>-8.20 [-11.90, -1.08]</td>
</tr>
<tr>
<td>TOHP Collaborative Research Group, 1999[168]</td>
<td>NR</td>
<td>57 (mmol/24h)*</td>
<td>NR</td>
<td>-4 (mmol/24h)*</td>
<td>0.96 [-1.15, 2.18]</td>
</tr>
</tbody>
</table>

Random effects model
Heterogeneity: $P=98%$

Mean difference in diastolic blood pressure

Adults

Potassium supplements vs. placebo

Parallel RCTs

Twelve parallel RCTs that met inclusion criteria reported on the effects of potassium supplements, typically potassium chloride, to increase potassium status compared with placebo controls on diastolic BP in adults (overall RoB high), 69, 73, 119, 197, 161, 203, 216, 235, 238, 248, 251, 256 Of the seven RCTs that reported urinary potassium excretion, all reported increases in the intervention groups compared with controls. Two RCTs did not report the levels but reported that they were increased and correlated with supplementation. The random effects pooled estimate of the mean difference in diastolic BP showed a significant beneficial effect of potassium supplements (MD -4.06, 95% CI -7.58, -0.54; $I^2$ 96%; low RoB) (Figure 42a).
Crossover RCTs

Eight crossover RCTs that met inclusion criteria reported on the effects of potassium supplements vs. placebo on diastolic BP.\textsuperscript{63, 65, 115, 123, 180, 209, 218, 270} Five RCTs reported increased urinary potassium excretion compared with the control groups, and one trial did not report on urinary potassium. The random effects pooled estimate of the mean difference in diastolic BP (that included seven of the studies) showed a non-significant beneficial effect of increased potassium intake on diastolic BP (MD $-1.67$, 95% CI $-4.76$ to $1.44$, I\textsuperscript{2} 59%; low RoB).

Pooled Parallel and Crossover RCTs

Eighteen of 20 RCTs could be pooled. The random effects pooled effect estimate for both parallel and crossover RCTs showed a significant beneficial effect of increased potassium intake on diastolic BP but high heterogeneity (MD $-3.43$, 95% CI $-5.87$ to $-0.99$; I\textsuperscript{2} 93%).

Controlled Clinical Trials

Two non-randomized placebo controlled trials assessed the effects of increased potassium intake on diastolic BP.

The UK study that provided daily potassium gluconate/potassium citrate supplements to half of a group of healthy adults and placebo to the remainder reported increases in urinary potassium excretion but no significant change in diastolic BP (high RoB).\textsuperscript{187}

The study conducted in Italy administered 30mmol potassium aspartate daily to half of a group of adults with mild HTN and placebo to the remainder. At 4 weeks, diastolic BP was significantly decreased in the potassium supplemented group (95.0 ± 5.6 vs. 87.2 ± 4.3 mmHg, P < 0.001).\textsuperscript{108}

Potassium from foods vs. usual diet

Parallel RCTs

A 2-month RCT that used coaching about dietary choices and food vouchers to increase potassium intake among urban blacks in Baltimore with controlled hypertension found increases in urinary potassium excretion in the intervention group (compared with baseline and the control group) but no change in diastolic BP.\textsuperscript{186}

Crossover RCTs

A 1.5 month crossover RCT conducted in the UK compared the use of a diet enriched with fruits and vegetables to raise potassium levels to that of potassium citrate supplements and placebo controls among individuals with mild (early) hypertension.\textsuperscript{65} This study reported no effects of increased potassium on diastolic BP.

Potassium salts compared

Parallel RCTs

A 1.5-month parallel RCT conducted in the UK randomized 85 healthy participants to 30mmol potassium chloride, 30mmol potassium citrate, or placebo.\textsuperscript{69} Both potassium chloride and citrate significantly reduced diastolic BP compared with placebo (MD $-4.30$, CI $-6.39$ to $-2.20$ and $-4.26$, CI $-6.31$ to $-2.21$, respectively); urinary potassium excretion was significantly increased in both intervention groups compared with the placebo group.\textsuperscript{69}
**Crossover RCTs**

He and colleagues reported no difference in the effects of potassium bicarbonate, potassium chloride, and placebo on diastolic BP (moderate RoB for urinary potassium excretion assessment). Vongpatanasin reported that 4 weeks of KCl supplementation decreased diastolic BP but potassium magnesium citrate and potassium citrate did not.

**Children**

Sinaiko and colleagues reported a small, statistically insignificant mean difference in diastolic BP (−1.14, 95% CI −5.34, 3.07) (Figure 42b).

The CCT that enrolled twins found no difference in diastolic BP between the potassium gluconate and potassium citrate mixture and placebo.

---

**Figure 42a. Effect of increased potassium intake on mean difference in diastolic BP for adults**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Pot Intervention</th>
<th>Achieved Sodium Control</th>
<th>Achieved Pot Control</th>
<th>MD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Type = 1: Parallel RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breschi, 2006[1156]</td>
<td>122 (mmHg/24h)</td>
<td>89 (mmHg/24h)</td>
<td>120 (mmHg/24h)</td>
<td>65 (mmHg/24h)</td>
<td>−0.39 [−0.58, −0.21]</td>
</tr>
<tr>
<td>Buxton, 1995[1157]</td>
<td>149 (mmHg/24h)</td>
<td>95 (mmHg/24h)</td>
<td>139 (mmHg/24h)</td>
<td>55 (mmHg/24h)</td>
<td>4.40 [−3.11, 12.71]</td>
</tr>
<tr>
<td>Cox, 2001[1158]</td>
<td>185 (mmHg/24h)</td>
<td>54 (mmHg/24h)</td>
<td>163 (mmHg/24h)</td>
<td>34 (mmHg/24h)</td>
<td>−0.19 [−2.14, 1.77]</td>
</tr>
<tr>
<td>Knipricht, 2003[1159]</td>
<td>165 (mmHg/24h)</td>
<td>NR</td>
<td>151 (mmHg/24h)</td>
<td>NR</td>
<td>−0.67 [−0.78, −0.54]</td>
</tr>
<tr>
<td>Nowcon, 1988[1160]</td>
<td>145 (mmHg/24h)</td>
<td>96 (mmHg/24h)</td>
<td>156 (mmHg/24h)</td>
<td>70 (mmHg/24h)</td>
<td>−2.18 [−0.29, −1.99]</td>
</tr>
<tr>
<td>Oster, 1998[1161]</td>
<td>NR</td>
<td>102 (mmHg/24h)</td>
<td>NR</td>
<td>95 (mmHg/24h)</td>
<td>3.06 [−10.26, −14.30]</td>
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<tr>
<td>Rahem, 2005[1162]</td>
<td>−92 (mmHg/24h)*</td>
<td>105 (mmHg/24h)</td>
<td>NR</td>
<td>9 (mmHg/24h)</td>
<td>−10.56 [−15.52, −5.61]</td>
</tr>
<tr>
<td>Seki, 1991[1163]</td>
<td>184 (mmHg/24h)</td>
<td>NR</td>
<td>164 (mmHg/24h)</td>
<td>52 (mmHg/24h)</td>
<td>−1.10 [0.11, 2.39]</td>
</tr>
<tr>
<td>Seki, 1991[1163]</td>
<td>184 (mmHg/24h)</td>
<td>73 (mmHg/24h)</td>
<td>165 (mmHg/24h)</td>
<td>52 (mmHg/24h)</td>
<td>−2.83 [−5.38, −0.29]</td>
</tr>
<tr>
<td>Schmidt, 1997[1164]</td>
<td>96 (mmHg/24h)</td>
<td>NR</td>
<td>90 (mmHg/24h)</td>
<td>56 (mmHg/24h)</td>
<td>−2.92 [−7.40, 1.56]</td>
</tr>
<tr>
<td>Svedmyr, 1997[1165]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>−0.34 [−1.37, 0.69]</td>
</tr>
<tr>
<td>TOHP Collaborative Research Group, 1992[1166]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>−4 (mmHg/24h)*</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: $I^2 = 35%$

---

**Figure 42b. Effect of increased potassium intake on mean difference in diastolic BP for children**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Achieved Sodium Intervention</th>
<th>Achieved Pot Intervention</th>
<th>Achieved Sodium Control</th>
<th>Achieved Pot Control</th>
<th>MD 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Type = 1: Parallel RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinaiko, 1993[1167]</td>
<td>176 (mmHg/24h)</td>
<td>100 (mmHg/24h)</td>
<td>176 (mmHg/24h)</td>
<td>63 (mmHg/24h)</td>
<td>−1.60 [−3.54, 0.34]</td>
</tr>
<tr>
<td>Sinaiko, 1993[1167]</td>
<td>173 (mmHg/24h)</td>
<td>93 (mmHg/24h)</td>
<td>126 (mmHg/24h)</td>
<td>41 (mmHg/24h)</td>
<td>−1.14 [−1.34, 0.09]</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: $I^2 = 0%$

---

135
Summary
Evidence is insufficient to draw a conclusion regarding moderating effects of age on the effects of increased potassium intake or increased dietary potassium on diastolic blood pressure. No studies directly compared individuals of different ages.

A moderate strength of evidence supports a beneficial effect of increased potassium intake on diastolic blood pressure in adults, based on 11 parallel RCTs and 7 crossover RCTs. Studies had a low risk of bias.

Evidence is insufficient to draw a conclusion regarding the effects of increasing potassium through dietary changes on diastolic BP in adults, based on two RCTs with high risk of bias.

Evidence is insufficient to draw any conclusions regarding superiority of one form of potassium supplement over another for lowering diastolic BP in adults, based on single studies with high risk of bias.

Evidence is insufficient to draw a conclusion regarding a beneficial effect of increased potassium intake on diastolic BP in children, based on two conflicting studies with high risk of bias.

Percent participants at blood pressure goal
No studies that met inclusion criteria reported on the actual proportion of participants who achieved a prespecified blood pressure goal. However, one study assessed the effect of increased potassium on the continued need for antihypertensive medication. A study conducted in Italy randomized 54 patients with hypertension to receive advice to improve dietary potassium intake or to usual diet for 1 year.235 Urinary potassium excretion increased significantly in the potassium-rich diet group compared with the usual diet group. At the end of the year, the average number of antihypertensive medications used per day decreased by 76 percent in the intervention group, compared with a 40 percent decrease in the usual diet group. Some 81 percent of intervention patients had their HTN managed on less than half of their baseline dosage, compared with 29 percent of the usual diet group.

Summary
Evidence is insufficient based on one study to draw conclusions regarding effects of increased potassium intake on achievement of a prespecified blood pressure goal.

Kidney Stones
Only one RCT that assessed the effect of increased potassium intake on kidney stone incidence or recurrence met inclusion criteria. A US RCT, reported by Barcelo and colleagues, randomized 57 patients with active idiopathic hypocitraturic calcium nephrolithiasis to 30-60 mmol/d potassium citrate supplementation for 3 years to assess the effect on the risk for kidney stone recurrence.59 Potassium citrate significantly decreased the incidence of kidney stone recurrence (MD –1.00, CI –1.16, –0.84) in the supplemented group.

Summary
Evidence is insufficient based on one study to draw conclusions regarding effects of increased potassium intake on risk for kidney stones.
Adverse Events

Six RCTs reported on adverse events associated with potassium supplement interventions.\textsuperscript{73, 197, 251, 59, 115, 209}

All six described minor gastrointestinal discomfort, but in at least one study,\textsuperscript{197} no difference was seen between active intervention and control groups.

One study reported no increase in LDL cholesterol with increased potassium intake.\textsuperscript{73}

Summary

A low strength of evidence based on six RCTs suggests minor gastrointestinal discomfort associated with use of potassium supplements.

Effect of Sex

One RCT reported outcomes of increased potassium intake on BP by sex in adults\textsuperscript{256} and one in children.\textsuperscript{238} The study on children is reported above. No RCTs reported on outcomes of increased potassium intake on incidence of HTN, percent of participants who achieve a prespecified goal, incidence of kidney stones, or AEs, by sex.

The TOHP-I trial randomized 353 US men and women to 6 months’ 60mmol potassium chloride supplementation or placebo. Women constituted 23 percent of the intervention group and 30 percent of the controls.\textsuperscript{256, 274}

Mean difference in systolic blood pressure

The TOHP-I found no significant differences between men and women in the lack of effect of increased potassium intake on systolic blood pressure at 6 months.\textsuperscript{256, 274}

Mean difference in diastolic blood pressure

The TOHP-I found no significant differences between men and women in the lack of effect of increased potassium intake on diastolic blood pressure at 6 months.\textsuperscript{256, 274}

Summary

Evidence is insufficient (based on one RCT) to draw a conclusion regarding the moderating effect of sex on the effects of increased potassium intake on BP in adults (high risk of bias for assessment of sodium and potassium exposure).

Effects of Race/ethnicity

Description of Included Studies

Two RCTs assessed effects of increased potassium intake on BP separately for black adults and the adult study population as a whole or for white and black adults,\textsuperscript{251, 256, 274} and two additional studies included only black adult participants.\textsuperscript{186, 203} No RCTs reported on outcomes of increased potassium intake on incidence of HTN, percent of participants who achieve a prespecified goal, incidence of kidney stones, or AEs, by race/ethnicity.

Svetkey randomized 101 US adults with mild hypertension to 120mmol potassium chloride or placebo for 2 months; 11 percent of the intervention group and 17 percent of the placebo control group identified as black.
As just described, the TOHP-I randomized 353 adults with high-normal BP to 6 months’ increased potassium intake. Seven percent of the intervention group and 11 percent of the control group identified themselves as black.\textsuperscript{256, 274} Obel assigned 48 black adult patients with mild hypertension in Kenya to a daily supplement of 64 mmol potassium (salt not identified) or placebo for 4 months.\textsuperscript{203} Miller and colleagues conducted a 2-month parallel RCT (the “Five Plus Nuts and Beans” trial) among US urban blacks to assess the effect of increasing dietary potassium through counseling and consumption of specific foods.

**Mean difference in systolic blood pressure**

In their study of the effects of 2 months of oral potassium chloride supplementation (120 mEq/d), Svetkey found a significant decrease in systolic BP in response to increased potassium intake among the small number of black participants (MD $-20.00$, 95% CI $-41.67$, $-1.67$), larger than that for the overall group (MD $-6.29$, 95% CI $-11.50$, $-1.08$) (low risk of bias).\textsuperscript{251}

In a study of 48 black patients with mild hypertension, Obel reported that 4 months of oral supplementation with 64mmol potassium decreased systolic BP significantly (MD $-39.00$, CI $-43.88$, $-34.12$) (high risk of bias for potassium exposure determination).\textsuperscript{203}

A 2-month RCT that used coaching about dietary choices and food vouchers to increase potassium intake among urban blacks in Baltimore with controlled hypertension found increases in urinary potassium excretion in the intervention group (compared with baseline and the control group) but no change in systolic BP (high risk of bias for potassium exposure determination).\textsuperscript{186}

The TOHP-I found no significant differences between white and black participants in the lack of effect of increased potassium intake on systolic blood pressure at 6 months (high risk of bias for potassium exposure determination).\textsuperscript{256, 274}

**Mean difference in diastolic blood pressure**

Svetkey found a significant decrease in diastolic BP in response to increased potassium intake among black participants (MD $-13.00$, 95% CI $-22.83$, $-3.17$), higher than the overall response of the group (MD $-2.50$, 95% CI $-5.39$, 0.39)\textsuperscript{251}

The TOHP-I found no significant differences between white and black participants in the lack of effect of increased potassium intake on diastolic blood pressure at 6 months.\textsuperscript{256, 274}

Among 48 black patients, Obel reported a significant decrease in diastolic BP with 2 months of increased potassium intake, compared with placebo (MD $-17.00$, CI $-19.26$, $-14.74$).\textsuperscript{203}

The dietary intervention among hypertensive urban black patients reported no improvement in diastolic blood pressure.\textsuperscript{186}

**Summary**

Evidence is insufficient to draw a conclusion regarding a moderating effect of race/ethnicity on the effect of dietary or supplemental potassium on BP-related outcomes (four RCTs with high RoB, only one of which directly compared blacks with the total population).
Key Question 5c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.

