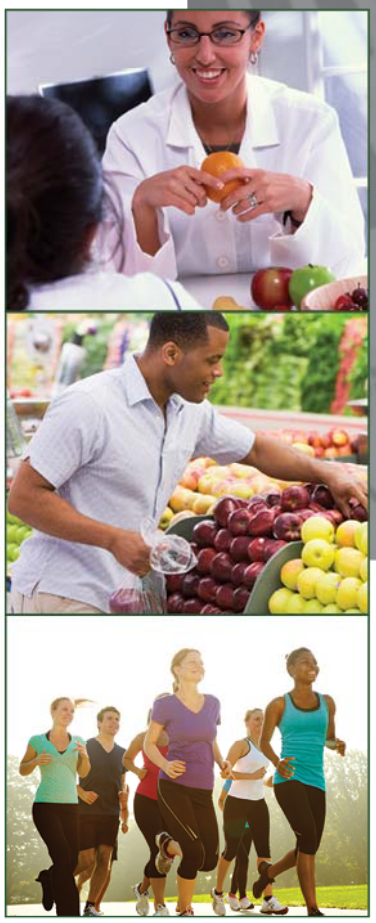
EVIDENCE REPORT



Lifestyle Interventions to Reduce Cardiovascular Risk

Systematic Evidence Review From the Lifestyle Work Group, 2013

U.S. Department of Health and Human Services
National Institutes of Health
National Heart, Lung, and Blood Institute

http://www.nhlbi.nih.gov/guidelines

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NIH National Heart, Lung, and Blood Institute

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Foreword

In 1977, the National Heart, Lung, and Blood Institute (NHLBI) issued the first of several clinical practice guidelines (CPGs) as part of its core mission, which is to provide global leadership for a research, training, and education program to promote the prevention and treatment of heart, lung, and blood diseases and enhance the health of all individuals so that they can live longer and more fulfilling lives. Guidelines from the National High Blood Pressure Education Program, the National Cholesterol Education Program, the Obesity Education Initiative, as well as from other similar programs and initiatives, have addressed a variety of topics, including, but not limited to, cholesterol, blood pressure, obesity, asthma, and von Willebrand disease. Over the years, health care systems and providers have used these guidelines for the prevention, detection, evaluation, and treatment of cardiovascular disease risk factors, and lung and blood diseases.

In 2008, NHLBI convened expert panels to update the existing clinical guidelines on cholesterol, blood pressure, and overweight/obesity, by conducting rigorous systematic evidence reviews. At the same time, three crosscutting work groups—on lifestyle, risk assessment, and implementation—were convened to develop additional systematic evidence reviews to support the work of the expert panels. The impetus for these guidelines was the recognition that despite the enormous progress over the last 60 years, cardiovascular disease remains the leading cause of death in the United States.

While the updates were underway, the Institute of Medicine (IOM) issued two reports that established new "best practice" standards for generating systematic evidence reviews and developing clinical guidelines. The reports underscore that these are two distinct, yet related, activities that require careful intersection and coordination. Accordingly, NHLBI's role in the guidelines updates transitioned to completing a systematic evidence review for each topic and collaborating with other organizations to prepare and issue the related clinical guidelines.

Since implementing the new collaborative partnership model for developing guidelines based upon NHLBI-sponsored systematic evidence reviews, four of the five Expert Panels/Work Groups have worked successfully with the American Heart Association (AHA), the American College of Cardiology (ACC), The Obesity Society (TOS), and other professional societies to develop new cardiovascular disease prevention CPGs for lifestyle, risk assessment, cholesterol, and obesity. The new guidelines—published in November 2013 by the AHA, ACC, and TOS, and endorsed by other professional societies—provide a valuable updated roadmap to help clinicians and patients manage CVD prevention and treatment challenges.

We appreciate the outstanding work and dedication of the expert panels and work groups that developed the systematic evidence reviews that formed the basis for the guidelines. These systematic evidence reviews are the products of one of the most rigorous evidence-based systematic reviews conducted to date. We look forward to continuing to develop accurate and timely evidence reviews, fueled by our investment in primary research on the prevention and treatment of cardiovascular disease as well as implementation science, to improve public health.

The following systematic evidence report is available as a public resource.

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Section 1: Background and Description of the NHLBI Cardiovascular Risk Reduction Project

A. Background

Since the 1970s, the National Heart, Lung, and Blood Institute (NHLBI) has sponsored the development of clinical practice guidelines that have helped to accelerate the application of health research to strategies and programs for the prevention, detection, and treatment of cardiovascular, lung, and blood diseases. In 2005, NHLBI recognized the need to update the most recent cardiovascular guidelines, namely those on high blood cholesterol, high blood pressure (BP), and overweight/obesity in adults. NHLBI convened stakeholder groups to provide input on the development process for the next generation of clinical practice guidelines.

The stakeholders emphasized the following needs:

- Maintain guidelines that focus on specific risk factors.
- Take a standardized and coordinated approach to updating the risk factors.
- Take a more evidence-based approach to development and implementation.
- Give more attention to dissemination and implementation issues.
- Work closely with stakeholders in health care and community systems to translate and disseminate the evidence base.

In 2008, NHLBI established three expert panels that would use a rigorous systematic evidence review process to update the guidelines for high blood cholesterol, high BP, and overweight/obesity. Additionally, three work groups were formed around risk assessment, lifestyle, and implementation to develop reports and provide crosscutting input to the expert panels. A Guidelines Executive Committee—comprised of co-chairs from the expert panels and work groups—coordinated the work of the expert panels and work groups. Efforts resulted in six topic-specific yet complementary reports: blood cholesterol, BP, overweight/obesity, lifestyle, risk assessment, and implementation. This report summarizes the evidence review findings of the Lifestyle Work Group.

While the expert panels and work groups were undertaking a rigorous, systematic, evidence-based approach to updating the guidelines, the Institute of Medicine (IOM) convened experts to examine the methodology for developing guidelines. In 2011, IOM issued two reports that established new "best practices" for generating systematic evidence reviews[1] and developing clinical practice guidelines.[2] The reports from IOM stress that these are two distinct but related activities that require careful intersection and coordination.

Because of these developments and the changing approaches to developing guidelines, in June 2012, the NHLBI Advisory Council recommended that the Institute transition to a new model in accordance with the best practice standards established by IOM. In mid-2013, NHLBI adopted a new collaborative partnership model whereby it will focus on generating high-quality systematic evidence reviews and developing subsequent clinical practice guidelines by partnering with professional societies and other organizations.[3] The systematic review components of the five adult clinical practice guidelines (including this systematic evidence review by the Lifestyle Work Group) will be

released as a public resource to complement the associated publication of the corresponding clinical practice guidelines in collaboration with partner organizations. The American Heart Association (AHA) and the American College of Cardiology (ACC) have agreed to spearhead the collaborative development of the CVD prevention guidelines utilizing the Adult CVD evidence reviews. The Lifestyle Work Group recommendation were published by AHA and ACC in the "2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines."[4]

B. Lifestyle Work Group Report

A healthy lifestyle is important in the prevention and reduction of CVD. CVD is the leading cause of morbidity and mortality in Americans. The majority of adults in the United States have at least one of the following risk factors; the frequency of these risk factors increases with age:

- Elevated low-density lipoprotein cholesterol (LDL-C) (33.5 percent)[5]
- Hypertension (31 percent) and prehypertension (29.7 percent)[6,7]
- Diabetes (11.3 percent)[8]

The Lifestyle Work Group evaluated evidence on the roles that particular dietary patterns, nutrient intake (e.g., macronutrients, sodium, and potassium), and levels and types of physical activity—through effects on such modifiable CVD risk factors as high BP and lipids—reducing CVD risk. The target audience of this report is primary care providers. Results from the Lifestyle Work Group's report will be incorporated into reports from the Expert Panels on BP and Blood Cholesterol.

Content in the body of this report addresses several critical questions (CQs). For each CQ,

- The rationale for its selection is provided and methods are described.
- The body of evidence is summarized.
- Evidence statements are presented, along with supporting rationale and a rating for quality.

This evidence review examines the following CQs:

LIFESTYLE WORK GROUP—CRITICAL QUESTIONS

No.	Question
CQ1.	Among adults, what is the effect of dietary patterns and/or macronutrient composition on CVD risk factors, when compared to no treatment or to other types of interventions?
CQ2.	Among adults, what is the effect of dietary intake of sodium and potassium on CVD risk factors and outcomes, when compared to no treatment or to other types of interventions?
CQ3.	Among adults, what is the effect of physical activity on blood pressure and lipids, when compared to no treatment, or to other types of interventions?

The results of this evidence review will be used to establish clinical recommendations that are directed at patients with CVD risk factors (i.e., abnormal lipids and/or prehypertension and hypertension). Implementation of clinical recommendations based on this evidence review has the potential to greatly reduce CVD risk factors in America.

Section 2: Process and Methods Overview

A. Evidence-Based Approach

i. Overview of the Evidence-Based Methodology

To continually improve the quality and impact of the evidence reviews sponsored by NHLBI, the evidence review process was updated to ensure rigor and minimize bias. This new effort involved the use of a rigorous evidence-based methodology and the development of evidence statements that are based on a systematic review of the biomedical literature for specific periods of time.

All of the expert panels and work groups followed the same methods, aside from variations needed to reflect the evidence in the field. The methodology involved numerous components and followed a prespecified development process. Expert panels and work groups consisting of cardiologists, primary care clinicians, nutritionists, and other clinical and nonclinical experts were convened to develop the evidence review. Directed by NHLBI, with support from a methodology contractor and a systematic review and general support contractor, the expert panels and work groups:

- Constructed CQs most relevant to clinical practice. CQs followed the PICOTS (population, intervention/exposure, comparison group, outcome, timing, and setting) format.
- Identified (*a priori*) inclusion/exclusion (I/E) criteria for each CQ.

Directed by NHLBI, with input from the expert panels and work groups, the contractor staff:

- Developed a search strategy, based on I/E criteria, for each CQ.
- Executed a systematic electronic search of the published literature from relevant bibliographic databases for each CQ.
- Screened—by two independent, masters/Ph.D.-level reviewers—thousands of abstracts or full-text articles returned from the search to identify relevant original articles, systematic reviews, and/or meta-analyses. Rigorous validation procedures were applied to ensure that the selected articles met pre-established I/E criteria before being included in the final review.
- Determined—by two independent raters on the methodology team—the quality (good, fair, or poor) of each study. With input from NHLBI, methodology staff adapted study-rating instruments and trained study raters on the use of these instruments. Six quality assessment tools were designed to assist reviewers in the critical appraisal of a study's internal validity.
- Abstracted relevant information from the included studies into an electronic database.
- Supported abstractions by constructing templates with lists of data elements that were pertinent to I/E criteria.
- Constructed detailed evidence tables as a way of organizing the data from the abstraction database.
- Analyzed the evidence tables and constructed summary tables, which displayed the evidence in a manageable format to answer specific parts of each CQ.

The expert panels and work groups:

- Used summary tables to develop evidence statements for each CQ. The quality of evidence for each evidence statement was graded as high, moderate, or low. The grade was based on scientific methodology, scientific strength, and consistency of results.
- Drafted a report that was reviewed by external Federal agencies and a group of experts selected by NHLBI.

ii. System for Grading the Body of Evidence

NHLBI adapted a system developed by the U.S. Preventive Services Task Force (USPSTF) to grade the body of evidence. Evidence statements were graded as high, moderate, or low quality (table 1).

Table 1. Evidence Quality Grading System

Type of Evidence	Strength of Evidence Grade
■ Well-designed, well-executed randomized controlled trials (RCTs) that adequately represent populations to which the results are applied and directly assess effects on health outcomes. ■ Meta-analyses of such studies. ■ High confidence that the evidence reflects the true effect. ■ Further research is unlikely to change the high confidence in the estimate of effect.	High
■ RCTs with minor limitations that affect confidence in, or applicability of, the results, including minor flaws in design or execution. ■ Well-designed, well-executed non-RCTs and well-designed, well-executed observational studies. ■ Meta-analyses of such studies. ■ Moderate confidence that the evidence reflects the true effect. ■ Further research may change the moderate confidence in the estimate of effect and may change the estimate.	Moderate
■ RCTs with major limitations. ■ Nonrandomized intervention studies and observational studies with major limitations that affect confidence in, or applicability of, the results. ■ Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). ■ Physiological studies in humans. ■ Meta-analyses of such studies. ■ Low confidence that the evidence reflects the true effect. ■ Further research is likely to change the low confidence in the estimate of effect and is likely to change the estimate.	Low

The grades provide guidance to primary care providers, clinicians, and other stakeholders on how much support the evidence provided for the evidence statement. The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. Appendix A describes four domains—risk of bias, consistency, directness, and precision—of the body of evidence that were used to grade the strength of evidence. Appendix A provides additional details about the methodology, including the four quality assessment tools that were designed to help reviewers address a study's internal validity.

Peer-Review Process

A formal peer-review process was undertaken that included inviting several scientific experts and representatives from multiple Federal agencies to review and comment on the draft documents. NHLBI selected scientific experts with diverse perspectives to review the reports. Potential reviewers were asked to sign a confidentiality agreement, but NHLBI did not collect COI information from the reviewers. DARD staff collected reviewers' comments and forwarded them to the respective panels and work groups for consideration. Each comment received was addressed—either by a narrative response and/or a change to the draft document. A compilation of the comments received and the panels' and work groups' responses was submitted to the NHLBI Advisory Council working group; individual reviewers did not receive responses.

B. Critical Question-Based Approach

The Lifestyle Work Group developed an initial set of questions based on its expertise and a brief literature review to identify topics of the greatest relevance and impact for the target audience of the evidence review—primary care providers. Due to time and resource limitations, the work group prioritized the final three CQs (see table on p. 4).

To reduce scope, several diet and physical activity interventions of interest to the work group are not included in this report: calcium, magnesium, alcohol, cardiorespiratory fitness, single behavioral intervention or multicomponent lifestyle interventions, the addition of lifestyle intervention to pharmacotherapy, and smoking. Additionally, the following risk factors of interest to the work group were not covered in this evidence review: diabetes- and obesity-related measurements, incident diabetes, metabolic syndrome, high-sensitivity C-reactive protein, and other inflammatory markers. The work group was interested in reviewing the evidence for CVD outcomes in all of the CQs; however, the evidence for mortality and CVD outcomes was reviewed as part of only CQ2. Appendixes B–D document the search strategies and results from the search of the published literature for each CQ.

Section 3: CQ1—Dietary Patterns and Macronutrients: Blood Pressure and Lipids

CQ1:
Among adults, what is the effect of dietary patterns and/or macronutrient composition on CVD risk factors, when compared to no treatment or to other types of interventions?

A. Introduction/Rationale

Research has repeatedly emphasized the importance of nutrition in modifying the risk for CVD.[9-13] Historically, research has focused mainly on the role of dietary components; however, foods are typically consumed in combinations rather than individually. Over the past few years, studies have begun to pay greater attention to dietary patterns and their relationships with health outcomes, including CVD.[14-22]

Intervention studies identify specific dietary patterns of defined macronutrient composition based on expert evidence and *a priori* hypotheses (such as DASH (Dietary Approaches to Stop Hypertension) or Mediterranean-style (MED) dietary patterns) that are then evaluated through RCTs. Observational studies assess associations between intake and risk factors. Because of limited resources, CVD morbidity and mortality were not outcomes included in the evidence review of CQ1. The work group was charged with informing the treatment of lipids and BP; therefore, those risk factors were the outcomes of focus.

B. Selection of Inclusion/Exclusion Criteria

Members of the work group developed eligibility criteria, based on a PICOTS approach, to screen potential studies for inclusion in this evidence review. Table 2 presents the details of the PICOTS approach for CQ1.

CQ1 examined studies that assessed either the impact on or the association between dietary patterns or changes in macronutrient composition with regard to CVD risk factors (systolic BP, diastolic BP, plasma LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG)). Studies were included that assessed effects after a minimum of 1 month of exposure in any geographic location and clinical or research setting. Studies that were evaluated included adults (≥18 years of age) with or without established CVD; with or without CVD risk factors; with or without tobacco use; and who were of normal weight, overweight, or obese. Studies were excluded if they focused on the use of dietary supplements or non-oral routes of nutrient delivery or the primary outcome of the nutritional intervention was weight change or when the weight change was greater than 3 percent (so that the effects would be independent of weight change).

Table 2 lists the dietary patterns that were included in the search terms. The work group focused on studies that assessed macronutrients (types and amount) and included the effects of saturated fatty acids (SFAs),

polyunsaturated fatty acids (PUFAs), monounsaturated fatty acids (MUFAs), *trans* fatty acids, dietary cholesterol, and the glycemic index.

Table 2. PICOTS Approach for CQ1

PICOTS Category	I/E Criteria
Population	Adults, ≥18 years of age
Intervention (RCTs, meta-analyses, observational studies)	1. Dietary pattern interventions or different dietary patterns. Studies that identified dietary pattern interventions or different dietary patterns prospectively or retrospectively (list is not exhaustive): ■ Isocaloric diets ■ DASH ■ Optimal Macronutrient Intake Strategies Against Heart Disease (OmniHeart) ■ MED diets (defined broadly) ■ Therapeutic Lifestyle Changes ■ Vegetarian ■ Vegan ■ Ornish diet ■ Pritikin diet ■ American Diabetes Association Diet for patients with diabetes or metabolic syndrome ■ Low-fat ■ High-protein ■ High-carbohydrate ■ Low-carbohydrate ■ High-fiber ■ Low-glycemic index ■ Glycemic load ■ Atkins ■ Portfolio ■ Ketogenic ■ National Cholesterol Education Program diet ■ American Heart Association diet ■ Step 1 diet and Step 2 diet ■ Meal replacement ■ Seventh Day Adventist diet ■ Raw food diet 2. Macronutrient composition interventions. Studies that identified controlled diets with the isocaloric substitution of a macronutrient (types and amount) and compared their effects on reducing plasma lipids: ■ Dietary fats: The effects of SFA, unsaturated fatty acids, omega-6 polyunsaturated fatty acids, omega-3 polyunsaturated fatty acids, MUFAs, *trans* fatty acids, alpha-linolenic acid, and dietary cholesterol.

PICOTS Category	I/E Criteria
Comparator	■ May be no predetermined comparison group for observational studies ■ Placebo ■ Usual care ■ No treatment ■ Other dietary pattern or macronutrient interventions ■ Drugs ■ Nondietary lifestyle interventions (e.g., physical activity or smoking cessation)
Outcomes	■ Risk factors and other outcomes ■ Cholesterol/lipid-related measurements: LDL-C, HDL-C, TG, non-HDL-C, apolipoprotein B (ApoB), lipoprotein (a) (Lp (a)), LDL particle number (LDL-P), Apo A–1, and percent at lipid goal ■ BP-related measurements: systolic BP, diastolic BP, or hypertensive/nonhypertensive, and percent at BP goal ■ Incident hypertension
Timing	■ Intervention/exposure time period: Risk factors and other outcomes for ≥4 weeks of treatment in RCTs and of exposure in observational studies ■ Followup time period: Risk factors and other outcomes for ≥4 weeks
Setting	■ Any geographic location ■ Any clinical or research setting

C. Literature Search Yield

i. Dietary Pattern Evidence

In all, 17 studies (28 citations) met the final inclusion criteria for CQ1 and were rated good or fair quality.[23-50]

CQ1 summary tables B–1 through B–8 summarize data on the included studies. The tables are organized by dietary pattern/macronutrient composition or subpopulations of interest, as defined by age, sex, race, or comorbid condition. Some studies appear in more than one summary table because they addressed more than one corresponding dietary pattern comparison or macronutrient composition.

D. CQ1 Evidence Statements

i. Dietary Patterns

a. Mediterranean-style dietary pattern

Three RCTs (conducted in free-living populations) and one prospective cohort study that analyzed the effects of the MED dietary pattern on CVD risk factors met criteria for inclusion.[27,28,39,41] Summary table B–1 summarizes the design, characteristics, and results of these studies.

Mediterranean-style dietary pattern description: The RCTs and cohort studies did not uniformly define the MED diet. However, the studies identified several common features of MED diets: higher in fruits (particularly

fresh), vegetables (emphasizing root and green varieties), whole grains (cereals, breads, rice, or pasta), and fatty fish (rich in omega-3 fatty acids); lower in red meat (and emphasizing lean meats); substituted lower fat or fat-free dairy products for higher fat dairy foods; and used oils (olive or canola), nuts (walnuts, almonds, or hazelnuts) or margarines blended with rapeseed or flaxseed oils in lieu of butter and other fats. The MED dietary patterns in these studies tended to be moderate in total fat (32–35 percent of total calories), lower in saturated fat (9–10 percent of total calories), high in fiber (27–37 g/day), and increased in PUFAs, particularly omega-3s.

Blood Pressure

ES1. Counseling to eat a MED dietary pattern, compared with minimal advice to consume a low-fat dietary pattern, in free-living middle-aged or older adults (with type 2 diabetes or at least three CVD risk factors), reduces BP by 6–7/2–3 mmHg. In an observational study of healthy younger adults, adherence to a MED dietary pattern is associated with lower BP (2–3/1–2 mmHg).

Strength of evidence: ***Low***

Lipids

ES2. Counseling to eat a MED dietary pattern, compared with minimal or no dietary advice, in free-living middle aged or older adults (with or without CVD or at high risk for CVD) results in no consistent effect on LDL-C, HDL-C, and plasma TG, in part because of substantial differences and limitations in the studies.

Strength of evidence: ***Low***

Rationale for ES1 and ES2: Four studies examined a MED dietary pattern in relation to BP and lipid outcomes under weight-stable conditions. Although none were randomized feeding studies in which exact nutrient intake could be determined, the three behavioral intervention trials and one observational study—all in free-living populations—provide some evidence of the effects of a MED diet on BP and lipids (as summarized in tables 3 and 4), although the strength of this evidence is low.

The first of the four studies providing evidence for ES1 and ES2 was a 3-month RCT called PREDIMED (Prevención con Dieta Mediterránea).[39] It compared changes in BP and lipids among those counseled on two energy-balanced MED diets and those in a control group (minimal advice to reduce all types of fat). The MED diets were generally comparable in composition but differed in the primary fat sources of either virgin olive oil or mixed tree nuts (walnuts, hazelnuts, almonds). Participants were 762 Spanish men (55–80 years old) and women (60–80 years old) with either type 2 diabetes or at least three CVD risk factors. Those on the MED pattern received weekly supplies of either virgin olive oil or mixed tree nuts and intensive ongoing dietary counseling; control group participants received minimal instruction and written information. Physical activity was consistent across all groups. At 3 months under weight-stable conditions, systolic BP fell by 6–7 mmHg (millimeter of mercury) and diastolic BP fell by 2–3 mmHg among participants on the MED diets compared with those in the control group. Compared with those in the control group, levels of HDL-C differed slightly among each group on the MED diet: +3 mg/dL among those receiving olive oil and +2 mg/dL among those receiving mixed tree nuts. Levels of LDL-C did not differ among the study groups, and levels of TG differed (–13 mg/dL, $p<.022$) between those in the mixed tree nut MED group and the control group.

The second source of evidence was a prospective cohort study that evaluated the effects on BP of adhering to a MED diet.[41] Conducted in Spain, the study examined BP outcomes in 9,408 professional men and women (20–90 years of age), with a mean followup of 4 years. Compliance with the MED diet was based on scores

derived from validated, self-administered food frequency questionnaires (FFQs). Compared with low compliance scores, better levels of compliance with the MED diet were associated with lower levels of systolic BP (–2 mmHg, moderate compliance scores; –3 mmHg, high compliance scores) and diastolic BP (–1 mmHg, moderate compliance scores; –2 mmHg, high compliance scores). Effects on plasma lipids were not reported.

The third source was an RCT that compared the effects on lipids between those who were counseled and crossed over for 12 weeks on an MED diet (in combination with simvastatin or placebo) and those who maintained habitual eating behaviors.[27] Conducted in Finland, the study examined 120 free-living weight-stable male industrial plant and government workers (35–64 years of age) with previously untreated hypercholesterolemia (total cholesterol $\geq$232 mg/dL fasting; TG <266 mg/dL) and a body mass index (BMI) below 32 kg/m^2. As part of the intervention, the MED diet encouraged a reduction in saturated fat intake (10 percent of energy or less), *trans* fats, and cholesterol (no more than 250 mg); enriched omega-3 fatty acids from plants (alpha-linolenic acid) and marine origin; fruits; vegetables; soluble fiber; leaner meats; low-fat cheese and yogurt; and fat-free milk and sour milk. Participants were supplied with fish, rapeseed margarine and oils (to replace butter, butter-vegetable oil mixtures, or sunflower margarine), oat bran, and frozen berries. Dietary adherence achieved target levels. Compared with habitual dietary patterns (which tended to be higher in total and saturated fat), adherence to a 12-week MED dietary intervention lowered LDL-C (–19 mg/dL, 10.8 percent; p<.001) and HDL-C (–2 mg/dL, 4.9 percent; p<.01) but there were no differences in TG levels compared with no dietary change, independent of simvastatin. Effects on BP were not reported.

The final source of evidence for ES1 and ES2 was an RCT that compared the 12-month effects on lipids among those who received an intensive outpatient MED dietary and lifestyle intervention with those in a control group.[28] The control group received only written information about basic MED diet principles and stress management. Conducted in Germany, the study examined 105 free-living participants who were being treated for coronary artery disease (>79% on statins) and had a BMI below 33 kg/m^2. Compared with those in the control group, participants in the intensive intervention group achieved a MED dietary pattern that was higher in fruits and low-fat dairy products, whole grain breads and pastas, fish, walnuts, and margarine and lower in meat, sausage, and butter. At 12 months, compliance with the MED pattern was generally good, but changes in nutrient profiles, albeit improved, were relatively modest compared with controls; weight was stable. Differences in the levels of LDL-C, HDL-C, or TG were not observed between the study groups. Effects on BP were not reported.

Table 3. Summary of Supporting Evidence for ES1 and ES2

Study	Change in Blood Pressure
Estruch et al., 2006 (PREDIMED)[39]	■ Intervention vs. control group ■ Systolic BP: –6–7 mmHg (p<.001) ■ Diastolic BP: –2–3 mmHg (p=.048; p=.001)
Núñez-Cordoba et al., 2009[41]	■ High and moderate MED dietary pattern score groups vs. low score referent group ■ Systolic BP: –2 to –3 mmHg; p (trend) = .01 ■ Diastolic BP: –1 to –2 mmHg; p (trend) = .05

Table 4. Summary of Supporting Evidence for ES1 and ES2

Study	Change in Levels of Lipids
Estruch et al., 2006 (PREDIMED)[39]	■ Intervention vs. control group ■ HDL-C levels: – +3 mg/dL (olive oil MED group) – +2 mg/dL (mixed tree nut MED group) ■ TG levels: – –13 mg/dL (p<.022) (mixed tree nut MED group vs. control group only)
Jula et al., 2002[27]	■ Intervention vs. control group ■ LDL-C level: –19mg/dL, 10.8 percent, p<.001 ■ HDL-C level: –2 mg/dL, 4.9 percent, p<.01
Michalsen et al., 2006[28]	No differences observed in lipid levels

b. DASH dietary pattern

Two RCTs (six citations) that evaluated the DASH pattern met eligibility criteria.[30-35] Summary table B–2 summarizes the design, characteristics, and results of these studies.

DASH dietary pattern description: The DASH dietary pattern is high in vegetables, fruits, and low-fat dairy products, whole grains, poultry, fish, and nuts and low in sweets, sugar-sweetened beverages, and red meats. Regarding macronutrients, the DASH dietary pattern is low in saturated fat, total fat, and cholesterol and rich in potassium, magnesium, and calcium, as well as protein and fiber.

DASH and Blood Pressure

ES3. When all food is supplied to adults with BP 120–159/80–95 mmHg and both body weight and sodium intake are kept stable, the DASH dietary pattern, when compared with a typical American diet of the 1990s, lowers BP by 5–6/3 mmHg.

Strength of evidence: High

Rationale: The DASH trial tested the hypothesis that the specific DASH dietary pattern lowers BP. The DASH study was a multicenter RCT of 459 participants with unmedicated Stage 1 hypertension or prehypertension. Participants were assigned at random to one of three diet-specific groups: DASH diet, a control diet similar to the usual dietary pattern in the United States in the 1990s, or to a diet high in fruits and vegetables but otherwise the same as the control diet. Each study group included 151–154 participants. The study population was 50 percent women, 60 percent African American, and 29 percent hypertensive. The average participant was 45 years of age and had a BMI of 28 kg/m^2 and a baseline BP of 132/85 mmHg.

Participants received complete diets for 8 weeks. Body weight at baseline was maintained throughout the trial by adjusting amounts of food given daily. Each diet contained 3,000 mg/day of sodium. The DASH diet and its effects did not involve weight loss or sodium reduction. A DASH dietary pattern was provided, including both foods and beverages, for 8 weeks. Tables 5 and 6 show the daily amounts (standard portions) of foods and macronutrients in the DASH diet compared with those in the control diet.

The DASH diet lowered BP in the entire study population by an average of 5.5/3.0 mmHg. Significant effects were observed in men and women, African Americans, and non-Hispanic Whites and in those with and without hypertension. The effects on BP of the fruits and vegetables diet were approximately half that of the DASH diet. The effects of the diets on BP were evident after 2 weeks and persisted as long as the diets were provided. A subsequent trial, DASH-Sodium, confirmed the BP-lowering effect of the DASH diet at various levels of dietary sodium intake (see description in CQ2).