No studies that met inclusion criteria compared the effects of potassium supplementation or increased dietary potassium on blood pressure between healthy individuals and those with hypertension or other chronic conditions within the same study. However, three RCTs assessed the effects of potassium on blood pressure in healthy adults, and 18 RCTs assessed these effects in adults with pre-HTN or HTN. No studies that met inclusion criteria assessed the impact of diabetes, obesity, or renal health status on the effects of potassium interventions.

Hypertension

Two parallel RCTs and one crossover RCT assessed the effects of potassium on blood pressure in healthy participants.\(^69, 180, 197\) Eleven parallel RCTs\(^{73, 119, 203, 216, 235, 236, 248, 251, 256}\) and seven crossover RCTs\(^{63, 115, 123, 209, 218, 270}\) reported on the effects of increased potassium intake on BP in participants with prehypertension, or mild-, moderate-, or more advanced hypertension.

Detailed Synthesis

Hypertension

Mean Difference in Systolic Blood Pressure

Healthy people

Three RCTs that enrolled only normotensive participants and assessed effects of potassium interventions on systolic BP were eligible for pooling.\(^69, 180, 197\) The random effects pooled estimate for the studies showed that potassium lowered systolic BP but the effect was not statistically significant (MD \(-4.42, 95\%\ CI{-13.85, 5.02}; I^2 41\%\); n=173; low RoB) (Figure 43).

People with Prehypertension or Hypertension

The random effects pooled estimate for the parallel and crossover studies that enrolled participants with prehypertension or hypertension showed that increasing potassium intake through use of potassium supplements had a statistically significant beneficial effect on lowering systolic BP but studies were highly heterogeneous (MD \(-6.01, 95\%\ CI{-11.07, -0.95}; I^2 97\%\); n=1,051; low RoB) (Figure 43).

Three RCTs assessed the effects of increasing potassium intake through dietary modification on blood pressure among adults with hypertension.\(^65, 186, 235\) Two of the RCTs showed no effects of increased dietary potassium on BP among participants (low and moderate RoB).\(^65, 186\) A third study, which randomized 47 adults on antihypertensive medications to receive advice to increase potassium-rich foods or to usual care, reported a significant decrease in the need for antihypertensive medications among individuals in the high-potassium diet group (low RoB).\(^235\)
Figure 43. Effects of increased potassium intake on mean difference in Systolic BP for populations with hypertension and those with normal blood pressure

Mean Difference in Diastolic Blood Pressure

Healthy People

The random effects pooled effect size for the RCTs that assessed the effect of increased potassium intake on diastolic BP in normotensive individuals showed no significant beneficial effect (MD = -3.35, -12.79, 6.10; I² 88%; low RoB) (Figure 44).

People with Prehypertension or Hypertension

The random effects pooled estimate for the parallel RCTs that enrolled populations with prehypertension or HTN and assessed effects of potassium interventions on diastolic BP showed that potassium had a small but statistically significant beneficial effect on diastolic BP; studies were highly heterogeneous (MD = -3.18, 95% CI = -5.92, -0.43; I² 94%; n=1,051; low RoB for assessment of potassium exposure) (Figure 44).
Summary

Evidence is insufficient to draw conclusions regarding the moderating effect of hypertension on the effects of increased potassium intake or increased dietary potassium on blood pressure (no studies directly compared findings in normotensive populations and those with hypertension).

A low strength of evidence suggests a lack of beneficial effect of potassium on blood pressure in healthy populations (based on three RCTs).

A moderate strength of evidence supports a beneficial effect of potassium supplements on blood pressure in populations with prehypertension or hypertension (based on 11 parallel RCTs and 7 crossover RCTs, some with inconsistent findings).

Key Question 5a. Do other minerals (e.g., sodium, calcium, magnesium) modify the effect of potassium?

Description of Included Studies

Three RCTs, one parallel and two crossover, assessed the potential moderating effects of calcium, magnesium, or reduced sodium on the effects of increased potassium intake on blood pressure. Rahimi and colleagues randomized 103 patients in Iran with hypertension or high-normal blood pressure to one of four interventions for 1 month: an 800mg (20 mmol) calcium diet, a 4000mg (100mmol) potassium diet, a combination of high calcium and high potassium diet, or a control (usual) diet. The sources of the minerals were foods; no description was provided regarding whether the intervention included instruction, provision of menus, or
provision of foods, and it was not possible to estimate. Urinary potassium excretion increased significantly compared with the controls (units were not reported). Patki and colleagues \(^{209}\) randomized 37 Indian adults with mild hypertension to potassium chloride (30mmol/d) or potassium chloride and magnesium (15mmol) for 2 months, followed by a 2-week crossover and 2 months on the other regimen.

No studies assessed the influence of other minerals on the effects of potassium on other outcomes of interest for this key question (i.e., incident hypertension, percentage at goal, or incident kidney stones)

**Detailed Synthesis**

**Calcium**

Rahimi’s study found significant decreases in systolic blood pressure for the intervention groups receiving potassium (MD \(-6.40, \text{CI} \ (-11.58, -1.22)\) and calcium plus potassium (MD \(-11.00, \text{CI} \ (-17.80, -4.20)\)) but not calcium alone, compared with the control group. \(^{216}\) Systolic blood pressure decreased slightly but not significantly more in the group that increased both calcium and potassium compared to those who consumed diets enriched in one or the other.

The study found significant decreases in diastolic blood pressure for the intervention groups receiving potassium (\(-4.40, \text{CI} \ (-8.01, -0.79)\)) and calcium (MD \(-5.60, \text{CI} \ (-9.29, -1.91)\)) but the decrease in diastolic blood pressure for calcium plus potassium just missed significance (MD \(-4.20, \text{CI} \ (-8.44, 0.04)\)), compared with the control group. \(^{216}\) Systolic blood pressure decreased slightly but not significantly more in the group that increased both calcium and potassium compared to those who consumed diets enriched in one or the other.

**Magnesium**

The crossover study conducted by Patki reported that supplementation with potassium alone and potassium plus magnesium reduced systolic blood pressure, with no significant difference between them (MD \(-8.90, \text{CI} \ (-13.75, -4.05)\)) compared with placebo vs. \(-12.10, \text{CI} \ (-18.69, -5.51)\). \(^{209}\)

This study reported that supplementation with potassium alone and potassium plus magnesium reduced diastolic blood pressure, with no significant difference between them (MD \(-10.10, \text{CI} \ (-15.60, -4.60)\) compared with placebo vs. \(-13.60, \text{CI} \ (-21.00, -6.20)\). \(^{209}\)

**Sodium Reduction**

A crossover RCT conducted in Australia randomized adult twins with or without HTN who were consuming a low-sodium, high-potassium diet to receive sodium pills, aimed at returning sodium intake to usual levels, or placebo pills to assess the effects of low vs. usual sodium intake on the effects of higher potassium intake (high RoB for assessment of sodium and potassium status). \(^{202}\) The combination of low sodium and high potassium resulted in significantly lower systolic BP than did usual sodium and high potassium when measured at home but no difference when measured in the clinic. In addition, the study did not report whether the higher potassium, usual sodium diet lowered BP from that of usual diet.
Summary

Evidence from three studies is insufficient to draw conclusions regarding the modifying effect of other minerals (one study each on calcium, magnesium, and reduced sodium) on the effects of dietary or supplemental potassium (high risk of bias based on assessment of potassium and sodium exposure).
Key Question 6. Among children and adults, what is the association between potassium intake and blood pressure and kidney stone formation?

Key Points

- A low strength of evidence suggests a lack of association between potassium exposure status and adjusted BP in adults. Across seven studies (six with high RoB), three studies observed associations only for diastolic BP, and one study observed no association.
- Evidence is insufficient, based on lack of direct comparisons, to draw conclusions regarding sex differences in the association between potassium exposure and BP, risk for incident HTN, or risk for kidney stones.
- Evidence is insufficient, based on lack of direct comparisons, to draw conclusions regarding age differences in the association between potassium exposure and BP, risk for incident HTN, or risk for kidney stones.
- Evidence is insufficient, based on only one study that met inclusion criteria, to draw conclusions regarding an association between potassium exposure and BP, risk for HTN, or risk for kidney stones in children.
- A low strength of evidence supports a lack of association between potassium exposure status and risk for incident hypertension in adults. Across five studies (four with high RoB), two studies observed an inverse association.
- A low strength of evidence suggests higher potassium exposure may be associated with lower risk for kidney stones in adults. Among four cohorts (analyzed in two publications), all had high risk of bias.
- Evidence is insufficient, based on lack of direct comparisons and only one study, to draw conclusions regarding a moderating effect of hypertension on the association between potassium exposure and BP, achievement of a prespecified blood pressure goal, or incidence of kidney stones.
- Evidence is insufficient, based on lack of direct comparisons and only one study, to draw conclusions regarding a moderating effect of obesity on the association between potassium exposure and BP, risk for incident HTN, achievement of a prespecified blood pressure goal, or risk for kidney stones.

Key Question 6a. Among subpopulations defined by sex, race/ethnicity, and age (children, adolescents, young adults, older adults, elderly).

Description of Included Studies

Of the studies that met the inclusion criteria for this key question, two studies included only females, and reported on BP and incident HTN, respectively; two included only males.
and reported on BP and incident HTN and kidney stones. Three studies compared the findings for males with those for females (on BP and kidney stones, respectively).

We identified 12 prospective cohort studies that addressed the association of potassium status with blood pressure, hypertension, or the incidence of kidney stones in adults or children. One study included only young people (age 17 or less). The rest followed adults. One study compared changes in BP and incidence hypertension between men under 50 and those 50 and over.

No studies compared findings by race/ethnicity.

**Detailed Synthesis**

**Effect of Sex**

**Blood Pressure**

The NHLBI Growth and Health study followed a cohort of 10-year old girls in the U.S. over 10 years. After adjusting for race, height, activity levels, screen time, energy intake (and percentage of calories from solid fats and added sugar), and dietary fiber, they reported a small association between the highest quartile of potassium intake and decreased systolic and diastolic BP among the young women at 10 years’ followup (ages 17 to 21 years) (high RoB).

The Health Professionals’ Followup Study (HPFUS) followed a cohort of male physicians. At 4 years, they found no association of dietary potassium (assessed using a semi-quantitative food frequency questionnaire [FFQ]) with BP (high RoB).

The Rancho Bernardo Study was a prospective cohort study of 859 men and women, 50 to 79. At 12 years’ follow up, this study found comparably small associations between potassium intakes (assessed via 24-hour dietary recall) and systolic and diastolic BP for men and women (moderate RoB).

**Incident Hypertension**

At 4 years’ followup, the Nurses’ Health Study (NHS) assessed the association between self-reported HTN and various dietary factors among some 6,930 participants, ages 34 to 59 (high RoB).

Neither the Nurses’ Health Study (all women) nor the HPFUS (all men) found an association between potassium and HTN incidence.

**Incidence of Kidney Stones**

One study assessed findings from three large cohorts: the HPFUS, Nurses’ Health Study (NHS)-I, and NHS-II. The cohorts included the HPFUS (42,919 enrolled), the NHS-I (60,128 enrolled), and the NHS-II (90,629 enrolled). They reported comparable decreases in the risk for incident kidney stones among men and women with increasing dietary potassium: Men experienced a nonsignificantly lower risk than did women in the highest quintile (high RoB).

**Summary**

Evidence is insufficient, based on lack of direct comparisons, to draw conclusions regarding sex differences in the association between potassium exposure and BP, risk for incident HTN, or risk for kidney stones.
Effects of Age
Blood Pressure
Adults

24-hour or estimated 24-hour urinary potassium excretion
Chien and colleagues followed a cohort of 1,520 healthy men and women (mean age 52) in a Taiwan village over a median of 8 years (the Chin-Shan Community Cardiovascular Cohort Study [CCCC]). They found no association between estimated 24-hour urinary potassium (based on overnight urine) and SBP but a small inverse correlation with age- and sex-adjusted DBP (high RoB). Multivariate analysis of the results of the TOHP-I (which randomized 353 men and women with high-normal BP to 60mmol/d potassium or placebo), adjusted for age, race, sex, baseline BP, 24-hour urinary sodium, post-randomization z, and changes in body weight, showed no association between urinary potassium and SBP (the mean of the 3- and 6-month change in SBP from baseline). Compared to those in the lowest quartile, change in 24-hour urinary potassium excretion for the highest quartile of excretion was associated with a 1.49-mm Hg larger reduction in DBP. Multiple linear regression with a continuous term for urinary potassium excretion showed a p coefficient of change in DBP (-0.015, P = 0.021) for each unit change in 24-hour urinary potassium excretion (low RoB).

Multivariate analysis of the results of the PAPSS, which supplemented Chinese adults with mild HTN with potassium (60mmol/d) found a significant association of 24-hour urinary potassium excretion (single measurement) with reduction in SBP after adjustment for sex, baseline DBP, baseline body weight, and changes in sodium during the intervention. The study found no association of urinary potassium excretion with reduction in DBP (low overall RoB).

Potassium intake assessment via dietary records
The association of dietary potassium and other nutritional factors (determined via FFQ) with self-reported blood pressure was assessed at 4 years’ followup in the Health Professionals’ Follow-Up Study. Multivariate analysis adjusted for age, BMI, alcohol consumption, and intakes of calcium, magnesium, and fiber showed no association of potassium intake with SBP or DBP. However, controlling for four nutrients (magnesium, calcium, sodium, and fiber) simultaneously showed a significant inverse association between potassium intake and DBP (high RoB based on dietary assessment method).

As described above, the NHLBI Study found that the highest quartile of potassium intakes (from multiple 3-day diet records) was associated with lower adjusted SBP and DBP (low RoB).

At 12 years’ followup, potassium intake in the Rancho Bernardo Study, determined from 24-hour dietary recall, was weakly inversely correlated with systolic BP (high RoB).

Children
One cohort study assessed the association of potassium exposure with blood pressure in children 17 and younger after an average of 7 years’ follow up. Geleijnse and coworkers followed a cohort of children 5 to 17 who resided in a small Netherlands town and found a small
association of potassium, assessed via overnight urine samples, with SBP but not DBP (low RoB).

**Summary**

Findings from six prospective cohort studies in adults and one study among children suggest a lack of consistent associations between potassium exposure status and BP in adults (low strength of evidence). Evidence is insufficient to assess association in children or to compare associations in children with those in adults.

**Incident Hypertension**

**Adults**

*24-hour urinary potassium excretion*

The Prevention of Renal and Vascular End-Stage Disease (PREVEND) Study has followed 8,592 men and women since the late 1990s. At a median follow-up of 7.6 years, they assessed factors associated with risk for incident HTN (Systolic BP of ≥140 mm Hg, a diastolic BP of ≥90 mmHg, or the use of antihypertensive drugs). Adjusting for age, sex, BMI, smoking status, alcohol consumption, parental history of HTN, urinary sodium excretion, education, and urinary magnesium and calcium excretion, multivariate analysis showed that the lowest tertile of 24-hour potassium excretion was associated with a significant increase in HTN risk, which they reported as a non-linear inverse association between urinary potassium excretion and risk for HTN (high RoB).

At a median follow-up of 7.9 years, the CCCC, described above, reported no significant difference in incidence rates for HTN across quartiles of potassium intake and no difference in relative risk using four different adjustment models (high RoB).

*Potassium intake assessment via dietary records*

The Health Professionals’ Followup Study assessed self-reported incident HTN at 4 years. Adjusting for age, BMI, alcohol consumption, and intakes of three other nutrients (magnesium, sodium, and fiber), they found a stronger association between dietary potassium and risk for HTN in men under 50 than in men 50 and over; but the overall effect disappeared in multivariate analysis. Thus, they found no significant association between potassium intake and risk for HTN (high RoB).

At 4 years’ followup, the Nurses’ Health Study assessed the association between self-reported HTN and various dietary factors among some 6,930 participants, ages 34 to 59. Adjusting for age, BMI, alcohol consumption, and energy intakes, they found that increased potassium intake was associated with a slight decrease in relative risk for HTN (RR 0.77 at ≥3200mg/d, p<0.001). However, further adjustment for magnesium and calcium intakes eliminated the effect of potassium (high RoB).

The Chinese Health and Nutrition Survey (CHNS) has followed 16,869 healthy adults over 10 years. Dietary potassium intake was assessed using three 3-day food diaries. Results were adjusted for sodium intake, energy intake, age, sex, education, income, region, BMI, physical activity, smoking status, and alcohol consumption. At a median follow-up of 10 years, the second (1.2-1.4 g/d) through fifth quintiles (≥2.2g/d) of potassium intake were associated with lower risk for incident HTN compared with the lowest quintile (<1.2g/d) (HR for highest potassium intake 0.66, CI .56, 0.78) (moderate RoB).
No studies assessed the association of potassium exposure and incident HTN among younger persons. A low strength of evidence suggests a lack of association between potassium exposure and risk for HTN among adults.

**Incidence of Kidney Stones**

**Adults**

Two studies assessed the association between potassium exposure and first incidence of kidney stones in adults.\(^{104,131}\) The Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study (ATBC) assessed the association between intakes of potassium (and other nutrients, based on baseline FFQ) and first-time physician diagnosis of a kidney stone over 5 to 8 (median 6) years.\(^{131}\) Before adjustment for magnesium intake, higher potassium intake was significantly associated with a lower incidence of kidney stones but after adjusting for magnesium, the association with potassium became nonsignificant.

The association between potassium intake and risk for incident kidney stones was examined across three large prospective cohort studies at approximately 25 years followup as part of an assessment of the role of dietary protein and potassium.\(^{104}\) The cohorts included the HPFUS (42,919 enrolled), the Nurses’ Health Study I (60,128 enrolled), and the Nurses’ Health Study II (90,629 enrolled). Higher potassium intake was associated with lower risk for kidney stones in all 3 cohort studies assessed together and separately, adjusted for age alone or for age, BMI, history of DM, history of HTN, use of diuretics, supplemental calcium, and dietary intakes of fluids, calcium, sodium, fructose, oxalates, phytates, alcohol, and protein. Multivariate adjusted hazard ratios ranged from 0.44 (CI 0.36, 0.53) for the HPFS to 0.67 (CI 0.57, 0.78) for the NHS II.

**Summary**

Evidence is insufficient, based on lack of direct comparisons, to draw conclusions regarding age differences in the association between potassium exposure and BP, risk for incident HTN, or risk for kidney stones.

Evidence is insufficient, based on only one study that met inclusion criteria, to draw conclusions regarding an association between potassium exposure and BP, risk for HTN, or risk for kidney stones in children.

A low strength of evidence suggests a lack of association between higher potassium exposure status and lower adjusted BP in adults. Across seven studies (six with high RoB), three studies observed associations only for diastolic BP, and one study observed no association.

A low strength of evidence supports a lack of association between high potassium exposure status and risk for incident hypertension in adults. Across five studies (four with high RoB), two studies observed an inverse association.

A low strength of evidence suggests higher potassium exposure may be associated with lower risk for kidney stones in adults. Among four cohorts (analyzed in two publications), all had high risk of bias.
Key Question 6b. Among subpopulations defined by hypertension, diabetes, and obesity health status

Description of Included Studies

Only one study that met inclusion criteria to respond to this key question enrolled a population all of whom had HTN. The remainder enrolled entirely or mostly healthy people.

One study compared the association of potassium status and incident hypertension in obese participants (BMI≥29) with that in men with BMI less than 29.

No studies that met inclusion criteria assessed the potential moderating role of DM or kidney disease.

Detailed Synthesis

Hypertension

No studies assessed the modifying effects of hypertension on the association of potassium status with achievement of a prespecified goal or with incidence of kidney stones.

Blood Pressure

No studies assessed the modifying effects of hypertension on associations of potassium status with BP by comparing participants with HTN and normotensives within the same study.

Multivariate analysis of the PAPSS cohort (Chinese adults with mild HTN, half of whom were supplemented with potassium [60mmol/d]) found a significant association of urinary potassium excretion with reduction in SBP and DBP after adjustment for sex, baseline DBP, baseline body weight, and changes in sodium during the intervention (high RoB).

Summary

Evidence is insufficient, based on lack of direct comparisons and only one study, to draw conclusions regarding a moderating effect of hypertension on the association between potassium exposure and BP, achievement of a prespecified blood pressure goal, or incidence of kidney stones.

Obesity

No studies assessed the modifying effects of weight status on associations of potassium status with BP, achievement of a prespecified goal, or kidney stones.

Incident Hypertension

The HPFUS compared the association of potassium and risk for HTN in obese and non-obese adults. In bivariate analysis, the lowest tertile of potassium intake among overweight and normal weight men—but not obese men—was associated with increased HTN risk. In multivariate analysis, this relationship did not hold.

Summary

Evidence is insufficient, based on lack of direct comparisons and only one study, to draw conclusions regarding a moderating effect of obesity on the association between potassium
exposure and BP, risk for incident HTN, achievement of a prespecified blood pressure goal, or risk for kidney stones.

**Key Question 7. Among adults, what is the effect of interventions aimed at increasing potassium intake on CVD, and kidney disease morbidity and mortality, and total mortality?**

**Key Points**
- Evidence was insufficient to assess the effect of potassium supplementation on the risk for all-cause mortality, CVD/CHD morbidity or mortality, or renal morbidity or mortality.

**Description of Included Studies**
One RCT met inclusion criteria for this question. Chang and colleagues block-randomized 1,981 male veterans in a retirement home in northern Taiwan by the kitchen in which they had their meals to receive potassium-enriched salt substitute (49% sodium chloride, 49% potassium chloride, 2% other) or sodium chloride and followed them for approximately 2 to 3 years. Forty percent of the veterans had HTN. This study reported only on all-cause, CVD-, CHD- and other causes of mortality and had moderate RoB.

**Detailed Synthesis**

**All-cause mortality**
At three months, the urinary sodium to creatinine ratio (available for approximately one fourth of participants) decreased in the salt substitute group and increased in the control group; urinary sodium and sodium/potassium were not reported. At 31 months, the potassium salt-supplemented group showed a significant decrease in cumulative age-adjusted all-cause mortality compared with the control group (RR 0.68, 95% CI 0.58, 0.80).

**CVD Mortality**
Chang reported a significantly lower age-adjusted rate of CVD-related mortality among men who received the potassium-enriched salt substitute (RR 0.42, 95% CI 0.27, 0.66), which translated to an additional 4 to 11 months of life.

**CHD Mortality**
Chang also reported a significantly lower age-adjusted rate of CHD-related mortality among men who received the potassium-enriched salt substitute (RR 0.45, 95% CI 0.21, 0.99).
Key Question 7a. Do other minerals modify the effect of potassium (e.g., sodium, calcium, magnesium)?

Description of Included Studies
We identified no studies other than the one reported above.

Key Question 7b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).

Description of Included Studies
No studies that met inclusion criteria stratified by subpopulations.

Key Question 7c. Among subpopulations defined by hypertension, diabetes, obesity and renal health status.

Description of Included Studies
No studies that met inclusion criteria stratified by the populations of interest.
Key Question 8. 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?

Key Points

- Evidence is insufficient to identify associations of potassium intake with longterm chronic disease outcomes of interest.

Overview

Detailed Synthesis

Total Mortality

A total of 10 studies⁹⁹, ¹¹¹, ¹₂₅, ¹₅₅, ¹₇₄, ²₀₄, ²₀₅, ²₃₁, ²₆₂, ²₈₂ that reported analyses examining the associations between potassium intake levels and total mortality outcome were included. These studies included six among generally healthy adult populations,¹¹¹, ¹₅₅, ²₀₄, ²₃₁, ²₆₂, ²₈₂ and four studies among people with existing diseases such as CVD,²⁰⁵ type 2 diabetes⁹⁹ and CKD.¹₂₅, ¹₇₄ The latter are described in the response to Subquestion 8c.

Five prospective cohort studies¹⁵₅, ²₀₄, ²₃₁, ²₆₂, ²₈₂ and one case-cohort study¹¹¹ examined the associations between potassium intake levels and total mortality outcomes among generally healthy adult populations. These cohorts are PREVEND,¹⁵₅ the Scottish Heart Health study,²₆₂ WHI Observational Study (WHI-OS),²³¹ NHANES III,²₈₂ PURE,²⁰⁴ and the Rotterdam study.¹¹¹ Except for the WHI Observational Study, all studies included both adult men and women at baseline (mean ages ranged from 50 to 69.2 years old). The WHI OS enrolled only postmenopausal women (mean age = 63.6 years old). Mean or median follow-up times ranged from 3.7 to 14.8 years.

Potassium intake levels were assessed by 24-hour urinary potassium excretion in the PREVEND and the Scottish Heart Health studies,¹⁵₅, ²₆₂ by spot-urine samples in the PURE and the Rotterdam studies,¹¹¹, ²₀₄ by food frequency questionnaire in the WHI-OS and the Rotterdam study,¹¹¹, ²₃₁ and by 24-hour dietary recalls in NHANES III.²₈₂ The potassium intake ranged from 27.5 mmol/d (1075 mg/d) to 116.4 mmol/d (4551 mg/day). Individual study results are shown in Table 68 and Table 15.

Overall Results

The relationships between potassium intake levels and total mortality are inconsistent among the four studies that examined urinary potassium levels and total mortality.¹¹¹, ¹₅₅, ²₀₄, ²₆₂ On the contrary, three studies consistently showed an inverse relationship between dietary potassium intake and total mortality.¹¹¹, ²₃₁, ²₆₂ In the Rotterdam study, levels of both urinary potassium (by spot-urine estimated 24-hour urinary potassium excretion) and dietary potassium were assessed.¹¹¹ All studies, except for the Scottish Heart Health study, controlled for various demographics, lifestyle factors, and medical history or medications. Among these, the PREVEND,¹⁵₅ ONTARGET and TRANSCEND cohort studies,²⁰⁵ and the Rotterdam study¹¹¹ also adjusted for urinary sodium excretion in their analyses. The Scottish Heart Health study
adjusted only for age in their analyses so the results are at high risk for confounding. The overall risk of bias was rated moderate.

**Urinary Potassium Excretion and Total Mortality**

Four studies that examined urinary potassium levels and total mortality showed inconsistent results. Among these, PREVEND measured 24-hour urinary potassium excretion. The PREVEND cohort, which oversampled individuals with albuminuria (n=7795), did not find significant associations between 24-hour urinary potassium excretion (examined as a continuous measure and in quartiles) and total mortality in multivariable adjusted models that included urinary sodium excretion as a covariate (adjusted hazard ratio = 1.02; 95% CI 0.88, 1.19). In contrast, the Scottish Heart Health study showed a significant inverse relationship between 24-hour urinary potassium excretion and total mortality among both men (n=5754) and women (n=5875). However, because the Scottish Heart Health study adjusted only for age in their analyses, the results are at high risk for confounding.

The association between estimated 24-hour urinary potassium excretion and total mortality was examined in PURE and the Rotterdam study. The PURE cohort study was a large, multi-center, multi-country study, and the Rotterdam study is a population-based study of men and women living in the Netherlands. The PURE study showed significantly decreasing risk of total mortality with increasing levels of 24-hour urinary potassium excretion estimated by Kawasaki equation in the primary multivariable model (adjusted OR 0.76, 95% CI 0.65, 0.89; 0.72 [0.62, 0.85], 0.71 [0.60, 0.85], and 0.60 [0.48, 0.74] comparing quintile 2, 3, 4, and 5 to the lowest quintile, respectively, n=101945), whereas no significant linear relationship was found between estimated 24-hour urinary excretion based on an overnight urine sample and total mortality in a multivariable adjusted model that included urinary sodium as a covariate in the Rotterdam study (adjusted RR 1.08 per SD increase; 95% CI 0.91, 1.28; n=5531).

**Dietary Potassium Intake and Total Mortality**

Three studies consistently showed an inverse relationship between dietary potassium intake and total mortality outcome. Using 24-hour dietary recall data with NCI methods for estimating usual intake, both categorical and continuous analyses of NHANES III showed that higher potassium intake was significantly associated with lower total mortality in the general US population (adjusted HR 0.8 per 1000 mg/d increase; 95% CI 0.67, 0.94; n=12267). There were no significant interactions by sex, race/ethnicity, or presence of hypertension. Similar to NHANES III, the WHI OS, which enrolled postmenopausal women living in the U.S. (n=90137), also showed that the second, third, and fourth quartiles of potassium intake were significantly associated with a decreased risk of total mortality when compared to the lowest quartile of potassium intake in fully adjusted models (adjusted HR 0.91, 95% CI 0.86, 0.96 [0.79, 0.89], and 0.90 [0.85, 0.95], respectively). Unlike the analyses using urinary potassium levels, the analyses using dietary potassium intake measured by a semi-quantitative food frequency questionnaire found an inverse relationship between dietary potassium intake and total mortality in the Rotterdam study (adjusted RR = 0.78 per SD increase; 95% CI 0.65, 0.94; n=5531) (Figure 45).
Figure 45. Categorical analysis of the association between potassium levels and total mortality outcome in generally healthy populations.
Table 15. Continuous analyses of the association between potassium levels and total mortality outcome in generally healthy populations

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate 95% CI</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
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<tbody>
<tr>
<td>Kieneker, 2016</td>
<td>PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>493/7795</td>
<td>0.063</td>
<td>24-hour urinary potassium excretion</td>
<td>Median 70 mmol/24h (IQR: 56–84 mmol/24h)</td>
<td>per 26-mmol/24-h increase</td>
<td>HR</td>
<td>1.02</td>
<td>0.88</td>
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<td>Geleijnse, 2007</td>
<td>Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Dietary potassium intake</td>
<td>Random subsample mean 3.6 (SD 0.8) g/d</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.78</td>
<td>0.65</td>
<td>0.94</td>
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<tr>
<td></td>
<td></td>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>Random subsample mean 3.6 (SD 0.8) g/d</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.71</td>
<td>0.51</td>
<td>1.00</td>
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<td></td>
<td></td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>Random subsample mean 45 (SD 22) mmol/24h</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.08</td>
<td>0.91</td>
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<td></td>
<td></td>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>Random subsample mean 45 (SD 22) mmol/24h</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.95</td>
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<td>Yang, 2011</td>
<td>NHANES III</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>2270/12267</td>
<td>0.185</td>
<td>Dietary potassium intake</td>
<td>median 2780 (IQR 2164-3502; range 609-8839) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.8</td>
<td>0.67</td>
<td>0.94</td>
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<td></td>
<td></td>
<td>Male</td>
<td>Male</td>
<td>median 14.8 y</td>
<td>1267/5899</td>
<td>0.215</td>
<td>Dietary potassium intake</td>
<td>median 3272 (IQR 2660-3964) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.89</td>
<td>0.73</td>
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<td></td>
<td></td>
<td>Female</td>
<td>Female</td>
<td>median 14.8 y</td>
<td>1003/6368</td>
<td>0.158</td>
<td>Dietary potassium intake</td>
<td>median 2367 (IQR 1177-2932) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.55</td>
<td>0.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Author, Year Cohort name</td>
<td>Subgroup</td>
<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric</td>
<td>Estimate</td>
<td>Lower 95% CI</td>
<td>Upper 95% CI</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1253/2269</td>
<td>0.552</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.8</td>
<td>0.66</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>527/1540</td>
<td>0.342</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.73</td>
<td>0.54</td>
<td>0.99</td>
<td></td>
</tr>
<tr>
<td>Mexican American</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>449/1859</td>
<td>0.241</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.65</td>
<td>0.43</td>
<td>0.96</td>
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<tr>
<td>Hypertensive</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1155/NR</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.83</td>
<td>0.66</td>
<td>1.06</td>
<td></td>
</tr>
<tr>
<td>Non-hypertensive</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1115/NR</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.74</td>
<td>0.61</td>
<td>0.91</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
CVD Mortality

A total of four studies\textsuperscript{111, 204, 205, 282} that reported analyses examining the associations between potassium intake levels and total mortality outcome were included. These studies analyzed data from three studies among generally healthy adult populations,\textsuperscript{111, 204, 282} and one study among people at high risk of CVD (previous medical history of myocardial infarction, stroke/TIA, hypertension, or diabetes).\textsuperscript{205}

Two prospective cohort studies\textsuperscript{204, 282} and one case-cohort study\textsuperscript{111} examined the associations between potassium intake levels and CVD mortality outcome among generally healthy adult populations. These cohorts are PURE,\textsuperscript{204} the Rotterdam study,\textsuperscript{111} and NHANES III.\textsuperscript{282} All studies included both adult men and women at baseline (mean ages ranged from 51 to 69.2 years old). Mean or median follow-up time ranged from 3.7 to 14.8 years.