Table 5. Food Composition of DASH Diet vs. Control Diet

Food	DASH Diet* Number of Servings/Day	Control Diet Number of Servings/Day
Fruits	5.2	1.6
Vegetables	4.4	2.0
Low-Fat Dairy	2.0	0.1
Regular-Fat Dairy	0.7	0.4
Nuts and Beans	0.7	0.0
Red Meat	0.5	1.5
Fish	0.5	0.2
Snacks and Sweets	0.7	4.1

* A DASH dietary pattern was provided as food or beverage for 8 weeks to adults.

Table 6. Macronutrient Composition of DASH Diet vs. Control Diet

Macronutrient	DASH Diet Percent of Energy	Control Diet* Percent of Energy
Total Fat	26	36
Saturated Fat	7	14
MUFA(s)	10	12
PUFA(s)	7	6
Carbohydrate	57	51
Protein	18	14

* The macronutrient composition of the control diet was based on the typical American diet of the early 1990s.

DASH and Lipids

ES4. When food is supplied to adults with a total cholesterol level <260 mg/dL and an LDL-C level <160 mg/dL and when body weight is kept stable, the DASH dietary pattern, when compared with a typical American diet of the 1990s, lowers LDL-C by 11 mg/dL, lowers HDL-C by 4 mg/dL, and has no effect on TG.

Strength of evidence: ***High***

Rationale: The rationale and study design of the DASH trial was described in the ES3 rationale. Blood lipids were measured at baseline and at the end of the 8-week dietary intervention in 436 participants. All randomized participants provided fasting blood at baseline, and 95 percent of those also provided fasting blood at the end of the intervention. Diet groups included 145 or 146 participants. For eligibility, participants had to have a total cholesterol level <260 mg/dL and an LDL-C level <160 mg/dL. Baseline LDL-C was 119 mg/dL, HDL-C was 49 mg/dL, and TG was 93 mg/dL. Less than 1 percent of the participants were taking cholesterol-lowering medication. When compared with a typical American diet of the 1990s, the DASH dietary pattern lowered LDL-C by 11 mg/dL and HDL-C by 4 mg/dL. DASH did not affect TG levels. The fruits and vegetables diet did not affect blood lipids, reflecting the similar content of saturated and unsaturated fat and cholesterol compared with the control diet. The reduction in LDL-C by DASH is consistent with its lower content of saturated fat and cholesterol, and the reduction in HDL-C is consistent with its higher content of carbohydrates.

The effects of the DASH trial were confirmed and extended to three dietary sodium levels in the DASH-Sodium trial, described in CQ2. In that trial, the DASH diet lowered LDL-C by 13 mg/dL, lowered HDL-C by 4 mg/dL, and did not affect TG levels.[34] The OmniHeart trial, described below, tested macronutrient variations of the DASH dietary pattern.[40] When carbohydrates were replaced with MUFAs, effects similar to those of the original DASH trial were observed on BP and LDL-C but HDL-C improved with the MUFA substitution.

c. DASH dietary pattern subpopulations

Two studies (eight citations) that evaluated the DASH dietary patterns on subpopulations met criteria for inclusion.[30-32,45-49] Summary tables B–3 (sex), B–4 (race ethnicity), B–5 (hypertension status), and B–6 (age) summarize the design, characteristics, and results of these studies on subgroups.

DASH and Blood Pressure Among Subpopulations

ES5. When all food is supplied to adults with BP 120–159/80–95 mmHg and body weight is kept stable, the DASH dietary pattern, compared with the typical American diet of the 1990s, lowers BP in women and men, African American and non-African American adults, older and younger adults, and hypertensive and nonhypertensive adults.

Strength of evidence: ***High***

Rationale—Women and men: The rationale and study design of the DASH trial and details of the diets tested are described in the DASH Dietary Pattern background. Compared with a typical American diet of the 1990s, the DASH dietary pattern lowered BP by similar amounts in men (5/3 mmHg) and women (6/3 mmHg).[30,32,45] A subsequent DASH-Sodium trial found a similar BP-lowering effect in men and women. At the higher sodium intake level (mean urinary sodium 3,300 mg/day), the DASH dietary pattern, compared with a typical American diet of the 1990s, lowered BP by 5/3 mmHg in men and 7/3 mmHg in women; differences by sex were not statistically significant.[49]

Rationale—African American and non-African American: Compared with a typical American diet of the 1990s, the DASH dietary pattern lowered BP more in African Americans (7/4 mmHg) than in non-African Americans (3/2 mmHg).[30-32,45] In contrast, the subsequent DASH-Sodium trial found a similar BP-lowering effect by race/ethnicity. At the higher sodium intake level (mean urinary sodium of 3,300 mg/day), the DASH dietary pattern, compared with a typical American diet of the 1990s, lowered BP by 6/3 mmHg in African Americans and 6/2 mmHg in non-African Americans; differences by race were not statistically significant.[49] Thus, the effects of DASH on BP do not appear to differ consistently between African American and non-African American adults.

Rationale—Older and younger adults: Compared with a typical American diet of the 1990s, the DASH dietary pattern lowered BP by 5/4 mmHg in participants 45 years of age and younger and by 7/3 mmHg in participants 45 years of age and older.[30,32,45] The subsequent DASH-Sodium trial found a similar BP-lowering effect by age. At the higher sodium intake level (mean urinary sodium of 3,300 mg/day), the DASH dietary pattern, compared with a typical American diet of the 1990s, lowered BP by 4/2 mmHg in adults 45 years of age and younger and by 7/3 mmHg in adults older than 45 years of age.[49]

Rationale—Hypertensive and nonhypertensive adults: Compared with a typical American diet of the 1990s, the DASH dietary pattern lowered BP more in adults with hypertension (11/6 mmHg) than in those without hypertension (4/2mmHg).[30,31,45] In contrast, the subsequent DASH-Sodium Trial found a similar BP-lowering effect among adults with and without hypertension. At the higher sodium intake level (mean urinary sodium of 3,300 mg/day), the DASH dietary pattern, compared with a typical American diet of the 1990s, lowered BP by 7/3 mmHg in adults with hypertension and 5/3 mmHg in adults without hypertension; differences by hypertension status were not statistically significant.[49] Thus, the effects of DASH on BP do not appear to differ consistently between adults with and without hypertension.

DASH and Lipids Among Subpopulations

ES6. When all food is supplied to adults with a total cholesterol level <260 mg/dL and an LDL-C level <160 mg/dL and when body weight is kept stable, the DASH dietary pattern, compared with a typical American diet of the 1990s, lowers LDL-C similarly in subgroups: African American and non-African American and adults with and without hypertension.

Strength of evidence: ***Low***

ES7. When all food is supplied to adults with a total cholesterol level <260 mg/dL and an LDL-C level <160 mg/dL and when body weight is kept stable, the DASH dietary pattern, compared with a typical American diet of the 1990s, lowers HDL-C similarly in subgroups: African American and non-African American, adults with and without hypertension, and men and women.

Strength of evidence: ***Low***

Rationale: One secondary analysis of the DASH trial[32] met inclusion criteria and was rated fair for assessing the effects on lipid levels of a DASH dietary pattern compared with a typical American diet of the 1990s. The analysis examined several subpopulations, including hypertensive and nonhypertensive adults, men and women, and African Americans and non-African Americans. Participants had a mean BMI of 28 kg/m^2.

Compared with the typical American diet, the DASH diet resulted in lower mean LDL-C and HDL-C in all participants. However, compared with women, men had greater reductions in LDL-C. Changes in total cholesterol, LDL-C, HDL-C, and TG did not differ significantly by race.

d. DASH variations

One RCT[40] (OmniHeart) that examined variations in the DASH eating pattern met eligibility criteria. The design, characteristics, and results of the OmniHeart trial are summarized in summary table B–2.

Background: The OmniHeart trial compared two variations of the DASH dietary pattern with DASH: one replaced 10 percent of total daily energy from carbohydrates with protein, and the second replaced the same amount of carbohydrates with unsaturated fat. These patterns were studied in an adequately powered crossover trial of 164 adults in which the participants were given all of their daily food.

ES8. In adults with BP 120–159/80–95 mmHg, modifying the DASH dietary pattern by replacing 10 percent of calories from carbohydrates with the same amount of either protein or unsaturated fat (8 percent monounsaturated and 2 percent polyunsaturated) lowers systolic BP by 1 mmHg compared with the DASH dietary pattern. Among adults with BP 140–159/90–95 mmHg, these replacements lower systolic BP by 3 mmHg compared with the DASH dietary pattern.

Strength of evidence: Moderate

ES9. In adults with average baseline LDL-C 130 mg/dL, HDL-C 50 mg/dL, and TG 100 mg/dL, modifying the DASH dietary pattern by replacing 10 percent of calories from carbohydrates with 10 percent of calories from protein lowers LDL-C by 3 mg/dL, HDL-C by 1 mg/dL, and TG by 16 mg/dL compared with the DASH dietary pattern. Replacing 10 percent of calories from carbohydrates with 10 percent of calories from unsaturated fat (8 percent monounsaturated and 2 percent polyunsaturated) lowers LDL-C similarly, increases HDL-C by 1 mg/dL, and lowers TG by 10 mg/dL compared with the DASH dietary pattern.

Strength of evidence: Moderate

Rationale: DASH had favorable effects on BP and LDL-C but neutral or slightly adverse effects on HDL-C and TG. An RCT was performed to determine whether partially replacing carbohydrates with either unsaturated fat or protein could improve the effect of DASH on lipid risk factors while maintaining the favorable effects of DASH on BP risk factors.[40] The OmniHeart trial compared the effects of three diets that were composed of the same foods in DASH but with different macronutrient compositions. Because the effects of the DASH diet were known from two previous controlled feeding trials, the high-carbohydrate DASH diet was used as the control and compared with the low-carbohydrate variations of DASH: the "protein diet" and the "unsaturated fat" diet. The macronutrient composition of the carbohydrate diet (DASH) was 58 percent carbohydrates, 27 percent fat, and 15 percent protein; the protein diet was 48 percent carbohydrates, 27 percent fat, and 25 percent protein; and the unsaturated fat diet was 48 percent carbohydrates, 37 percent fat, and 15 percent protein. Saturated fat was 8 percent for all diets. MUFA was 13 percent on the carbohydrate (DASH) and protein diets compared with 21 percent on the unsaturated fat diet. Polyunsaturated fat was 8 percent on the carbohydrate (DASH) and protein diets compared with 10 percent on the unsaturated fat diet. The carbohydrate diet (DASH) had more fruit and fruit juices, desserts, and other sweets than the other two diets. Meat and plant sources provided the additional protein in the protein diet. The sodium content was 2,300 mg for all diets. Weight was maintained by adjusting calorie intake as needed.

The OmniHeart trial design was crossover with randomized sequence of the three diets, with each being provided for 6 weeks. Study design and feeding were otherwise comparable to the DASH and DASH-Sodium trials. Compared with the DASH dietary pattern, both the protein and unsaturated fat diets lowered systolic BP significantly by an average of 1 mmHg. Among adults with BP 140–159/90–95 mmHg, both variations lowered systolic BP by 3 mmHg. Compared with baseline measurements taken when participants were eating their usual diets, the carbohydrate diet (DASH) lowered BP by 8/4 mmHg and the protein and unsaturated fat variations lowered BP by 9/5 mmHg. BP in adults with hypertension was lower by 13/6 mmHg (protein diet) and 16/8–9 mmHg (unsaturated fat diet), and BP in adults with prehypertension was lower by 7/4 mmHg (protein diet) and 8/4 mmHg (unsaturated fat diet).

Replacing 10 percent of daily calories from carbohydrates with 10 percent of calories from protein lowered LDL-C by 3 mg/dL, HDL-C by 1 mg/dL, and TG by 16 mg/dL compared with the DASH dietary pattern. Replacing 10 percent of calories from carbohydrates with 10 percent of calories from unsaturated fat (8 percent MUFA and 2 percent PUFA) lowered LDL-C similarly, increased HDL-C by 1 mg/dL, and lowered TG by 10 mg/dL compared with the DASH dietary pattern. Compared to the baseline period, the control diet (DASH)

lowered LDL-C by 12–14 mg/dL and reduced HDL-C by 3 mg/dL and did not reduce HDL-C with the unsaturated fat substitution.

In summary, the OmniHeart trial found that the beneficial effects on BP and LDL-C of the DASH dietary pattern are modestly enhanced by replacing some carbohydrates with either protein or unsaturated fat while maintaining the healthy foods that are hallmarks of the DASH approach. The combined findings from the DASH and OmniHeart studies provide a range of macronutrient intakes and foods that substantially improve BP and LDL-C.

e. Glycemic index/load dietary approaches

Three RCTs that evaluated glycemic index met criteria for inclusion.[29,38,44] Summary table B–7 summarizes the design, characteristics, and results of these studies.

ES10. Evidence is not sufficient to determine whether low-glycemic diets versus high-glycemic diets affect BP or lipids in adults without diabetes mellitus. The evidence for this relationship in adults with diabetes mellitus was not reviewed.

Rationale: Carbohydrate content is an important determinant of glycemic control in adults with diabetes. The glycemic index is a system of ranking the degree to which dietary carbohydrates, in equal amounts, raise blood glucose. However, the glycemic load defines the glycemic effect of a regular serving size of food with the amount of carbohydrates in a single serving. Carbohydrate foods that result in a lower postprandial blood glucose, tend to be those with higher fiber and more complex carbohydrates, such as non-starchy vegetables and legumes. The popularity of low-glycemic diets arose from a concern that the increase in type 2 diabetes in tandem with the rise in obesity was due, at least in part, to an increase in large portions of foods that were low in fiber and high in simple sugars.

No studies that compared low- and high-glycemic diets in adults without diabetes met inclusion criteria for CQ1. Therefore, the available data are not sufficient to recommend a diet based on glycemic index as being better or worse at improving cardiovascular health in adults without diabetes mellitus. Diabetes mellitus-related outcomes were not reviewed at this stage of the evidence review because of limited resources. Therefore, the work group did not review the evidence of the effect of glycemic index on cardiovascular risk factors in people with diabetes mellitus.

ii. Dietary Fat and Cholesterol

Five trials (six citations) that evaluated saturated and *trans* fat and dietary cholesterol met inclusion criteria.[30,33,36,37,42,43] Summary table B–8 summarizes the design, characteristics, and results of these studies. In addition, based on a search of meta-analyses and systematic reviews from 1990 to 2009, four systematic reviews and meta-analyses met inclusion criteria.[23-26]

a. Saturated fat

ES11. When food was supplied to adults in a dietary pattern that achieved a macronutrient composition of 5–6 percent saturated fat, 26–27 percent total fat, 15–18 percent protein, and 55–59 percent carbohydrates, compared with a control diet (14–15 percent saturated fat, 34–38 percent total fat, 13–15 percent protein, and 48–51 percent carbohydrate), LDL-C was lowered 11–13mg/dL in two studies and 11 percent in one study.

Strength of evidence: ***High***

Rationale: Three feeding trials (DASH, DASH-Sodium, and DELTA (Dietary Effects on Lipoproteins and Thrombogenic Activity)) with dietary patterns of varying saturated fat levels examined the effect on LDL-C.[30,33,36] The dietary patterns used in the DASH and DASH-Sodium trials were described previously. The patterns in the three studies were compared with those observed among a control group of participants who received a typical American diet and had a baseline LDL-C less than 160 mg/dL or were described as "healthy." The achieved level of saturated fat in the DASH groups was 6 percent of total calories compared with 14–15 percent of total calories in the control group. LDL-C decreased 11mg/dL ($p<.0001$) in the DASH trial and 13 mg/dL ($p<.0001$) in the DASH-Sodium trial. The DELTA trial tested three dietary patterns: low saturated fat; Step 1; and 5 percent, 9 percent, and 15 percent of calories from saturated fat (control group). Compared with the control group, LDL-C decreased by 4 percent ($p<.01$) among those in the low saturated fat group and by 7 percent ($p<.1$) among participants in the Step 1 group, totaling an 11 percent reduction. Of note, in the DASH trials, the effect of saturated fat on LDL-C could not be isolated because macronutrients and other nutrients, such as dietary cholesterol, were not held constant. In the DELTA trial, dietary cholesterol and protein were held constant but other nutrients, including total fat and carbohydrates, differed in the comparison groups (table 7). In the DASH trials, LDL-C lowering is consistent with the lower saturated fat dietary pattern resulting in lower LDL-C. In DELTA, the greater reduction in saturated fat led to greater LDL-C lowering.

Table 7. Macronutrient Composition and Lipid Effects in DASH, DASH-Sodium, and DELTA

	Total Fat (% kcal)	SFA (% kcal)	Carbohydrate (% kcal)	Protein (% kcal)	Baseline LDL-C of Participants	Effect on LDL-C (Compared With Control)	Effect on HDL-C and/ or TG (Compared With Control)
DASH	27	6	55	18	<160 mg/dL	–11 mg/dL	HDL-C: –4 mg/dL
DASH: Control	36	14	51	14			
DASH-Sodium	27	6	58	15	<160 mg/dL	–13 mg/dL	HDL-C: –4 mg/dL TG: +5 mg/dL
DASH-Sodium: Control	38	15	49	13			
DELTA: Low Saturated Fat	26	5	59	15	"Healthy"	–11%	HDL-C: –11% TGs: No change
DELTA: Step 1	29	9	55	15		–7%	HDL-C: –7% TG: +9%
DELTA: Control	34	15	48	15			

ES12. In controlled feeding trials among adults, for every 1 percent of energy from SFA that is replaced by 1 percent of energy from carbohydrate, MUFA, or PUFA:

- LDL-C decreases by an estimated 1.2, 1.3, and 1.8 mg/dL, respectively; and
- HDL-C decreases by an estimated 0.4, 1.2, and 0.2 mg/dL, respectively.

For every 1 percent of energy from SFA that is replaced by 1 percent of energy from:

- Carbohydrate and MUFA, TG increases by an estimated 1.9 and 0.2 mg/dL, respectively; and
- PUFA, TG decreases by an estimated 0.4 mg/dL.

Strength of evidence: Moderate

ES13. In controlled feeding trials among adults, for every 1 percent of energy from carbohydrates that is replaced by 1 percent of energy from:

- MUFA, LDL-C decreases by 0.3 mg/dL, HDL-C increases by 0.3 mg/dL, and TG decreases by 1.7 mg/dL; and
- PUFA, LDL-C decreases by 0.7 mg/dL, HDL-C increases by 0.2 mg/dL, and TG decreases by 2.3 mg/dL.

Strength of evidence: Moderate

Rationale: When restricting saturated fat, it is helpful to understand the effects of replacing it with other macronutrients. Two of the meta-analyses were from the same authors and published 11 years apart.[23,24] The authors used the same I/E criteria and generated predictive equations to estimate changes in plasma lipids when substituting dietary fat types with carbohydrates or other fat types. The first meta-analysis included 27 RCTs (682 volunteers) and covered the period between January 1970 and December 1991.[23] The second meta-analysis included 60 trials (1,672 participants) and covered the period between January 1970 and December 1998.[24] In both meta-analyses, inclusion criteria were controlled intervention studies in which the sole variable was macronutrient content, with dietary cholesterol held constant. Eligible study designs included parallel, crossover, or Latin-square under metabolic ward conditions, with a feeding period greater than 13 days. All participants were 21–72 years of age and did not have disturbances of lipid metabolism or diabetes. Studies were excluded if they focused on omega-3 fatty acids or medium-chain fatty acids. The search identified a third review that addressed dietary advice to reduce total fat intake or change PUFA to SFA ratio.[26] However, this review was not used to develop the evidence statement because the effect of changing SFA intake could not be isolated.

The authors found that replacing 1 percent of SFA with an equal amount of carbohydrates, MUFA, or PUFA led to comparable LDL-C reductions: 1.2, 1.3, and 1.8 mg/dL, respectively. Replacing 1 percent of SFA with carbohydrates, MUFA, or PUFA also lowered HDL-C by 0.4, 1.2, and 0.2 mg/dL, respectively. TG increased by an estimated 1.9 and 0.2 mg/dL when replacing SFA with carbohydrates or MUFA, respectively, but TG decreased when SFA was replaced by PUFA. Replacing 1 percent of carbohydrates by an equal amount of MUFA or PUFA raised LDL-C by 0.3 and 0.7 mg/dL, raised HDL-C by 0.3 and 0.2 mg/dL, and lowered TG by 1.7 and 2.3 mg/dL, respectively. Despite 30 studies in this methodologically strong meta-analysis, the evidence statement is rated moderate because of the relatively small number of participants (n=1,672).

b. *Trans* fat

ES14. In controlled feeding trials among adults, for every 1 percent of energy from *trans* MUFAs replaced with 1 percent of energy from:

- MUFA or PUFA, LDL-C decreases by 1.5 mg/dL and 2.0 mg/dL, respectively; and
- SFA, MUFA, or PUFA, HDL-C increases by an estimated 0.5, 0.4, and 0.5 mg/dL, respectively; and
- MUFA or PUFA, TG decreases by an estimated 1.2 and 1.3 mg/dL, respectively.

Strength of evidence: Moderate

ES15. In controlled feeding trials among adults, the replacement of 1 percent of energy as *trans* MUFAs with carbohydrates decreases LDL-C levels by 1.5 mg/dL but has no effect on HDL-C and TG levels.

Strength of evidence: Moderate

Rationale: During the past two decades, increasing evidence has accumulated that the intake of *trans* fat causes unfavorable modifications of plasma lipids, lipoproteins, and CVD risk. The *trans* fat evidence statements are based on two meta-analyses.[20,21]

The first meta-analysis included 13 trials that were published through January 2008.[25] Inclusion criteria were controlled dietary trials reporting data on plasma lipid and lipoprotein response at the end of each dietary phase, with each phase lasting at least 2 weeks. In this meta-analysis, replacing 1 percent of energy as *trans* fatty acids with 1 percent of energy from MUFA lowered LDL-C levels by 1.5 mg/dL ($p<.05$), increased HDL-C levels by 0.4 ($p<.05$), and lowered TG levels by 1.2 mg/dL ($p<.05$). Replacing 1 percent of energy from *trans* fatty acids with 1 percent energy from PUFA lowered LDL-C levels by 2.0 mg/dL ($p<.05$), increased HDL-C levels by 0.5 mg/dL ($p<.05$), and lowered TG levels by 1.3 mg/dL ($p<.05$). Replacing 1 percent of energy from *trans* fatty acids with 1 percent energy from SFA increased HDL-C levels by 0.5mg/dL ($p<.05$).

The second meta-analysis included eight studies and covered the period between January 1970 and December 1998.[24] Inclusion criteria were controlled intervention studies in which the sole variable was the dietary fatty acid prolife, with dietary cholesterol held constant. Study designs included parallel, crossover, or Latin-square in which the feeding period was at least 13 days. All participants were 21–72 years of age and had no lipid metabolism disturbances or diabetes mellitus. Studies were excluded if they focused on dietary omega-3 fatty acids or medium-chain fatty acids. In this meta-analysis, replacing 1 percent of energy as *trans* MUFA with carbohydrates decreased LDL-C levels by an estimated 1.5 mg/dL ($p=.02$) but had no effect on HDL-C or TG levels.

c. Dietary cholesterol

ES16. Evidence is not sufficient to determine whether lowering dietary cholesterol reduces LDL-C.

Rationale: Dietary cholesterol has been a controversial topic for years. Reasons include the variable effect of increases in dietary cholesterol on LDL-C levels and the inconsistent relationship between dietary cholesterol intake and CVD. No systematic reviews or meta-analyses met inclusion criteria. In the absence of other evidence, two poorly rated meta-analyses were reviewed.[51, 52] Most of the published studies that were included in each meta-analysis examined the independent effect of dietary cholesterol on total concentrations of plasma cholesterol, not lipoprotein cholesterol or TG. In six of the studies, data for LDL-C were reported for 128 participants. Dietary cholesterol ranged from 130–200 mg/day to 700–1,700 mg/day over intervals that ranged from 10 days to 8 weeks. Because these studies predated the search and the impact of more moderate intakes of dietary cholesterol on lipoprotein cholesterol over a broad range of individuals with normocholesterolemia and hypercholesterolemia had not been addressed adequately, the work group concluded that data are not sufficient to make such an evidence statement.

Section 4: CQ2—Sodium and Potassium: Blood Pressure and CVD Outcomes

CQ2:

Among adults, what is the effect of dietary intake of sodium and potassium on CVD risk factors and outcomes, when compared to no treatment or to other types of interventions?

A. Introduction/Rationale

Vitamins and minerals typically are consumed in foods. However, sometimes individual minerals can be isolated to determine their effects on health outcomes. Therefore, the work group decided that a systematic review was warranted to determine the individual effects of sodium and potassium, which have been associated with CVD risk factors and outcomes. Other minerals, such as calcium and magnesium, also were considered, but were not included in the systematic review because their consumption is limited to relatively few specific foods or food groups (e.g., calcium and dairy products), and a recommendation to increase or decrease consumption of the mineral rather than the food could not likely be implemented.

Sodium was reviewed as a single nutrient because little sodium is found naturally in food, and it is primarily added to foods in preparation, preservation, and/or at the time of consumption. Therefore, individuals can alter sodium intake without altering intake of specific foods or an overall dietary pattern.

Potassium was reviewed as a single nutrient because it has been hypothesized that dietary potassium intake may lower BP independent of other nutrients or foods. In addition, the effect of sodium on BP may be modulated by concomitant potassium intake.

Most of the evidence from clinical trials pertains to effects of minerals on risk factors (i.e., BP and plasma lipids) that are relevant, intermediate outcomes for CVD. In addition, data primarily from observational studies provide evidence on the effects of dietary sodium and potassium on CVD outcomes.

B. Selection of Inclusion/Exclusion Criteria

Members of the work group developed eligibility criteria, based on a PICOTS approach, to screen potential studies for inclusion in this evidence review. Table 8 presents the details of the PICOTS approach for CQ2.

CQ2 was established to examine studies that assessed the impact of sodium and potassium on BP and cardiovascular morbidity and mortality. The studies included adults with or without established CVD; with or without CVD risk factors; with or without tobacco use; and who were of normal weight, overweight, or obese. In addition to the criteria in table 8, to be included in this evidence review, biomarker and risk factor studies had to have an intervention sample size of at least 50, and cardiovascular morbidity and mortality studies had to

have an intervention sample size of at least 500. Because a separate Obesity Panel is reviewing evidence on the effect of weight loss on CVD risk factors and outcomes, this review excluded studies in which weight change was more than 3 percent.

Table 8. PICOTS Approach for CQ2

PICOTS Category	I/E Criteria
Population	Adults, ≥18 years of age
Intervention (RCTs, observational studies)	■ RCTs—intervention alters nutrient intake ■ Observational studies—exposure to two different levels of nutrient intake (for hard health outcomes (listed below) only) ■ Trials that identify well-defined diets with the substitution of a mineral (types and amount) The work group considered the following list of dietary or oral minerals: ■ Sodium, sodium chloride (salt) ■ Potassium ■ Sodium-to-potassium ratio
Comparator	■ May be no predetermined comparison group for observational studies ■ Placebo ■ Usual care ■ No treatment ■ Other dietary interventions ■ Drugs ■ Nondietary lifestyle interventions (e.g., physical activity or smoking cessation)
Outcomes	1. Hard health outcomes: CVD-related morbidity or mortality: ■ Acute coronary syndrome: unstable angina, myocardial infarction ■ Fatal or nonfatal stroke ■ Fatal or nonfatal myocardial infarction (ST-segment elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI)). ■ Coronary revascularization procedures: angioplasty, coronary stent placement, coronary artery bypass ■ Other atherosclerotic revascularization procedures (carotid endarterectomy) ■ Fatal heart failure or hospitalization for heart failure ■ Hospitalization for any cause of coronary heart disease (CHD) or CVD 2. Risk factors and other outcomes: ■ Plasma lipid-related measurements: LDL-C, HDL-C, TG, non-HDL-C, ApoB, Lp (a), LDL-P, Apo A–1, percent at lipid goal ■ BP-related measurements: systolic BP, diastolic BP, hypertensive/nonhypertensive, or percent at BP goal ■ Urinary excretion of albumin sodium or potassium ■ Change in medication dose ■ Incident hypertension

PICOTS Category	I/E Criteria
Timing	1. Intervention/exposure time period: ■ Risk factors and other outcomes for ≥2 weeks ■ Hard health outcomes for ≥3 mo 2. Followup time period: ■ Risk factors and other outcomes for ≥4 weeks ■ Hard health outcomes for ≥6 mo
Setting	■ Any geographic location ■ Any clinical or research setting ■ Any nontreatment setting

C. Literature Search Yield

Thirty-four studies (47 citations) met the final inclusion criteria for CQ2 and were rated good or fair quality.[33,34,48,49,53-94]

CQ2 summary tables C–1 through C–8 summarize data on the included studies. The tables are organized by mineral (sodium or potassium), outcomes (BP or CVD), sodium subquestions (overall results, different levels of sodium, and sodium and other dietary changes), and subpopulations (sex (summary table C–4a), race/ethnicity (summary table C–4b), age (summary table C–4c), and hypertension status (summary table C–4d)). Some studies appear in more than one summary table because they addressed more than one corresponding mineral or subquestion.

D. CQ2 Evidence Statements

i. Sodium and Blood Pressure

A note about the unit of measure presented for dietary and urinary sodium: Sodium is presented in studies in mmol (millimoles), g (grams), and mg (milligrams). The work group chose to convert the sodium results to milligrams for the evidence statements and rationales so that data from different studies would be displayed in a consistent unit. Also, U.S. dietary recommendations and the Nutrition Facts label display sodium in milligrams, and this unit (mg) is easier for health care providers to communicate with patients. Urinary and dietary sodium are portrayed in the original units from each published study in the summary tables.

a. Overall effect of dietary intake of sodium on blood pressure

Three RCTs (seven citations) that examined the overall effect of dietary intake of sodium on blood pressure met inclusion criteria.[33,53,55,56,59,64,65] Summary table C–1 summarizes the design, characteristics, and results of these studies.