Potassium intake levels were assessed by spot-urine samples in PURE and the Rotterdam study,\textsuperscript{111} by food frequency questionnaire in the Rotterdam study,\textsuperscript{111} and by 24-hour dietary recalls in NHANES III.\textsuperscript{282} The potassium intake ranged from 30.7 mmol/d (1197 mg/d) to 104 mmol/d (4069 mg/day). Individual study results are shown in Figure 46 and Table 16.

Overall Results for Potassium and CVD Mortality

Inverse relationships were observed between potassium intake levels and CVD mortality in two studies,\textsuperscript{204, 282} but no significant associations were shown between urinary potassium (by spot-urine estimated 24-hour urinary potassium excretion) or dietary potassium and CVD mortality in the Rotterdam study.\textsuperscript{111} All three studies controlled for various demographics, lifestyle factors, and medical history or medications. The Rotterdam study\textsuperscript{111} also adjusted for urinary sodium excretion in their analyses. The overall risk of bias was rated low to moderate.

Urinary Potassium Excretion and CVD Mortality

The association between estimated 24-hour urinary potassium excretion and total mortality was examined in the PURE and the Rotterdam studies.\textsuperscript{111, 204} The PURE cohort study was a large, multi-center, multi-country study, and the Rotterdam study is a population-based study of men and women living in the Netherlands. The PURE study showed significantly decreasing risk of CVD mortality with increasing levels of 24-hour urinary potassium excretion estimated by Kawasaki equation in the primary multivariable model (adjusted OR 0.64, 95% CI 0.51, 0.80, 0.57 [0.44, 0.75], 0.45 [0.32, 0.64], and 0.48 [0.32, 0.71] comparing quintile 2, 3, 4, and 5 to the lowest quintile, respectively, n=101945),\textsuperscript{204} whereas no significant linear relationship was found between estimated 24-hour urinary excretion based on an overnight urine sample and CVD mortality in a multivariable adjusted model including urinary sodium as a covariate in the Rotterdam study (adjusted RR 1.23 per SD increase; 95% CI 0.94, 1.6; n=5531).\textsuperscript{111}

Dietary Potassium Intake and CVD Mortality

The association between estimated dietary potassium intake and CVD mortality was examined in the NHANES III and the Rotterdam study.\textsuperscript{111, 282} Using 24-hour dietary recall data with NCI methods for estimating usual intake, both categorical and continuous analyses of NHANES III found that higher potassium intake was significantly associated with lower CVD mortality in the general US population (adjusted HR 0.63 per 1000 mg/d increase; 95% CI 0.46, 0.87; n=12267).\textsuperscript{282} There were no significant interactions by sex, race/ethnicity, or presence of hypertension. Similar to the analyses using urinary potassium levels, the analyses using dietary
potassium intake (measured by a semi-quantitative food frequency questionnaire) did not find a significant association between dietary potassium intake and CVD mortality in the Rotterdam study (adjusted RR = 0.97 per SD increase; 95% CI 0.72, 1.31; n=5531).\textsuperscript{111}

**Figure 46. Categorical analysis of the association between dietary potassium intake and CVD mortality outcome in generally healthy populations**
Table 16. Continuous analyses of the association between dietary potassium intake and CVD mortality outcome in generally healthy populations

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate Lower 95% CI</th>
<th>Estimate Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geleijnse, 2007</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Dietary potassium intake</td>
<td>Random subsample mean 3.6 (SD 0.8) g/d</td>
<td>per SD increase</td>
<td>RR</td>
<td>0.97</td>
<td>0.72</td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>Random subsample mean 3.6 (SD 0.8) g/d</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.43</td>
<td>0.67</td>
<td>3.03</td>
</tr>
<tr>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>Random subsample mean 45 (SD 22) mmol/24h</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.23</td>
<td>0.94</td>
<td>1.6</td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>Random subsample mean 45 (SD 22) mmol/24h</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.45</td>
<td>0.84</td>
<td>2.54</td>
</tr>
<tr>
<td>Yang, 2011</td>
<td>All</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>2270/12267</td>
<td>0.185</td>
<td>Dietary potassium intake</td>
<td>median 2780 (IQR 2164-3502; range 609-8839) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.63</td>
<td>0.46</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Male</td>
<td>median 14.8 y</td>
<td>1267/5899</td>
<td>0.215</td>
<td>Dietary potassium intake</td>
<td>median 3272 (IQR 2660-3964) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.73</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>Female</td>
<td>median 14.8 y</td>
<td>1003/6368</td>
<td>0.158</td>
<td>Dietary potassium intake</td>
<td>median 2367 (IQR 1177-2932) mg/d</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.69</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>Non-Hispanic White</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1253/2269</td>
<td>0.552</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.68</td>
<td>0.48</td>
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<tr>
<td></td>
<td>Non-Hispanic Black</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>527/1540</td>
<td>0.342</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.52</td>
<td>0.33</td>
</tr>
<tr>
<td>Author, Year Cohort name</td>
<td>Subgroup</td>
<td>Sex</td>
<td>Follow-up duration</td>
<td>Number of events / Total N</td>
<td>Cumulated Incidence</td>
<td>Exposure assessment</td>
<td>Exposure ranges</td>
<td>Analysis unit</td>
<td>Metric</td>
<td>Estimate</td>
<td>Lower 95% CI</td>
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<tr>
<td>Mexican American</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>449/1859</td>
<td>0.241</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.36</td>
<td>0.18</td>
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<tr>
<td>Hypertensive</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1155/NR</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.64</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-hypertensive</td>
<td>Both</td>
<td>Both</td>
<td>median 14.8 y</td>
<td>1115/NR</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>per 1000 mg/d increase</td>
<td>HR</td>
<td>0.66</td>
<td>0.46</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
**CHD Mortality**

A total of two prospective cohort studies\(^\text{262, 282}\) examined the associations between potassium intake levels and CHD or IHD mortality outcomes among generally healthy adult populations. These cohorts are the Scottish Heart Health study\(^\text{262}\) and NHANES III.\(^\text{282}\) Mean or median follow-up time were 7.6 and 14.7 years, respectively.

Potassium intake levels were assessed by 24-hour urinary excretion in one study,\(^\text{262}\) and by 24-hour dietary recall in another.\(^\text{282}\) The potassium intakes ranged from 27.5 mmol/d (1075 mg/d) to 104 mmol/d (4069 mg/d). Individual study results are shown in Figure 47.

**Overall Results for CHD Mortality**

Both cohort studies showed inverse relationships between potassium intake levels and risks of CHD or IHD mortality.\(^\text{262, 282}\) However, one study (the Scottish Heart Health study) adjusted only for age in their analyses, so the results may be at increased risk for confounding. The overall risk of bias was rated as moderate.

**Urinary Potassium Excretion and Total CHD Mortality**

**24-hour urinary potassium**

The Scottish Heart Health Study\(^\text{262}\) reported that baseline 24-hour urinary potassium excretion levels were inversely associated with risks of CHD mortality in men (age-adjusted HR 0.57, 0.76, 0.59, 0.60 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875), but not in women (age-adjusted HR 0.73, 0.51, 0.62, 0.45 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754). The overall risk of bias was rated as high.

**Dietary Potassium Intake and CHD Mortality**

The NHANES III followup study showed that higher dietary potassium intake levels were associated with lower risks of CHD mortality for both categorical and continuous analyses (adjusted HR 0.51 per 1000 mg increase; 95% CI 0.32, 0.81; n=12267).\(^\text{282}\) The overall risk of bias was rated as low.

**Figure 47. Categorical analysis of the association between urinary or dietary potassium levels and CHD mortality outcome in generally healthy populations**
Stroke

A total of 15 studies that analyzed the associations between potassium intake levels and stroke were included. These studies analyzed data from 13 studies among generally healthy adult populations, and two studies among people with existing diseases such as CKD and CVD (described in subquestion 8c). Three studies that examined urinary potassium levels and stroke outcome. Overall Results

Twelve prospective cohort studies, and one case-control study examined the associations between potassium intake levels and stroke among generally healthy adult populations. These studies included 12 non-overlapping cohorts: the PREVEND cohort, the Rancho Bernardo California cohort, the PURE cohort, the Rotterdam study, NHANES I, EPIC-Netherland cohort, a pooled analysis of NHS I and II, Swedish Mammography cohort, WHI-OS, HPFS, Cardiovascular Health Study, and the ATBC cohort. Among these, six cohorts (PREVEND, the Rancho Bernardo California cohort, PURE, the Rotterdam study, EPIC-Netherland cohort, and NHANES) included both adult men and women (mean ages ranged from 48.6 to 69.2 years). The Cardiovascular Health Study enrolled older men and women (>65 years) living in four US communities. Three studies (a pooled analysis of NHS I and II, the Swedish Mammography cohort, and WHI-OS) exclusively enrolled adult women (mean ages ranged from 60.7 to 63.6 years), and two studies (HPFS and the ATBC cohort) exclusively enrolled adult men (mean ages ranged from 57.3 to 57.8 years). Mean or median follow-up times ranged from 3.7 to 19 years.

Potassium intake levels were assessed by 24-hour urinary potassium excretion in one study, by spot-urine samples in two studies, and by 24-hour dietary recalls in three studies. Among these, the Rotterdam study assessed both urinary and dietary potassium intake levels. The potassium intake ranged from 28 mmol/d (1424 mg/d) to 149 mmol/d (5859 mg/day). Individual study results are shown in Figures 48 and 49, and Table 17.

Overall Results for Stroke

The relationships between potassium intake levels and stroke are inconsistent among the three studies that examined urinary potassium levels and stroke outcome. Five of the 11 studies showed an inverse relationship between dietary potassium intake levels and risks of stroke, while the other six found no significant associations. Except for the Rancho Bernardo California study, all studies controlled for various demographics, lifestyle factors, and medical history or medications. Among these, the PREVEND cohort and the Rotterdam study also adjusted for urinary sodium excretion in their analyses. One of the NHANES I analyses adjusted only for age and race. The overall risk of bias was rated moderate.

Urinary Potassium Excretion and Stroke

Only one study examined the relationships between baseline 24-hour potassium excretion levels and risks of stroke. Specifically, the PREVEND cohort found no significant associations between baseline 24-hour potassium excretion levels and risks of stroke in both categorical and continuous analyses (adjusted HR 1.13; 95% CI 0.88, 1.46; n=7795).
The association between estimated 24-hour urinary potassium excretion and stroke outcome was examined in two studies. The PURE cohort (n=101945) found that the second quintile of urinary potassium excretion (<1.5-1.99 g/d; median = 44.6 mmol/d) was associated with a reduced risk of stroke compared to the lowest quintile (<1.5 g/d) of urinary potassium excretion (adjusted OR = 0.82; 95% CI 0.68, 0.99). The risks of stroke were not statistically significant when comparing the third (2.0-2.49 g/d; median = 57.4 mmol/d), fourth (2.5-3.5 g/d; median = 70.3 mmol/d), and the highest quintile (>3 g/d) levels to the lowest quintile (adjusted OR [95% CI] = 0.85 [0.70, 1.03], 0.81 [0.63, 1.05], and 0.97 [0.72, 1.31], respectively. The other study is the Rotterdam study, which showed no significant linear relationships between levels of estimated 24-hour urinary excretion (based on an overnight urine sample) and risks of stroke (adjusted RR = 1.17 per SD increase; 95% CI 0.86, 1.58; n=5531).

**Dietary Potassium Intake and Stroke**

Eleven studies examined the relationship between dietary potassium intake and stroke outcome. Three studies (a pooled analysis of NHS I and II, the Swedish Mammography cohort, and the EPIC-Netherlands cohort) exclusively enrolled adult men. The Cardiovascular Health Study enrolled older men and women (≥65 years) living in four U.S. communities. Three studies (a pooled analysis of the Rotterdam study, the EPIC-Netherlands cohort, and the NHANES I cohort) exclusively enrolled adult women, and two studies (HPFS and the ATBC cohort) exclusively enrolled adult men.

Assessment of the Rancho Bernardo California cohort found that higher baseline dietary potassium excretion levels were significantly associated with lower risks of stroke mortality (adjusted HR 0.60; 95% CI 0.44, 0.81; n=859). The associations were similar in men (adjusted RR = 0.65; 95% CI 0.41, 1.00; n=356) and in women (adjusted RR = 0.56; 95% CI 0.03, 0.82; n=503). Furthermore, categorical analyses of the NHANES I follow-up study showed that higher potassium intake levels were associated with lower risks of stroke (adjusted HR 0.75 95% CI 0.63, 0.88, 0.85 [0.71, 1.01], and 0.76 [0.58, 1.01] comparing the second, third, and the highest quartile to the lowest quartile, respectively; n=9805). Subgroup analyses of NHANES I showed increased risk of stroke mortality (comparing the lowest to highest tertile of dietary potassium intake) in black men (age-adjusted RR = 4.27; 95% CI 1.88, 9.19) compared with white men (age-adjusted RR = 1.66; 95% CI 1.32, 2.14), but risk was higher in white women (age-adjusted RR 1.13, 95% CI 0.84, 1.66) than in black women (age-adjusted RR 0.80, 95% CI 0.21, 2.01). On the contrary, both the Rotterdam study (adjusted RR 1.02 per SD increase; 95% CI 0.71, 1.46; n=5531) and the EPIC-Netherlands cohort study (adjusted HR 0.97 per 1 g increase; 95% CI 0.83, 1.13; n=36094) showed no significant linear relationships between dietary potassium intake and stroke outcome.