ES1. In adults, 25–80 years of age with BP 120–159/80–95 mmHg, reducing sodium intake lowers BP.

Strength of evidence: ***High***

Rationale: Three RCTs with different study designs examined the overall effect of dietary intake of sodium on BP. Two of the studies were behavioral interventions designed to reduce sodium intake in free-living populations: Trial of Nonpharmacologic Interventions in the Elderly (TONE)[55] and Trials of Hypertension Prevention II (TOHP II).[59] The third study, DASH-Sodium, was a randomized feeding study that provided prepared foods to participants in the study.[33] The two different study designs demonstrate what can be achieved in controlled settings with provision of food and known nutrient intake and what is achievable in a less-controlled setting (i.e., real-world) with behavioral counseling to lower sodium intake. In each of these studies, weight was kept stable during the intervention arms reviewed for this specific evidence statement; therefore the effect of sodium reduction on BP could be isolated from changes in body weight.

In all three studies, reductions in sodium intake were associated with reductions in BP. In each study, estimation of dietary intake of sodium was confirmed by 24-hour urinary excretion of sodium. (Of note, observed urinary sodium excretions serve as a marker of dietary sodium intake that represents approximately 90 percent of ingested sodium.) Although the achieved sodium intake levels varied by study, the relative reductions in sodium intake led to consistent findings across the studies.

TONE was designed to test the effect of a behavioral intervention for sodium reduction in older adults (60–80 years of age) who were taking one antihypertensive medication, which was withdrawn at the beginning of the trial.[55] The intervention achieved a 920 mg reduction in urinary sodium excretion from a baseline of 3,312 mg/day. This reduction in sodium was associated with a 4/2 mmHg decrease in BP at a mean of 3.5 months of followup.

TOHP II examined overweight adults, 30–54 years of age, with undedicated baseline BP of <140/83–89 mmHg.[59] The adults were randomized to receive (or not) a behavioral intervention with a target of decreasing sodium intake by 1,840 mg/day. The average 24-hour urinary sodium excretion among participants at baseline was 4,278 mg. Compared with the control group, the behavioral intervention group achieved 24-hour urinary sodium levels that were approximately 1,012 mg lower at 18 months and 874 mg lower at 36 months. These reductions were associated with decreases in BP: 4/5 mmHg at 18 months and 1/3 mmHg at 36 months.

The DASH-Sodium trial tested the effects of sodium reduction in adults who consumed a typical American dietary pattern and were not on BP medication.[33] Using a controlled feeding design, sodium intake was targeted to be reduced initially from 3,450 mg/day to 2,300 mg/day and then further to 1,150 mg/day. Although all food was provided to participants, achieved sodium intake levels differed somewhat from targeted intake levels. The work group decided to use achieved sodium intake levels based on 24-hour urinary sodium excretion to determine the extent to which certain sodium intake levels would effectively lower BP. BP decreased with each reduction in sodium intake. Reducing sodium excretion to a mean of 2,461 mg/day lowered BP by an average of 2/1 mmHg. Lowering sodium intake to a urinary excretion of 1,495 mg/day on average (or an additional 966 mg/day) led to an additional decrease in BP of 5/2 mmHg.

In summary, adults with BP 120–159/80–95 mmHg who reduced their sodium intake experienced decreases in BP. This result was seen consistently in the three RCTs, including the one feeding study in which nutrient intake was carefully controlled; the effect was independent of changes in body weight or other dietary manipulations. However, it should be noted that in all studies, the study populations were not taking BP medication; the evidence statement, strictly speaking, applies only to similar adult populations. Therefore, it may be reasonable to expect that the BP-lowering effects of reduced sodium intake could also be applied to adults taking BP medications, and reducing sodium intake while taking BP medications could lead to better BP control and/or reduced medication needs.

b. Comparison of different levels of dietary intake of sodium on blood pressure

One RCT (four citations) that evaluated the overall effect of different levels of dietary sodium on BP met inclusion criteria.[33,48,49,57] Summary table C–2 summarizes the design, characteristics, and results of this study.

ES2. In adults, 25–75 years of age with BP 120–159/80–95 mmHg, reducing sodium intake that achieves a mean 24-hour urinary sodium excretion of approximately 2,400 mg/day, relative to approximately 3,300 mg/day, lowers BP by 2/1 mmHg, and reducing sodium intake that achieves a mean 24-hour urinary sodium excretion of approximately 1,500 mg/day, lowers BP by 7/3 mmHg.

Strength of evidence: Moderate

Rationale: The DASH-Sodium trial was the only RCT that specifically compared various levels of sodium intake to each other with regard to the effect on BP.[33] The DASH-Sodium trial studied the effect of sodium intake at low, medium, and high levels in adults with BP 120–159/80–95 mmHg who were not taking BP medication. After adjusting for caloric intake, the target intakes of low, medium, and high sodium levels led to 24-hour urinary sodium excretion of 1,495 mg/day, 2,438 mg/day, and 3,337 mg/day, respectively. To isolate the effects of sodium reduction at each level, participants were fed a typical American diet, and body weight was kept stable. The achieved intake levels of sodium were separated by approximately 1,000 mg, meaning nearly 2,000 mg difference between the highest and lowest levels. When sodium was reduced from the highest intake level, BP in participants whose baseline BP was 120–159/80–95 mmHg decreased by 2/1 mmHg at the medium level and decreased further by 5/2 mmHg at the lowest level. Overall, reducing sodium intake from the highest intake level to the lowest level led to a decrease in BP of 7/3 mmHg.

ES3. In adults, 30–80 years of age with or without hypertension, counseling to reduce sodium intake by an average of 1,150 mg/day reduces BP by 3–4/1–2 mmHg.

Strength of evidence: High

Rationale: Two RCTs (three citations) offer evidence that providing counseling to reduce dietary sodium reduces BP.[55,56,58] The trials started at various levels of sodium in the diet, conducted different interventions to lower sodium intake, and achieved varying levels of reduction in dietary sodium. Both trials showed a reduction in systolic BP of at least 3 mmHg in those assigned to counseling intervention groups. TOHP II[58] and TONE[55] showed a reduction in diastolic BP of at least 1 mmHg.

For TOHP II, in nine clinical centers across the United States, overweight men and women (30–54 years of age) were randomly allocated to receive either education and counseling about how to reduce sodium (intervention group) or no counseling (control group).[58] The goal of the intervention was to decrease the group average sodium intake to less than 1,840 mg/24 hours by 6 months. The intervention included an individual counseling session of 60–90 minutes, 10 weekly group sessions, and four monthly group sessions—with additional in-person, telephone, and mail contacts as needed. Content included identifying sodium sources in foods, preparing low-sodium items, modifying recipes, making lower sodium selections at and between meals and away from home, and general relapse and behavioral techniques. Registered dietitians or other nutrition counselors delivered the intervention with support from behavioral psychologists. Dietary sodium and 24-hour urinary samples were collected at 6, 18, and 36 months. Systolic BP decreased more in the intervention group at 6, 18, and 36 months than in the control group: 6 mmHg vs. 2 mmHg ($p<.001$), 4 mmHg vs. 2 mmHg ($p<.01$), and 0.7 mmHg vs. 0.6 mmHg. The reduction in diastolic BP also was significant at 6 months (4 mmHg vs. 3 mmHg ($p<.001$)) and at 18 months (4 mmHg vs. 3 mmHg ($p<.002$)). Incident hypertension was reduced by 18 percent in the intervention group.[58]

For TONE, healthy adults, 60–80 years of age with BP <145/85 mmHg and on one or more hypertensive medications that were weaned during the screening phase, were randomly allocated to one of four groups: weight loss and reduced sodium, reduced sodium alone, weight loss alone, and usual lifestyle. The intervention goal for sodium reduction was to achieve and maintain 24-hour dietary sodium of 1,840 mg as measured by 24-hour urine collection. The intervention for sodium included an individual session with a registered dietitian, 4 months of weekly small group (9–12 participants) meetings (individual sessions each fourth week), a 3-month extended phase of biweekly meetings, and a maintenance phase. Content included learning about sources of sodium, alternative foods, and adaptation of the reduced sodium recommendations to individualized lifestyles. A registered dietitian typically administered the intervention. From baseline to 3 months before medication withdrawal, sodium reduction was associated with reductions in systolic BP (4 mmHg) and diastolic BP 2 mmHg net of control (p<.001). Mean followup at 30 months was associated with a mean reduction in sodium intake of 1,035 mg/day. In adults taking a single medication, this reduced the need for antihypertensive medication by 32 percent.[55]

c. Sodium and blood pressure in subpopulations defined by sex, race/ethnicity, age, and hypertension status

Summary tables provide the design, characteristics, and results of the studies evaluating the effect of sodium on BP in the following subpopulations: sex (summary table C–4a), race/ethnicity (summary table C–4b), age (summary table C–4c), and hypertension status (summary table C–4d).

ES4. In adults with prehypertension or hypertension, reducing sodium intake lowers BP in women and men, African American and non-African American adults, and older and younger adults.

Strength of evidence: ***High***

Rationale: Three RCTs (five citations) of 3–6 months' duration examined the effect of lowering sodium intake in subgroups that included men and women, African Americans and non-African Americans, and older and younger adults.[33,48,49,55,58] In all three trials, which included adults with prehypertension and hypertension, reductions in sodium levels were associated with reductions in systolic and diastolic BP (table 9). As noted in ES1, TONE, TOHP II, and the DASH-Sodium trial involved different populations, interventions, and varying levels of achieved reductions in sodium; yet these studies led to consistent findings across trials. All three trials examined adults 25–80 years of age.

Table 9. Effects of Sodium Reduction on Systolic/Diastolic Blood Pressure (mmHg) in the DASH-Sodium Trial

Population	Typical American Diet: Reducing Sodium From 3,300 mg to 2,400 mg	Typical American Diet: Reducing Sodium From 2,400 mg to 1,500 mg	DASH: Reducing Sodium From 3,300 mg to 2,400 mg	DASH: Reducing Sodium From 2,400 mg to 1,500 mg
Women	–2†/–1	–6*/–3*	–2†/–1‡	–2*/–1†
Men	–3†/–1†	–3*/–2*	–1/–1	–1/–1
African Americans	–2†/–2*	–6*/–3*	–2†/–1‡	–2*/–1†
Non-African Americans	–2†/–1	–3*/–2*	–1/–0.3	–1/–1‡

Population	Typical American Diet: Reducing Sodium From 3,300 mg to 2,400 mg	Typical American Diet: Reducing Sodium From 2,400 mg to 1,500 mg	DASH: Reducing Sodium From 3,300 mg to 2,400 mg	DASH: Reducing Sodium From 2,400 mg to 1,500 mg
>45 years of age	–3*/–2*	–5*/–2*	–1‡/–1‡	–3*/–1*
≤45 years of age	–1/–0.2	–4*/–3*	–1/–1	–0.1/–1

Note: Results (mmHg) for systolic BP are presented first, followed by diastolic BP (e.g., –2/–1).
* $p<.01$
† $p<.05$
‡ $p<.10$

Rationale—Women: In the context of the typical American diet in the DASH-Sodium trial, reductions in urinary sodium from an average of 3,300 mg to 2,400 mg per 2,100 kilocalories on average lowered BP in women by an average of 2/1 mmHg. Further reductions in urinary sodium to 1,500 mg reduced BP by an additional 6/3 mmHg. In the context of the DASH dietary pattern, reductions in urinary sodium excretion from an average of 3,300 mg to 2,400 mg/day lowered systolic BP by an average of 1 mmHg, and further reducing urinary sodium excretion to 1,500 mg reduced systolic BP by an additional 4 mmHg and diastolic BP by an additional 2 mmHg. In TONE, among women 60–80 years of age with hypertension, counseling to reduce sodium intake to less than 1,800 mg/day lowered BP by 3/1 mmHg compared with those receiving usual care ($p<.2$) at a mean followup of 28 months. In TOHP II, counseling to reduce sodium intake to <1,840 mg/day lowered BP by 3–5/2 mmHg in women at 6 months, 2–5/2–4 mmHg at 18 months, and 2–3/1–2 mmHg at 36 months.

Rationale—Men: In the context of the typical American diet in the DASH-Sodium trial, reductions in urinary sodium from an average of 3,300 mg to 2,400 mg lowered BP in men by an average of 3/1 mmHg. Further reductions in urinary sodium to 1,500 mg led to a BP reduction of an additional 3/2 mmHg. In the context of the DASH dietary pattern, reductions in urinary sodium excretion from about 3,300 mg to 1,500 mg/day on average lowered systolic and diastolic BP by 2 mmHg, although the systolic BP lowering was not significant. In TONE, reducing sodium to <1,800 mg/day lowered BP by 5/3 mmHg compared with those receiving usual care ($p<.01$) at a mean followup of 28 months. In TOHP II, counseling to reduce sodium intake to <1,840 mg/day lowered BP by 2–5/1–2 mmHg at 6 months, 2/1 mmHg at 18 months, and 1/1mmHg at 36 months.

Rationale—African Americans: In the context of the typical American diet in the DASH-Sodium trial, reductions in urinary sodium from an average of 3,300 mg to 2,400 mg lowered BP by an average of 2/2 mmHg in African Americans. Further reductions of urinary sodium excretion to 1,500 mg lowered BP in African Americans by an additional 6/3 mmHg. In the context of the DASH dietary pattern, reductions in 24-hour urinary sodium excretion from about 3,300 mg/day to 2,400 per/day lowered systolic BP by 2 mmHg and diastolic BP by 1 mmHg (nonsignificant); further reductions in urinary sodium to 1,500 mg/day lowered BP an additional 2/1 mmHg. In TONE, reducing sodium to <1,800 mg/day lowered BP by 5/3 mmHg in African Americans who received counseling compared with those who received usual care ($p<.05$). In TOHP II, counseling to reduce sodium to 1,840 mg/day lowered BP by 5/2–3 mmHg at 6 months, 1–5/1–4mmHg at 18 months, and 1–3/1–2 mmHg at 36 months.

Rationale—Non-African Americans: In the context of the typical American diet in the DASH-Sodium trial, reductions in urinary sodium from an average of 3,300 mg to 2,400 mg lowered BP by 2/1 mmHg. Further reductions in urinary sodium excretion to 1,500 mg lowered BP by an additional 3/2 mmHg. In the context of the DASH dietary pattern, reductions in urinary sodium excretion from an average of 3,300 mg to 2,400 mg/day

lowered systolic BP by 1 mmHg and diastolic BP by 0.3 mmHg (nonsignificant); further reductions in urinary sodium excretion to 1,500 mg/day lowered BP an additional 2/1mmHg. In TONE, reducing sodium to <1,800 mg lowered BP by 4/2 mmHg in non-African Americans who received counseling compared with usual care. (p<.01). In TOHP II, counseling to reduce sodium to 1,840 mg/day lowered BP by 2–3/1–2 mmHg at 6 months, 2/1–2 mmHg at 18 months, and 1–2/1 mmHg at 36 months.

Rationale—>45 years of age: In the context of the typical American diet in the DASH-Sodium trial, reductions in urinary sodium from an average of 3,300 mg to 2,400 mg lowered systolic BP by an average of 3/2 mmHg. Further reductions in urinary sodium excretion to 1,500 mg lowered BP in those over 45 years of age by an additional 5/2 mmHg. In the context of the DASH dietary pattern, reductions in urinary sodium excretion from about 3,300 mg/day to 1,500 mg/day lowered BP by 5/2 mmHg; further reductions in urinary sodium excretion from about 2,400 mg to 1,500 mg per day lowered BP 3/1 mmHg. In TONE, reducing sodium to 1,800 mg/day lowered BP by 5/2mmHg in those 60–69 years of age and by 2/1 mmHg in those 70–80 years of age.

Rationale—≤45 years of age: In the context of the typical American diet in the DASH-Sodium trial, reductions in urinary sodium from an average of 2,400 mg to 1,500 mg lowered systolic BP by an average of 4/3 mmHg (p<.01).

ES5. Reducing sodium intake lowers BP in adults with either prehypertension or hypertension when eating either the typical American diet or the DASH dietary pattern. The effect is greater in those with hypertension.

Strength of evidence: ***High***

Rationale: Three studies (four citations) examined the effects on BP of reducing dietary sodium intake in adults with either prehypertension or hypertension.[48,55,57,58]

Prehypertension: Findings from two studies (three citations) provide evidence that reducing dietary sodium intake lowers BP in adults with prehypertension.[48,57,58] In the context of a typical American diet in the DASH-Sodium trial, reductions in 24-hour urinary sodium excretion from an average of about 3,300 mg/day to 2,400 mg/day lowered BP by an average of 2/1 mmHg. Further reductions in urinary sodium excretion to 1,500 mg/day lowered BP by an additional 3/2 mmHg.[48,57] In the context of the DASH dietary pattern, reductions in urinary sodium excretion from about 3,300 mg/day to 2,400 mg/day in adults with prehypertension lowered BP by an average of 1/1 mmHg; further reductions in urinary sodium excretion to 1,500 mg/day did not lower BP.[48,57] Among adults with prehypertension in TOHP II, counseling to reduce sodium intake to ≤1,840 mg/day lowered BP by about 3/2 at 6 months, 2/1 at 18 months, and 1/1 mmHg at 36 months, net of control.[58]

Hypertension: Findings from two studies (three citations) provide evidence that reducing dietary sodium intake lowers BP in adults with hypertension.[48,55,57] In the context of a typical American diet in the DASH-Sodium trial, reductions in urinary sodium excretion from an average of 3,300 mg/day to 2,400 mg/day lowered BP by an average of 2/2 mmHg among adults with BP 140–159/90–95 mmHg; further reductions in urinary sodium excretion to 1,500 mg/day lowered BP an additional 6/3 mmHg.[48,57] In the context of the DASH dietary pattern, reductions in urinary sodium excretion from 3,300 mg/day to 2,400 mg/day lowered systolic BP by an average of 2 mmHg; further reduction of urinary sodium to 1,500 mg lowered BP an additional 3/2 mmHg.[48,57] In TONE, among adults 60–80 years of age with hypertension (defined as taking a BP medication for BP <145/85 mmHg), counseling to reduce sodium intake to <1,800 mg/day lowered BP by 4/2 mmHg, net of control (p<.001), after a mean of 3.5 months.[55]

Prehypertension and hypertension: One study—the DASH-Sodium trial—included adults with prehypertension and adults with hypertension, allowing a direct comparison of effects in both subgroups.[33] The effects of reducing sodium intake on BP lowering were greater among adults with BP 140–159/90–95 mmHg compared with those with BP 120–139/80–90 mmHg on both the typical American diet (p=.01) and the DASH dietary pattern (p=.003).

d. Sodium and blood pressure in the context of dietary pattern changes

Summary table C–3 summarizes the design, characteristics, and results of the studies evaluating the effect of dietary sodium on BP in the context of other dietary changes.[33,53,55,56,60-62]

ES6. In adults, 25–80 years of age with BP 120–159/80–95 mmHg, the combination of reducing sodium intake and eating the DASH dietary pattern lowers BP more than reducing sodium intake alone.

Strength of evidence: Moderate

Rationale: This statement is based on the DASH-Sodium trial.[29] Although the DASH-Sodium trial was a single RCT, it involved a large and diverse study population of prehypertensive or hypertensive adults who were not on BP medication, and it was a well-designed RCT with high followup rates. The intervention provided all foods and beverages to the participants of the study, which allowed the actual intake of nutrients and food groups to be assessed. Sodium intake was estimated from 24-hour urinary excretion, which in steady-state generally represents about 90 percent of actual sodium intake.

In the DASH-Sodium trial, the effect of reducing sodium intake while eating the DASH dietary pattern was compared with eating a typical American diet and typical intake of sodium (i.e., a mean 24-hour urinary sodium excretion of approximately 3,300 mg). Relative to this "typical" state, following both the DASH dietary pattern and reducing sodium intake to a level that achieved a mean 24-hour urinary sodium excretion of approximately 2,400 mg/day lowered BP by 7/4 mmHg. Furthermore, following both the DASH dietary pattern and reducing sodium intake to a level that achieved a mean 24-hour urinary sodium excretion of approximately 1,500 mg lowered BP by 9/5 mmHg.

e. Sodium and blood pressure in the context of other minerals

Summary table C–3 summarizes the design, characteristics, and results of the studies evaluating the effect of dietary sodium on BP in the context of dietary changes designed to alter minerals.[33,53,55,56,60-62]

ES7. Evidence from RCTs is not sufficient to determine whether reducing sodium intake and changing dietary intake of any other single mineral (e.g., increasing potassium, calcium, or magnesium) lowers BP more than reducing sodium intake alone.

Rationale: No RCTs or meta-analyses met inclusion criteria that examined whether reducing sodium intake plus changing dietary intake of any other single mineral lowers BP more than reducing sodium intake alone. However, several studies that included modifications of multiple minerals were identified and are described briefly below.

In a study of Black South African adults with mild- to moderate hypertension, commonly consumed foods were altered to achieve approximately 41 percent reduction in sodium intake, 826 percent increase in potassium intake, 388 percent increase in calcium intake, and 368 percent increase in magnesium intake.[62] Following consumption of these altered foods for 8 weeks, systolic BP was lowered by 6 mmHg (p<.05) (with no

significant change in diastolic BP), compared with a group of adults that consumed unaltered foods. Urinary sodium excretion was not different between the intervention groups, but urinary potassium and magnesium were higher in the group eating altered foods, which suggested that the BP effect was due to changes in intake of minerals other than sodium. In any case, the effect of changing sodium intake in the context of changing intake of other minerals cannot be determined from this study because the sodium intake (reflected in sodium excretion) was not different between the intervention and control groups.

In the China Salt Substitute Study, the household use of a salt substitute that included 25 percent potassium chloride, 10 percent magnesium sulfate, and 65 percent sodium chloride for 1 year reduced systolic BP by 4 mmHg ($p<.001$) relative to usual salt usage.[61] Differences in diastolic BP were not detected. Significant differences were not observed in the first-morning urinary sodium concentrations between the intervention and control groups. The first-morning urinary potassium concentration was higher at 6 months and 12 months, but no measurements of magnesium were reported. Thus, it was not possible to identify the impact of any single mineral.

A secondary analysis of TONE reported that when using pooled estimates of sodium and potassium intake with hierarchical measurement error models, an independent, graded influence on nonpharmacologic BP control was observed.[56] The study interventions in TONE inadvertently led to changes in potassium intake, and higher potassium intake was associated with greater BP reduction. However, the intervention was not designed to specifically influence the level of potassium intake, and the changes that took place were in association with changes to facilitate sodium reduction in the diet. Within the report of this secondary analysis, no urinary excretion data were provided to allow additional estimates of change in sodium and potassium intake. The pooled estimates used to derive the relationships with BP control appeared to include participants in the trial who were assigned to all four interventions in the parent trial (sodium only intervention, combined sodium/weight loss intervention, weight loss only intervention, and usual care). Thus, the work group concluded that the observed results from this analysis had limited implications.

ii. Sodium and CHD/CVD Outcomes

Effect of dietary intake of sodium on CVD outcomes

To examine the effects of dietary intake of sodium on CVD outcomes, the work group reviewed both randomized trials and observational studies. Observational studies were included for this question and not in others due to the paucity of trials with CVD outcomes and the work group's opinion that, given the implications of changing sodium intake for individuals, institutions, and potentially for public policy, it was critical to address what evidence was available, even if it was only observational. Summary table C–5 summarizes three trials that examined the effect of dietary intake of sodium on CVD outcomes.[55,66,67] Summary table C–6 summarizes observational studies[72,76,79] that were not included in the meta-analysis[85] in addition to newer observational citations.[77,78,80-84]

ES8. A reduction in sodium intake by approximately 1,000 mg/day reduces CVD events by about 30 percent.
Strength of evidence: Low

Rationale: Three RCTs tested the effect of reduction in sodium intake on CVD or mortality.[55,66,67] In 1,981 elderly male military veterans in a retirement home in Taiwan, substitution of sodium with potassium-enriched salt that reduced sodium intake from 5,200 mg/day to 3,800 mg/day for 31 months lowered death from CVD by 41 percent.[67] In TONE, 975 elderly patients in the United States who had hypertension lowered their sodium intake by about 1,000 mg/day for 29 months.[55] The sodium reduction group experienced 36

cardiovascular events compared with 46 in the control group, which was not statistically significant. In an extended observational followup study of 3,126 prehypertensive men and women who participated in either an 18-month or 36- to 48-month trial to reduce sodium intake, participants who received interventions had a 30 percent reduction in relative risk for cardiovascular events, compared with control participants, during 12–15 years of followup.[66] Sodium intake was reduced by about 800 mg/day after the initial intervention.

Several features in these trials limit a conclusive interpretation, rendering the quality of the strength of evidence as "low": small sample sizes for a disease or mortality outcomes; insufficient duration of sodium reduction or of followup for sufficient events to accumulate; a small reduction in sodium intake; the concomitant increase in potassium intake (one trial);[67] and the inclusion of one observational study in the evidence base.

ES9. Higher dietary sodium intake is associated with a greater risk for fatal and nonfatal stroke and CVD.
Strength of evidence: Low

Rationale: Fifteen observational studies published from 1998 to 2009 examined the relationship between dietary sodium intake and stroke and/or CVD. All but two of these studies[78,79] were included in one good-quality systematic review and meta-analysis that summarized the observational studies from January 1966 to December 2008;[85] hence, the estimated risks from the meta-analysis are summarized along with data from the additional two studies. The meta-analysis included data from 13 studies, with a total of 177,025 participants followed 3.5–19 years from six different countries. Studies using fatal, nonfatal, or combined fatal and nonfatal outcomes were combined to produce incident stroke or CVD outcomes. Based on 5,346 stroke events from 10 studies, each 2,000 mg/day higher sodium intake was associated with a 23 percent greater risk for stroke. Similarly, based on 5,044 CVD events from nine studies, each 2,000 mg/day higher sodium intake was associated with a 17 percent greater risk for CVD. These risk reductions are likely to be underestimated because of possible misclassification due to the use of a single baseline sodium assessment with no adjustment for day-to-day variability or changes in sodium intake over time, as well as other limitations of the various sodium assessment methods used in some of these studies, most of which provide inadequate estimates of sodium intake.

One of the two studies not included in the meta-analysis was a small Finnish study (n=755) that found no relationship between sodium intake and stroke mortality.[79] The second study, which followed participants in the first National Health and Nutrition Examination Survey (NHANES), found an inverse relationship between sodium intake and age- and sex-specific CVD mortality rates.[72] However, in multivariate analyses, sodium intake was not associated with CVD mortality (p=.09). The latter study presents with several methodological concerns: inclusion of participants with existing CVD and simultaneous inclusion of sodium, energy intake, and sodium-to-energy ratio in the model, which likely led to colinearity. A re-analysis of the same dataset excluding participants with preexisting CVD and the sodium-to-energy ratio had opposite findings and was included in the meta-analysis.[85]

Because of the timeliness and importance of this question, an updated search was conducted to include studies published from 2010 to April 2012. As a result, six additional studies were identified that met the inclusion criteria. In a study following participants from two population-based cohorts without CVD (n=3,681) for an average of 7.9 years, the lowest tertile of sodium excretion (mean of 2,185 mg/day in men; 2,760 mg/day in women) was associated with higher CVD mortality (hazard ratio (HR)=1.56, confidence interval (CI)=1.02–2.36) but not with combined fatal and nonfatal CVD.[84] The study's findings contradict themselves, and the methodology has been criticized. Concerns include a large amount of missing data but no sensitivity analyses using imputation to assess the impact of missing data, and perhaps more importantly, a

nonstandard approach in which the reference group is the entire study population instead of the group with the highest or lowest urinary sodium excretion.

In the second study, patients who had CVD or were at high risk for CVD and enrolled in two randomized drug trials conducted in 40 countries, were followed for a median of 56 months.[78] Although sodium excretion at both >7,000 mg/day and <3,000 mg/day were associated (in a J-shaped relationship) with increased risk for fatal and nonfatal CVD, this study has been criticized for several reasons. First, the authors used a first-morning void instead of a 24-hour urine sample to estimate urinary sodium excretion over a 24-hour period. A partial urine sample is suboptimal because sodium excretion varies greatly throughout the day and can be affected by diurnal variations in sodium intake, the use of loop diuretics, older age, and hypertension status—most of which were characteristic of patients in this study. Furthermore, the equation used to estimate total sodium excretion was developed specifically for an Asian population. Although the authors validated the equation for their study population, they provided only correlation coefficients, which are not sufficient to assess validity. Finally, many patients were ill and may have been advised to reduce sodium intake before taking part in the study; thus, those with lower sodium intake may have already had CVD.

A NHANES III analysis of 12,267 randomly selected U.S. adults examined the estimated usual intakes of sodium and potassium and their ratio in relation to risk for CVD mortality.[77] The findings suggest that a higher sodium-to-potassium ratio is associated with CVD mortality. The HR comparing the highest quartile of sodium-to-potassium ratio with the lowest quartile was 1.46 (95% CI, 1.11–1.92). In this analysis, it is impossible to determine whether the association is related to higher sodium intake or lower potassium intake.

Another study was a population-based study of 2,657 adults living in Manhattan, New York, who were followed for a mean of 10 years.[82] In this study, each 500 mg/day higher sodium intake was associated with a 17 percent increase in the risk for stroke (HR=1.17, CI=1.07–1.27). Compared with an intake ≤1,500 mg/day, a dietary sodium intake greater than 4,000 mg/day was associated with an increased risk for stroke (HR=2.59, CI=1.27–5.28) and combined stroke, myocardial infarction, and vascular death (HR=1.68, CI=2.67). Sodium intake between these values was not associated with stroke, but intake of 1,501–2,300 mg/day resulted in an increased risk for combined stroke, myocardial infarction, and vascular death (HR=1.35, CI=1.00–1.82), compared with an intake of ≤1,500 mg/day. One major limitation of this study was the estimate of sodium intake by FFQ, a method that does not provide enough details about each food to be a sensitive method for measuring sodium intake.

Two additional studies were conducted in Asian populations with much higher sodium intake than populations in the United States. A study following 77,500 Japanese adults for 7–9 years found that the highest quintile of sodium intake (median 6,844 mg/day) was associated with a higher risk for CVD (HR=1.19, CI=101–1.40) and stroke (HR=1.21, CI=1.01–1.43) compared with the lowest quintile of intake (median 3,084 mg/day).[80] One major limitation of this study was the use of an FFQ, which does not provide enough details about each food to be a sensitive method for measuring sodium intake. Although the authors reported that their FFQ was validated for estimating sodium intake, the correlation with urinary sodium excretion was quite low (r=0.42 in men and r=0.3 in women). A case-control study of 374 cases and 464 age-matched controls from three Chinese hospitals found no relationship between sodium intake and ischemic stroke.[81] Sodium intake was estimated from an FFQ. Additionally, the results from case-control studies may be biased by measuring sodium intake after the stroke has occurred, and in this case, the controls were not matched for sex, although sodium intake is usually higher in men than women.

Although one additional study examined the association between sodium intake and the risk for CVD mortality among people with type 2 diabetes,[83] the work group considered this study insufficient to assess the association between sodium intake and CVD in this subpopulation.

In sum, most studies reported that higher dietary sodium intake was associated with higher risk for stroke and CVD, but findings were inconsistent across studies. Some of the inconsistencies may be due to the observational nature of the studies, along with other general limitations and weaknesses. For example, in the majority of studies, the estimated sodium intake may be misclassified because of the use of a single baseline assessment with no adjustment for day-to-day variability or changes in sodium intake over time, as well as other limitations of the varying assessment methods used (i.e., many were self-reported and are known to provide inadequate estimates of sodium intake). In addition, morbidity and mortality outcomes may be under-ascertained, thereby reducing power. Some studies failed to exclude participants with existing CVD, who may have already reduced their sodium intake because of their disease. Finally, findings may be influenced by confounding of variables not included in the analyses or for those measured with error. On the other hand, observational studies often are population-based samples, allowing the results to be broadly generalized, and usually follow participants for longer than is feasible in randomized trials. After considering the strengths and limitations of each study, the work group concluded that the observational studies suggest that higher dietary sodium intake is associated with higher risk for stroke and CVD. However, because of the methodological limitations of these observational studies, the strength of the evidence was rated low instead of moderate, which is the highest level possible using observational studies.

ES10. Evidence is not sufficient to determine the association between sodium intake and the development of heart failure.

Rationale: One observational study that met inclusion criteria examined the relationship between dietary sodium intake and incidence of congestive heart failure.[76] However, the work group considered the evidence insufficient to make a statement about dietary sodium intake on the development of heart failure.

ES11. Evidence is not sufficient to determine the effect of reducing dietary sodium intake on cardiovascular outcomes in patients with existing heart failure.

Rationale for evidence statement 11: Of three studies[95-97] that examined dietary sodium intake in heart failure patients, two failed to meet inclusion criteria because of inadequate sample size for observational studies (n<500). One trial examined the effect of two levels of sodium on hospital readmissions in heart failure patients;[95] however, not enough evidence was available to make a graded statement on the topic.

iii. Potassium and Blood Pressure and CHD/CVD Outcomes

Summary tables C–7 and C–8 include details on studies evaluating the effect of potassium on BP and CVD outcomes.[61,62,87-94]

ES12. Evidence is not sufficient to determine whether increasing dietary potassium intake lowers BP.

Rationale: Overall, the work group concluded that the evidence of a BP-lowering effect of dietary potassium alone was suggestive but not compelling. No RCTs isolated the effect of dietary potassium on BP. However, three trials suggest a BP-lowering effect of increasing dietary potassium intake, but in each of these trials, changes in potassium intake occurred in the context of other dietary changes:

In the DASH study, a fruit and vegetable dietary pattern that was high in potassium but otherwise similar to a typical American diet lowered BP compared with the typical American diet, but not as much as the DASH

diet.[30] The effect of potassium cannot be isolated because of differences in fiber intake and the possibility that fruits and vegetables lower BP independent of potassium intake.

In the China Salt Substitute Study, the use of a salt substitute that included 25 percent potassium chloride, 10 percent magnesium sulfate, and 65 percent sodium chloride for 1 year reduced systolic BP by 3.7 mmHg ($p<.001$) relative to usual salt usage.[57] Urinary sodium excretion did not differ between participants in the intervention group and those in the control group. However, urinary potassium intake was higher in the intervention group than in the control group, raising the possibility that the BP effect was due to increased potassium intake. Changes in magnesium intake may have contributed to the effect, making it impossible to isolate the effect of potassium.

In a study of Black South African adults, commonly consumed foods were altered to achieve approximately 40 percent reduction in sodium intake, 800 percent increase in potassium intake, 400 percent increase in calcium intake, and 400 percent increase in magnesium intake.[62] These altered foods lowered systolic BP by 6 mmHg (with no significant change in diastolic BP), compared with a group that ate unaltered foods. Urinary sodium excretion did not differ between intervention groups, but urinary potassium and magnesium levels were higher in the group eating altered foods, raising the possibility that the BP effect was due to changes in intake of potassium and/or other minerals.

In contrast, meta-analyses of potassium supplementation (i.e., in pill form), with doses ranging from 40 to 120 mmol/day, resulted in inconsistent effects on BP (no significant effect in one analysis).[98] Other meta-analyses suggested BP-lowering effects of 2–6/1–3 mmHg.[99-101]

ES13. In observational studies with appropriate adjustments (e.g., BP, sodium intake, etc.), higher dietary potassium intake is associated with lower risk for stroke.

Strength of evidence: Low

Rationale: Several large observational studies, with a wide range of potassium intake and a large number of stroke events, fairly and consistently demonstrated an inverse association between potassium intake and risk for stroke, on the order of 20–50 percent reduction in risk compared with the highest and lowest intakes.[71,79,88,90,91] Although several of these studies adjusted for age, sex, race, and BP, the independence of this relationship cannot be established firmly.[68,87,88,90,92,94] In addition, as in all observational studies, causality cannot be assessed.

ES14. Evidence is not sufficient to determine an association between dietary potassium intake and CHD, heart failure, and cardiovascular mortality.

Rationale: The association between dietary potassium intake and heart disease or overall cardiovascular morbidity and/or mortality has not been extensively studied, but the little observational data that exist suggest no significant relationship.[89,93]

Section 5: CQ3—Physical Activity: Lipids and Blood Pressure

CQ3:
Among adults, what is the effect of physical activity on BP and lipids, when compared to no treatment or to other types of interventions?

A. Introduction/Rationale

Data from a large body of observational studies show an association between higher levels of physical activity and lower rates of many chronic diseases, including CVD, and enhanced longevity.[102-104] Furthermore, an inverse dose-response relationship exists, with increasing higher levels of activity associated with commensurately lower rates of CVD in a curvilinear fashion.[105,106] A recent analysis has estimated that by eliminating physical inactivity, 6 percent of CHD worldwide may be eliminated, and life expectancy of the world may be increased by 0.68 years.[107]

Among the mechanisms proposed to mediate the relationship between physical activity and decreased CVD rates are beneficial effects of exercise on BP and lipids.[108] One study estimated that the effects of physical activity on BP, and the development of hypertension reduction explained some 27 percent of the activity-related reduction in CVD rates observed, while 19 percent of the reduction in CVD rates could be explained by the beneficial effects of physical activity on traditional lipids and 16 percent on novel lipids.

Below, we elaborate on findings from meta-analyses of physical activity on changes in lipid profile and BP.

B. Selection of Inclusion/Exclusion Criteria

Due to resource limitations, the work group included only systematic reviews and meta-analyses of RCTs or controlled clinical trials published from 2001 to 2011. The work group identified I/E criteria in eight categories for CQ3 (table 10). The criteria were based on a PICOTS approach and several others related to study design, type of publication, and timeframe for publication.

For each of these I/E criteria, members of the work group developed detailed specifications related to each component. The population of interest was defined as all adults, 18 years of age and older. For CQ3, the intervention was defined as physical activity interventions of any type. However, studies where the primary outcome was weight change were excluded, to focus on the independent effect of physical activity on two CVD risk factors: BP and lipids. A separate Obesity Panel is reviewing evidence of the effect of weight loss on CVD risk factors and outcomes.

Table 10. PICOTS Approach for CQ3

PICOS Category	I/E Criteria
Population	■ Adults, ≥18 years of age
Intervention (meta-analysis or systematic review of RCTs)	■ For RCTs, include physical activity interventions of any type, except for those with a primary outcome of weight change.
Comparator	■ May be no predetermined comparison group for observational studies. ■ For RCTs, the comparison is a group (or groups) of people with varying levels of physical activity or people receiving pharmacotherapy. ■ For an RCT, the comparison group could receive one or more of the following: – Usual care – No treatment – Nonphysical activity intervention – Pharmacotherapy
Outcomes	Risk factors and other outcomes: ■ Lipid-related measurements: LDL-C; HDL-C; TG; non-HDL-C; ApoB; Lp (a); LDL-P; Apo A–1; and percent at lipid goal ■ BP-related measurements: systolic BP, diastolic BP, hypertensive/nonhypertensive, and percent at BP goal ■ Incident hypertension
Setting	■ Any geographic location ■ Any clinical or research setting ■ Any nontreatment setting

C. Literature Search Yield

Forty-two systematic reviews and meta-analyses were identified that met inclusion criteria and quality assessment requirements for CQ3. Of these, 16 studies were rated poor in quality assessment and were excluded from the final body of evidence for CQ3. Ten were rated fair, and 16 were rated good. Two studies were meta-analyses, and five were systematic reviews.

The work group members next identified the systematic reviews and meta-analyses that contained detailed data on lipid outcomes. They identified 14 studies with data on lipid outcomes, including 10 meta-analyses and four systematic reviews.

The work group members next identified the systematic reviews and meta-analyses that contained detailed data on BP outcomes. They identified 11 studies with data on BP outcomes. Ten meta-analyses and one systematic review examined the effects of aerobic exercise. One study, a systematic review, looked at the effects of resistance training.

The next step in the evidence review process for systematic reviews and meta-analyses was to develop evidence statements from the included studies and present them to the full Lifestyle Work Group for consideration and voting. Because these systematic review and meta-analysis articles each summarize evidence from a number of

studies, NHLBI staff and work group members determined that the development of formal evidence tables and summary tables of individual articles by methodologists was not necessary.

CQ3 summary tables summarize the evidence on physical activity and lipids: aerobic exercise and LDL-C (summary table D–1), resistance exercise and LDL-C (summary table D–2), aerobic exercise and HDL-C (summary table D–3), and resistance exercise and HDL-C (summary table D–4), aerobic exercise and blood pressure (summary table D–5), and resistance exercise and blood pressure (summary table D–6).

D. CQ3 Evidence Statements

i. Physical Activity and Lipids

This section examines evidence supporting the use of physical activity alone (i.e., not in combination with other interventions, such as dietary interventions or weight loss) versus no physical activity or other type of intervention, for improvements in selected lipids: HDL-C, LDL-C, TG, and non-HDL-C. The 2008 *Physical Activity Guidelines Advisory Committee Report* was used as the starting point for the evidence review.[102] Additionally, a systematic search identified eight meta-analyses and five systematic reviews (from 2001 to 2011) that were rated fair to good, addressed the evidence statements, and were included as the evidence base.

a. Aerobic exercise training and lipids

ES1. Among adults, aerobic physical activity, as compared to control interventions, reduces LDL-C by 2.5 mg/dL on average to 6.0 mg/dL.

Strength of evidence: ***Moderate***

Rationale: Evidence from meta-analyses and systematic reviews was examined with regard to the effect of aerobic exercise on changes in LDL-C, along with conclusions of the Physical Activity Guidelines Advisory Committee.[102] A meta-analysis that included studies involving healthy adults 18 years of age and older, showed that aerobic exercise results in a significant decrease in LDL-C of 6 mg/dL.[109] Studies involving only women 18 years of age and older, showed a significant decrease in LDL-C of 4 mg/dL,[110] with the decrease in older adults being 4 mg/dL.[111] A nonsignificant decrease was observed in a meta-analysis of overweight and obese adults (3 mg/dL),[112] with a significant decrease of 6 mg/dL in a meta-analysis that included adults with type 2 diabetes.[113] In a meta-analysis of studies that included only patients with known CVD or who had undergone a medical procedure for CVD, aerobic exercise resulted in a nonsignificant decrease in LDL-C of 8 mg/dL.[114] These observed changes are present when exercise is 15 weeks or more in duration, more than 3 days per week, 35–50 minutes per session, at a vigorous intensity (>60 percent of maximal oxygen consumption). A systematic review of outpatient adult studies also concluded that an average increase of 2,492 steps/day resulted in a significant reduction in LDL-C.[115] However, other systematic reviews[116,117] have concluded that the effect of aerobic exercise on changes in LDL-C are inconsistent, with some studies showing a significant improvement in LDL-C and others not supporting these findings. The *Physical Activity Guidelines Advisory Committee Report* concluded that there is inconsistent evidence of favorable improvements in LDL-C resulting from exercise.[102] Although the results from two systematic reviews and from the report of the Advisory Committee for the Physical Activity Guidelines for Americans are not consistent with the meta-analyses, the totality of the evidence suggests that physical activity reduces LDL-C. This conclusion is based on the results from meta-analyses that were published between 2001 and 2011, which reported significant reductions in LDL-C with physical activity,[109,110,111,113] and on an additional two meta-analyses that reported nonstatistically significant reductions in LDL-C with physical activity that were of similar magnitude.[112,114]

ES2. Among adults, aerobic physical activity alone, as compared to control interventions, reduces non-HDL-C 6 mg/dL on average.

Strength of evidence: Moderate

Rationale: Evidence from one meta-analysis was examined with regard to the effect of aerobic exercise on changes in non-HDL-C.[118] This meta-analysis included studies of healthy adults, 18 years of age and older, and showed a significant decrease in non-HDL-C of 6 mg/dL. This observed change was present when aerobic exercise was 23 ±18 weeks' duration, 5 ±3 days/week, and 38 ±16 minutes/session, at a vigorous intensity (65 ±9 percent of maximal oxygen consumption).

ES3. Among adults, aerobic physical activity alone, as compared to control interventions, has no consistent effect on TG.

Strength of evidence: Moderate

Rationale: Evidence from five meta-analyses and four systematic reviews was examined with regard to the effect of aerobic exercise on TG, along with a review of the conclusions of the Physical Activity Guidelines Advisory Committee.[102] A meta-analysis that included studies of healthy adults, 18 years of age and older, showed that aerobic exercise led to nonsignificant increases in TG of 0.2 mg/dL[118] and 1 mg/dL.[110] Studies involving only women, 18 years of age and older, showed a significant decrease of 4 mg/dL,[109] with the nonsignificant decrease in older adults being 7 mg/dL.[111] A significant decrease was observed in a meta-analysis of overweight and obese adults (16 mg/dL),[112] with a nonsignificant decrease of 10 mg/dL observed in a meta-analysis that included adults with type 2 diabetes.[113]

A meta-analysis of studies observed a significant decrease in TG of 20 mg/dL among only patients with known CVD or who had undergone a medical procedure for CVD.[114] These observed changes were present when exercise was 15 weeks or more in duration, more than 3 days per week, 35–50 minutes per session, at a vigorous intensity (>60 percent of maximal oxygen consumption). One systematic review concluded that aerobic exercise has a consistent effect on reducing TG,[116] but another systematic review concluded that the effect is inconsistent.[117] The *Physical Activity Guidelines Advisory Committee Report 2008* concluded that exercise results in favorable improvements in TG.[102] A systematic review concluded that an average increase of 2,492 steps/day resulted in a nonsignificant decrease in TG in outpatient adult studies.[115] These findings also show no deleterious effect of physical activity on TG.

ES4. Among adults, aerobic physical activity alone, as compared to control interventions, has no consistent effect on HDL-C.

Strength of evidence: Moderate

Rationale: Evidence from eight meta-analyses and three systematic reviews published between 2001 and 2011, along with conclusions of the Physical Activity Guidelines Advisory Committee, was examined with regard to the effect of aerobic exercise on changes in HDL-C.[102] Meta-analyses studies of healthy adults, 18 years of age and older, showed nonsignificant increases in HDL-C of 1 mg/dL.[110,118] One meta-analysis of adults (20 years of age and older) that excluded studies in which participants may have been taking medication or prescribed a diet that may have influenced HDL-C, reported a significant increase of 3 mg/dL.[114] Studies involving only women, 18 years of age and older, showed a significant increase of 2 mg/dL,[109] with the increase in older adults being 3 mg/dL.[111] A nonsignificant increase was observed in a meta-analysis of overweight and obese adults

(2 mg/dL),[112] with a nonsignificant increase of 1 mg/dL observed in a meta-analysis that included adults with type 2 diabetes.[113] In a systematic review of studies that included only patients with known CHD who engaged in exercise-based cardiac rehabilitation, a nonsignificant decrease in HDL-C of 1.9 mg/dL was observed.[119]

The observed changes in HDL-C reported in meta-analyses are present when exercise is 15 weeks or more in duration, more than 3 days per week, 35–50 minutes per session, and at a vigorous intensity (>60 percent of maximal oxygen consumption). Systematic reviews[116,117] have concluded that the effect of aerobic exercise on increasing HDL-C are consistent, and the *Physical Activity Guidelines Advisory Committee Report 2008* concluded that exercise results in favorable improvements in HDL-C.[102] A systematic review concluded that an average increase of 2,492 steps/day resulted in a nonsignificant increase in HDL-C in outpatient adult studies.[115]

The conclusion of no consistent effect of physical activity on change in HDL-C may be a result of differences in patient demographics among the studies included in the meta-analyses and systematic reviews; the inability to examine meta-analyses or systematic reviews published before 2001, which may have limited the inclusion of earlier studies that showed a favorable influence on physical activity on HDL-C; or the insufficient dose of physical activity in some studies that would influence a change in HDL-C. These findings also show no deleterious effect of physical activity on HDL-C.

b. Resistance exercise training and lipids

ES5. Among adults, resistance training, as compared to control interventions, reduces LDL-C, TG, and non-HDL-C by 6 to 9 mg/dL on average and has no effect on HDL-C. Typical interventions shown to reduce LDL-C, TG, and non-HDL-C and have no effect on HDL-C include resistance physical activity programs that average 24 weeks in duration and include ≥3 days per week, 9 exercises performed for 3 sets and 11 repetitions at an average intensity of 70 percent of one maximal repetition.

Strength of evidence: Low

LDL-C: Evidence from one meta-analysis and one systematic review was examined with regard to the effect of resistance exercise on changes in total cholesterol. The meta-analysis involved studies of healthy adults, 18 years of age and older, and showed a significant decrease in LDL-C of 6.1 mg/dL.[120] These observed changes were present when resistance exercise was 24 ±19 weeks' duration and involved 2.9 ±0.4 days per week of exercise, with the average session lasting 48 ±12 minutes. Specifics of the resistance exercise sessions included performing 9 ±3 different exercises and engaging in 3 ±1 sets of 12 ±7 repetitions for these exercises. The intensity was 70 ±10 percent of one maximal repetition. A systematic review of the literature for the effects of resistance exercise on changes in LDL-C in patients with type 2 diabetes concluded that LDL-C generally improves with this form of exercise.[121] The resistance exercises in these studies were typically performed over a range of 4 weeks to 12 months and were typically performed 3 days per week. The dose of resistance exercises varied between the studies, with less detail provided in the systematic review.

Triglycerides: Evidence from one meta-analysis and one systematic review was examined with regard to the effect of resistance exercise on changes in lipids. The meta-analysis included studies of healthy adults, 18 years of age and older, and showed a significant decrease in TG of 8.1 mg/dL.[122] These observed changes were present when resistance exercise was 24 ±19 weeks' duration and involved 2.9 ±0.4 days/week of exercise, with the average session lasting 48 ±12 minutes. Specifics of the resistance exercise sessions included performing 9.2 ±3.1 different exercises and engaging in 3 ±1 sets of 12 ±7 repetitions. The intensity was 70 ±10 percent of one maximal repetition. A systematic review of the literature for the effects of resistance exercise on changes in TG in patients with type 2 diabetes concluded that TG generally improves with resistance exercise.[121] The resistance exercises in these studies were typically performed over a range of 4 weeks to 12 months and were

typically performed 3 days per week. The dose of resistance exercises varied between the studies, with less detail provided in the systematic review.

Non-HDL-C: Evidence from one meta-analysis was examined with regard to the effect of resistance exercise on changes in non-HDL-C. The meta-analysis included studies of healthy adults, 18 years of age and older, and showed a significant decrease in non-HDL-C of 9 mg/dL.[122] These observed changes were present when resistance exercise was 24 ±19 weeks' duration and involved 3 days/week of exercise, with the average session lasting 48 ±12 minutes. Specifics of the resistance exercise sessions included performing 9 ±3 different exercises and engaging in 3 ±1 sets of 12 ±7 repetitions. The intensity was 70 ±10 percent of one maximal repetition.

HDL-C: Evidence from one meta-analysis and one systematic review was examined with regard to the effect of resistance exercise on changes in total cholesterol. The meta-analysis included studies of healthy adults, 18 years of age and older, and showed a nonsignificant increase in HDL-C of 1 mg/dL.[120] These observed changes were present when resistance exercise was 24 ±19 weeks' duration and involved 3 days/week of exercise, with the average session lasting 48 ±12 minutes. Specifics of the resistance exercise sessions included performing 9 ±3 different exercises and engaging in 3 ±1 sets of 12 ±7 repetitions. The intensity was 70 ±10 percent of one maximal repetition. A systematic review of the literature for the effects of resistance exercise on changes in HDL-C in patients with type 2 diabetes concluded that HDL-C generally improves with resistance exercise.[121] The resistance exercises in these studies were typically performed over a range of 4 weeks to 12 months and were typically performed 3 days per week. The dose of resistance exercises varied between the studies, with less detail provided in the systematic review.

ii. Physical Activity and Blood Pressure

This section examines evidence supporting the use of physical activity alone (i.e., not in combination with such other interventions as dietary interventions or weight loss) versus no physical activity or other types of intervention to reduce BP. The *Physical Activity Guidelines Advisory Committee Report 2008* was used as the starting point for the evidence review.[102] Additionally, a systematic search identified 15 meta-analyses and reviews (from 2001 to 2011) that addressed the evidence statements and were rated fair or good. Details of the search are provided in CQ3 search strategy.[119,121,123-135] Four of these were not used because one examined a combination of exercise and diet versus usual recommendations;[133] one examined lifestyle counseling—as opposed to intervention directly targeting physical activity—versus no counseling for BP reduction;[131] one was a meta-analysis of observational studies rather than RCTs;[125] and the relevant data from one review were obtained from a cross-sectional study.[129] The remaining 11 meta-analyses and reviews served as the basis for the evidence statements.

a. Aerobic exercise training and blood pressure

ES6. Among adult men and women at all BP levels, including hypertensive individuals, aerobic physical activity decreases systolic and diastolic BP, on average, by 2–5 mmHg and 1–4 mmHg, respectively. Typical interventions shown to be effective for lowering BP include aerobic physical activity of, on average, at least 12 weeks duration, 3 to 4 sessions per week, lasting on average 40 minutes per session, and involving moderate- to vigorous intensity physical activity.

Strength of evidence: High

Rationale: The 2008 Physical Activity Guidelines Advisory Committee reviewed the data from 10 meta-analyses and concluded that: "Both aerobic and progressive resistance exercise yields important reductions in systolic and diastolic BP in adult humans, although the evidence for aerobic exercise is more convincing.

Traditional aerobic training programs of 40 minutes of moderate-to-high intensity exercise three to five times per week that involve more than 800 metabolic equivalent task (MET)-minutes of aerobic exercise per week appear to have reproducible effects on BP reduction."[102] Of note, the 2008 Physical Activity Guidelines Advisory Committee focused primarily on hard clinical end points, such as CVD, and BP was considered a secondary end point. Thus, evidence for physical activity and BP reduction was obtained from a search of reviews on the topic, with no assessment of the quality of the reviews used. For example, the committee emphasized the most recent and inclusive meta-analysis,[136] which was not included in the present review because it ranked "poor" in current search strategy. Nonetheless, the conclusions of the *Physical Activity Guidelines Advisory Committee Report 2008* are congruent with the conclusions from the present review, as described below.

For the present review, the largest meta-analysis combined data from 54 RCTs that lasted at least 2 weeks and included 2,419 participants.[135] The median trial duration was 12 weeks, and the average resting BP at baseline was 127/77 mmHg. Three trials included participants on hypertension medication. Among all participants, the average reduction in systolic BP was 4 mmHg (3–5 mmHg) and in diastolic BP was 3 mmHg (2–3 mmHg). Larger reductions were observed when only trials with supervised exercise were included.

Weight change in the intervention group was small (median: –0.4 kg; p=.09). Among normotensive participants, the corresponding BP reduction in systolic BP was 4 mmHg (3–5 mmHg) and in diastolic BP was 2 mmHg (2–3 mmHg); among hypertensive participants, reductions were 5 mmHg (3–7 mmHg) and 4 mmHg (2–6 mmHg), respectively. No significant differences in BP reductions were achieved among White, African American, or Asian participants (p>.2); those with different BMIs (<24.5, 24.5–26.4, or >26.4 kg/m^2; p=.12); and those with different net weight change during the trial (<–1.5, –1.5 to +0.2, or >0.2 kg; p>.2). The characteristics of the aerobic training program did not predict BP change; shorter study trials tended to show larger effects than longer trials (<10, 10–24, or >24 weeks; p=.05). Compliance typically declined with longer trial duration, suggesting that exercise needs to be sustained for BP reduction.

In addition to this meta-analysis, other meta-analyses have reached similar overall conclusions. Additional information provided by these other meta-analyses relates to the following:

- **Specific modalities of exercise:** Walking and qigong (a practice of aligning breath, movement, and awareness for exercise, healing, and meditation).[124,127,130,132]
- **Specific subgroups:** Older adults, post-menopausal women, and adults with CHD or type 2 diabetes.[119,123,126,128,134]

Two meta-analyses specifically examined walking interventions. One meta-analysis pooled data from 16 studies and 650 participants.[127] Adults in the intervention group, whose baseline resting BP averaged 128/80 mmHg, experienced significant decreases in systolic BP of 3 mmHg (2–5 mmHg) and in diastolic BP of 2 mmHg (1–3 mmHg). The average intervention was 25 weeks' duration, with adults in the intervention group walking 4 days per week for 42 minutes each day at 63 percent of maximum VO_2 (oxygen consumption). Another meta-analysis examined 24 RCTs and 1,128 participants in relation to walking and cardiovascular risk factors.[132] The average intervention was 35 weeks' duration, with adults in the intervention group walking 4 days per week for 38 minutes each day at 56 percent of maximum VO_2. For the BP-specific outcomes, data were pooled from nine studies and 356 adults. The participants were primarily women (88 percent in the BP studies), and baseline resting BP averaged 127/78 mmHg. The pooled data showed that walking was not related to systolic BP change (–1 mmHg; p=.32) but was related to diastolic BP change (–2 mmHg; p=.03).

Two meta-analyses compared qigong compared with no intervention (wait-list control), conventional aerobic exercise, or drug treatment with regard to BP.[117,123] Several of the same trials were used in both meta-

analyses.[124,130] The data are limited because of the small number of studies available and the small number of participants in each trial (e.g., 130[124] and 94[130]), yielding results with wide CIs. Qigong significantly reduced systolic BP and diastolic BP compared with no intervention but not compared with drug treatment or conventional aerobic exercise (jogging 4–5 km/day in one study; "exercise" 120 minutes per day, 2 days per week in another).

With regard to specific population groups, a meta-analysis examined data from RCTs of aerobic exercise training versus no exercise among persons 50 years of age and older.[128] The meta-analysis examined seven trials with 802 participants; the mean age was 68.5 years. Initial mean BP was 128/77 mmHg in the intervention group. The average intervention was 35 weeks' duration, 3 days per week for 40 minutes each day, at 63 percent of maximum VO_2. Exercise reduced systolic BP by 2 mmHg (1–4 mmHg); the reduction in diastolic BP was of borderline significance: change –1 mmHg (–2–0 mmHg). The BMI of participants did not change significantly as a result of the intervention.

A qualitative review of RCTs that examined the effect of exercise on BP in post-menopausal women provided mixed results.[123] Seven trials assessed 976 women. Aerobic exercise had no effect on BP in normotensive women; however, compliance with exercise sessions was only moderate (73 percent).

Two analyses examined the effects of cardiac rehabilitation on BP.[119,126] One analysis examined exercise-based cardiac rehabilitation among adults with CVD.[119] The study pooled data from RCTs that lasted at least 6 months. Participants in the intervention group received exercise-based cardiac rehabilitation, and care provided to those in comparison groups did not involve exercise but could include standard care involving drugs. The effect of exercise-based cardiac rehabilitation on systolic BP was examined across eight trials with 744 participants. Exercise-based cardiac rehabilitation (which also may have targeted such other risk factors as diet, stress management, smoking, and group support) decreased systolic BP by 3 mmHg (1–5 mmHg). The effect on diastolic BP was examined across five trials with 482 participants. Exercise-based cardiac rehabilitation reduced diastolic BP by 1.18 mmHg. However, this change (–1 mmHg (–3 to +0.32 mmHg)) was not statistically significant, possibly because of the small sample. Another analysis compared home-based cardiac rehabilitation with supervised rehabilitation.[126] Based on only two studies, systolic BP did not differ significantly with either type of program.