The Cardiovascular Health Study found that lower potassium intake (≤2.34 g/d), compared to higher potassium intake (>2.34 g/d) was associated with an increased risk of stroke among older men and women (≥65 years). Three studies examined the associations between dietary potassium intake levels and risks of stroke among adult women. Only the WHI-OS study showed statistically significant results, that is, compared to the lowest potassium intake quartile (<1925.5 mg/d), the second, third, and highest potassium intake quartiles were associated with lower risks of stroke (adjusted HR 0.88, 95% CI 0.79, 0.98, 0.85 [0.76, 0.94], and 0.88 [0.79, 0.98], respectively; n=90137) among postmenopausal women. The analyses of the Swedish Mammography Cohort showed similar but smaller, non-significant associations (adjusted HR [95% CI] 0.90 [0.77, 1.06], 0.94
[0.79, 1.11], 0.85 [0.71, 1.03], and 0.89 [0.72, 1.10] comparing the second, third, fourth, and highest quintile to the lowest quintile, respectively; n=34670)\textsuperscript{170} The pooled analysis of NHS I and II did not find significant associations (adjusted HR [95% CI] = 1.0 [0.89, 1.12], 0.92 [0.81, 1.05], 0.91 [0.79, 1.05], and 0.91 [0.78, 1.06] comparing the second, third, fourth, and highest quintile to the lowest quintile, respectively; n=34670)\textsuperscript{38}

The ranges of dietary potassium intake levels were greater in the two studies in adult men: the HPFS study (2400 to 4300 mg/d)\textsuperscript{55} and the ATBC study\textsuperscript{171} of adult male smokers (3919 to 5859 mg/d). The higher potassium intake levels were associated with small, but not statistically significant, reduced risks of stroke in the HPFS study (adjusted HR [95% CI] 0.86 [0.61, 1.18], 0.82 [0.56, 1.2], 0.83 [0.56, 1.24], and 0.69 [0.45, 1.07] comparing the second, third, fourth, and highest quintile to the lowest quintile, respectively; n=43738).\textsuperscript{55} In the ATCB study, no significant associations were shown (adjusted HR [95% CI] = 1.07 [0.96, 1.21], 0.94 [0.83, 1.06], 0.95 [0.84, 1.08], and 0.92 [0.81, 1.04], respectively; n=26556).\textsuperscript{171}

\textbf{Figure 48. Categorical analysis of the association between urinary or dietary potassium levels and stroke outcome in generally healthy populations}
Figure 49. Categorical analysis of the association between dietary potassium levels and stroke outcome in generally healthy adult women or men.

Adebamowo, 2015 Pooled analysis of NHS I and II

Larsson, 2011 Swedish Mammography Cohort

Seth, 2014 WHI–OS

Ascherio, 1998 HPFS

Larsson, 2008 ATBC

Stroke: 3780/180684

Stroke: 1680/34870

Stroke: 3046/96197

Stroke: 3284/43738

Cerebral infarction: 2702/265556
Table 17. Continuous analyses of the association between potassium levels and stroke outcome in generally healthy populations

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kieneker, 2016 PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5y (IQR 9.9 - 10.8y)</td>
<td>493/7795</td>
<td>0.063</td>
<td>24-hour urinary potassium excretion</td>
<td>Median 70 mmol/24h (IQR: 56–84 mmol/24h)</td>
<td>per 26- mmol/24- h increase</td>
<td>HR</td>
<td>1.13</td>
<td>0.88</td>
<td>1.46</td>
</tr>
<tr>
<td>Geleijnse, 2007 Rotterdam Study</td>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Dietary potassium intake</td>
<td>Random subsample mean 3.6 (SD 0.8) g/d</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.17</td>
<td>0.86</td>
<td>1.58</td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Dietary potassium intake</td>
<td>Random subsample mean 3.6 (SD 0.8) g/d</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.11</td>
<td>0.61</td>
<td>2.04</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>795/5531</td>
<td>0.144</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>Random subsample mean 45 (SD 22) mmol/24h</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.02</td>
<td>0.71</td>
<td>1.46</td>
<td></td>
</tr>
<tr>
<td>Initially free of CVD and HTN</td>
<td>Both</td>
<td>median 5.5 y</td>
<td>NR/783</td>
<td>--</td>
<td>Estimated 24-hour urinary potassium excretion (spot urine)</td>
<td>Random subsample mean 45 (SD 22) mmol/24h</td>
<td>per SD increase</td>
<td>RR</td>
<td>1.06</td>
<td>0.50</td>
<td>2.29</td>
<td></td>
</tr>
<tr>
<td>Khaw, 1987</td>
<td>All</td>
<td>Both</td>
<td>12 y</td>
<td>24/859</td>
<td>0.028</td>
<td>Dietary potassium intake</td>
<td>mean 64 (range 17-154) mmol/d</td>
<td>per 10 mmol/d increase</td>
<td>RR</td>
<td>0.60</td>
<td>0.44</td>
<td>0.81</td>
</tr>
<tr>
<td>Sluijs, 2014</td>
<td>All</td>
<td>Both</td>
<td>12 y</td>
<td>631/36094</td>
<td>0.017</td>
<td>Dietary potassium intake</td>
<td>mean 3672 (SD 903) mg/d</td>
<td>Per 1 g/d increase</td>
<td>HR</td>
<td>0.97</td>
<td>0.83</td>
<td>1.13</td>
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166
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimate</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green, 2002</td>
<td>EPIC-Netherlands</td>
<td>&gt;65 years</td>
<td>Both</td>
<td>Median 7.3 y</td>
<td>NR</td>
<td>NR</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>≤2.34 g/d vs. &gt;2.34 (reference)</td>
<td>RR</td>
<td>1.3</td>
<td>1.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Fan, 2000</td>
<td>NHANES I</td>
<td>White</td>
<td>Male</td>
<td>mean 16.7 y</td>
<td>93/3169</td>
<td>0.029</td>
<td>Dietary potassium intake</td>
<td>mean 2557 mg/d</td>
<td>&lt;2003 mg/d vs. &gt;2879 mg/d</td>
<td>RR</td>
<td>1.66</td>
<td>1.32</td>
<td>2.14</td>
</tr>
<tr>
<td>Black</td>
<td>Male</td>
<td>mean 16.7 y</td>
<td>28/595</td>
<td>0.047</td>
<td>Dietary potassium intake</td>
<td>mean 1884 mg/d</td>
<td>&lt;1260 mg/d vs. &gt;2206 mg/d</td>
<td>RR</td>
<td>4.27</td>
<td>1.88</td>
<td>9.19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>Female</td>
<td>mean 16.7 y</td>
<td>136/5073</td>
<td>0.027</td>
<td>Dietary potassium intake</td>
<td>mean 1942 mg/d</td>
<td>&lt;1508 mg/d vs. &gt;2207 mg/d</td>
<td>RR</td>
<td>1.13</td>
<td>0.84</td>
<td>1.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>Female</td>
<td>mean 16.7 y</td>
<td>47/1029</td>
<td>0.046</td>
<td>Dietary potassium intake</td>
<td>mean 1469 mg/d</td>
<td>&lt;1017 mg/d vs. &gt;1641 mg/d</td>
<td>RR</td>
<td>0.8</td>
<td>0.21</td>
<td>2.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>Male</td>
<td>mean 16.7 y</td>
<td>45/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;2003 mg/d vs. &gt;2879 mg/d</td>
<td>RR</td>
<td>2.13</td>
<td>1.09</td>
<td>6.78</td>
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<td></td>
</tr>
<tr>
<td>HTN</td>
<td>Female</td>
<td>mean 16.7 y</td>
<td>93/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;1260 mg/d vs. &gt;2206 mg/d</td>
<td>RR</td>
<td>1.16</td>
<td>0.86</td>
<td>3.59</td>
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</tr>
<tr>
<td>Non-HTN</td>
<td>Male</td>
<td>mean 16.7 y</td>
<td>76/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;1508 mg/d vs. &gt;2207 mg/d</td>
<td>RR</td>
<td>1.23</td>
<td>0.84</td>
<td>3.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HTN</td>
<td>Female</td>
<td>mean 16.7 y</td>
<td>90/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;1017 mg/d vs. &gt;1641 mg/d</td>
<td>RR</td>
<td>1.11</td>
<td>0.85</td>
<td>3.54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Myocardial infarction

A total of two publications\textsuperscript{111, 204} that reported analyses examining the associations between potassium intake levels and myocardial infarction (MI) among generally healthy adult populations.

The two studies are the PURE prospective cohort study\textsuperscript{204} and the Rotterdam case-cohort study.\textsuperscript{111} Both studies included both adult men and women at baseline (mean ages were 51 and 69.2 years, respectively). Mean or median follow-up times were 3.7 and 5.5 years. Potassium intake levels were assessed by spot-urine samples in both studies, ranging from 104 mmol/d (2392 mg/d) to 365 mmol/d (8395 mg/d). In addition to urinary potassium measures, the Rotterdam study also assessed dietary potassium intake using a food frequency questionnaire. Individual study results are shown in Figure 50.

Overall Results

The two studies both showed non-significant results for relationship between estimated 24-hour urinary potassium excretion and MI.\textsuperscript{111, 204} One study also showed no significant linear relationship between dietary potassium intake and MI.\textsuperscript{111} Both studies controlled for various demographics, lifestyle factors, and medical history or medications. One study\textsuperscript{111} also adjusted for urinary potassium excretion in their analyses. The overall risk of bias was rated high based on exposure assessment and low to moderate for the other criteria.

Urinary Potassium Excretion and MI

Estimated 24-hour urinary potassium excretion

The analyses that used the PURE cohort (n=101945) showed no significant associations between 24-hour urinary potassium excretion levels (estimated by Kawasaki equation) and risks of MI (adjusted HR [95% CI] = 1.03 [0.83, 1.27], 0.85 [0.67, 1.07], 0.93 [0.72, 1.19], and 0.89 [0.66, 1.2] comparing the second, third, fourth, and highest quintile levels of urinary potassium excretion to the lowest quintile [<1.5 g/day], respectively).\textsuperscript{204}

The Rotterdam study also showed no significant linear relationship between estimated 24-hour urinary excretion based on an overnight urine sample and MI (adjusted RR = 1.11 per SD increase; 95% CI 0.87, 1.43; n=5531).\textsuperscript{111}

Dietary Potassium Intake and MI

The Rotterdam study showed no significant linear relationship between dietary potassium intake and MI outcome (adjusted RR = 0.90 per SD increase; 95% CI 0.65, 1.24; n=5531).\textsuperscript{111}
Combined CHD Morbidity and Mortality

A total of two prospective cohort studies\textsuperscript{155, 262} reported analyses examining the associations between potassium intake levels and combined CHD morbidity and mortality outcome among generally healthy adult populations. These cohorts are the Scottish Heart Health study\textsuperscript{262} and PREVEND.\textsuperscript{155} Both studies included both adult men and women at baseline. Mean or median follow-up times were 7.6 and 10.5 years, respectively. Potassium intake levels were assessed by 24-hour urinary potassium excretion in both studies, ranging from 27.5 mmol/d (1075 mg/d) to 112 mmol/d (4379 mg/d). Individual study results are shown in Figure 51.

Overall Results

The two studies showed inconsistent associations between urinary potassium levels and combined CHD mortality outcomes.\textsuperscript{155, 262} However, one controlled for various demographics, lifestyle factors, medical history or medications, and urinary sodium excretion,\textsuperscript{155} whereas the other adjusted only for age in their analyses.\textsuperscript{262} The latter study may be at increased risk for confounding. The overall risk of bias was rated low for exposure assessment but moderate for all other criteria.

Urinary Potassium Excretion and Combined CHD Morbidity and Mortality

24-hour urinary potassium

The two studies showed inconsistent associations between urinary potassium levels and combined CHD mortality outcomes.\textsuperscript{155, 262} Specifically, the PREVEND study did not find a significant association between baseline 24-hour potassium excretion and CHD events for either categorical or continuous analyses (adjusted HR = 0.9; 95% CI 0.77, 1.04; n=7795). The Scottish Heart Health study showed a positive relationship between quintiles of 24-hour urinary potassium excretion levels and all CHD outcome in men (age-adjusted HR = 0.62, 0.87, 0.58, 0.66 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754),
but no significant association in women (age-adjusted HR = 0.91, 0.57, 0.79, 0.67 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875). Again, because the Scottish Heart Health study adjusted only for age in their analyses, these results are at higher risk for confounding.

Figure 51. Categorical analysis of the association between urinary potassium levels and combined CHD morbidity and mortality outcome in generally healthy populations

Combined CVD morbidity and mortality

Potassium intake

A total of three publications\textsuperscript{93, 155, 204} were identified that reported on the associations between potassium intake levels and combined CVD morbidity and mortality outcome among generally healthy adult populations. These studies included three non-overlapping cohorts: the TOHP (I and II) cohort,\textsuperscript{93} PREVEND,\textsuperscript{155} and PURE cohort.\textsuperscript{204} All studies included both adult men and women at baseline. Mean or median follow-up time ranged from 3.7 to 10.5 years.

Sodium intake levels were assessed by 24-hour urinary potassium excretion in two studies,\textsuperscript{93, 155} and by spot-urine samples in one study.\textsuperscript{204} The potassium intake ranged from 30.7 mmol/d (1200 mg/d) to 100 mmol/d (3910 mg/d). Individual study results are shown in Figure 52 and Table 18.

Overall Results

No significant associations were found between urinary potassium levels and combined CVD morbidity and mortality outcomes.\textsuperscript{93, 155, 204} All studies controlled for various demographics, lifestyle factors, and medical history. Among these, the TOHP I and II follow-up study\textsuperscript{93} and PREVEND,\textsuperscript{155} also adjusted for urinary sodium excretion in their analyses. The overall risk of bias was rated low to moderate.
Urinary Potassium Excretion and Combined CVD Morbidity and Mortality

24-hour urinary potassium

Two studies examined the relationships between baseline 24-hour urinary potassium excretion levels and risks of combined CVD morbidity and mortality outcomes. Both showed non-significant results.\(^93\),\(^155\) Specifically, the TOHP (I and II) follow-up study, which enrolled the control groups from the original sodium reduction trials, showed no significant associations between baseline 24-hour urinary potassium excretion levels and risks of total cardiovascular events in both categorical and continuous analyses (adjusted RR per 50 mmol/d increase = 0.67; 95% CI 0.41, 1.10).\(^93\) The PREVEND study\(^155\) also did not show significant associations between the baseline 24-hour urinary potassium excretion levels and risks of composite cardiovascular outcomes in both categorical and continuous analyses (adjusted RR per 26 mmol/d increase = 0.99; 95% CI 0.88, 1.13)

Estimated 24-hour urinary potassium excretion

The association between estimated 24-hour urinary sodium excretion and combined CVD morbidity and mortality outcomes was examined in one study.\(^204\) The PURE cohort showed that higher levels of urinary potassium excretion were associated with mostly non-significant, reduced risks of major cardiovascular events compared to the lowest quintile (adjusted OR [95% CI] = 0.9 [0.79, 1.03], 0.84 [0.73, 0.97], 0.87 [0.74, 1.03], and 0.87 [0.72, 1.06] compared second, third, fourth, and fifth quintile to the lowest quintile, respectively; n=101945).\(^204\)

Figure 52. Categorical analysis of the association between urinary potassium levels and combined CVD morbidity and mortality outcome in generally healthy populations

Other CVD outcomes

Potassium intake

One study\(^121\) that examined the association between dietary potassium intake and other CVD outcomes was included. The Strong Heart Study (SHS) is a longitudinal population-based survey of cardiovascular risk factors and disease in young adult American Indians.\(^121\) The mean age in the SHS was 28.4 years and follow-up time was 4 years.

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Overall Results

The SHS study found that potassium intake (assessed by a food frequency questionnaire) was not associated with changes in left atrium diameter, LV diameter, or LV mass. The overall risk of bias of this study was rated high.
Table 18. Continuous analyses of the association between potassium levels and combined CVD morbidity and mortality outcome in generally healthy populations

<table>
<thead>
<tr>
<th>Author, Year Cohort name</th>
<th>Subgroup</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric Estimate</th>
<th>Lower 95% CI</th>
<th>upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cook, 2009&lt;sup&gt;193&lt;/sup&gt; TOHP I &amp; II control groups</td>
<td>All</td>
<td>Both</td>
<td>median 5 y (TOHP I) 4 y (TOHP II)</td>
<td>166/2084</td>
<td>0.080</td>
<td>24-hour urinary potassium excretion</td>
<td>NR</td>
<td>per 50 mmol/d increase</td>
<td>RR</td>
<td>0.67</td>
<td>0.41</td>
</tr>
<tr>
<td>Kieneker, 2016&lt;sup&gt;135&lt;/sup&gt; PREVEND</td>
<td>All</td>
<td>Both</td>
<td>median 10.5 y (IQR 9.9 - 10.8y)</td>
<td>785/7795</td>
<td>0.101</td>
<td>24-hour urinary potassium excretion</td>
<td>Median 70 (IQR 56–84) mmol/24h</td>
<td>per 26-mmol/d increase</td>
<td>HR</td>
<td>0.99</td>
<td>0.88</td>
</tr>
</tbody>
</table>

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; NR = not reported; RR = relative risk; SD = standard deviation; y = years
Mean difference between groups in estimated Glomerular Filtration Rate

The PREVEND study followed 5315 Dutch adults free of CKD, aged 28 to 75 years, for a median of 10.3 years. Using a multi-variable adjusted model, this study found that a 1 SD (21 mmol/24hr) decrease in urinary potassium excretion was associated with a 16% higher risk of developing CKD, with risk of CKD defined as eGFR < 60 ml/min per 173 m^2, or urinary albumin excretion of >30 mg/24 h, or both (adjusted HR per 21 mmol/d increase = 1.16; 95% CI 1.06, 1.28). The overall risk of bias was rated low.