Limited data are available on the effect of physical activity on BP in adults with type 2 diabetes. A meta-analysis examined four RCTs with 127 participants for the effect of physical activity on systolic BP, and three trials with 78 participants for the effect of physical activity on diastolic BP.[134] Compared with no intervention, systolic BP among participants that received the exercise-based intervention decreased by 4.16 mmHg (–10 to +1.14 mmHg), which was not statistically significant; diastolic BP showed little change: –0.13 mmHg (–4 to +3 mmHg).

Thus, although not every meta-analysis observed statistically significant decrements in systolic and diastolic BP with exercise (e.g., because of small total sample size or limited compliance), the totality of evidence provides strong support for the role that aerobic exercise training can play in reducing BP.

b. Resistance exercise training and blood pressure

The 2008 Physical Activity Guidelines Advisory Committee focused on data from a meta-analysis of nine RCTs of resistance training that included 341 participants.[137] However, given the limited parameters of the systematic search for CQ3, only one review was identified. A qualitative review of clinical trials—randomized, nonrandomized, and uncontrolled studies—examined the effect of resistance exercise training on the metabolic health of adults with type 2 diabetes.[121] Ten of these studies assessed BP. Investigators concluded that

resistance exercise training results in beneficial changes to systolic BP and to diastolic BP (less frequently observed). The magnitude of reduction was not specified.

Thus, the review did not provide consistent evidence that resistance exercise training reduces BP.

c. Combination of aerobic and resistance exercise training and blood pressure

No meta-analyses or reviews have been published that specifically examine the effect of a combined regimen of aerobic exercise and resistance training on BP. However, in some of the meta-analyses and reviews described previously, studies with aerobic and resistance components were included in pooled data related to aerobic exercise training.[123,134]

Section 6: Gaps in Evidence and Future Research Needs

A. Diet

- Interaction between dietary modification and statin treatment.
- Relative effects of SFAs, MUFAs, PUFAs, *trans* fatty acids, and omega-3 fatty acids on lipids; inflammation; microbiome; and other newer, potential CVD risk factors.
- Relative effects of naturally occurring fiber (cereal (whole grains) and vegetable/fruit) and supplemental fiber on lipids; inflammation; microbiome; and other newer, potential CVD risk factors.
- Effects of dietary cholesterol on LDL-C and HDL-C over the current ranges of cholesterol and saturated fat intakes (5th and 95th percentiles).
- Effects of minerals in combination other than sodium on BP.
- Studies of HDL function in studies that modify HDL-C by changes in diet.
- Is the minimal effect of dietary carbohydrate on plasma TG harmful?
- The effect of sodium reduction in adults with diabetes, heart failure, and chronic kidney disease.
- Effect of dietary pattern and sodium intake in adults who take BP and/or lipid-lowering medications (e.g., effects on BP/lipids, achieving BP/lipid goals, medication needs/costs, outcomes).
- Effect of dietary pattern and sodium intake in adults with CVD (e.g., post-myocardial infarction or post-stroke or with coronary artery disease, heart failure, or chronic kidney disease).
- Strategies for effectively (and cost-effectively) implementing evidence-based recommendations. How can primary care providers, health systems, public health agencies, local and Federal Governments, community organizations, and other stakeholders help adults adopt diet and sodium intake recommendations?
- Increased understanding of racial/ethnic/socioeconomic factors that may influence (a) the effects of dietary pattern and sodium on BP and lipids and (b) the adoption of diet and/or sodium recommendations.

B. Physical Activity

- The results from meta-analyses and systematic reviews demonstrate that exercise, when performed at a sufficient dose and intensity, will reduce LDL-C and non-HDL-C. However, additional research is needed to understand the pattern of exercise that may be associated with the reduction in LDL-C and non-HDL-C. Such research may lead to improved understanding of whether exercise performed at a lower dose or intensity or different modes of exercise can impact these outcomes. It is also important to further understand the characteristics of individuals for whom exercise of a certain dose and/or intensity can reduce LDL-C and non-HDL-C.
- The results from meta-analyses and systematic reviews show inconsistent effects of exercise on HDL-C and TG. It is important to understand the source of these inconsistent findings to better understand under what conditions exercise can increase HDL or decrease TG. This may include additional research to understand the optimal dose that will result in the desired changes in these outcomes or to understand whether exercise performed at a lower dose or intensity or different modes of exercise can impact these outcomes. It is also

important to further understand the characteristics of individuals for whom exercise of a certain dose, intensity, or mode can increase HDL-C or reduce TG.

- Although data clearly show that physical activity lowers BP, most of the evidence comes from studies of Whites, with limited data on ethnic minorities. Additionally, it is unclear what specific aspects of an aerobic exercise program (e.g., length, frequency, duration, and intensity) are related to greater reductions in BP; that is, the shape of the dose-response curve between physical activity and BP is not clear. Furthermore, data are limited on whether resistance exercise training lowers BP, and whether a combination of aerobic and resistance exercise training offers any added BP lowering, compared with aerobic exercise only.
- Additional research is needed to determine how combining diet and physical activity factors affect BP and lipids.
- Effect of physical activity in adults taking BP and/or lipid-lowering medications (e.g., effects on BP/lipids, achieving BP/lipid goals, medication needs/costs, outcomes).
- Effect of physical activity in adults with CVD (e.g., post-myocardial infarction or post-stroke or with coronary artery disease, heart failure, or chronic kidney disease).
- Strategies for effectively (and cost-effectively) implementing evidence-based recommendations. How can primary care providers, health systems, public health agencies, local and Federal Governments, community organizations, and other stakeholders help adults adopt physical activity recommendations?
- Increased understanding of racial/ethnic/socioeconomic factors that may influence (a) the effect of physical activity on BP and lipids and (b) the adoption of physical activity recommendations.

Appendixes

APPENDIX A.

Methods for Lifestyle Questions

Appendix A. Methods for Lifestyle Questions

i. Description of How Expert Panel and Work Group Members Were Selected

NHLBI initiated a public call for nominations for work group membership to ensure adequate representation of key specialties and stakeholders and appropriate expertise among expert panel and work group members. A nomination form was posted on the NHLBI Web site for several weeks and was also distributed to a leadership group that had given advice to NHLBI on its guideline efforts. Information from nomination forms, including contact information and areas of clinical and research expertise, was entered into a database.

After the close of the call for nominations, NHLBI staff reviewed the database and selected a potential chair and co-chair for each expert panel and work group. The potential chairs and co-chairs provided to NHLBI Conflict of Interest disclosures and a copy of their curriculum vitae. The NHLBI Ethics Office reviewed the conflict of interest disclosures and cleared or rejected persons being considered as chairs and co-chairs. The selected chairs then were formed into a Guidelines Executive Committee, which worked with NHLBI to select expert panel members from the list of nominees.

NHLBI received 440 nominations for potential expert panel members with appropriate expertise for the task. Expert panel selection focused on creating a diverse and balanced composition of members. Expert panel members were selected based on their expertise in the specific topic area (e.g., high BP, high blood cholesterol, and obesity), as well as in such specific disciplines as primary care, nursing, pharmacology, nutrition, exercise, behavioral science, epidemiology, clinical trials, research methodology, evidence-based medicine, guideline development, guideline implementation, systems of care, or informatics. The expert panels also included, as voting ex officio members, senior scientific staff from NHLBI and other Institutes from the National Institutes of Health who are recognized experts in the topics under consideration.

ii. Development and Prioritization of Questions

After expert panels were convened, members were invited to submit topic areas or questions for systematic review. Members were asked to identify topics of the greatest relevance and impact for the target audience of the guideline, primary care providers.

Proposed questions and topic areas were collected from expert panel members over a period of several months. The number of CQs was scoped, and questions were prioritized based on resource constraints. After group discussion, expert panel members ranked priority CQs through a combination of collaborative dialogue and voting. The rationale for each priority CQ is in the main body of the report.

With support from the methodologist and systematic review team, priority CQs were formulated. I/E criteria were defined and formatted using the PICOTS framework. PICOTS is a framework for developing a structured research question. It includes the following components in the statement of the CQ or in the question's I/E criteria:

P Population
I Intervention, Exposure
C Comparator
O Outcome
T Timing
S Setting

I/E criteria define the parameters for the selection of literature for a particular CQ. I/E criteria were developed with input from the methodologist and systematic review team to ensure that criteria were clear and precise and could be applied consistently across literature identified in the search.

The final CQs and criteria were submitted to the literature search team for search strategy development.

iii. Literature Search Infrastructure, Search Strategy Development, and Validation

The literature search was performed using an integrated suite of search engines that explored a central repository of citations and full-text journal articles. The central repository, search engines, search results, and Web-based modules for literature screening and data abstraction were integrated within a technology platform called the virtual collaborative workspace (VCW). VCW was custom-developed for the NHLBI systemic review initiative.

The central repository consisted of 1.9 million citations and 71,000 full-text articles related to CVD risk reduction. Citations were acquired from several databases: PubMed, EMBASE, CINAHL®, Cochrane, PsycINFO®, Wilson Science, and Biological Abstracts®. Literature searches were conducted using a collection of search engines, including TeraText®, Content Analyst, Collexis, and Lucene. These engines were used for executing search strategies, and Lucene was used to correlate the search with screening results.

For every CQ, a literature search and screening were conducted according to the understanding of the question and the I/E criteria that provided specific characteristics of studies relevant to the question. Criteria were framed in the PICOTS format—specifying population, intervention/exposure, comparison group, outcome, time, and setting. The question and PICOTS components were translated into a search strategy involving Boolean and conceptual queries.

A Boolean query encodes both inclusion and exclusion rules. It grants access to the maximum quantity of citations, which are then analyzed by text analytics tools and ranked to produce a selection for literature screening that was conducted by two independent reviewers in VCW's Web-based module. Boolean queries select citations by matching words in titles and abstracts, as well as Medical Subject Headings (MeSH) and subheadings. The number of citations resulting from Boolean queries has ranged from a few hundred to several thousand depending on the question. The text analytics tools suite included:

- A natural language processing module for automated extraction of data elements in support of application of I/E criteria. Frequently extracted and utilized data elements were study size and intervention followup period.
- Content Analyst for automatically expanding vocabulary of queries, conceptual retrieval, and conceptual clustering. The conceptual query engine employed in Content Analyst leverages word frequency features and co-occurrence in similar contexts to index, select, and rank results. The indexing utilizes the Singular Value Decomposition algebraic method.
- TeraText for ranking search results and a variety of fast operations on the inverted index.

Search strategy development was intertwined with the results of literature screening, which provided feedback on search quality and context. Screened literature was categorized into two subsets: relevant or not relevant to the question. Next, results were analyzed to determine the characteristics of relevant versus not relevant citations. Additional keywords and MeSH terms were used to expand or contract the scope of the query as driven by characteristics of relevant citations. If the revised search strategy produced citations that did not undergo the screening process, then a new batch of citations was added for review. The search strategy refinement/literature review cycle was repeated until all citations covered by the most recent Boolean query had been screened.

Each search strategy was developed and implemented in VCW. The search strategy was reviewed by the methodologist and work group members and was available for viewing and printing at any time by work group members and staff collaborating on the systematic review. It was available for execution and supplying literature updates until the literature search and screening cut-off date.

Search strategies for a sample of questions were validated by an independent methodology team. For this validation process, the methodology team developed and executed a separate search strategy and screened a random sample of citations against I/E criteria; these results were compared with the search and screening results developed by the systematic review team. As an additional validation method, studies identified in systematic reviews and meta-analyses were cross-checked against a CQ's "include" list to ensure completeness of the search strategy.

iv. Process for Literature Review and Application of I/E Criteria

Using results from the search strategy, criteria were applied to screen literature for inclusion or exclusion in the evidence base for the CQ. I/E criteria address the parameters in the PICOTS framework and determine what types of studies are eligible and appropriate to answer the CQ. Additional criteria, such as sample size restrictions, were included by the expert panel to fit the context of the CQ.

a. Pilot literature screening mode

In the pilot literature screening mode, two reviewers independently screened the first 50 titles or abstracts in the search strategy results by applying I/E criteria. Reviewers voted to include or exclude the publication for full-text review. Reviewers compared their results to ensure that I/E criteria were applied consistently. Discrepancies in votes were discussed, and clarification on criteria was sought from the expert panel when appropriate. For example, if criteria were not specific enough to be clearly applied to include or exclude a citation, then guidance was sought to word criteria more explicitly.

During this phase, reviewers provided feedback to the literature search team about the relevance of search strategy results; this feedback was used to further refine and optimize the search.

b. Phase 1: Title and abstract screening phase

After the completion of the pilot mode phase, two reviewers independently screened search results at the title and abstract level by applying I/E criteria. Reviewers voted to include or exclude the publication for full-text review.

Titles and abstracts where one or both reviewers voted to include the publication advanced to Phase 2, full-text screening. Titles and abstracts where both reviewers voted to exclude were excluded and not reviewed further; these citations were maintained in VCW and marked as "excluded at title/abstract phase."

c. Phase 2: Full-text screening phase

Titles and abstracts where at least one reviewer voted to include were reviewed at the full-text level in Phase 2. In this phase, two reviewers independently applied I/E criteria to the full-text article and voted for "include," "exclude," or "undecided." The reviewer had to specify the rationale for exclusion (i.e., population, intervention, etc.) in this phase.

Articles where both reviewers voted to include were moved to the "include" list. Articles where both reviewers voted to exclude were moved to the "exclude" list; these citations were maintained in VCW and identified as "excluded at the full article phase" and the rationale for exclusion was noted. Any article with discrepant votes (i.e., one include and one undecided, one include and one exclude, etc.) advanced to Phase 3.

d. Phase 3: Resolution and consultation phase

In this phase, reviewers discussed their vote for "include," "exclude," or "undecided" and cited the relevant criteria for their decision. The two reviewers attempted to achieve consensus through collaborative discussion. If a decision was not reached between the two reviewers, input was sought from the methodologist. If a decision was not reached after consultation with the methodologist, then input was sought from the expert panel; however, the methodologist had the final decision. The final disposition of the article ("include" or "exclude") was recorded in VCW along with comments from the adjudication process.

Similar to search strategies being posted and available for viewing on VCW, all citations screened for a CQ were maintained in VCW with their reviewer voting status and all collected comments.

v. Quality Assessment of Individual Studies

The methodology team assessed the quality (internal validity) of all studies meeting the I/E criteria after the three-phase literature review process. Separate quality rating tools were used for each study design.

a. Design of the quality assessment tools

Appraisal of individual study quality was based on tailored quality assessment tools developed jointly by methodologists from NHLBI and Research Triangle Institute International. The tools were based on quality assessment methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centers, the Cochrane Collaboration, the USPSTF, the Scottish Intercollegiate Guidelines Network, and the National Health Service Centre for Reviews and Dissemination, as well as consulting epidemiologists and others working in evidence-based medicine, with adaptations by methodologists and NHLBI staff for this project.

The tools were designed to assist reviewers in focusing on concepts that are key for critical appraisal of the internal validity of a study. The tools were not designed to provide a list of factors comprising a numeric score. The tools were specific to individual types of included study designs and are described in more detail below.

The tools included items for evaluating potential flaws in study methods or implementation, including sources of bias (e.g., patient selection, performance, attrition, and detection), confounding, study power, the strength of causality in the association between interventions and outcomes, and other factors. Quality reviewers could select "yes," "no," or "cannot determine/not reported/not applicable" in response to each item on the tool. For each item where "no" was selected, reviewers were instructed to consider the potential risk of bias that could be introduced by that flaw in the study design or implementation. Cannot determine and not reported were also noted as representing potential flaws.

Each of the quality assessment tools had a detailed guidance document, which was also developed by the methodology team and NHLBI. The guidance documents were specific to each tool and provided more detailed descriptions and examples of application of the items, as well as justifications for each item's inclusion. For some items, examples were provided to clarify the intent of the question and the appropriate rater response. The four quality assessment tools and guidance documents used in this evidence review are included in tables A–1 through A–4 below.

b. Significance of the quality ratings of good, fair, or poor

Reviewers used the study rating tools on the range of items included in each tool to judge each study to be of "good," "fair," or "poor" quality. The ratings on the different items were used by the reviewers to assess the risk of bias in the study due to flaws in study design or implementation.

In general terms, a "good" study has the least risk of bias, and results are considered to be valid. A "fair" study is susceptible to some bias deemed not sufficient to invalidate its results. The fair quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses.

A "poor" rating indicates significant risk of bias. Studies rated poor were excluded from the body of evidence to be considered for each CQ. The only exception allowed was if there was no other evidence available, then poor quality studies could be considered. However, this exception was not applied in this project because there were no situations found where only poor quality studies were available for a body of evidence for a particular CQ.

c. Training for application of the quality assessment tools

The methodology team conducted a series of training sessions on the use of four of the quality assessment tools. Initial training consisted of two 2-day, in-person training sessions. Reviewers trained in the quality rating were master's or doctorate-level staff with a background in public health or health sciences. Training sessions provided instruction on identifying the correct study designs, the theory behind evidence-based research and quality assessment, explanations and rationales for the items in each tool, and methods for achieving overall judgments regarding quality ratings of good, fair, or poor. Participants engaged in interactive evaluation of multiple example articles, both with the instructors and during group work. Reviewers were also instructed to refer to related articles on study methods if such papers were cited in the articles being rated.

Following the in-person training sessions, the methodology team assigned several articles with pertinent study designs to test the abilities of each reviewer. The reviewers were asked to individually identify the correct study design, complete the appropriate quality assessment tool, and submit it to the methodology team for grading against a methodologist-developed key. A second round of training sessions was then conducted via telephone to review the results and resolve any remaining misinterpretations. Based on the results of these evaluations, a third round of exercises and training sessions was sometimes convened.

The before-after and case series studies quality assessment tools were only applied for the Obesity Panel's CQ5, which addresses bariatric surgery interventions. This CQ included those types of study designs due to the different types of issues addressed for this surgical intervention. As a result, a formal training program for using these quality assessment tools was not conducted. The training efforts were more individual and focused on reviewing the tool and guidance document with staff working on quality assessment for this CQ.

d. Quality assessment process

For all studies except systematic reviews and meta-analyses, each article that met the CQ's inclusion criteria was independently rated for quality by two reviewers using the appropriate tool. If the ratings differed, then reviewers discussed the article in an effort to reach consensus. If consensus was not achieved, then the article was forwarded to a methodologist for quality adjudication.

Quality rating of systematic reviews and meta-analyses was performed independently by two methodologists. If ratings differed, then reviewers discussed the article in an effort to reach consensus. When consensus was not achieved, the article was forwarded to a third methodologist for adjudication.

Expert panel members could appeal the quality of a particular study or publication, subsequent to the initial rating reported to the expert panel members. However, to enhance the objectivity of the quality rating process, the final decision on quality ratings was made by the methodology team, and not by the expert panel members.

vi. Guidance for Assessing the Quality of Controlled Intervention Studies

The quality assessment tool for controlled intervention studies is included in table A–1. The guidance document for that tool is also included in table A–1. This tool was developed by the methodology team and NHLBI based

in part on criteria from AHRQ's Evidence-Based Practice Centers, the USPSTF, and the National Health Service Centre for Reviews and Dissemination.

This tool addresses 14 elements of quality assessment. They include randomization and allocation concealment, similarity of compared groups at baseline, use of intention-to-treat (ITT) analysis (i.e., all patients randomized were analyzed even if some were lost to followup), adequacy of blinding, the overall percentage of subjects lost to followup, the differential rates of lost to followup between the intervention and control groups, and other factors.

Table A–1. Quality Assessment Tool for Controlled Intervention Studies

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?			
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?			
3. Was the treatment allocation concealed (so that assignments could not be predicted)?			
4. Were study participants and providers blinded to treatment group assignment?			
5. Were the people assessing the outcomes blinded to the participants' group assignments?			
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?			
7. Was the overall drop-out rate from the study at its endpoint 20% or less than the number originally allocated to treatment?			
8. Was the differential drop-out rate between groups at the study's endpoint 15% or less?			
9. Was there high adherence to the intervention protocols for each treatment group?			
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			
14. Were all randomized participants analyzed in the group to which they were originally assigned (i.e., did they use an intention-to-treat analysis)?			

Quality Rating (Good, Fair, Poor) (see guidance)
Rater #1 initials:
Rater #2 initials:
Additional Comments (If POOR, please state why):

Note: CD = cannot determine; NA = not applicable; NR = not reported.

The guidance document below is organized by question number from the tool for quality assessment of controlled intervention studies.

Question 1. Described as randomized

Literally, was the study described as randomized? A study does not satisfy quality criteria as randomized simply because the authors call it *randomized*. But as a first step, did the authors of the study say it was randomized?

Questions 2 and 3. Treatment allocation—two interrelated pieces

- Adequate randomization: The randomization is adequate if it occurred according to the play of chance (e.g., computer-generated sequence in more recent studies, or random number table in older studies).

Inadequate randomization: "Randomization" is inadequate if there is a pre-set plan (e.g., alternation where every other subject is assigned to treatment arm or another method of allocation is used such as time or day of hospital admission or clinic visit, ZIP Code, phone number, etc.). In fact, this is not randomization at all—it is another method of assignment to groups. If assignment is not by the play of chance, then the answer is *no*.

There may be some tricky scenarios that will require careful reading and consideration for the role of chance in assignment. For example, sites are randomized to receive treatment or not so all individuals at the site are thereby assigned to a treatment group. This scenario is used for group-randomized trials, which can be truly randomized, but often are "quasi-experimental" studies with comparison groups rather than true control groups. (Few, if any, group-randomized trials are anticipated for this evidence review.)

- Allocation concealment: This means that one does not know in advance, or cannot guess accurately, to what group the next person eligible for randomization will be assigned. Methods include sequentially numbered opaque sealed envelopes, numbered or coded containers, central randomization by a coordinating center, computer-generated randomization that is not revealed ahead of time, etc.

Questions 4 and 5. Blinding

Blinding means that one does not know to which group—intervention or control—the participant is assigned. It is also sometimes called "masking." You are looking to see if each of the following is blinded to knowledge of treatment assignment: the person assessing the primary outcome(s) for the study (e.g., taking the measurements, examining medical records to determine type of event as in an adjudication committee, etc.); the person receiving the intervention (e.g., the patient or volunteer participant); and the person providing the intervention (e.g., the physician, nurse, or behavioral interventionist).

Generally, placebo-controlled medication studies are blinded to patient, provider, and outcome assessors; behavioral or lifestyle studies may often be blinded only to the outcome assessors. Sometimes the person providing the intervention is the same person doing the outcome assessment. If so, make note of it in your comments section.

Question 6. Similarity of groups at baseline

This question relates to whether the intervention and control groups have similar characteristics on average. The whole point of doing a randomized trial is to create similar groups to enable valid comparisons of intervention effects between groups. If there is a significant difference, you should see it when you abstract baseline characteristics. Baseline characteristics for intervention groups are usually presented in a table in the article (often table 1).

Groups can differ at baseline without raising red flags if (1) the differences would not be expected to have any bearing on the interventions and outcomes or (2) the differences are not statistically significant. If you have any

concerns about baseline difference in the groups, write them down in the comments section and consider them in your overall determination of the study quality.

Questions 7 and 8. Dropout

Here, "dropout" means participants for whom there are no end point measurements—the most common reason being that they dropped out of the study (for whatever reason) and were lost to followup.

Generally, an acceptable overall dropout rate is considered 20 percent or less of participants who were randomized/allocated into each group, and an acceptable differential dropout is considered an absolute difference between groups of 15 percentage points at most (calculated by subtracting the dropout rate of one group minus the dropout rate of the other group). However, these are general rates. Higher overall dropout rates may be acceptable. If you are conducting a systematic review on comparative efficacy of antidepressants, then setting the cap at 20 percent for overall dropout makes sense. On the other hand, if you are looking at joint space narrowing for targeted immune modulators, then you may be able to raise the cap for what you define as an overall acceptable dropout rate. Studies comparing targeted immune modulators for this outcome are going to be of longer duration, which means dropouts are more likely. This is the kind of thing that should be decided by the experts for your systematic review. It may or may not be the same cap for all expert panels that are involved in the systematic evidence reviews for NHLBI.

Differential dropout, however, is not flexible. Stick with the 15 percent cap. If you have a differential dropout rate of 15 percent or higher between arms, then you have serious potential for bias, and this constitutes a fatal flaw resulting in a *poor* quality rating for the study.

Question 9. Adherence

Did participants in each treatment group adhere to the protocols for assigned interventions? For example, if Group 1 was assigned to 10 mg/day of Drug A, did most of them take 10 mg/day of Drug A? Another example is a study evaluating the difference between a 30-pound weight loss and a 10-pound weight loss on specific clinical outcomes (e.g., heart attacks), but the 30-pound weight loss group did not achieve its intended weight loss target. A third example is whether a large percentage of participants assigned to one group "crossed over" and got the intervention provided to the other group. A final example is when one group that was assigned to receive a particular drug at a particular dose had a large percentage of participants who did not end up taking the drug or the dose as designed in the protocol.

Question 10. Avoid other interventions

Changes that occur in the study outcomes being assessed should be attributable to the interventions being compared in the study. If participants in any of the groups receive other interventions that are not part of the study protocol and that could affect the outcomes being assessed, and they receive these interventions differentially, there is cause for concern, as it could bias the results. For example, if a study is comparing two different dietary interventions on serum cholesterol, but one of the groups had a significantly higher percentage of participants taking statin drugs, it could unduly influence the results of the study because you would not know whether the difference in outcome was due to the dietary intervention or the drugs.

Question 11. Outcome measures assessment

What tools or methods were used to measure outcomes in the study? Were the tools/methods accurate and reliable—for example, have they been validated, or are they objective? This is important because it indicates the confidence you can have in the reported outcomes. Perhaps even more important is whether the outcomes were assessed in the same manner within groups and between groups. One example is that a self-report of dietary salt intake is not as valid and reliable as testing urine for sodium content. Another example is measurement of BP that only uses clinicians' usual measurement approaches rather than measurers being trained on a standard

approach using the same instrument and taking BP multiple times. In each of these cases, the question would get a "no" for the former and a "yes" for the latter scenario. Another example of a "no" is when an intervention group is seen much more often, enabling more opportunities to report clinical events, than the control group.

Question 12. Power calculation

Generally, a paragraph in the methods section of the study will explain sample size needed to detect differences in primary outcomes. The current standard is at least 80 percent power to detect a clinically relevant difference in an outcome using a two-sided alpha of 0.05. Often, however, older studies will not report anything about power.

Question 13. Prespecified outcomes

Outcomes reported in the study must have been prespecified in order to be hypothesis testing, which is the whole purpose of doing a RCT. If they are not prespecified, then the study may be reporting ad hoc analyses, simply looking for differences that support the findings they wanted. In addition to outcomes, the subgroups being examined should be prespecified in order to be considered hypothesis testing. Most RCTs conduct numerous post hoc analyses as a way of exploring findings and generating additional hypotheses. The intent of this question is to give more weight to reports that are not simply exploratory in nature.

Question 14. Intention-to-treat analysis

ITT analysis means everybody who was randomized is analyzed according to the original group to which they are assigned. This is an extremely important concept, because doing an ITT analysis preserves the reason for doing a randomized trial—that is, to compare groups that differ only in the intervention being tested. Once the ITT analysis philosophy is not followed, you are not really sure that the main reason for doing an RCT is upheld because the groups being compared may no longer be the same. If a study does not use an ITT analysis, it should probably be rated as poor. However, if some other analysis is used and you think it is valid, explain that in the "other" box of the quality review form. Some studies will use a *completers analysis* (which analyzes only the participants that completed the intervention and the study); this type of analysis introduces significant potential for bias. Characteristics of participants who do not complete the study are unlikely to be the same as those who do. The likely impact of participants who withdraw from the study treatment must be considered carefully. ITT analysis provides a more conservative (potentially less biased) estimate of effectiveness.

General guidance for determining the overall quality rating of controlled intervention studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity is the extent to which the results (effects) reported in a study can truly be attributed to the intervention being evaluated and not to flaws in the design or conduct of the study—in other words, the ability for the study to make causal conclusions about the effects of the intervention being tested. Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk of potential for allocation bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other—examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above). High potential for risk of bias translates to a rating of poor quality. Low potential for risk of bias translates to a rating of good quality. (Again, the greater the risk of bias, the lower the quality rating of the study.)

Fatal flaws: If a study has a "fatal flaw," then risk of bias is significant and the study is of poor quality. Examples of fatal flaws in RCTs include high drop-out, high differential drop-out, no ITT analysis or/unsuitable statistical analysis (e.g., completers-only analysis).

Generally, when you evaluate a study, you will not see a fatal flaw, but you will find some risk of bias. By focusing on the concepts underlying the questions in the tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask what the potential for bias is as a result. That is, does this factor cause you to doubt the results that are reported in the study?

We can provide some background reading for you on critical appraisal, but the best approach is for you to think about the questions in the tool and how each tells you something about the potential for bias for any study. We are reluctant to give you general rules as each study has nuances. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal.

We will provide you some examples of studies that fall into each of the categories: good/fair/poor. But again, these will be examples. Each study must be assessed on its own given the details that are reported.

vii. Guidance for Quality Assessment of Systematic Reviews and Meta-Analyses

The quality assessment tool for systematic reviews and meta-analyses is included in table A–2. The guidance document for that tool is also included in table A–2. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-Based Practice Centers and the Cochrane Collaborative.