Number of patients with end stage renal disease

The U.S. National Institutes of Health–American Association of Retired Persons Diet and Health Study followed US adults, ages 51 to 70 years, for an average of 14.3 years. This study found that being in the highest quintile of potassium intake (assessed by a food frequency questionnaire) was associated with a decreased risk of dying from a renal cause (adjusted HR = 0.78; 95% CI 0.67, 0.90), and with an increased risk of self-reported dialysis (adjusted HR = 1.27; 95% CI 1.02, 1.57). The overall risk of bias was rated high.

Key Question 8a. Do other minerals (e.g., sodium, calcium, magnesium) modify the association with potassium?

Description of Included Studies

No studies were identified that addressed this question.

Key Question 8b. Among subpopulations defined by sex, race/ethnicity, age (young adults, older adults, elderly), and for women (pregnancy and lactation).

Description of Included Studies

Effect of Sex

All-cause mortality

Using 24-hour dietary recall data with NCI methods for estimating usual intake, both categorical and continuous analyses of NHANES III showed that higher potassium intake was significantly associated with lower total mortality in the general US population (adjusted HR 0.8 per 1000 mg/d increase; 95% CI 0.67, 0.94; n=12267), but no significant interactions by sex.

Similarly, the WHI OS also showed that the second, third, and fourth quartiles of potassium intake were significantly associated with a decreased risk of total mortality when compared to the lowest quartile of potassium intake in fully adjusted models (adjusted HR 0.91, 95% CI 0.86, 0.96, 0.84 [0.79, 0.89], and 0.90 [0.85, 0.95], respectively).
Stroke

Subgroup analyses of NHANES I showed increased risk of stroke mortality (comparing the lowest to highest tertile of dietary potassium intake) in black men (age-adjusted RR = 4.27; 95% CI 1.88, 9.19) compared with white men (age-adjusted RR = 1.66; 95% CI 1.32, 2.14), but risk was higher in white women (age-adjusted RR 1.13, 95% CI 0.84, 1.66) than in black women (age-adjusted RR 0.80, 95% CI 0.21, 2.01).\textsuperscript{103}

Total CHD Mortality

The Scottish Heart Health Study\textsuperscript{262} reported that baseline 24-hour urinary potassium excretion levels were inversely associated with risks of CHD mortality in men (age-adjusted HR 0.57, 0.76, 0.59, 0.60 comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5875), but not in women (age-adjusted HR 0.73, 0.51, 0.62, 0.45 [CIs were not reported] comparing quintiles 2, 3, 4, and 5 to the lowest quintile; n=5754). The overall risk of bias was rated as high.

Assessment of the Rancho Bernardo California cohort found that higher baseline dietary potassium excretion levels were significantly associated with lower risks of stroke mortality and that the associations were similar in men (adjusted RR = 0.65; 95% CI 0.41, 1.00; n=356) and in women (adjusted RR = 0.56; 95% CI 0.03, 0.82; n=503).\textsuperscript{153}

Effects of Race/Ethnicity

Stroke

Subgroup analyses of NHANES I showed increased risk of stroke mortality (comparing the lowest to highest tertile of dietary potassium intake) in black men (age-adjusted RR = 4.27; 95% CI 1.88, 9.19) compared with white men (age-adjusted RR = 1.66; 95% CI 1.32, 2.14), but risk was higher in white women (age-adjusted RR 1.13, 95% CI 0.84, 1.66) than in black women (age-adjusted RR 0.80, 95% CI 0.21, 2.01).\textsuperscript{103}

Effects of Age

No studies that met inclusion criteria conducted subgroup analyses by age.

Key Question 8c. Among subpopulations defined by hypertension, diabetes, and obesity health status

Description of Included Studies

Eight publications examined the associations between potassium intake and total mortality, CVD, CHD, stroke, or kidney disease morbidity and mortality exclusively among people with existing diseases such as hypertension,\textsuperscript{40} history of CVD,\textsuperscript{205} Type 2 DM,\textsuperscript{51, 98, 99} and CKD.\textsuperscript{125, 174, 189} Individual study results are shown in Figure 53, Figure 54 and Table 19.

The results from these studies are described together with subgroup analyses\textsuperscript{103, 282} in this section. The findings are categorized by comorbidity, rather than by outcome.
Detailed Synthesis

Hypertension

One study examined the associations between 24-hour urinary potassium levels and risk for MI among hypertensive men in a worksite HTN program in New York City. After an average of 3.8 years of followup, no significant linear associations were observed between baseline 24-hour urinary potassium excretion levels and risk of MI (adjusted HR per SD [26.4 mmol/d] increase = 1.29; 95% 0.93, 1.79; n=1900).40

Two subgroup analyses of two population-based cohort studies in the U.S. examined the associations between dietary potassium levels and total mortality, CVD mortality, or stroke outcome among hypertensive adults.103,282 Subgroup analyses of NHANES I showed an inverse relationship between dietary potassium intake levels and risks of stroke among men and women adjusting for age and race. Comparing the lowest to highest tertile of dietary potassium intake, the age-adjusted risk of stroke mortality was 2.13 (95% CI 1.09, 6.78) in hypertensive men, and 1.16 (95% CI 0.86, 3.59) in hypertensive women.103 Significant inverse linear relationships also were observed between baseline dietary potassium take levels and risks of total mortality or CVD mortality (adjusted HR [95% CI] = 0.83 [0.66, 1.06] and 0.64 [0.38, 1.06], respectively) among adults with HNT in subgroup analyses of NHANES III.282

History of CVD

One study examined the associations between estimated urinary potassium excretion levels and total mortality, CVD, CHD, or stroke outcomes among adults with history of CVD (including HTN).205 ONTARGET and TRANSCEND were two large, multi-center, multi-country cohorts of people at high risk of CVD; both cohorts reported on all-cause mortality, CVD mortality, MI incidence, and stroke incidence. This study found no significant associations between higher levels of 24-hour urinary potassium excretion (estimated by Kawasaki equation) and total mortality (adjusted HR was 1.06 [0.92, 1.21], 1.09 [0.95, 1.26], 1.07 [0.90, 1.25], and 1.01 [0.83, 1.24] comparing quintiles 2, 3, 4, and 5 to the lowest quintile, respectively; n=28880), CVD mortality (adjusted HR was 0.97 [0.82, 1.16], 0.99 [0.83, 1.19], 1.01 [0.82, 1.23], and 1.05 [0.81, 1.34] comparing quintile 2, 3, 4, and 5 to lowest quintile, respectively), and MI (adjusted HR was 1.18 [0.93, 1.50], 1.11 [0.87, 1.42], 1.10 [0.84, 1.43], and 1.07 [0.78, 1.47] comparing quintile 2, 3, 4, and 5 to lowest quintile, respectively). However, inverse relationships were found between estimated urinary potassium excretion levels and risks of stroke (adjusted HR was 0.77 [0.63, 0.94], 0.73 [0.59, 0.90], 0.71 [0.56, 0.91], and 0.68 [0.49, 0.92] comparing quintiles 2, 3, 4, and 5 to the lowest quintile, respectively).205

History of Diabetes

Three publications examined the associations between 24-hour potassium excretion levels and total mortality or kidney disease morbidity and mortality outcomes among patients with type 2 diabetes.51,98,99 Among these, two studies had overlapping study populations.98,99

Among a subsample of ONTARGET participants who were diagnosed with vascular disease or Type 2 diabetes with end-organ damage, the second and third tertiles of 24-hour urinary potassium excretion were significantly associated with a decreased risk of total mortality.
(adjusted odds ratio [95% CI] was 0.89 [0.81, 0.99] and 0.77 [0.71, 0.98], respectively; n=3088). This study did not find a significant association between potassium excretion and risk of CKD. Comparing the second and third tertiles to the lowest tertile, risk of CKD was 0.94 (95% CI=0.87 – 1.01) and 0.87 (95% CI=0.73 – 1.03), respectively. However, another observational study followed a subsample of ONTARGET participants who were diagnosed with Type 2 diabetes but without macroalbuminuria, for 5.5 years. This study reported on the incidence or progression of CKD and found that the 2nd and 3rd tertiles of potassium excretion were significantly associated with reduced risk of CKD compared to the lowest tertile (adjusted OR=.90 [0.85, 0.95] and 0.78 [0.69, 0.88], respectively. The Shiga Prospective Observational Follow-up Study followed patients with Type 2 diabetes and eGFR>=60 ml/min per 1.73 m2 in Japan for a median of 11 years. This study reported on three outcomes related to renal function: incidence of a 50% decline in eGFR, progression to stage 4 CKD, and the rate of annual decline in eGFR. The highest quartile of urinary potassium excretion was significantly associated with a lower incidence of 50% decline in eGFR (adjusted HR=0.24 [0.08, 0.70] and slower progression to CKD stage 4 (adjusted HR=0.08 [0.01, 0.50] when compared to the lowest quartile. The 2nd and 3rd quartiles were not significantly different from the lowest quartile for these outcomes. The annual rate of decline in eGFR was significantly lower in the highest quartile (-1.3 [-1.4, -1.0] when compared to the 1st (-2.2 [-2.4, -1.8] and 2nd (-1.9 [-2.0, -1.8]) quartiles, but not when compared to the 3rd quartile (-1.7 [-2.0, -1.5]).

**Chronic Kidney Disease**

Three publication examined the associations between 24-hour urinary potassium excretion levels and total mortality or kidney disease morbidity and mortality outcomes among patients with CKD. Of these, two publications analyzed data from the CRIC study and reported on all-cause mortality outcome, composite CVD incidence, MI incidence, and stroke incidence outcomes. The third publication was an analysis of the MDRD study on risk of kidney failure and all-cause mortality. The CRIC study followed patients with CKD and reported on all-cause mortality. In the CRIC study of patients with CKD in the U.S., no significant association was found between levels of 24-hour urinary potassium excretion and total mortality (adjusted HR [95%CI] 0.92 [0.72, 1.18], 0.81 [0.61, 1.08], and 0.89 [0.64, 1.23] comparing quartile 2, 3, and 4 to the lowest quartile, respectively; n=3757). Another publication from the CRIC cohort study also reported no significant associations between levels of 24-hour urinary potassium excretion and composite CVD outcomes (adjusted HR [95%CI] 1.04 [0.84, 1.29], 1.02 [0.81, 1.30], and 1.26 [0.98, 1.63] comparing quartile 2, 3, and 4 to lowest quartile, respectively), MI (adjusted HR [95%CI] was 1.08 [0.75, 1.56], 0.98 [0.66, 1.45], and 1.04 [0.68, 1.583] comparing quartile 2, 3, and 4 to lowest quartile, respectively), and stroke (adjusted HR [95%CI] was 1.03 [0.64, 1.66], 1.04 [0.61, 1.77], and 1.41 [0.80, 2.48] comparing quartiles 2, 3, and 4 to the lowest quartile, respectively). The MDRD study followed patients with CKD and reported on all-cause mortality and risk of kidney failure. This study identified a non-significant trend of increased kidney failure events in lower quartiles of baseline urinary potassium excretion. However, lower quartiles of potassium excretion were significantly associated with increased risk of all-cause mortality compared to the highest quartile of urinary potassium excretion (adjusted HR [95%CI] was 1.71
[1.23, 2.38], 1.70 [1.25, 2.31], and 1.53 [1.15, 2.02] comparing quartile 1, 2, and 3 to highest quartile, respectively n=812). Furthermore, continuous analyses also showed that both baseline 24-hour urinary potassium excretion levels (adjusted HR = 0.83 per 1 SD increase; 95% CI 0.74, 0.94) and a time-updated average of 24-hour urinary excretion levels (adjusted HR = 0.83 per 1 SD increase; 95% CI 0.71, 0.97) were significantly associated with a decreased risk for total mortality.174

**Obesity**

No studies were identified that assessed associations of potassium intake with risks of total mortality, CVD, CHD, stroke, or kidney disease morbidity and mortality in this population.

**Figure 53. Categorical analyses of the association between potassium levels and total mortality and CVD mortality outcomes in non-healthy populations**
Figure 54. Categorical analyses of the association between potassium levels and stroke outcome in non-healthy populations

Mills, 2016 CRIC [CKD]

O’Donnell, 2011 ONTARGET and TRANSCEND [CVD]
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Cohort name</th>
<th>Populatio n</th>
<th>Sex</th>
<th>Follow-up duration</th>
<th>Number of events / Total N</th>
<th>Cumulated Incidence</th>
<th>Exposure assessment</th>
<th>Exposure ranges</th>
<th>Analysis unit</th>
<th>Metric</th>
<th>Estimat e</th>
<th>Lower 95% CI</th>
<th>Upper 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leonberg-Yoo, 2016</td>
<td>CKD</td>
<td>Both</td>
<td>median 19.2 (IQR 10.8-20.6) y</td>
<td>430/812</td>
<td>0.529</td>
<td>Baseline 24-hour urine potassium excretion</td>
<td>mean 2.39 (SD 0.89) g/d</td>
<td>per SD increase</td>
<td>HR</td>
<td>0.83</td>
<td>0.74</td>
<td>0.94</td>
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</tr>
<tr>
<td>CKD</td>
<td>Both</td>
<td>median 19.2 (IQR 10.8-20.6) y</td>
<td>390/812</td>
<td>0.480</td>
<td>Time-updated average 24-hour urine potassium excretion</td>
<td>NR</td>
<td>per SD increase</td>
<td>HR</td>
<td>0.83</td>
<td>0.71</td>
<td>0.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fan, 2000</td>
<td>HTN</td>
<td>Male</td>
<td>mean 16.7 y</td>
<td>45/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;2003 mg/d vs. &gt;2879 mg/d</td>
<td>RR</td>
<td>2.13</td>
<td>1.09</td>
<td>6.78</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>Female</td>
<td>mean 16.7 y</td>
<td>93/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;1260 mg/d vs. &gt;2206 mg/d</td>
<td>RR</td>
<td>1.16</td>
<td>0.86</td>
<td>3.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HTN</td>
<td>Male</td>
<td>mean 16.7 y</td>
<td>76/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;1508 mg/d vs. &gt;2207 mg/d</td>
<td>RR</td>
<td>1.23</td>
<td>0.84</td>
<td>3.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-HTN</td>
<td>Female</td>
<td>mean 16.7 y</td>
<td>90/NR</td>
<td>-</td>
<td>Dietary potassium intake</td>
<td>NR</td>
<td>&lt;1017 mg/d vs. &gt;1641 mg/d</td>
<td>RR</td>
<td>1.11</td>
<td>0.85</td>
<td>3.54</td>
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</table>

CKD = chronic kidney disease; CI = confidence interval; HR = hazard ratio; IQR = interquartile rage; MDRD = Modification of Diet in Renal Disease; NR = not reported; SD = standard deviation; y = years
Discussion

**Summary of Key Findings and SoE**

The key points for each outcome appear in the Results section, organized by key question. Key points (primarily those for which the strength of evidence is moderate or higher are summarized below, along with the strength of evidence ratings (the factors that contributed to the ratings are reported in full in Appendix F). In general, the key questions were organized, first, by exposure: key questions 1 through 4 considered sodium exposure and sodium to potassium ratio, whereas key questions 5 through 8 considered potassium exposures. The questions were then further organized by study design: Key questions 1, 3, 5, and 7 assessed the findings of RCTs on the effects of studies intended to reduce sodium or increase potassium intake for the outcomes of interest, whereas the even-numbered questions assessed the associations between sodium or potassium exposures and the outcomes of interest in prospective cohort studies. The questions are then further organized by outcomes:

Key questions 1 and 2 address the relationships between sodium intake and BP, achievement of a prespecified BP goal, incident HTN, and adverse effects.