This tool addresses eight elements of quality assessment. They include the use of prespecified eligibility criteria, use of a comprehensive and systematic literature search process, dual review for abstracts and full-text articles, quality assessment of individual studies, assessment of publication bias, and other factors.

Table A–2. Quality Assessment Tool for Systematic Reviews and Meta-Analyses

Criteria	Yes	No	Other (CD, NR, NA)
1. Is the review based on a focused question that is adequately formulated and described?			
2. Were eligibility criteria for included and excluded studies predefined and specified?			
3. Did the literature search strategy use a comprehensive, systematic approach?			
4. Were titles, abstracts, and full-text articles dually and independently reviewed for inclusion and exclusion to minimize bias?			
5. Was the quality of each included study rated independently by two or more reviewers using a standard method to appraise its internal validity?			
6. Were the included studies listed along with important characteristics and results of each study?			
7. Was publication bias assessed?			
8. Was heterogeneity assessed? (This question applies only to meta-analyses.)			

Quality Rating (Good, Fair, or Poor):
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

Note: CD = cannot determine; NA = not applicable; NR = not reported.

A systematic review is a study that attempts to answer a question by synthesizing the results of primary studies using strategies to limit bias and random error.[138-141] These strategies include a comprehensive search of all potentially relevant articles and the use of explicit, reproducible criteria in the selection of articles included in the review. Research designs and study characteristics are appraised, data are synthesized, and results are interpreted using a predefined systematic approach that adheres to evidence-based methodological principles.

Systematic reviews can be qualitative or quantitative. A qualitative systematic review summarizes the results of the primary studies but does not combine the results statistically. A quantitative systematic review, or meta-analysis, is a type of systematic review that employs statistical techniques to combine the results of the different studies into a single pooled estimate of effect, often given as an odds ratio.

The guidance document below is organized by question number from the tool for quality assessment of systematic reviews and meta-analyses.

Question 1. Focused question

The review should be based on a question that is clearly stated and well formulated. An example would be a question that uses the PICO (population, intervention/exposure, comparison group, outcome) format, with all the components clearly described.

Question 2. Eligibility criteria

The eligibility criteria used to determine whether studies were included or excluded from the review should be clearly specified and predefined. It should be clear to the reader why studies were included or excluded.

Question 3. Literature search

The search strategy should employ a comprehensive, systematic approach in order to capture all of the evidence possible that pertains to the question of interest. At a minimum, a comprehensive review has the following attributes:

- Electronic searches were conducted using multiple scientific literature databases such as MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, PsychLit, and others as appropriate for the subject matter.
- Manual searches of references found in articles and textbooks should supplement the electronic searches.

Additional search strategies that may be used to improve the yield include the following:

- Studies published in other countries
- Studies published in languages other than English
- Identification by experts in the field of studies and articles that may have been missed
- Search of the grey literature, which includes technical reports and other papers from government agencies or scientific groups or committees, presentations and posters from scientific meetings, conference proceedings,

unpublished manuscripts, etc. A search of the grey literature is important (whenever feasible) because sometimes only positive studies with significant findings are published in the peer-reviewed literature, which can bias the results of a review.

The literature search strategy should be described clearly in the review and be reproducible by others with similar results.

Question 4. Dual review for determining which studies to include and exclude

Titles, abstracts, and full-text articles (when indicated) should be reviewed by two independent reviewers to determine which studies to include and exclude in the review. Disagreements between the reviewers should be resolved by discussion and consensus or with third party involvement. The process for review, including methods for adjudicating disagreements, should be clearly stated.

Question 5. Quality appraisal for internal validity

Each included study should be appraised for internal validity (study quality assessment) using a standardized approach for rating the quality of the individual studies. Ideally, this should be done by at least two independent reviewers. However, because there is not one commonly accepted, standardized tool for rating the quality of studies, what we are looking for is that individual study quality was assessed, and details as to how this was done should be clearly stated by the authors.

Question 6. List and describe included studies

All of the included studies should be listed in the review, along with descriptions of their key characteristics. This can be presented in narrative or table format.

Question 7. Publication bias

Publication bias is when studies with positive results have a higher likelihood of being published, being published rapidly, being published in higher impact journals, being published in English, being published more than once, or being cited by others.[138,139] Publication bias can be linked to favorable or unfavorable treatment of research findings due to the investigators, editors, industry, commercial interests, or peer reviewers. A strategy that can minimize the potential for publication bias is to conduct a very comprehensive literature search that includes the strategies discussed in Question 3.

A funnel plot is a commonly used graphical method for detecting publication bias. The funnel plot is a scatter plot of component studies in a meta-analysis. The graph looks like a symmetrical inverted funnel if there is no significant publication bias.

The likelihood of publication bias should be assessed in the review. This can be done in a number of different ways, but an assessment should be conducted and clearly described.

Question 8. Heterogeneity

Heterogeneity is used to describe important differences in the included studies of a meta-analysis that may make it inappropriate to combine the studies.[140] Heterogeneity can be clinical (e.g., important differences between study participants, baseline disease severity, interventions), methodological (e.g., important differences in the design and conduct of the study), or statistical (e.g., important differences in the quantitative results or reported effects).

Clinical or methodological heterogeneity is usually assessed qualitatively by determining whether it makes sense to combine studies.

For example:

- Should a study evaluating the effects of an intervention on CVD risk that involves elderly male smokers with hypertension be combined with a study that involves healthy adults age 18–40? (Clinical Heterogeneity)
- Should a study that uses a randomized controlled trial design be combined with a study that uses a case-control study design? (Methodological Heterogeneity)

Statistical heterogeneity describes the degree of variation in the effect estimates from a set of studies and is assessed quantitatively. The two most common methods used to assess statistical heterogeneity are the Q test (also known as the χ^2 or chi-square test) or I^2 test.

An assessment for heterogeneity should be conducted and clearly described. If the studies are found to be heterogeneous, the investigators should explore and explain the causes of the heterogeneity, and they should determine what influence, if any, the study differences had on the overall study results.

viii. Guidance for Assessing the Quality of Observational Cohort and Cross-Sectional Studies

The quality assessment tool for cohort and cross-sectional studies is included in table A–3. The guidance document for that tool is also included in table A–3. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-Based Practice Centers, the USPSTF, consultation with epidemiologists, and other sources.

This tool addresses 13 elements of quality assessment. They include the clarity of the research question or research objective; the definition, selection, composition, and participation of the study population; the definition and assessment of exposure and outcome variables; the measurement of exposures before outcome assessment; the study timeframe and followup; study analysis and power; and other factors.

Table A–3. Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this study clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this study, were the exposures of interest measured prior to the outcome(s) being measured?			
7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			

Criteria	Yes	No	Other (CD, NR, NA)
8. For exposures than can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as a continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Were the exposures assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposures and outcomes?			

Quality Rating (Good, Fair, or Poor):
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

Note: CD = cannot determine; NR = not reported; NA = not applicable.

The guidance document below is organized by question number from the tool for quality assessment of observational cohort and cross-sectional studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Questions 2 and 3. Study population

Did the authors describe the group of people from which the study participants were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know who to recruit, from where, and from what time period? Is the cohort population free of the outcomes of interest at the time they were recruited?

An example would be men over 40 years old with type 2 diabetes who began seeking medical care at Phoenix Good Samaritan Hospital between January 1, 1990 and December 31, 1994. In this example, the population is clearly described as: (1) who (men over 40 years old with type 2 diabetes); (2) where (Phoenix Good Samaritan Hospital); and (3) when (between January 1, 1990 and December 31, 1994). Another example is women ages 34 to 59 years of age in 1980 who were in the nursing profession and had no known coronary disease, stroke,

cancer, hypercholesterolemia, or diabetes, and were recruited from the 11 most populous States, with contact information obtained from State nursing boards.

In cohort studies, it is crucial that the population at baseline is free of the outcome of interest. For example, the nurses' population above would be an appropriate group in which to study incident coronary disease. This information is usually found either in descriptions of population recruitment, definitions of variables, or inclusion/exclusion criteria.

You may need to look at prior papers on methods in order to make the assessment for this question. Those papers are usually in the reference list.

If fewer than 50% of eligible persons participated in the study, then there is concern that the study population does not adequately represent the target population. This increases the risk of bias.

Question 4. Groups recruited from the same population and uniform eligibility criteria

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the subjects involved? This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Most cohort studies begin with the selection of the cohort; participants in this cohort are then measured or evaluated to determine their exposure status. However, some cohort studies may recruit or select exposed participants in a different time or place than unexposed participants, especially retrospective cohort studies—which is when data are obtained from the past (retrospectively), but the analysis examines exposures prior to outcomes. For example, one research question could be whether diabetic men with clinical depression are at higher risk for cardiovascular disease than those without clinical depression. So, diabetic men with depression might be selected from a mental health clinic, while diabetic men without depression might be selected from an internal medicine or endocrinology clinic. This study recruits groups from different clinic populations, so this example would get a "no."

However, the women nurses described in the question above were selected based on the same inclusion/exclusion criteria, so that example would get a "yes."

Question 5. Sample size justification

Did the authors present their reasons for selecting or recruiting the number of people included or analyzed? Do they note or discuss the statistical power of the study? This question is about whether or not the study had enough participants to detect an association if one truly existed.

A paragraph in the methods section of the article may explain the sample size needed to detect a hypothesized difference in outcomes. You may also find a discussion of power in the discussion section (such as the study had 85 percent power to detect a 20 percent increase in the rate of an outcome of interest, with a 2-sided alpha of 0.05). Sometimes estimates of variance and/or estimates of effect size are given, instead of sample size calculations. In any of these cases, the answer would be "yes."

However, observational cohort studies often do not report anything about power or sample sizes because the analyses are exploratory in nature. In this case, the answer would be "no." This is not a "fatal flaw." It just may indicate that attention was not paid to whether the study was sufficiently sized to answer a prespecified question—i.e., it may have been an exploratory, hypothesis-generating study.

Question 6. Exposure assessed prior to outcome measurement

This question is important because, in order to determine whether an exposure causes an outcome, the exposure must come before the outcome.

For some prospective cohort studies, the investigator enrolls the cohort and then determines the exposure status of various members of the cohort (large epidemiological studies like Framingham used this approach. However, for other cohort studies, the cohort is selected based on its exposure status, as in the example above of depressed diabetic men (the exposure being depression). Other examples include a cohort identified by its exposure to fluoridated drinking water and then compared to a cohort living in an area without fluoridated water, or a cohort of military personnel exposed to combat in the Gulf War compared to a cohort of military personnel not deployed in a combat zone.

With either of these types of cohort studies, the cohort is followed forward in time (i.e., prospectively) to assess the outcomes that occurred in the exposed members compared to nonexposed members of the cohort. Therefore, you begin the study in the present by looking at groups that were exposed (or not) to some biological or behavioral factor, intervention, etc., and then you follow them forward in time to examine outcomes. If a cohort study is conducted properly, the answer to this question should be "yes," since the exposure status of members of the cohort was determined at the beginning of the study before the outcomes occurred.

For retrospective cohort studies, the same principal applies. The difference is that, rather than identifying a cohort in the present and following them forward in time, the investigators go back in time (i.e., retrospectively) and select a cohort based on their exposure status in the past and then follow them forward to assess the outcomes that occurred in the exposed and nonexposed cohort members. Because in retrospective cohort studies the exposure and outcomes may have already occurred (it depends on how long they follow the cohort), it is important to make sure that the exposure preceded the outcome.

Sometimes cross-sectional studies are conducted (or cross-sectional analyses of cohort-study data), where the exposures and outcomes are measured during the same timeframe. As a result, cross-sectional analyses provide weaker evidence than regular cohort studies regarding a potential causal relationship between exposures and outcomes. For cross-sectional analyses, the answer to Question 5 should be "no."

Question 7. Sufficient timeframe to see an effect

Did the study allow enough time for a sufficient number of outcomes to occur or be observed, or enough time for an exposure to have a biological effect on an outcome? In the examples given above, if clinical depression has a biological effect on increasing risk for CVD, such an effect may take years. In the other example, if higher dietary sodium increases BP, a short timeframe may be sufficient to assess its association with BP, but a longer timeframe would be needed to examine its association with heart attacks.

The issue of timeframe is important to enable meaningful analysis of the relationships between exposures and outcomes to be conducted. This often requires at least several years, especially when looking at health outcomes, but it depends on the research question and outcomes being examined.

Cross-sectional analyses allow no time to see an effect, since the exposures and outcomes are assessed at the same time, so those would get a "no" response.

Question 8. Different levels of the exposure of interest

If the exposure can be defined as a range (examples: drug dosage, amount of physical activity, amount of sodium consumed), were multiple categories of that exposure assessed? (for example, for drugs: not on the medication, on a low dose, medium dose, high dose; for dietary sodium, higher than average U.S. consumption, lower than

recommended consumption, between the two). Sometimes discrete categories of exposure are not used, but instead exposures are measured as continuous variables (for example, mg/day of dietary sodium or BP values).

In any case, studying different levels of exposure (where possible) enables investigators to assess trends or dose-response relationships between exposures and outcomes—e.g., the higher the exposure, the greater the rate of the health outcome. The presence of trends or dose-response relationships lends credibility to the hypothesis of causality between exposure and outcome.

For some exposures, however, this question may not be applicable (e.g., the exposure may be a dichotomous variable like living in a rural setting versus an urban setting, or vaccinated/not vaccinated with a one-time vaccine). If there are only two possible exposures (yes/no), then this question should be given an "NA," and it should not count negatively towards the quality rating.

Question 9. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable—for example, have they been validated or are they objective? This issue is important as it influences confidence in the reported exposures. When exposures are measured with less accuracy or validity, it is harder to see an association between exposure and outcome even if one exists. Also as important is whether the exposures were assessed in the same manner within groups and between groups; if not, bias may result.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP, where there may be quite a difference between usual care, where clinicians measure BP however it is done in their practice setting (which can vary considerably), and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged). In each of these cases, the former would get a "no" and the latter a "yes."

Here is a final example that illustrates the point about why it is important to assess exposures consistently across all groups: If people with higher BP (exposed cohort) are seen by their providers more frequently than those without elevated BP (nonexposed group), it also increases the chances of detecting and documenting changes in health outcomes, including CVD-related events. Therefore, it may lead to the conclusion that higher BP leads to more CVD events. This may be true, but it could also be due to the fact that the subjects with higher BP were seen more often; thus, more CVD-related events were detected and documented simply because they had more encounters with the health care system. Thus, it could bias the results and lead to an erroneous conclusion.

Question 10. Repeated exposure assessment

Was the exposure for each person measured more than once during the course of the study period? Multiple measurements with the same result increase our confidence that the exposure status was correctly classified. Also, multiple measurements enable investigators to look at changes in exposure over time, for example, people who ate high dietary sodium throughout the followup period, compared to those who started out high then reduced their intake, compared to those who ate low sodium throughout. Once again, this may not be applicable in all cases. In many older studies, exposure was measured only at baseline. However, multiple exposure measurements do result in a stronger study design.

Question 11. Outcome measures

Were the outcomes defined in detail? Were the tools or methods for measuring outcomes accurate and reliable—for example, have they been validated or are they objective? This issue is important because it influences

confidence in the validity of study results. Also important is whether the outcomes were assessed in the same manner within groups and between groups.

An example of an outcome measure that is objective, accurate, and reliable is death—the outcome measured with more accuracy than any other. But even with a measure as objective as death, there can be differences in the accuracy and reliability of how death was assessed by the investigators. Did they base it on an autopsy report, death certificate, death registry, or report from a family member? Another example is a study of whether dietary fat intake is related to blood cholesterol level (cholesterol level being the outcome), and the cholesterol level is measured from fasting blood samples that are all sent to the same laboratory. These examples would get a "yes." An example of a "no" would be self-report by subjects that they had a heart attack, or self-report of how much they weigh (if body weight is the outcome of interest).

Similar to the example in Question 9, results may be biased if one group (e.g., people with high BP) is seen more frequently than another group (people with normal BP) because more frequent encounters with the health care system increases the chances of outcomes being detected and documented.

Question 12. Blinding of outcome assessors

Blinding means that outcome assessors did not know whether the participant was exposed or unexposed. It is also sometimes called "masking." The objective is to look for evidence in the article that the person(s) assessing the outcome(s) for the study (for example, examining medical records to determine the outcomes that occurred in the exposed and comparison groups) is masked to the exposure status of the participant. Sometimes the person measuring the exposure is the same person conducting the outcome assessment. In this case, the outcome assessor would most likely not be blinded to exposure status because they also took measurements of exposures. If so, make a note of that in the comments section.

As you assess this criterion, think about whether it is likely that the person(s) doing the outcome assessment would know (or be able to figure out) the exposure status of the study participants. If the answer is no, then blinding is adequate. An example of adequate blinding of the outcome assessors is to create a separate committee, whose members were not involved in the care of the patient and had no information about the study participants' exposure status. The committee would then be provided with copies of participants' medical records, which had been stripped of any potential exposure information or personally identifiable information. The committee would then review the records for prespecified outcomes according to the study protocol. If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Followup rate

Higher overall followup rates are always better than lower followup rates, even though higher rates are expected in shorter studies, whereas lower overall followup rates are often seen in studies of longer duration. Usually, an acceptable overall followup rate is considered 80 percent or more of participants whose exposures were measured at baseline. However, this is just a general guideline. For example, a 6-month cohort study examining the relationship between dietary sodium intake and BP level may have over 90 percent followup, but a 20-year cohort study examining effects of sodium intake on stroke may have only a 65 percent followup rate.

Question 14. Statistical analyses

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in cohort studies, because statistical analyses need to control for potential confounders, in contrast to an RCT, where the randomization process controls for potential confounders. All key factors that

may be associated both with the exposure of interest and the outcome—that are not of interest to the research question—should be controlled for in the analyses.

For example, in a study of the relationship between cardiorespiratory fitness and CVD events (heart attacks and strokes), the study should control for age, BP, blood cholesterol, and body weight, because all of these factors are associated both with low fitness and with CVD events. Well-done cohort studies control for multiple potential confounders.

Some general guidance for determining the overall quality rating of observational cohort and cross-sectional studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for cohort studies is the extent to which the results reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study—in other words, the ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes. Any such flaws can increase the risk of bias.

Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or confounding (the mixture of exposures that one cannot tease out from each other). Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above. High risk of bias translates to a rating of poor quality. Low risk of bias translates to a rating of good quality. (Thus, the greater the risk of bias, the lower the quality rating of the study.)

In addition, the more attention in the study design to issues that can help determine whether there is a causal relationship between the exposure and outcome, the higher quality the study. These include exposures occurring prior to outcomes, evaluation of a dose-response gradient, accuracy of measurement of both exposure and outcome, sufficient timeframe to see an effect, and appropriate control for confounding—all concepts reflected in the tool.

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no" you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study or doubt the ability of the study to accurately assess an association between exposure and outcome?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and consideration of the concepts for minimizing bias.

ix. Guidance for Assessing the Quality of Case-Control Studies

The quality assessment tool for case-control studies is included in table A–4. The guidance document for that tool is also included in table A–4. This tool was developed by the methodology team and NHLBI based in part on criteria from AHRQ's Evidence-Based Practice Centers, consultation with epidemiologists, and other factors.

This tool includes 12 items for assessment of study quality. They include the clarity of the research objective or research question; the definition, selection, composition, and participation of the study population; definition and assessment of case or control status; exposure and outcome variables; use of concurrent controls; confirmation that the exposure occurred before the outcome; statistical power; and other factors.

Table A–4. Quality Assessment Tool for Case-Control Studies

Criteria	Yes	No	Other (CD, NR, NA)
1. Was the research question or objective in this study clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was an appropriate target population clearly defined per the research question? Did the cases adequately represent the cases that arose in the target population?			
4. Did the authors include a sample size justification?			
5. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same time frame)?			
6. Were the definitions, inclusion and exclusion criteria, algorithms, or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
7. Were the cases clearly defined and differentiated from controls?			
8. If not all eligible cases and/or controls (e.g., fewer than100 percent) were selected for the study, were the cases and/or controls randomly selected from those that were eligible?			
9. Was there use of concurrent controls?			
10. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
11. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
12. Were the assessors of exposure/risk blinded to the case or control status of participants?			
13. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

Quality Rating (Good, Fair, or Poor):
Reviewer #1 initials:
Reviewer #2 initials:
Comments:

Note: CD = cannot determine; NR = not reported; NA = not applicable.

The guidance below is organized by question number from the tool for quality assessment of case-control studies.

Question 1. Research question

Did the authors describe their goal in conducting this research? Is it easy to understand what they were looking to find? This issue is important for any scientific paper of any type. Higher quality scientific research explicitly defines a research question.

Question 2. Study population

Did the authors describe the group of people from which the cases and controls were selected or recruited, using demographics, location, and time period? If you were to conduct this study again, would you know exactly who to recruit, from where, and from what time period?

Case-control study populations are determined by the location, time period, and inclusion criteria for cases (people with the disease or problem) and controls (people without the disease or health problem). An example population for a study of lung cancer and chemical exposure would be all incident cases of lung cancer diagnosed in patients ages 35 to 79 from January 1, 2003 to December 31, 2007, in 6 regions of northern France, as well as lung-cancer-free controls recruited from the same population during that time. The population is clearly described as: (1) who (men and women ages 35 to 79 with (cases) and without (controls) incident lung cancer); (2) where (6 regions of northern France); and (3) when (between January 1, 2003 and December 31, 2007).

Other studies may use disease registries or data from cohort studies to identify cases, in which case the populations are people in the area covered by the disease registry, or included in a cohort study (i.e., nested case-control or case-cohort). For example, a study of the relationship between vitamin D intake and myocardial infarction might use patients identified via the GRACE registry, a database of heart attack patients.

You may need to look at prior papers on methods in order to make this assessment. Those papers are usually in the reference list.

Question 3. Target population and case representation

In order for a study to truly address the research question, the target population—the population from which the study population is drawn, and to which study results are believed to apply—should be carefully defined. Some authors may compare characteristics of the study cases to characteristics to cases in the target population, either in text or in a table. When study cases are shown to be representative of cases in the appropriate target population it increases the likelihood that the study was well-designed per the research question.

However, because these statistics are frequently difficult or impossible to measure, publications should not be penalized if case representation is not shown. For most papers, the response to question 3 will be "NR." These subquestions are combined because the answer to the second subquestion—case representation—determines the response to this item. However, it cannot be determined without considering the response to the first subquestion. For example, if the answer to the first subquestion is "yes," and the second, "CD," then the response for item 3 is "CD."

Question 4. Sample size justification

Did the authors discuss their reasons for selecting or recruiting the number of people included? Do they discuss the statistical power of the study? This question concerns whether or not the study was sufficiently sized to see an association if one exists.

Generally, a paragraph in the methods section of the article will explain sample size needed to detect differences in exposures. However, you may also find a discussion of power in the discussion section.

Question 5. Groups recruited from the same population

In order to determine whether cases and controls were recruited from the same population, one can ask hypothetically, "If a control was to develop the outcome of interest (the condition that was used to select cases), would that person have been eligible to become a case?" Case-control studies begin with the selection of the cases (those with the outcome of interest) and controls (those in whom the outcome is absent). Cases and controls are then evaluated and categorized by their exposure status. For the lung cancer example, cases and controls are recruited from hospitals in a given region. It may be reasonable to assume that controls in the catchment area for the hospitals, or those already in the hospitals for a different reason, would attend those hospitals if they became a case; therefore, the controls are drawn from the same population as the cases. If controls are recruited or selected from a different region or time period, then the cases and controls are recruited from different populations.

Another example: Eligible cases may be men and women between the ages of 18 and 39 who were diagnosed with atherosclerosis at hospitals in Perth, Australia, between July 1, 2000 and December 31, 2007. Appropriate controls for these cases might be sampled using voter registration information for men and women 18–39 years of age living in Perth (population-based controls); they could also be sampled from patients without atherosclerosis at the same hospitals (hospital-based controls). As long as the controls are people that would have been eligible to be included in the study as cases (if they had been diagnosed with atherosclerosis), then the controls are considered to be selected appropriately from the same source population as cases.

In a prospective case-control study, people are enrolled as cases at the time they are found to have the outcome of interest; the number of cases usually increases as time progresses. In this type of study, controls may be recruited or selected from the population without the outcome of interest at the time the case is diagnosed. Cases may be identified or recruited through a surveillance system, with controls selected from the population covered by that surveillance system—this would be an example of population-based controls. Controls may also be sampled from a cohort study population, in which cases should be the cases that are identified in that cohort study population, and controls should be selected from outcome-free individuals in the same cohort study. This is known as a nested case-control study.

Question 6. Inclusion and exclusion criteria prespecified and applied uniformly

Were the inclusion and exclusion criteria developed prior to recruitment or selection of the study population? Were the same underlying criteria used for all of the groups involved? The same selection criteria should be used except, of course, for whether or not they had the disease/condition, which would be different for cases and controls by definition. Often, therefore, the same age (or age range), gender, race, etc., is used to select cases and controls. This issue is related to the description of the study population, above, and you may find the information for both of these questions in the same section of the paper.

Question 7. Case and control definitions

Was a specific description of "case" and "control" provided? Is there a discussion of the validity of the case and control definitions and the processes or tools used to identify study participants as such? Were the tools or methods accurate, reliable, and objective? For example, cases might be identified as "adult patients admitted to a Veterans Administration hospital from January 1, 2000 to December 31, 2009, with an ICD–9 discharge diagnosis code of acute myocardial infarction and at least one of the following confirmatory findings in their medical records: at least 2 mm of ST elevation changes in two or more ECG leads, an elevated troponin level." Investigators might also use ICD–9 or CPT codes to identify patients. All cases should be identified using the

same methods. Study results cannot be used to draw valid conclusions unless the distinction between cases and controls is accurate and reliable.

Question 8. Random selection of study participants

If a case-control study did not use 100 percent of eligible cases and controls (e.g., not all *disease-free participants* were included as controls), did the authors indicate that random sampling was used to select controls? When it is possible to identify the source population fairly explicitly (e.g., in a nested case-control study, or in a registry-based study), then random sampling of controls is preferred. If consecutive sampling was used, as frequently occurs for cases in prospective studies, then study participants were not randomly selected, so the answer would be "no." This would not be considered a fatal flaw.

If all eligible cases and controls were included as study participants, then mark "NA."

Question 9. Concurrent controls

A concurrent control is a control selected at the time another person became a case, usually on the same day. This means that one or more controls are recruited or selected from the population without the outcome of interest at the time a case is diagnosed. This can be done in both prospective case-control studies and retrospective case-control studies. For example (assuming our study of adenocarcinoma of the colon was performed retrospectively using data from hospital records), if hospital records indicate that Person A was diagnosed with adenocarcinoma of the colon on June 22, 2002, then one or more controls would be selected from the population of patients *without* adenocarcinoma of the colon on June 22, 2002. One might also imagine this study to have been performed using patient records from a cohort study instead of from a hospital database, in which case it would be a nested case-control study.

The use of concurrent controls can be done in the presence or absence of matching, and vice versa. Just because a study incorporates matching, does not mean that concurrent controls were used.

Question 10. Exposure assessed prior to outcome measurement

Because case or control status is determined first (based on presence or absence of outcome of interest), and then exposure history of the case or control is assessed, it is important to make sure that the exposure preceded the outcome. For example, if tissue samples were used to determine exposure, were the tissue samples collected from patients prior to their diagnosis? If hospital records were used, did investigators verify that the date that a patient was exposed (e.g., received medication for atherosclerosis) occurred prior to the date that a person became a case (e.g., was diagnosed with type 2 diabetes)? In order for an association between an exposure and an outcome to be considered causal, the exposure *must* occur prior to the outcome.

Question 11. Exposure measures and assessment

Were the exposure measures defined in detail? Were the tools or methods used to measure exposure accurate and reliable—for example, have they been validated, or are they objective? This is important as it influences confidence in the reported exposures. As important is whether the exposures were assessed in the same manner within groups and between groups.

For example, retrospective self-report of dietary salt intake is not as valid and reliable as prospectively using a standardized dietary log plus testing participants' urine for sodium content. Another example is measurement of BP in a study assessing BP as an exposure potentially affecting a particular outcome. There may be quite a difference in BP measurements between usual care, where clinicians measure BP as it is done is their practice setting, and use of trained BP assessors using standardized equipment (e.g., the same BP device which has been tested and calibrated) and a standardized protocol (e.g., patient is seated for 5 minutes with feet flat on the floor, BP is taken twice in each arm, and all four measurements are averaged).

Question 12. Blinding of exposure assessors

Blinding means that persons assessing the exposure status of study participants did not know whether the participant was a case or control. It is also sometimes called "masking." The objective is to look for evidence in the article that the person assessing the exposure(s) (for example, examining medical records to determine the exposures that occurred in the cases and controls) is masked to the case/control status of the participant. Sometimes the person measuring the exposure is the same person conducting case ascertainment. If so, make a note of that in the comments section.

One way to ensure good blinding of exposure assessment is to have a separate committee, whose members have no information about the study participants' status as cases or controls. As you assess this criterion, think about whether it is likely that the person doing the exposure assessment would know whether the study participant was a case or control. If the answer is no, then the blinding should be adequate. For example, if the investigators were using medical records to assess exposure, you would want them to: (1) Not be directly involved in the care of the study subjects, because they would probably have knowledge of the conditions of their patients; and (2) If the medical record contained information on the patient's condition that identified him/her as a case (which is likely), that information would have to be removed before the exposure assessors reviewed the records.

If blinding was not possible, which is sometimes the case, mark "NA" and explain the potential for bias.

Question 13. Statistical analysis

Were key potential confounding variables measured and adjusted for, such as by statistical adjustment for baseline differences? Logistic regression or other regression methods are often used to account for the influence of variables not of interest.