Key questions 3 and 4 address the relationships between sodium intake and all-cause mortality, CVD mortality, CHD mortality, stroke, MI, combined CVD morbidity and mortality, combined CHD morbidity and mortality, renal outcomes, any reported combination of CVD events, other CVD events, and adverse events.

Key questions 5 and 6 address the relationships between potassium status and BP, achievement of a prespecified BP goal, incident HTN, kidney stones, and adverse effects.

Key questions 7 and 8 address the relationships between potassium status and all-cause mortality, CVD mortality, CHD mortality, stroke, MI, combined CVD morbidity and mortality, combined CHD morbidity and mortality, renal outcomes, any reported combination of CVD events, other CVD events, and adverse events.

In this chapter, we discuss the overall findings for each outcome, considering all study designs together.

**Key Question 1: What is the effect (benefits and harms) of interventions to reduce dietary sodium intake on blood pressure?**

**Conclusions:**

- Sodium reduction decreases systolic and diastolic blood pressure significantly in adults (moderate SoE).
- Sodium reduction in adults increases the likelihood of achieving a prespecified blood pressure goal (moderate SoE).
- Sodium reduction decreases systolic BP in both those with hypertension and those with normal BP; the effect is greater in adults with HTN than in those with normal BP (moderate SoE).
- Sodium reduction decreases diastolic BP in those with hypertension (moderate SoE).
- Potassium-containing salt substitutes decrease systolic and diastolic BP (moderate SoE).
- Sodium reduction lowers BP in both men and women (moderate SoE).
Key Question 2 What is the association between dietary sodium intake and blood pressure?

Conclusions:
- Prospective cohort studies suggest that sodium exposure status is not associated with systolic or diastolic BP in adults (low SoE). All studies had high risk of bias based on the methods used to assess sodium intake (typically single 24-hour urine excretion with or without validation or estimated based on overnight urinary excretion), and findings were inconsistent across studies.
- Evidence from a small number of prospective cohort studies suggests that sodium exposure status is associated with incident hypertension in adults (low SoE: All studies had high risk of bias based on the methods used to assess sodium intake.

Sodium and Blood Pressure

Key questions 1 and 2 considered the relationship between sodium intake and systolic and diastolic blood pressure. We limited inclusion to RCTs with a minimum four-week intervention and observational studies to those with a minimum 4-week followup to increase the applicability of the study findings to individual patient- and community interventions.

RCTs designed to assess the effects of interventions to restrict sodium intakes had significant, although somewhat inconsistent, beneficial effects on reducing both systolic BP and diastolic blood pressure, compared with usual sodium intakes in adults; followup times were as long as 8 years, but most studies limited intervention duration and followup to a year or less. Pooled analyses showed high heterogeneity across studies (see below). Assessment of dose-response relationships between interventions, 24-hour urinary sodium excretion, and blood pressure showed significant positive effects in the DASH-Sodium trial but findings were inconsistent in smaller does-response studies. Observational studies generally reported inconsistent associations of sodium exposure with blood pressure at followup, however assessments of exposure relied on high RoB methods such as single 24-hour urinary excretion, estimated urinary excretion, or dietary assessments.

Few studies assessed the effects of sodium reduction on blood pressure in subgroups of interest, and even fewer studies conducted subgroup analyses within the same study. Evidence was insufficient to determine whether sex or race/ethnicity moderate the effect of sodium reduction on blood pressure.


Adults with HTN showed greater improvements in BP with sodium excretion interventions than did those with normal blood pressure (moderate strength of evidence for systolic BP; low strength of evidence for diastolic BP). The lower heterogeneity across studies included in these pooled analyses compared with that of the pooled analysis of studies of all adults suggest the latter might be attributable to the inclusion of studies of both those with HTN and those with normal BP. Evidence was insufficient from observational studies to determine whether the
association between sodium intake and blood pressure differs between those with HTN and those with normal BP.

A small number of RCTs assessed the impact of alteration of other minerals (potassium) on the effect of sodium reduction. Those that compared the effects of combining sodium reduction and increased potassium intake with that of sodium reduction alone suggested potassium has no moderating effect on that of sodium reduction for BP. Another group of studies, which compared the effects of using potassium-rich salt substitutes to limit sodium intake to usual diet, found significant beneficial effects of these salt substitutes on blood pressure (moderate strength of evidence). No studies assessed the impact of other minerals on the effects of sodium reduction. No observational studies assessed these associations.

**Sodium and Achievement of a Prespecified Goal**

Few studies assessed the effects of interventions on the likelihood of reaching a prespecified BP goal. Across six RCTs, sodium reduction interventions had a significant beneficial effect on the proportion of adult study participants achieving a prespecified blood pressure goal, although goals differed among the studies (moderate strength of evidence).

No RCTs assessed the potential moderating impact of subgroup status on this outcome. No observational studies assessed the association between sodium exposure and achievement of a prespecified BP goal.

**Sodium and Incident Hypertension**

RCTs showed a small, non-statistically significant beneficial effect of sodium reduction on the relative risk for incident HTN in adults (low SoE, because of the small number of studies and inconsistency). Observational studies suggested an association between urinary sodium excretion and risk for HTN (low strength of evidence due in part to high RoB and inconsistency). The small number of observational studies show mixed findings regarding the association between urinary sodium excretion and risk for HTN, ranging from no association to an association at higher exposure levels.

No studies of the moderating effects of potassium or potassium salt substitutes assessed effects on incident HTN.

No RCTs assessed the potential moderating effects of sex, race/ethnicity, age, or comorbidities on the effects of sodium reduction on incident hypertension. Sodium reduction during pregnancy had no effects on incident gestational hypertension, and urinary salt excretion was not associated with risk for gestational hypertension in one cohort study.

**Sodium and Adverse Events**

Few RCTs reported specific adverse events associated with sodium reduction to lower BP. Three studies, including the DASH-Sodium Trial, found no effects of sodium reduction on blood lipids (low strength of evidence). Evidence was insufficient regarding other adverse effects.
Sodium and Long-term Clinical Outcomes

Key Question 3: 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?

Conclusions:

- In adults, a low strength of evidence suggests that sodium reduction decreases the risk for all-cause mortality (based on three RCTs with low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not affect risk for CVD mortality (three RCTs) or stroke (three RCTs with low RoB).
- In adults, evidence is insufficient to assess the effect of sodium reduction on the risk for myocardial infarction (one RCT; low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not affect risk for a composite measure of “any CVD outcome” as reported by study authors (based on five RCTs; low RoB).
- In adults, a low strength of evidence suggests that sodium reduction does not significantly decrease risk for combined CVD morbidity and mortality (seven RCTs; low RoB). Evidence is insufficient to draw conclusions on the moderating effects of hypertension, diabetes, or renal disease on the effects of sodium reduction interventions on all-cause, CVD, or CHD mortality, CVD- or CHD morbidity, or other longer term CVD outcomes.
- Conflicting evidence from two RCTs is insufficient to draw conclusions regarding the moderating impact of overweight or obesity on the effect of sodium reduction on composite CVD outcomes (low RoB).
- Evidence was insufficient, based on one RCT, to draw conclusions on whether the effects of sodium reduction on clinical CVD, CHD, and renal outcomes as well as all-cause mortality are affected by higher dietary potassium.
- Evidence was insufficient, based on two RCTs, to draw conclusions on the moderating effects of potassium-containing salt substitutes on the effects of sodium reduction on clinical CVD, CHD, and renal outcomes and all-cause mortality.

Key Question 4: 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?

Conclusions:

- Although there appears to be an association between all-cause mortality and 24-hour sodium excretion at higher sodium levels (low SOE), the linearity of this relationship at lower sodium levels could not be determined (insufficient SOE).
- Data are insufficient to determine the linearity of the association of sodium intake levels with CVD mortality.
• A low level of evidence supports a lack of association of sodium intake levels and risk for stroke or combined CVD morbidity and mortality.
• Evidence is insufficient to assess effects of sex, race/ethnicity, age, or comorbidities on associations between sodium intake status and outcomes of interest.

**Sodium and All-cause Mortality**

Key Questions 3 and 4 consider the relationship between sodium intake and all-cause mortality. Only RCTs with followup of 6 months or longer and observational studies of 1 year or longer were included.

Decreasing dietary sodium reduced the risk for all-cause mortality slightly (low strength of evidence). The number of studies was small and outcomes were inconsistent. Differences in 24-hour urinary sodium excretion of 40mM or more showed a trend toward being associated with greater decreases in risk.

At 20 years’ followup, multivariate analysis of TOHP-I and TOHP-II data showed trends toward a dose-response relationship between 24-hour urinary sodium excretion and mortality. Among prospective cohort studies with followup times of 1 year or longer, 24-hour urinary sodium excretion showed an association with all-cause mortality (low strength of evidence) but the linearity of the relationship could not be assessed.

Too few RCTs assessed the potential moderating effects of sex, race/ethnicity, age, or comorbidities to draw any conclusions. Evidence was insufficient from prospective cohort studies that assessed sodium exposure using 24-hour urinary excretion to assess the potential moderating effects of sex, race/ethnicity, age, or comorbidities of interest.

**Sodium and Cardiovascular Disease Mortality**

Only three RCTs that met inclusion criteria assessed the effect of sodium reduction on CVD mortality. The TOHP-I and TOHP-II trials found no significant effects on CVD mortality over a 20-year followup. A third, much smaller RCT also found no effect (low strength of evidence). Two prospective cohort studies that conducted 24-hour urinary sodium excretion analyses (but had high risk of bias) found inconsistent effects of lower sodium intake and lower sodium-to-potassium ratios, as did studies that conducted dietary intake assessments. Several studies that relied on urinary sodium estimation showed a U-shaped relationship (small increases in CVD mortality at the lowest and highest intakes) but these findings were inconsistent, and data are insufficient to quantitatively estimate the limits above and below which risk begins to increase.

**Sodium and CHD Mortality**

No RCTs that met inclusion criteria assessed the effects of sodium reduction on CHD mortality. Two prospective cohort studies that assessed 24-hour urinary sodium excretion reported inconsistent associations of CHD mortality with sodium intake (insufficient evidence).
Sodium and Stroke

Three RCTs that met inclusion criteria reported on the incidence of stroke, although only one of the studies included stroke risk as a prespecified outcome. None of the studies reported significant differences in stroke risk (insufficient evidence to draw conclusions). Across prospective cohort studies that reported 24-hour urinary sodium excretion, no significant association with stroke risk for normotensives or those with HTN was found (low strength of evidence).

Sodium and Myocardial Infarction

Among three RCTs that reported on the incidence of MI, two reported no effect of sodium reduction on risk for stroke whereas in the third (TOHP-I), stroke risk was decreased by sodium reduction (insufficient strength of evidence). No observational studies that measured 24-hour sodium excretion assessed the association with MI risk.

Sodium and Combined CVD Morbidity and Mortality

Among the six RCTs that met inclusion criteria, sodium had a nonstatistically significant beneficial effect on the relative risk for this combined outcome. Four prospective cohort studies found no consistent associations between 24-hour urinary sodium excretion and this outcome (low strength of evidence for both RCTs and cohort studies).

Sodium and CHD Morbidity and Mortality

No RCTs that met inclusion criteria assessed the effect of sodium reduction on the combined outcomes of CHD morbidity and mortality. Four studies that assessed non-overlapping cohorts found inconsistent associations between 24-hour urinary sodium excretion and this outcome.

Sodium and Patients with Any CVD Event

Three large and two smaller RCTs reported on outcomes that included a CVD outcome. A pooled analysis showed a non-significant decrease in the relative risk for this outcome with sodium reduction (low strength of evidence). Prospective cohort studies did not include a comparable outcome.

- Stratified analysis by sex found no differences between males and females.
- Stratified analysis by race/ethnicity in the two TOHP trials combined found that only the response for white participants was statistically significant.
- Stratified analysis by age in one large RCT found a greater benefit of sodium reduction among adults in the 60 to 69 age group than among older adults. None of these findings have sufficient strength to permit conclusions.

Sodium and Mean Difference in eGFR and Number of Patients with End Stage Renal Disease

No RCTs that met inclusion criteria reported on these outcomes. One cohort study found no association between sodium excretion and mean difference in eGFR. Another cohort study found that lower sodium excretion was associated with a slower decline in kidney function among
individuals with HTN. Evidence was considered insufficient to draw any conclusions on sodium intake and renal outcomes.

**Sodium and Left Ventricular Hypertrophy**

Two RCTs reported no effect of sodium reduction on this outcome. No prospective cohort studies that met inclusion criteria reported on this outcome. Evidence is insufficient to draw conclusions.

**Key Question 5: What is the effect of interventions to increase potassium intake on blood pressure and kidney stone formation?**

**Conclusions:**

- Increased potassium intake has a beneficial effect on blood pressure in adults (moderate SoE based on 11 parallel RCTs and 7 crossover RCTs). However, evidence is insufficient to compare the effects of increasing potassium intake through dietary changes alone with the effects of a dietary supplement.
- Increasing potassium intake via potassium supplementation or increased dietary potassium from food has a beneficial effect on blood pressure in populations with prehypertension or hypertension (moderate strength of evidence based on 11 parallel RCTs and 7 crossover RCTs, some with inconsistent findings) but a low strength of evidence (based on three RCTs) suggests potassium supplementation does not affect blood pressure in normotensive populations.

**Key Question 6: Among children and adults, what is the association between potassium intake and blood pressure and kidney stone formation?**

**Conclusions:**

- A low strength of evidences suggests higher potassium exposure status is not associated with lower adjusted BP in adults (based on high risk of bias for six of seven studies; three studies observed associations only for diastolic BP, and one study observed no association).
- A low strength of evidence suggests high potassium exposure status is not associated with risk for incident hypertension in adults. (high RoB based on exposure assessment and inconsistency of findings).
- A low strength of evidence supports an association between higher potassium exposure and lower risk for kidney stones in adults (low SoE, based on four cohorts with high risk of bias for exposure assessment).

**Potassium and Blood Pressure**

Increased potassium intake significantly decreased systolic (by more than 5 mm Hg) and diastolic BP (by more than 3 mm Hg) in pooled analyses of 18 RCTs (moderate strength of
evidence) but the evidence is based predominantly on studies that employed dietary supplements. Prospective cohort studies and multivariate analyses found inconsistent associations between urinary potassium excretion and BP, and three additional prospective cohort studies found inconsistent associations with potassium intake based on dietary assessment.

Evidence was insufficient to determine whether the effect of potassium was moderated by sex, race/ethnicity, or age, or by baseline hypertensive status.

**Potassium and Incident Hypertension**

No RCTs that met inclusion criteria assessed the effect of increased potassium intake on incident HTN compared with placebo. Among five prospective cohort studies, one study found a significant association between the lowest quantile of potassium excretion and higher risk for HTN, whereas four studies found inconsistent associations with dietary potassium; this evidence was considered insufficient on which to base a conclusion.

**Potassium and Percent Participants at Blood Pressure Goal**

No RCTs that met inclusion criteria assessed the effect of increased potassium intake on potassium compared with placebo. No prospective cohort studies assessed this outcome.

**Potassium and Kidney Stones**

One RCT that met inclusion criteria reported that potassium (citrate) supplementation for 3 years significantly decreased the risk for kidney stone recurrence compared with placebo (insufficient strength of evidence). Multivariate analysis of a large RCT dataset found only a nonsignificant association between dietary potassium and kidney stone risk. Across three large prospective cohort studies assessed together, dietary potassium intake was inversely associated with risk for incidence kidney stones (low strength of evidence; high RoB based on dietary assessment).

**Potassium and Adverse Events**

Six RCTs reported greater risk for minor gastrointestinal discomfort associated with increased potassium intake from supplements (low strength of evidence).

**Key Question 7. What is the effect of interventions aimed at increasing potassium intake on CVD and kidney disease morbidity and mortality, and total mortality?**

- Evidence was insufficient to address this question (one RCT).
Key Question 8: 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?

- 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.

Potassium and All-Cause Mortality

One RCT reported that the use of a potassium-containing salt substitute in place of sodium chloride significantly reduced all-cause mortality at 2 ½ years (insufficient evidence).

Prospective cohort studies were inconsistent in their assessments of potassium status and all-cause mortality: four studies showed inconsistent associations between urinary potassium excretion and all-cause mortality, whereas three studies showed consistent associations between dietary potassium intake and adjusted all-cause mortality.

Potassium and CVD Mortality

The RCT described above reported that the potassium-containing salt substitute produced a significant decrease in age-adjusted CVD mortality compared with usual diet (insufficient evidence).

Prospective cohort studies reported no consistent association between potassium status and CVD mortality. Two of three cohort studies reported inverse associations between dietary potassium intake and CVD mortality, whereas two studies found no association between estimated 24-hour urinary excretion and CVD mortality.

Potassium and CHD Mortality

The salt substitute study also reported a significant decrease in age-adjusted CHD mortality at 2 ½ years (insufficient evidence).

Potassium status was inversely associated with CHD mortality risk across two cohort studies, one of which assessed 24-hour urinary potassium excretion (insufficient evidence).

Potassium and Stroke

No RCTs assessed the effect of increased potassium intake on the risk for stroke.

Among thirteen prospective cohort studies that assessed associations of potassium status with stroke risk among healthy cohorts, findings were inconsistent and could not be predicted by method used to assess potassium status (insufficient evidence).

Potassium and Myocardial Infarction

No RCTs assessed the effect of increased potassium intake on the risk for MI.

Two prospective cohort studies found no association between potassium status and risk for MI (insufficient evidence).
Potassium and Combined CVD Morbidity and Mortality

No RCTs assessed the effect of potassium supplementation on the combined outcome of CVD morbidity and mortality.

No significant associations were found between urinary potassium levels and combined CVD morbidity and mortality outcomes across three prospective cohort studies (insufficient evidence).

Potassium and Combined CHD Morbidity and Mortality

No RCTs assessed the effect of increased potassium intake on the combined outcome of CHD morbidity and mortality. Two prospective cohort studies showed inconsistent associations between 24-hour urinary potassium excretion and combined CHD morbidity and mortality outcomes (insufficient evidence).

Potassium and Any CVD Outcomes

No RCTs assessed the effect of increased potassium intake on “any CVD outcomes” as reported by authors.

One cohort study reported no association between potassium intake and a combination of outcomes that included left ventricular hypertrophy (insufficient evidence).

Potassium and Renal disease

No RCTs assessed the effect of increased potassium intake on risk for renal disease.

Two prospective cohort studies assessed the association between potassium status and renal outcomes. One study found that lower urinary potassium excretion was associated with an increased risk of developing chronic kidney disease (lower eGFR); the second study found that higher dietary potassium intake was associated with decreased risk of mortality from kidney disease.

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 status 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 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- (defined as a target of 100mmol/d) sodium interventions.³ ²³¹ Our report found similar effects of sodium reduction on BP in adults, but only statistically non-significant beneficial effects in children, possibly due to slight differences in analytic methods or studies that met inclusion criteria. The WHO report did not assess effects of sodium reduction on incident hypertension or achievement of specific BP goals. Our report limited inclusion of crossover RCTs to those with 2 weeks or more of washout or a process to ensure lack of carryover, whereas the WHO report did not exclude crossover studies on this basis. In addition, our review included sodium reduction
RCTs regardless of achieved sodium excretion, whereas the WHO excluded RCTs with a mean difference in achieved sodium excretion of less than 40 mmol/d. More recently, Graudal and colleagues systematically reviewed the literature on sodium reduction and BP and reached similar conclusions to those of Aburto and our current review.\textsuperscript{292} The current review corroborates the findings of the Graudal review regarding a larger effect of sodium reduction on individuals with HTN than on normotensive individuals. The Graudal review also identified studies that enabled comparisons across racial/ethnic groups; however, they included studies with a minimum of one-week follow up and did not limit inclusion of crossover studies.

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; our report identified three studies that corroborated the lack of effect of sodium reduction on blood lipids 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 much shorter follow-up of some included studies.\textsuperscript{292}

Several recent systematic reviews also reviewed 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 and only weak effects on CVD mortality and morbidity; they largely attributed the latter effect to one study that was excluded from our review because the intervention did not control for other dietary changes (the remaining seven RCTs were included in our review).\textsuperscript{14} 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 that increased sodium intake was linked to increased risk for stroke, stroke mortality, and CHD mortality.\textsuperscript{3} Graudal and colleagues conducted a subsequent meta-analysis of cohort studies that assessed the association between sodium exposures and mortality: They reported an increased mortality risk at both low- and high intakes of sodium (referred to as a “U-shaped curve.”)\textsuperscript{293} The review did not include RCTs, 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 current review adds to the evidence by demonstrating an effect of sodium reduction on reducing all-cause mortality, albeit with a small number of studies. Our review also corroborates the finding of the meta-analysis by Graudal regarding an association between lower intakes of sodium and risk for CVD mortality with a low level of evidence. However, the methods used to estimate sodium intake varied across the studies, and none used multiple 24-hour sodium excretion measures with validation to ensure complete collection; in addition, these studies could not rule out reverse causation: the possibility that individuals who had elevated BP or other risk factors at baseline were already reducing their intake of sodium.

McMahon and colleagues reviewed the evidence on effects of sodium reduction on cardiovascular outcomes in persons with CKD.\textsuperscript{294} However like our review, they identified no studies with long enough followup to assess long term chronic disease outcomes. Instead they reported on studies that assessed effects of sodium reduction on BP outcomes in persons with CKD, an outcome that was not included in our report. Of the eight studies they included, we included one in our assessment of effects of sodium reduction on BP in persons with DM, and the remaining seven would not have met inclusion criteria.

Aburto and colleagues subsequently reviewed the evidence for an association of potassium status with BP, HTN, and CVD for the WHO, concluding that higher potassium status was
associated with reduced BP in individuals with HTN but not in normotensive persons. That report found insufficient evidence to draw conclusions regarding the association of potassium status with risk for CVD or CHD morbidity or mortality. Our current review confirmed the association of potassium with BP lowering, by identifying randomized controlled trials that assessed the effects of increased potassium intake and also extended this 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 status 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, as reflected in reduced 24-hour urinary sodium intake. We did not assess the evidence regarding the most effective intervention design(s).

Most recent studies (e.g., those published from 1995 to the present) demonstrated an overall low RoB. However, older studies tended to omit many details of study design and conflict of interest, so actual RoB was unclear for some items. Nearly all observational studies that met inclusions 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 status in observational studies are discussed further below. Additional limitations are listed here, organized by a PICOTSS framework.

**Populations**

- Few to no studies conducted subgroup analyses by sex, age, race/ethnicity, or comorbidities.
- RCTs likely have highly selected populations, comprising highly motivated individuals.
- Studies defined prehypertension and mild-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, some 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 antihypertensive medications could have masked the effects of a reduced sodium diet.
- Observational studies had limited ability to control for pre-existing health conditions at study baseline. Thus, the association of sodium intake with risk for CVD mortality only at higher sodium exposures, as observed in some studies, could be the result of reverse causality.
- Observational studies may have residual confounding, as they could not adjust for all factors that may increase risk for HTN, CVD, CHD outcomes.
Interventions/Exposures

- 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.
- Few studies assess effects of natural experiments, community-, or government-level interventions, and of those that did, most did not meet inclusion criteria.
- 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 may be affected by factors that can’t be measured, such as intensity of counseling.
- No observational studies used multiple 24-hour urinary excretion analyses, although increasing evidence demonstrates that multiple, non-consecutive 24-hour urinary sodium excretion needs to be used as the indicator of compliance in RCTs and exposure in observational studies. 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, FFQ, 24-h recalls, and food records) and random error (e.g., single 24-hour or spot urine collections or single-day food recalls). Inconsistencies in apparent sodium intakes in studies over time may be attributable to changes in assessment methods used.
- Impaired kidney function could potentially affect changes in urinary sodium excretion in response to changes in sodium and potassium intake.
- Both RCTs and observational studies varied widely in baseline and achieved/observed sodium intake. Most RCTs employed 24-hour urinary sodium excretion as a measure of compliance with the intervention. Differences in baseline status could affect the potential to achieve sodium reduction goals through dietary interventions and introduce a source of heterogeneity among prospective cohort studies. Wide variation in achieved status 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. Greater decreases in 24-hour excretion from baseline or greater differences between intervention and control groups (e.g., exceeding 40 mmol/d) did not always correlate with outcomes of interest.
- 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 AI for adults is 62 mmol/d), introducing a potential source of heterogeneity across studies.

Comparators

- Contamination 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.
• 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 any effects.

Setting
• RCTs in academic 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, primarily because studies did not consistently report or adjust for such use. Thus, we could not eliminate the possibility that differences in sodium excretion or failure to see differences in sodium excretion might be due to use of drugs that affect Na excretion.

We did not conduct sensitivity analyses to determine the possible contribution of studies with high or moderate RoB to the findings.

Although we hoped to exclude prospective cohort studies that used methods other than multiple non-consecutive measures of 24-hour urinary sodium excretion to assess status, doing
so would have excluded most large cohort studies. Therefore, we included these studies but their risk of bias is higher.

The duration of interventions or exposures 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 exposure 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 may have excluded a small number of studies that could have increased strength of evidence. However, evidence suggests potential carryover needs to be considered.221

Conclusions

A systematic review of the evidence regarding the effects of dietary sodium reduction and increased potassium intake on (and their associations with) blood pressure and risk for chronic cardiovascular diseases finds that interventions that reduce dietary sodium intake (including use of potassium-containing salt substitutes) reduce blood pressure in both normotensive adults and those with hypertension. Interventions to reduce sodium intake increase the likelihood of reaching a prespecified blood pressure goal and appear to modestly decrease the incidence of hypertension, in agreement with prospective cohort studies, which show that higher sodium intakes are associated with greater risk for hypertension.

Increasing potassium intake significantly decreases blood pressure.

Interventions to reduce sodium intake may decrease risk for all-cause mortality slightly but studies are inconsistent and small in number. The effects of sodium reduction and increased potassium intake on mortality and morbidity due to CVD, CHD, and renal disease need more research.
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## Abbreviations / Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AE</td>
<td>Adverse effect</td>
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<tr>
<td>AI</td>
<td>Adequate Intake</td>
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<tr>
<td>ANHMRCDSSMC</td>
<td>Australia National Health and Medical Research Council Dietary Salt Study Management Committee</td>
</tr>
<tr>
<td>ATBC</td>
<td>Alpha-Tocopherol, Beta-Carotene Lung Cancer Prevention Study</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>CABG</td>
<td>Coronary artery bypass graft</td>
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<tr>
<td>CCCC</td>
<td>Chin-Shan Community Cardiovascular Cohort Study</td>
</tr>
<tr>
<td>CCT</td>
<td>Controlled clinical trial</td>
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<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
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<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
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<td>CHNS</td>
<td>Chinese Health and Nutrition Survey</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>CIRCS</td>
<td>Circulatory Risk in the Community Study</td>
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<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CrCl</td>
<td>Creatinine clearance</td>
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<td>CRIC</td>
<td>Chronic Renal Insufficiency Cohort Study</td>
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<tr>
<td>CV</td>
<td>Cardiovascular</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DBP</td>
<td>Diastolic blood pressure</td>
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<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
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<tr>
<td>DONALD</td>
<td>Dortmund Nutritional and Anthropometric Longitudinally Designed Study</td>
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<tr>
<td>DRI</td>
<td>Dietary Reference Intakes</td>
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<tr>
<td>EAR</td>
<td>Estimated Average Requirement</td>
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<tr>
<td>eGFR</td>
<td>Estimated glomerular filtration rate</td>
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<tr>
<td>EPC</td>
<td>Evidence-based Practice Center</td>
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<tr>
<td>ESRD</td>
<td>End Stage Renal Disease</td>
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<tr>
<td>GFR</td>
<td>Glomerular filtration rate</td>
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<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<td>HPFUS</td>
<td>Health Professionals Follow-Up Study</td>
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<td>HPT</td>
<td>Hypertension Prevention Trial</td>
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<td>Hypertension Prevention Trial Research Group</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<tr>
<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>IHD</td>
<td>Ischemic heart disease</td>
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<td>IOM</td>
<td>Institute of Medicine</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>K</td>
<td>Potassium</td>
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<tr>
<td>KCl</td>
<td>Potassium chloride</td>
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<tr>
<td>KQ</td>
<td>Key Question</td>
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<tr>
<td>LV</td>
<td>Left ventricular</td>
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<tr>
<td>MD</td>
<td>Mean difference</td>
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<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease trial</td>
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<tr>
<td>MI</td>
<td>Myocardial infarction</td>
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<tr>
<td>MMSHT</td>
<td>Minnesota Mount Sinai Hypertension Trial</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<td>---------</td>
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</tr>
<tr>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Na</td>
<td>Sodium</td>
</tr>
<tr>
<td>Na-K</td>
<td>Sodium-Potassium</td>
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<tr>
<td>NHLBI</td>
<td>National Heart, Lung, and Blood Institute</td>
</tr>
<tr>
<td>N/R</td>
<td>Not reported</td>
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<tr>
<td>NSTEMI</td>
<td>non-ST elevation myocardial infarction</td>
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<tr>
<td>PAPSS</td>
<td>Potassium and Protein Supplementation Study</td>
</tr>
<tr>
<td>PICOTSS</td>
<td>Population, intervention/exposure, comparison group, outcome, time, setting, and study design</td>
</tr>
<tr>
<td>PREVEND</td>
<td>Prevention of Renal and Vascular End-Stage Disease Study</td>
</tr>
<tr>
<td>PTCA</td>
<td>Percutaneous transluminal coronary angioplasty</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RDA</td>
<td>Recommended Daily Allowance</td>
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<tr>
<td>RoB</td>
<td>Risk of bias</td>
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<tr>
<td>RR</td>
<td>Relative risk</td>
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<tr>
<td>RRID</td>
<td>Renal Risk in Derby study</td>
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<tr>
<td>SBP</td>
<td>Systolic blood pressure</td>
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<tr>
<td>SCr</td>
<td>Serum creatinine</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<tr>
<td>SHS</td>
<td>Strong Heart Study</td>
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<tr>
<td>SoE</td>
<td>Strength of evidence</td>
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<tr>
<td>SRDR</td>
<td>Systematic Review Data Repository</td>
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<td>STEMI</td>
<td>ST-segment elevation myocardial infarction</td>
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<td>TCSSSCG</td>
<td>The China Salt Substitute Study Collaborative Group</td>
</tr>
<tr>
<td>TAIM</td>
<td>Trial of Antihypertensive Interventions and Management</td>
</tr>
<tr>
<td>TEP</td>
<td>Technical expert panel</td>
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<tr>
<td>TIA</td>
<td>Transient ischemic attack</td>
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<td>TOHP I</td>
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<tr>
<td>UL</td>
<td>Tolerable Upper Intake Level</td>
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<tr>
<td>WHI OS</td>
<td>Women's Health Initiative Observational Study</td>
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<td>WHO</td>
<td>World Health Organization</td>
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