This is a key issue in case-control studies, because the statistical analyses need to control for potential confounders, in contrast to a randomized controlled trial where the randomization process controls for potential confounders. All key factors that may be associated both with the exposure of interest and the outcome should be controlled for in the analyses. For example, in a study of the relationship between smoking and CVD events (heart attacks and strokes), the investigators need to control for age, gender, and body weight, because those are all associated both with smoking and with CVD events. Well-done case-control studies control for multiple potential confounders.

Matching is a technique used in an effort to improve study efficiency and control for known confounders. For example, in the study of smoking and CVD events, one might identify cases that have had a heart attack or stroke and then select controls of similar age, gender, and body weight to the cases. For case-control studies, it is important that if matching was performed during the selection or recruitment process, the variables used as matching criteria (e.g., age, gender, race) *should be controlled for in the analysis*.

Some general guidance for determining the overall quality rating of case-control studies

The questions on the form are designed to help you focus on the key concepts for evaluating the internal validity of a study. They are not intended to create a list that you simply tally up to arrive at a summary judgment of quality.

Internal validity for case-control studies is the extent to which the associations between disease and exposure reported in the study can truly be attributed to the exposure being evaluated and not to flaws in the design or conduct of the study. In other words, what is ability of the study to draw associative conclusions about the effects of the exposures being studied on outcomes? Any such flaws can increase the risk of bias. Critical appraisal involves considering the risk of potential for selection bias, information bias, measurement bias, or

confounding (the mixture of exposures that one cannot tease out from each other. Examples of confounding include co-interventions, differences at baseline in patient characteristics, and other issues throughout the questions above). High risk of bias translates to a rating of poor quality; low risk of bias translates to a rating of good quality. Thus, the greater the risk of bias, the lower the quality rating of the study.

If a study has a "fatal flaw," then risk of bias is significant and the study is deemed to be of poor quality. An example of a fatal flaw in case-control studies is a lack of a consistent standard process used to identify cases and controls. Examples of fatal flaws in RCTs include high dropout, high differential dropout, no ITT analysis, or unsuitable statistical analysis (e.g., completers-only analysis).

Generally, when you evaluate a study, you will not see a "fatal flaw," but you will find some risk of bias. By focusing on the concepts underlying the questions in the quality assessment tool, you should ask yourself about the potential for bias in the study you are critically appraising. For any box where you check "no," you should ask, "What is the potential risk of bias resulting from this flaw in study design or execution?" That is, does this factor cause you to doubt the results that are reported in the study?

The best approach is to think about the questions in the tool and how each one tells you something about the potential for bias in a study. Specific rules are not useful, as each study has nuances that are a bit different. The more you familiarize yourself with the key concepts, the more comfortable you will be with critical appraisal. Examples of studies rated good, fair, and poor are useful, but each study must be assessed on its own based on the details that are reported and must consider the concepts for minimizing bias.

x. Policy and Procedures for the Use of Existing Systematic Reviews and Meta-Analyses

Systematic reviews and meta-analyses are routinely used in evidence reviews, and well-conducted systematic reviews or meta-analyses of RCTs are generally considered to be among the highest forms of evidence. As a result, systematic reviews or meta-analyses could be used to inform the NHLBI CVD adult systematic review project if certain criteria were met. Guidance on using existing systematic reviews has been published by AHRQ as a chapter of the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* and helped to inform the development of the NHLBI criteria.[142]

To use existing systematic reviews or meta-analyses to inform the NHLBI evidence review, the project needed to identify (1) those systematic reviews and meta-analyses relevant to the topic of interest, (2) those where the risk of bias was low, and (3) those that were recent. Examining the research question and component studies in the systematic reviews or meta-analyses as they related to the NHLBI critical questions (CQs) addressed the first issue, using a quality assessment tool addressed the second issue, and examining publication dates addressed the third issue.

In general, for this project:

- Eligibility of systematic reviews and meta-analyses was determined by the methodologists, consulting with expert panels and work groups as needed.
- Data were not abstracted from systematic reviews or meta-analyses, so they were not included in evidence tables. However, if a systematic review or meta-analysis was used in the evidence review, a summary of the evidence was provided in the text, information from the systematic review or meta-analysis was included in a summary table or appendix, and the citation was included in the reference list.
- Systematic reviews or meta-analyses were rated using the quality assessment tool for this project. Systematic reviews or meta-analyses were used to develop evidence statements if they were rated "good" or

"fair" or were comprehensive reviews commissioned by the Federal Government. Systematic reviews or meta-analyses rated as "poor" were only used when there were no eligible "good" or "fair" publications.

If an existing systematic review or meta-analysis was used in the evidence review:

- Multiple eligible systematic reviews and meta-analyses addressing the same topic were identified through a systematic search to minimize bias. The systematic reviews or meta-analyses used were summarized in text, tables, or appendixes.
- Rating the body of evidence followed the same system used for the de novo systematic reviews conducted for this project and resulted in a high (systematic reviews/meta-analyses rated "good" only), moderate, or low rating based on number, type, and quality of the studies in the meta-analysis or systematic review.

Additional criteria were used to determine when systematic reviews or meta-analyses could be used. They are described in Situations 1–3 below.

SITUATION #1—When a systematic review or meta-analysis addresses a topic relevant to the NHLBI CVD systematic review that was not covered by an existing CQ (e.g., effects of physical activity on CVD risk):

A. In order for a systematic review or meta-analysis to be examined for relevance to the topic of interest, the topic needed to be prespecified in the form of a CQ using the PICO structure (population, intervention/exposure, comparator, and outcome). If only portion(s) of a systematic review are relevant, those relevant portions that are reported separately could be used. For example, in the U.S. Department of Health and Human Services' 2008 systematic review on physical activity, the effects of physical activity on CVD were relevant and were used in the evidence review because they were reported in a separate chapter. However, the effects of physical activity on mental health would not be relevant and therefore were not used in NHLBI evidence review.

B. Systematic reviews or meta-analyses could be used if they were recent (i.e., published within 3 years of the end date of the NHLBI systematic review publication window of December 31, 2009) or identified by the expert panel or work group if published after the end date of the project literature search and before the expert panel began deliberations on the evidence. If the end date of the systematic review or meta-analysis literature search was before December 31, 2009, then expert panels or work groups had the option of conducting a bridging literature search through December 31, 2009, if the expert panel or work group members believed it was necessary because relevant studies were published after the end date of the systematic review or meta-analysis. In this situation, the bridging literature search could cover the time period only up to 1 year before the literature search cut-off date of the systematic review or meta-analysis and extend to no later than December 31, 2009.

SITUATION #2—If the NHLBI literature review identified an existing systematic review or meta-analysis that could possibly replace the NHLBI review of a CQ or subquestion:

A. The systematic review or meta-analysis was examined for consistency between the studies in the systematic review or meta-analysis included studies and the CQ I/E criteria. Component studies had to meet the CQ I/E criteria; however, smaller sample sizes were allowed, as were studies published before the beginning of the project's search date window, as long as a truly systematic approach was used.

B. Systematic reviews or meta-analyses could be used if they were recent (i.e., published within 3 years of the end date of the NHLBI systematic review publication window), or identified by the expert panel or work group if published after the end date of the project literature search and before the expert panel began

deliberations on the evidence. If the end date of the systematic review or meta-analysis literature search was before December 31, 2009, the expert panel or work groups could conduct a bridging literature search through December 31, 2009, if the expert panel or work group members believed it was necessary because relevant studies were published after the end date of the systematic review or meta-analysis. In this situation, the bridging literature search could cover the time period only up to 1 year before the literature search cut-off date of the systematic review or meta-analysis and extend to no later than December 31, 2009.

SITUATION #3—If the NHLBI literature review identified an existing systematic review or meta-analysis that addressed the same or a similar CQ or subquestion as one undergoing NHLBI review:

A. Systematic review or meta-analysis component articles that **met all the I/E criteria for the CQ**, but were not identified in the NHLBI literature search could be added to the included studies in the NHLBI review and treated the same way (i.e., abstracted, quality rated, and added to evidence and summary tables).

xi. Data Abstraction and Review Process

Articles rated "good" or "fair" during the quality rating process were abstracted into VCW using a Web-based data entry form. Requirements for abstraction were specified in an evidence table template that was developed by the methodologist for each critical question. The evidence table template included data elements relevant to the critical question such as study characteristics, interventions, population demographics, and outcomes.

The abstractor carefully read the article and entered the required information into the Web-based tool. Once abstraction was complete, an independent quality control review was conducted. During this review, data were checked for accuracy, completeness, and the use of standard formatting.

xii. Development of Evidence Tables and Summary Tables

a. Evidence tables

For each critical question, methodologists worked with the expert panel or work group members to identify the key data elements needed to answer the question. Using the PICOTS criteria as the foundation, expert panel or work group members determined what information was needed from each study to be able to understand the design, sample, and baseline characteristics in order to interpret the outcomes of interest. A template for a standard evidence table was created and then populated with data from several example studies for review by the expert panel or work group to ensure that all of the appropriate study characteristics were being considered. Once a final template was agreed upon, evidence tables were generated by pulling the appropriate data elements from the master abstraction database for those studies that met the inclusion criteria for the CQ.

Only studies rated "good" and "fair" were included in the evidence tables.

Templates varied by each individual critical question but generally provided the following information:

- Study characteristics: Author, year, study name, country and setting, funding, study design, research objective, year study began, overall study *N*, quality rating
- Criteria and end points: I/E criteria, primary outcome, secondary outcome, composite outcomes
- Study design details: Treatment groups, descriptions of interventions, duration of treatment, duration of followup, run-in, wash-out, intervention N
- Baseline population characteristics: Demographics, biomarkers, other measures relevant to the outcomes
- Results: Outcomes of interest for the CQ with between-group *p* values or confidence intervals for risk ratios, adverse events, attrition, and adherence

Studies are presented in alphabetical order by the study name (if none, the first author's last name was used). Some expert panels combined all of the articles for a study and presented it as a single entry, but for those that did not, the articles were presented in chronological order within the group for the same study.

b. Summary Tables

To enable a more targeted focus on the specific aspects of a critical question, methodologists developed summary tables, or abbreviated evidence tables, in concert with the expert panels or work groups. A summary table might be designed to address a general population or a specific subpopulation, such as individuals with diabetes, women, or the elderly, but it presents only concise data elements. All of the available data in the evidence tables were reviewed to determine a consistent format to present the specific outcome of interest. For example, some lifestyle interventions have lengthy descriptions in the evidence tables, but only the key features would be concisely stated in the summary tables. Within an outcome, the time periods are clearly identified and the order of the different measures is consistently applied. For example, weight loss is always listed in order of percentage change, followed by kilogram change, and lastly by number of subjects losing a certain percent of their body weight. Templates varied by each aspect of the CQ being addressed but generally provide the following information:

- Study characteristics: Study name, author/year, design, overall study N, quality rating
- Sample characteristics: Relevant inclusion criteria and baseline characteristics
- Study design details: Intervention doses and duration
- Results: Change in outcomes by time periods, attrition, and adherence

Each expert panel or work group determined its own ordering of studies to present the evidence within each summary table. For some, trials were listed in chronological order; for others, it was listed by the type or characteristics of the intervention.

xiii. Process for the Development of Evidence Statements and Expert Panel Voting

Using the summary tables (and evidence tables as needed), evidence statements were collaboratively written by the expert panel or work group members with input from methodology staff and oversight of the process by NHLBI staff. Evidence statements aimed to summarize key messages from the evidence that could be provided to primary care providers and other stakeholders. In some cases, the evidence was too limited or inconclusive, so no evidence statement was developed, or a statement about insufficient evidence was made.

Methodology staff provided the expert panels with overarching guidance on how to grade the level of evidence (i.e., high, moderate, or low), and the expert panels used this guidance to grade each evidence statement. This guidance is documented in the following section.

Beginning in September 2011, the Guidelines Executive Committee set up its own approach to manage relationships with industry and other potential conflicts of interest (see http://www.nhlbi.nih.gov/guidelines/cvd_adult_coi-rwi_policy.htm).

Expert panel members who had relationships with industry or other possible conflicts of interest were allowed to participate in discussions leading up to voting as long as they declared their relationships, but they recused themselves from voting on any issue relating to relationships with industry or potential conflicts of interest. Voting occurred by an expert panel chair who asked each member to signify his or her vote. NHLBI project staff and contractors did not vote.

Voting could be open so that differing viewpoints could be identified easily and facilitate further discussion and revisions to address areas of disagreement (e.g., by wordsmithing or dividing an evidence statement into more than one statement). Voting could be by confidential ballot if the group chose.

A record of the vote count (for, against, or recusal) was made without attribution. The ideal was 100 percent consensus, but a two-thirds majority was considered acceptable.

xiv. Grading the Body of Evidence

The NHBLI Adult Cardiovascular Disease Evidence Review Project applied related but distinct processes for grading the bodies of evidence for CQs and for bodies of evidence for different outcomes included within CQs. Each of these processes is described in turn below.

In developing the system for grading the body of evidence, NHLBI reviewed a number of systems, including GRADE (Grading of Recommendations Assessment, Development, and Evaluation), USPSTF, AHRQ Evidence-Based Practice Centers, American College of Cardiology/American Heart Association, American Academy of Pediatrics, Strength of Recommendation Taxonomy, Canadian Task Force on Preventive Health Care, Scottish Intercollegiate Guidelines Network, and Center for Evidence Based Medicine in Oxford. In particular, GRADE, USPSTF, and American College of Cardiology/American Heart Association were considered at length. However, none of those systems fully met the needs of the NHLBI project. The NHLBI therefore developed its own hybrid version that incorporated features of those systems. The resulting system was strongly supported by expert panel and work group members. In using the system, decisions about evidence rating were made by the expert panel and work group members and the methodology team working collaboratively to apply the system and guidance in a thoughtful manner.

Two approaches were used for summarizing the body of evidence for each CQ. The first process was to conduct a de novo literature search and literature review for all of the individual studies that met a CQ's I/E criteria. This approach was used for most of the CQs. The second process, developed in response to resource limitations for the overall project, was to focus the literature search on existing systematic reviews and meta-analyses, that themselves summarized a broad range of the scientific literature. This was used for several CQs across expert panels and work groups. Additional information on the use of systematic reviews and meta-analyses is provided in the following section.

Once the expert panel and work group members reached consensus on the wording of the evidence statement, the next step was to assign a grade to the strength of the body of evidence to provide guidance to primary care providers and other stakeholders on how much support the evidence provided for the evidence statement. Three options were identified for grades for the strength of evidence: high, moderate, or low.

Table A–5 describes the types of evidence that were used to grade the strength of evidence as high, moderate, or low by the expert panel and work group members, with assistance from methodologists.

Table A–5. Evidence Quality Grading System

Type of Evidence	Strength of Evidence Grade
■ Well-designed, well-executed RCTs that adequately represent populations to which the results are applied and directly assess effects on health outcomes. ■ Meta-analyses of such studies. ■ High confidence that the evidence reflects the true effect. ■ Further research is unlikely to change the high confidence in the estimate of effect.	High
■ RCTs with minor limitations that affect confidence in, or applicability of, the results, including minor flaws in design or execution. ■ Well-designed, well-executed non-RCTs and well-designed, well-executed observational studies. ■ Meta-analyses of such studies. ■ Moderate confidence that the evidence reflects the true effect. ■ Further research may change the moderate confidence in the estimate of effect and may change the estimate.	Moderate
■ RCTs with major limitations. ■ Nonrandomized intervention studies and observational studies with major limitations that affect confidence in, or applicability of, the results. ■ Uncontrolled clinical observations without an appropriate comparison group (e.g., case series, case reports). ■ Physiological studies in humans. ■ Meta-analyses of such studies. ■ Low confidence that the evidence reflects the true effect. ■ Further research is likely to change the low confidence in the estimate of effect and is likely to change the estimate.	Low

The strength of the body of evidence represents the degree of certainty, based on the overall body of evidence, that an effect or association is correct. It is important to assess the strength of the evidence as objectively as possible. For rating the overall strength of evidence, the entire body of evidence for a particular summary table and its associated evidence statement was used.

Methodologists provided guidance to the expert panels and work groups for assessing the body of evidence for each outcome or summary table of interest using four domains: (1) risk of bias, (2) consistency, (3) directness, and (4) precision.[143,144] Each domain was assessed and discussed, and the aggregate assessment was used to increase or decrease the strength of the evidence, as determined by the NHLBI Evidence Quality Grading System shown above. The four domains are explained in more detail below:

a. Risk of bias

Risk of bias refers to the likelihood that the body of included studies for a given question or outcome is biased due to flaws in the design or conduct of the studies. Risk of bias and internal validity are similar concepts that are inversely correlated. A study with a low risk of bias has high internal validity and is more likely to provide correct results than one with high risk of bias and low internal validity. At the individual study level, risk of bias is determined by rating the quality of each individual study using standard rating instruments, such as the NHLBI study quality rating tools presented and discussed in the previous section of this report. Overall risk of

bias for the body of evidence regarding a particular question, summary table, or outcome is then assessed by the aggregate quality of studies available for that particular question or outcome. Expert panel and work group members reviewed the individual study quality ratings with methodologists to determine the aggregate quality of the studies available for a particular question, summary table, or outcome. If the risk of bias is low, then it increases the strength of evidence rating for the strength of the overall body of evidence; if the risk of bias is high, then it decreases the strength of evidence rating.

b. Consistency

Consistency is the degree to which reported effect sizes are similar across the included studies for a particular question or outcome. Consistency enhances the overall strength of evidence and is assessed through effect sizes being in the same direction (e.g., multiple studies demonstrate an improvement in a particular outcome) and the range of effect sizes across studies being narrow. Inconsistent evidence is reflected in (1) effect sizes that are in different directions, (2) a broad range of effect sizes, (3) non-overlapping confidence intervals, or (4) unexplained clinical or statistical heterogeneity. Studies included for a particular question or outcome can have effect sizes that are consistent, inconsistent, or unknown (or not applicable). The latter occurs in situations where only a single study is available. For the NHLBI project, consistent with the approach of AHRQ's Evidence-Based Practice Centers, evidence from a single study generally should be considered insufficient for a high strength of evidence rating because a single trial, no matter how large or well-designed, may not provide definitive evidence of a particular effect until confirmed by another trial. However, a very large, multicentered, well-designed, well-executed RCT that performs well in the other domains could in some circumstances be considered high quality evidence after thoughtful consideration.

c. Directness

Directness has two aspects: the direct line of causality and the degree to which findings can be extended from a specific population to a more general population. The first defines directness as whether the evidence being assessed reflects a single direct link between the intervention (or service, approach, or exposure) of interest and the ultimate health outcome under consideration. Indirect evidence relies on intermediate or surrogate outcomes that serve as links along a causal pathway. Evidence that an intervention results in changes in important health outcomes (e.g., mortality, morbidity) increases the strength of the evidence. Evidence that an intervention results in changes limited to intermediate or surrogate outcomes (e.g., a blood measurement) decreases the strength of the evidence. However, the importance of each link in the chain should be considered, including existing evidence that a change in an intermediate outcome affects important health outcomes.

Another example of directness involves whether the bodies of evidence used to compare interventions are the same. For example, if Drug A is compared with placebo in one study and Drug B is compared with placebo in another study, using those two studies to compare Drug A with Drug B yields indirect evidence and provides a lower strength of the evidence than direct head-to-head studies of Drug A versus Drug B.

The second aspect of directness refers to the degree to which participants or interventions in the study are different from those to whom the study results are being applied. This concept is referred to as applicability. If the population or interventions are similar, then the evidence is direct and strengthened. If they are different, then the evidence is indirect and weakened.

d. Precision

Precision is the degree of certainty about an estimate of effect for a specific outcome of interest. Indicators of precision are statistical significance and CIs. Precise estimates enable firm conclusions to be drawn about an intervention's effect relative to another intervention or control. An imprecise estimate is where the confidence interval is so wide that the superiority or inferiority of an intervention cannot be determined. Precision is related

to the statistical power of the study. An outcome that was not the primary outcome or not prespecified will generally be less precise than the primary outcome of a study. In a meta-analysis, precision is reflected by the CI around the summary effect size. For systematic reviews, where there are multiple studies but no quantitative summary estimate, the quantitative information from each study should be considered in determining the overall precision of the body of included studies, since some studies may be more precise than others. Determining precision across many studies without conducting a formal meta-analysis is challenging and requires judgment. A more precise body of evidence increases the strength of evidence, and less precision reduces the strength of a body of evidence.

Following discussion of the four criteria for the strength of evidence grading options, other considerations were also examined in some cases. For example, the objectivity of an outcome measure can be an issue in some cases. Total mortality is a very objective measure because it is usually recorded accurately. Determination of angina is less objective and may be considered to result in lower strength of evidence. Similarly, urinary sodium excretion is a more objective measure than dietary sodium intake reported by study subjects through recall. Another example is measured height and weight used to calculate a study subject's BMI versus self-reported weight and height that provide less reliable data.

Following the conclusion of review and discussion of this range of factors, the expert panel or work group members voted on the final grade for the strength of evidence for each evidence statement. Methodologists provided analysis and recommendations regarding strength of evidence grading but did not participate in the voting process. A simple majority vote was sufficient to identify the strength of evidence grade, although in most cases the expert panels and work groups discussed the results if there were dissenting opinions until consensus or large majorities were achieved for the votes on the strength of evidence.

xv. Search Strategy Overview and Syntax of Queries

This section describes how search strategies for the NHLBI Evidence Review initiative were constructed and explains how to interpret search strategies that are documented in the following section.

A search strategy is an expression of conditions connected by the logical operators AND, OR, and NOT. Parentheses are used to group conditions. Each condition is described by attributes, operators, and values. Table A–6 shows examples of queries and a description of results. A complete list of attributes used in search strategies with their explanation is listed in table A–7. Commonly used macro queries are defined in table A–8.

Table A–6. Examples of Simple Queries

Query	Results
title=blood pressure	Articles with phrase "blood pressure" in article title
title,abstract=blood pressure	Articles with phrase "blood pressure" in article title or its abstract
blood pressure	When attribute name is skipped, "title, abstract" is assumed; therefore, the results are equivalent to query: title, abstract=blood pressure
title=(blood pressure or cholesterol)	Articles with phrases "blood pressure" or "cholesterol" in article title

Query	Results
title=blood pressure and abstract=(mortality or morbidity)	Articles with "blood pressure" in the title and words "mortality" or "morbidity" in the abstract.
((subject=Cardiovascular Diseases) with (qualifier=(prevention or epidemiology))	Articles with MeSH heading "Cardiovascular Diseases" and subheadings 'prevention' or 'epidemiology'
qualifier=mortality	Articles with MeSH subheading 'mortality'
title,abstract,genre,subject=random?	Articles that include any word starting with 'random' (e.g., 'randomized,' 'randomised,' random, etc.)
abstract=?cholesterol?	Articles with abstracts including any word that includes subword 'cholesterol' (e.g., hypocholesterolemia)
qualifier=mortality	Articles with MeSH subheading 'mortality'
title,abstract,genre,subject=random?	Articles that include any word starting with 'random' (e.g., 'randomized,' 'randomised,' random, etc.)
abstract=?cholesterol?	Articles with abstracts including any word that includes subword 'cholesterol' (e.g., hypocholesterolemia)
not journalTitle="ACP journal club"	Exclude articles from "ACP journal club"
publicationYear >1997 and publicationYear <2010	Articles from 1998 to 2009
(CVD %2 event?)	Articles with 'CVD' word in proximity of two words from word stem 'event'

Table A–7. Attributes and Their Values

Attribute	Values
Abstract	Text of abstract
Title	Text of title
<no attribute specified>	Combined text of title and abstract
journalTitle	Journal name (as in PubMed)
publicationYear	Year of the publication (e.g., 2000)
genre	Publication type (as in PubMed)
language	eng for English
subject	MeSH subject headings
majorSubject	MeSH major subject headings
qualifier	MeSH subheadings
substance	MeSH substances
RecordContentSource	'PubMed,' 'embase,' 'cinahl,' for example
recordStatus	'delete,' for example
pubmedid	Pubmed identifier
uuid	Internal unique identifier

Table A–8. Common Macro Queries Used in Search Strategies

Macro Name	Query
RCT	(((RecordContentSource=pubmed AND (genre=randomized controlled trial OR subject=random allocation OR subject=double-blind method OR subject=single-blind method OR (subject="Randomized Controlled Trials as Topic" and abstract=? and (title=trial or ((title=study or subject,genre=stud?) and subject=outcome?))))) OR ((? NOT RecordContentSource=pubmed) AND (genre=randomized OR (title,abstract=randomized AND title,abstract=controlled AND title,abstract=trial) OR title,abstract=random? OR subject=random allocation OR title,abstract=placebo OR subject=double-blind method OR subject=single-blind method))) AND language=eng?) NOT (title= (case report or commentary) OR genre= (letter or abstract or newspaper article or comment?))
RCT	(((RecordContentSource=pubmed AND (genre=randomized controlled trial OR subject=random allocation OR subject=double-blind method OR subject=single-blind method OR (subject="Randomized Controlled Trials as Topic" and abstract=? and (title=trial or ((title=study or subject,genre=stud?) and subject=outcome?))))) OR ((? NOT RecordContentSource=pubmed) AND (genre=randomized OR (title,abstract=randomized AND title,abstract=controlled AND title,abstract=trial) OR title,abstract=random? OR subject=random allocation OR title,abstract=placebo OR subject=double-blind method OR subject=single-blind method))) AND language=eng?) NOT (title= (case report or commentary) OR genre= (letter or abstract or newspaper article or comment?))
Systematic review	(((title=systematic review OR genre=meta-analysis OR title=meta-analysis OR title=systematic literature review OR (title,abstract=systematic review AND genre=review) OR genre=consensus development conference OR genre=practice guideline OR journalTitle= ("Cochrane Database of Systematic Reviews" OR "Health technology assessment" OR "Evidence report/technology assessment (Summary)")) OR ((title=evidence based OR subject=evidence-based medicine OR title=best practice? OR title,abstract=evidence synthesis) AND (genre=review OR subject=diseases category OR subject=behavior and behavior mechanisms OR subject=therapeutics OR genre=evaluation studies OR genre=validation studies OR genre=guideline)) OR ((systematic OR systematically OR title,abstract=critical OR (study selection) OR (predetermined OR inclusion AND criteri?) OR exclusion criteri? OR "main outcome measures" OR "standard of care" OR "standards of care") AND (title,abstract=survey OR title,abstract=surveys OR overview? OR title,abstract=review OR title,abstract=reviews OR search? OR handsearch OR title,abstract=analysis OR title,abstract=critique OR appraisal OR (reduction AND risk AND (death OR recurrence))) AND (title,abstract=literature OR title,abstract=articles OR title,abstract=publications OR title,abstract=publication OR title,abstract=bibliography OR title,abstract=bibliographies OR title,abstract=published OR unpublished OR citation OR citations OR title,abstract=database OR title,abstract=internet OR title,abstract=textbooks OR references OR scales OR papers OR datasets OR title,abstract=trials OR meta-analy? OR (title,abstract=clinical AND title,abstract=studies) OR subject,title,abstract=treatment outcome))) AND language=eng?) NOT (title= (case report or commentary) OR genre= (letter or abstract or newspaper article or comment?))
CVDs	Term in parentheses is MeSH-exploded and matched against subject headings, titles, and abstracts

In order to increase the readability of search strategies, conditions are grouped in meaningful components. There are three major types of components: study type query, Boolean search, and Boolean filter. These three components are connected with the AND operator; thus, a citation must satisfy all three component queries in order to be retrieved. The I/E criteria for each question, which was defined using the PICOTS approach, are implemented in search strategies using the study type query, Boolean search, and Boolean filter.

- Study type query: Consists of expressions that retrieve the study designs that are eligible for inclusion in the body of evidence as defined in the criteria (i.e., RCTs, systematic reviews, prospective cohort studies, etc.)
- Boolean search: Implements expressions for population, intervention, outcomes, timing, and settings
- Boolean filter: Implements an extension of search or comparator criterion

Each of the components may use NOT queries to implement exceptions.

In addition to the strict Boolean strategy, results are ranked using keywords specified for integrated ranking of the TeraText Rank Engine and Content Analyst Conceptual Engine. Ranking helps to identify the most relevant citations first, as the titles and abstracts are analyzed for the presence and frequency of the keywords.

APPENDIX B.

Critical Question 1 Methods

Appendix B. Critical Question 1 Methods

i. Search Strategy

a. Among adults, what is the effect of dietary patterns and/or macronutrient composition on CVD risk factors or health outcomes, when compared to no treatment or to other types of interventions?

The search strategy presented here reflects original (broad) I/E criteria. The final criteria did not include hard outcomes or interventions pertaining to nondietary patterns.

b. Study type query

Study types eligible for this question: RCTs, systematic reviews or meta-analyses of RCTs or controlled clinical trials, observational or epidemiologic studies with time difference between interventions/exposures and outcomes (e.g., cohort studies, case-control studies).

Sample size: For biomarker assessment and risk factor studies, sample size ≥100

- (RCT) OR (Systematic Review) OR
- genre= (Controlled Clinical Trial) OR
- (subject= ("Controlled Clinical Trials as Topic") **and** (subject,abstract,title= (random?) or systematic? or critical or (study selection) or (predetermined or inclusion and criteri?) or exclusion criteri? or "main outcome measures" or "standard of care" or "standards of care")) OR
- (subject,title,abstract= (Case-Control Stud? or Retrospective Stud? or Cohort Stud? or Followup Stud? or Longitudinal Stud? or Prospective Stud? or Observational Stud?))

c. Boolean search

(

- (publicationYear>1997 and publicationYear<2010 and language=eng)
- AND (qualifier="diet therapy"
- or subject,title,abstract= (diet? %3 (pattern? or habit? or preference?))
- or subject= (Diet or "Diabetic Diet" or "Diet, Carbohydrate-Restricted" or "Diet Fads" or "Diet, Fat-Restricted" or "Diet, Gluten-Free" or "Diet, Mediterranean" or "Diet, Protein-Restricted" or "Diet, Reducing" or "Diet, Sodium-Restricted" or "Diet, Vegetarian" or "Diet, Macrobiotic" or "Energy Intake" or "Caloric Restriction" or "Ketogenic Diet" or "Diet Therapy")
- or isocaloric diet? or "DASH diet" or "OMNI diet" or Mediterranean diet? or therapeutic lifestyle change? or vegetarian diet? or vegan diet? or "Ornish diet" or Pritikin diet or "American Diabetes Association Diet" or "ADA Diet" or low-fat diet? or high protein diet? or high carbohydrate diet? or high-CHO or low carbohydrate diet? or low-CHO or high fiber diet? or low glycemic index diet? or "glycemic load" or "Atkins diet" or "portfolio diet" or Ketogenic diet or "NCEP diet" or "AHA Diet" or (step %2 diet) or meal replacement or adventist diet? or raw food diet?
- or (macronutrient %3 intervention) or isocaloric or controlled diet?
- or subject,title,abstract= ("Dietary Fats" or Butter or "Cholesterol, Dietary" or "Dietary Fats, Unsaturated" or "Cod Liver Oil" or "Corn Oil" or "Cottonseed Oil" or "Fatty Acids, Omega–3" or "alpha-Linolenic Acid" or "Docosahexaenoic Acids" or "Eicosapentaenoic Acid" or "Safflower Oil" or "Sesame Oil" or "Soybean Oil" or "Fat Emulsions, Intravenous" or Margarine or "Dietary Carbohydrates" or "Dietary Sucrose")

- or saturated fatty acid? or unsaturated fatty acid? or polyunsaturated fatty acid? or monounsaturated fatty acid? or trans fatty acid? or dietary cholesterol or sugar-sweetened beverages or ((complex or plant-based or animal based) %3 fiber?) or glycemic index
- or subject,abstract,title= (Dietary Proteins or "Egg Proteins, Dietary" or Conalbumin or Ovalbumin or Ovomucin or Phosvitin or Milk Proteins or Caseins or Lactalbumin or Lactoglobulins or Vegetable Proteins)
- or MeSHSubjectPhrase= ("Food" or "Food Preferences" or "Food Habits"))
- AND (subject,qualifier,title,abstract=mortality or death? or died or fatal? or subject= ("Cause of Death" or "Fatal Outcome" or "Survival Rate")
- or subject,title,abstract= ("Acute Coronary Syndrome" or "Myocardial Infarction" or "Shock Cardiogenic" or "Myocardial Stunning" or "No Reflow Phenomenon" or "Heart Arrest" or "Death Sudden Cardiac" or "Angina, Unstable" or "Heart Attack") or STEMI or NSTEMI or myocardial infarctions or unstable angina? or acute coronary syndromes
- or subject,abstract,title= ("Stroke" or "Brain Infarction" or "Brain Stem Infarctions" or "Lateral Medullary Syndrome" or "Cerebral Infarction" or "Dementia, Multi-Infarct" or "Infarction Anterior Cerebral Artery" or "Infarction Middle Cerebral Artery" or "Infarction Posterior Cerebral Artery")
- or ((CVD or CHD or HF or CHF or cardiovascular or coronary or heart failure or cardiac) and (subject,abstract,title= (hospitalization) or hospitalization? or rehospitalization? or subject,abstract,title= (inciden? or morbidity or prevalence)))
- or ((subject= (Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders)) with (qualifier=complications))
- or (lifetime %3 risk) or subject="Severity of Illness Index"
- or subject,title,abstract= (Angioplasty or Revascularization or Coronary Artery Bypass or Coronary Angiography or Stents or Endarterectomy) or CABG
- or subject= ("Kidney Failure, Chronic" or "Renal Insufficiency, Chronic") or Chronic Kidney Failure or CKD or Chronic Kidney Disease or End Stage Renal or ESRD or ((kidney or renal) %5 stage %5 (3 or 4 or 5 or III or IV or V))
- or risk score
- or subject="Metabolic Syndrome X" or metabolic syndrome
- or subject,abstract,title= (inciden? and (diabet? or hypertension))
- **or ((**
- ((subject="C-Reactive Protein") with (qualifier= (metabolism or analysis))) or hs-CRP or CRP or hsCRP or "C-reactive protein"
- or inflammatory marker? or subject,title,abstract= (Fibrinogen) or prothrombotic factor?
- or ((subject= (Triglycerides or "Cholesterol" or "Apolipoproteins B" or Apolipoprotein B? or "Apolipoprotein A-I" or "Apolipoproteins A" or Apolipoproteins or "Lipoprotein (a)" or "Apoprotein (a)")) with (qualifier= (blood or metabolism))) or Triglyceride? or HDL Cholesterol or HDL-C or Apolipoprotein B? or apoB or Apolipoprotein A? or apoA–1 or Lp (a) or "Lipoprotein (a)" or "Apoprotein (a)" or total cholesterol or LDL particle number or LDL-P or (LDL and subject,abstract,title="Particle Size") or lipid goal? or ?cholesterol? or ?lipid? or lipoprotein? or LDL-cholesterol or LDL-C or non-HDL-cholesterol or anticholesterol?
- or ((subject= (Hypertension or Cholesterol or Diabetes or Metabolic Syndrome X)) with (qualifier= (blood or diagnosis)))
- or subject,title,abstract= ("Blood pressure" or systol? or diastol?) or BP or SBP or DPB or hypertensive or nonhypertensive or blood pressure goal?

- or subject="Glucose Tolerance Test" or ((subject= (Blood Glucose or Insulin or "Hemoglobin A, Glycosylated")) with (qualifier= (blood or diagnostic))) or (fasting %2 glucose) or (fasting %2 insulin) or A1c or HOMA or IVGTT or OGTT or glycemic control goal?
- or ((subject=Obesity) with (qualifier=prevention)) or subject= ("Obesity, Abdominal" or "Obesity, Morbid") or subject,title,abstract= (Anthropometry or "Body Mass Index" or "Waist Circumference" or "Body Fat Distribution") or BMI or BMIs or weight change
- or Carotid intima-medial wall thickness or subject,abstract,title= ((carotid or tunica) and (intima medial or wall thickness?)) or (IMT? not (muscle training or memory task? or intensive mixture or intramuscularly or intrathecal morphine or myofibroblastic or tyrosine or immune modulation or immunotherapy or immunomodulat? or microthombosis or idiopathic macular))
- or Coronary calcium or ((calcium or Agatston) %2 score?)
- **)**
- **and (** subject,title,abstract= (risk? or marker? or biomarker? or indicator? or level? or concentration? or end point? or endpoint? or Treatment Outcome) **))**
)

)

NOT majorSubject= ("Dietary Supplements")

NOT majorSubject= (Fruit or Vegetables or Margarine or Butter or Phytotherapy or Phenols or Flavonoids or Carotenoids or "Diet, Sodium-Restricted")

NOT title= (fruit? or vegetable? or ((antioxidants or vitamin? or sodium or salt or potassium or magnesium or calcium or folate) %2 (dietary or intake or supplement? or consumption)) or tocopherol or phenol? or beta-carotene or caroten? or resveratrol or polyphenol or proanthocyanidins or selenium or garlic or chocolate or Phytosterol? or Ecdysteroid? or Ergosterol or Withanolid? or Sitosterol? or Stigmasterol or plant sterol? or campesterol? or sitostanol or campestanol? or Isoflavone? or flavonoid? or genestein or daidzein or equol)

NOT ((subject= (Fruit or Vegetables or Calcium or Magnesium or Potassium or Phytotherapy or Plant Extracts or Vitamins or Ascorbic Acid or Antioxidants or Carotenoids or Tocopherols or beta Carotene or Allyl Compounds or "Calcium, Dietary" or "Sodium, Dietary" or "Sodium Chloride, Dietary" or Phytosterol? or Ecdysteroid? or Ergosterol or Withanolid? or Sitosterol? or Stigmasterol)) with (qualifier= (administration or therapeutic use or pharmacology)))

NOT majorSubject= ("Digestive System Surgical Procedures" or "Bariatric Surgery" or "Gastric Bypass" or "Gastric Balloon" or Laparoscopy or Gastroplasty or Coronary Artery Bypass or Gastrectomy or "Biliopancreatic Diversion")

NOT (((subject= ("Digestive System Surgical Procedures" or "Bariatric Surgery" or "Gastric Bypass" or "Gastric Balloon" or Laparoscopy or Gastroplasty or Coronary Artery Bypass or Gastrectomy or Biliopancreatic Diversion)) with (qualifier= (instrumentation or methods or adverse effects or economics or standards or statistics))))

NOT subject= ("Postoperative Complications" or Reoperation or "Postoperative Period" or "Length of Stay" or "Reconstructive Surgical Procedures" or "Equipment and Supplies" or "Preoperative Care" or "Postoperative Care" or "Prenatal Care" or "Weight Gain and Pregnancy" or "Pregnancy Complications")

NOT subject= ("Equipment Design" or "Advertising as Topic")

NOT subject= (Heel or Foot diseases or Cosmetic techniques or Hair Removal or Hirsutism)

NOT majorSubject= ("Research Design")

NOT subject= (Animals or Venoms)

NOT title,abstract,subject=flax?

NOT ((?dialysis %5 patients) or subject= (renal dialysis) or hemodialysis)

NOT title= (Alcohol or red wine or Coffee)

NOT subject,title= (pregnan?)

d. Boolean Filter

None

ii. Search Strategy Results, PRISMA Diagram, and CQ1 Summary Tables

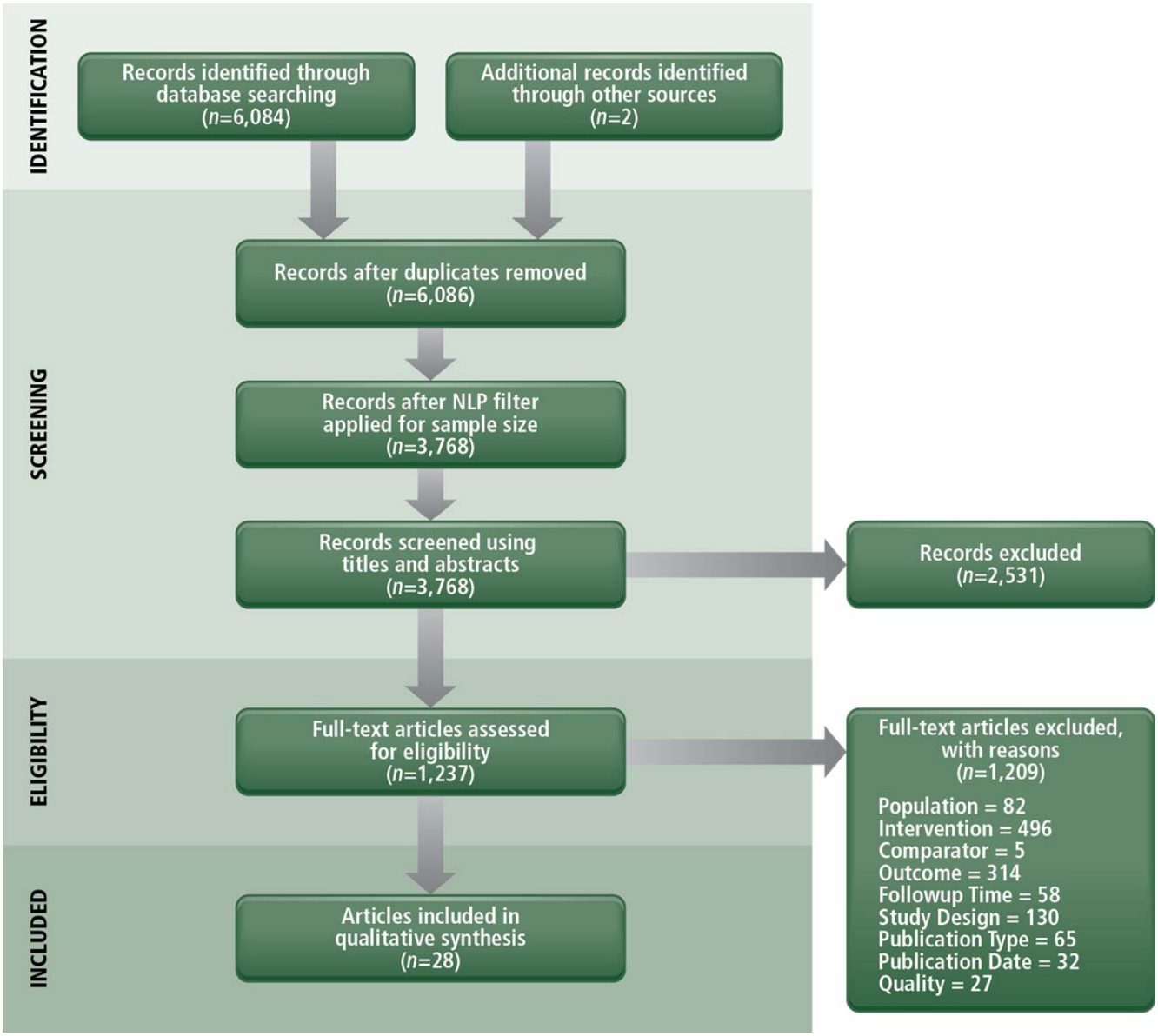
The databases listed below were searched for RCTs, controlled clinical trials, observational or epidemiologic studies with a time difference between interventions/exposures and outcomes (i.e., cohort studies, case-control studies), and systematic reviews and meta-analyses of these study designs to answer Question 1. Observational and epidemiologic studies or systematic reviews of such studies were eligible for hard health outcomes only.

- PubMed from January 1998 to December 2009
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008
- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

Duplicate citations which arise from the same citation being found in more than one database were removed from the Central Repository before screening. The search produced 6,084 citations. This number of citations includes results from a supplemental search of PubMed for systematic reviews and meta-analyses focused on fatty acids, with publication dates between 1990 and 2009.

A natural language processing filter was used to identify studies with sample sizes less than 500 for studies reporting hard health outcomes, and sample sizes less than 50 for biomarker assessment and risk factor studies. The natural language processing filter was executed against titles and abstracts, and 2,318 publications were automatically excluded because they were studies with less than the required sample size. The titles and abstracts of the 3,768 remaining publications were screened against I/E criteria independently by two reviewers, which resulted in the retrieval of 1,237 full-text papers. These papers were independently screened by two reviewers. Per figure B–1 and summary tables B–1 through B–8, 28 articles were included in the evidence base for Question 1—24 RCTs, 1 cohort study, and 3 systematic reviews or meta-analyses—and 1,209 publications were excluded on one or more I/E criteria. An additional 27 publications were excluded because they were rated as poor quality: 17 RCTs, 4 cohort studies, and 6 systematic reviews or meta-analyses (table B–9).

Figure B–1. PRISMA Diagram Showing Selection of Articles for Lifestyle Critical Question 1



Note: NLP = natural language processing

CQ1 Summary Table B–1. Mediterranean Style Dietary Pattern

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
Jula et al., 2002[27] RCT, crossover Turku, Southwestern Finland, 5 industrial plants and government offices Fair	**Treatment groups:** G1: Modified Mediterranean-style diet G2: Habitual diet G1: <10% energy from saturated and *trans* unsaturated fatty acids; cholesterol ≤250 mg/d; omega-3 fatty acid intake of plant origin (α-linolenic acid) and marine origin ≥4 g/d and ratio of omega-6/omega-3 polyunsaturated fatty acids <4; increase intake of fruits, vegetables, and soluble fiber Rapeseed margarine and oil, oat bran (20 g/d) and frozen berries (50 g/d) supplied free Individual session and 2 group counseling sessions at the beginning of the treatment and 5 subsequent monthly group 'brush-up' sessions during the dietary treatment G2: subjects advised to continue eating usual diet during study period; no formal intervention after baseline **Duration:** **Placebo run-in:** 4–6 weeks **Treatment:**12 weeks **Second randomized:** simvastatin vs. placebo	Adult males 35 to 64 years of age, previously untreated hypercholesterolemia (>232 mg/dL), BMI<32 ***n*:** G1: 60 G2: 60 **Mean age, yr (SD):** G1: 48.0 (6.2) G2: 48.4 (6.2) **Weight, Kg (SD):** G1: 82.4 (9.3) G2: 81.4 (9.7) **Total cholesterol, mg/dL (SD):** G1: 250 (21) G2: 259 (24) *p*=.04 **HDL-C, mg/dL (SD):** G1: 52 (12) G2: 49 (12) **LDL-C, mg/dL (SD):** G1: 175 (22) G2: 183 (23) *p*=.05 **APO B, mg/dL (SD):** G1: 129 (17) G2: 139 (21) *p*=.01	NR (Authors note that BP not affected by diet or simvastatin (data not presented)	**At 12 weeks** Mean (SE) [95% CI] G1–G2 **LDL-C, mg/dL** –19 (3) [–25 to –14] *p*<.001 **HDL-C, mg/dL** –2 (1) [–4 to –0.4] *p*=.01 **Triglycerides, mg/dL** –1 (5) [–12 to 10] *p*=.90 **APO A1, mg/dL** –3 (2) [–7 to 0] *p*=.08 **APO B, mg/dL** –8 (2) [–13 to –3] *p*=.003	**Withdrawals, *n* (%):** G1: 0 (0) G2: 2 (3.3) **Adherence:** NR (Descr' as 'good') **Actual nutrient intake:** **Fat,% of total energy (SD):** G1: 34.8 (5.6) G2: 36.9 (4.6) **Cholesterol, mg/d (SD):** G1: 214 (82) G2: 313 (101) **SFA, % of total energy (SD):** G1: 9.3 (2.1) G2: 14.6 (2.7) **MUFA, % of total energy (SD):** G1: 14.1 (3.0) G2: 12.6 (1.9) **PUFA, % of total energy (SD):** G1: 8.1 (1.6) G2: 5.9 (1.5) **Fiber, g/day (SD)** G1: 27.2 (7.8) G2: 19.6 (6.1)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
Michalsen et al., 2006[28] RCT Germany, outpatient medical setting Fair	**Treatment groups:** G1: Mediterranean-style diet G2: Control G1: Dietary recommendations for a diet rich in ALA, marine n–3 PUFA, MUFA, phytochemicals, and low in SFA. ≤5 portions of fruits and vegetables; daily emphasis on root and green vegetables (high ALA); >2 portions of fatty fish per week; whole-grains, flaxseed and walnuts; limit meat and sausage to 3 servings/week; replace beef, pork, lamb with poultry, fish, or vegetarian dishes; olive, canola, flaxseed, and walnut oils encouraged; margarine discouraged (unless from olive oil as no ALA-based products were available) **Duration:** **Treatment:** 1 yr **Intervention delivery:** G1: 3-day nonresidential retreat that included group counseling followed by weekly 3-h meetings for 10 weeks. Thereafter, 2-h meetings took place every other week for 9 mo. Participants were intensively (100 h/yr) informed about the Mediterranean diet, including group discussions, cooking classes, and group meals. If necessary a 1-h individual session presented customized instructions. Also received a practical stress management program. G2: Patients received less detailed written information about Mediterranean diet and lifestyle advice (stress reduction) leaflet by mail.	CAD patients treated with statins, aspirin, Coumadin, beta blockers or ACE inhibitors ***n*:** G1: 53 G2: 48 **Age, mean yr (SD):** G1: 59.0 (8.7) G2: 59.8 (8.6) **Sex, *n** (%):** Male G1: 42 (79.2) G2: 36 (75.5) **Race/ethnicity:** NR **Weight:** NR **BMI, Kg/m^2 (SD):** G1: 26.1 (3.2) G2: 27 (2.8) **SBP, mmHg (SD):** G1: 145.1 (19.1) G2: 145.1 (17.5) **DBP, mmHg (SD):** G1: 84.7 (13.4) G2: 82.7 (11.9)	NR	**At 1 yr** **Mean change in HDL-C, mmol/L (SD):** G1: 1.45 (0.37) G2: 1.39 (0.29) G1 vs. G2: 0.03 (95% CI): (–0.04,0.10) *p*=.360 **Mean change in LDL-C, mmol/L (SD):** G1: 3.12 (1.12) G2: 3.02 (0.72) G1 vs. G2: 0.22 (95% CI): (–0.10, 0.56) *p*=.224 **Mean change in non-HDL-C, mmol/L (SD):** G1: 3.44 (1.25) G2: 3.38 (0.82) G1 vs. G2: 0.22 (95% CI): (–0.12,0.58) *p*=.289 **Mean change in TG, mmol/L (SD):** G1: 1.45 (0.82) G2: 1.57 (0.95) G1 vs. G2:–0.03 (95% CI): (–0.34, 0.28) *p*=.646	**Withdrawals, *n* (%):** G1: 2 (3.77) G2: 1 (2.08) **Adherence:** NR **Actual nutrient intake:** **At 1 yr** **Energy kJ (SD):** G1: 9371 (2130) G2: 9351 (2254) **Fat,% of energy (SD):** G1: 32.2 (6.1) G2: 35.2 (6.1) **CHO, % of energy (SD):** G1: 46.6 (6.4) G2: 43.4 (6.3) **Protein, % of energy (SD):** G1: 16.8 (2.6) G2: 17.0 (3.1) **SFA, % of fat (SD):** G1: 31.4 (7.2) G2: 36.8 (5.8) **MUFA, % of fat (SD):** G1: 32.8 (5.5) G2: 34.6 (4.2) **PUFA, % of fat (SD)** G1: 19.0 (6.2) G2: 21.0 (6.3) DHA and EPA increased **Fiber, g/day (SD):** G1: 33.1 (9.2) G2: 30.9 (12.6)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
PREDIMED Estruch et al., 2006[39] RCT Spain, outpatient centers Good	**Treatment groups:** G1: Mediterranean diet with virgin olive oil G2: Mediterranean diet with mixed nuts G3: Recommended low-fat diet **Duration:** **Treatment:** 3 mo **Followup:** 4 yr **Intervention Delivery:** All groups: Dietitian had a 30-min personalized session with each participant, and provided recommendations on the desired frequency of intake of specific foods. G1 & G2: 1 week after inclusion, the dietitian delivered a 1-h group session with separate sessions for each Mediterranean diet group. Afterwards participants had free and continuous access to their center dietitian for advice and consultation. G1 & G2 also received free "3-mo supplies (with additional supplies for those in families) of typical" sources of Mediterranean fats (virgin olive oil or nuts (walnuts, hazelnuts, almonds) based on group assignment). G3: Reduce fat intake and given AHA leaflet. No further intervention.	Men 55 to 80 years, Women 60 to 80 years, Type 2 DM; or 3 or more CHD risk factors; 77% were hypertensive ***n*:** G1: 257 G2: 258 G3: 257 **Age, mean yr (SD):** G1: 68.6 (6.9) G2: 68.5 (6.2) G3: 69.5 (6.1) **Sex, *n* (%):** Male G1: 102 (40) G2: 128 (50) G3: 109 (42) **Race/ethnicity:** NR **Weight:** NR **BMI ≥25 *n* (%)** G1: 232 (90) G2: 233 (90) G3: 231 (90) **BMI:** NR **SBP:** NR **DBP:** NR	**At 3 mo** **Mean Changes in SBP, mmHg:** G1: –4.8 G2: –6.5 G3: 0.64 G1 vs. G3: –5.9 95% CI: (–8.7, –3.1); *p*<.001 G2 vs. G3: –7.1 95% CI: (–10.0, –4.1); *p*<.001 **Mean Changes in DBP, mmHg (95% CI)** G1: –2.5 G2: –3.6 G3: –0.85 G1 vs. G3: –1.60 95% CI: (–3.00, –0.01); *p*=.048 G2 vs. G3: –2.6 95% CI: (–4.2, 1.0); *p*=.001	**At 3 mo** **Mean change in HDL-C mmol/L:** G1: 0.62 G2: 0.02 G3: 0.01 G1 vs. G3: 0.08 95% CI: (0.04, 0.10) *p*<.001 G2 vs. G3: 0.04 95% CI: (0.01, 0.07) *p*=.006 **Mean changes in LDL-C, mmol/L:** G1: –0.15 G2: –0.10 G3: –0.15 G1 vs. G3: –0.10 95% CI: (–0.25, 0.04) *p*=.177 G2 vs. G3: –0.09 95% CI: (–0.23, 0.05) *p*=.119 **Mean changes in TG, mmol/L (95% CI):** G1: –0.03 G2: –0.09 G3: 0.03 G1 vs. G3: –0.08 95% CI: (–0.20, 0.04); *p*=.21 G2 vs. G3: –0.15 95% CI: (–0.26, –0.02) *p*=.022	**Withdrawals, *n* (%)** G1: 0 (0) G2: 1 (0.38) G3: 2 (0.77) **Adherence:** NR **Actual nutrient intake—Mean change from baseline at 3 mo** **Energy, kcal:** G1: –180 G2: –34 G3: –197 G1 vs. G3: 4.5 95% CI: (–139.0, 148.0); *p*=.95 G2 vs. G3: 161 95% CI: (12, 310); *p*=.034 **Energy from total protein, %:** G1: 0.36 G2: –0.28 G3: 0.83 G1 vs. G3: –0.47 95% CI: (–1.07, 0.13); *p*=.122 G2 vs. G3: –1.00 95% CI: (–1.60, –0.38) *p*=.002 **Energy from total carbohydrate, %:** G1: 0.33 G2: –2.9 G3: –0.36 G1 vs. G3: 0.22 95% CI: –1.30, 1.70); *p*=.84 G2 vs. G3: –3.6 95% CI: (–5.2, –2.1); *p*<.001 **Fiber, g/d:** G1: 0.98 G2: 3.8 G3: 0.60 G1 vs. G3: 0.49 95% CI: (–1.91, 2.90); *p*=.69 G2 vs. G3: 2.00

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
					95% CI: (–0.54, 4.50); *p*=.124 **Energy from total fat, %:** G1: –0.75 G2: 3.4 G3: –1.40 G1 vs. G3: 0.45 95% CI: (–1.00, 1.90); *p*=.55 G2 vs. G3: 5.0 95% CI: (3.5, 6.5) *p*<.001 **SFA,%:** G1: –0.77 G2: –1.00 G3: –0.74 G1 vs. G3: –0.09 95% CI: (–0.55, 0.36); *p*=.69 G2 vs. G3: 0.07 95% CI: (–0.40, 0.54); *p*=.78 **MUFA, %:** G1: 0.15 G2: 1.38 G3: –0.52 G1 vs. G3:0.58 95% CI: (–0.30, 1.45); *p*=.198 G2 vs. G3: 1.9 95% CI: (1.0, 2.8); *p*<.001 **PUFA, %:** G1: –0.11 G2: 3.0 G3: 0.14 G1 vs. G3: 0.03 95% CI: (0.53, 0.58); *p*=.93 G2 vs. G3: 3.0 95% CI: (2.4, 3.5); *p*<.001

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
SUN Núñez-Córdoba et al., 2009[41] Prospective cohort study Spain, University Fair	**Treatment groups:** G1: High adherence (score 7–9) G2: Moderate adherence (score 3–6) G3: Low adherence (score 0–2) Adherence scores assessed degree of adherence to the traditional Mediterranean dietary pattern. The score includes 9 components: vegetables, legumes, fruits and nuts, cereals, fish, meat and meat products, dairy products, alcohol, and the ratio of MUFA to SFA. Values of 0 or 1 were assigned to each of the 9 components. Consumption of vegetables, legumes, fruits and nuts, cereals, and fish: ≥median =1 pt; < the median = 0 pts. Consumption of meats, meat products and dairy: < median = 1 pt; ≥ median = 0 pts. Alcohol intake: 10–50 g/day for men, 5–25 g/day for women= 1 pt. MUFA:SFA ratio: < median = 0 pts; ≥ median= 1 pt. **Fruits: Mean (SD) servings/day:** G1: 3.5 (2.3) G2: 2.3 (1.9) G3: 1.2 (0.9) **Vegetables: Mean (SD) servings/day:** G1: 3.1 (1.5) G2: 2.2 (1.4) G3: 1.4 (0.8) **Legumes: Mean (SD) servings/day:** G1: 0.5 (0.3) G2: 0.4 (0.3) G3: 0.3 (0.3) **Nuts and dried fruits: Mean (SD) servings/day:** G1: 0.3 (0.4) G2: 0.2 (0.3) G3: 0.1 (0.1) **Cereals: Mean (SD) servings/day:** G1: 2.5 (1.4) G2: 1.9 (1.3) G3: 1.4 (1.1) **Meat: Mean (SD) servings/day:** G1: 1.5 (0.7) G2: 1.9 (0.9) G3: 2.2 (0.9)	Healthy adults ***n*:** G1: 1,143 G2: 6,730 G3: 1,535 **Mean yr (SD):** G1: 41 (12) G2: 36 (10) G3: 32 (9) **Sex, *n*:** NR by group For overall population Male: 5,825 Female: 3,583 **Race/ethnicity:** NR **Weight:** NR **BMI, kg/m^2 (SD):** G1: 24 (3) G2: 23 (3) G3: 23 (3) **SBP:** NR **DBP:** NR	**At 6 yr** ***n* (those without HTN at baseline):** G1: 175 G2: 1,109 G3: 229 **SBP, mean absolute change, mmHg:** G1: –0.5 G2: 0 G3: 1.3 *p*=NR **SBP mean relative change, mmHg (multivariate adjusted†):** G1: –3.1 G2: –2.4 G3: 0 *p* for trend=0.01 **DBP, mean absolute change, mmHg:** G1: 0.2 G2: 0.1 G3: 0 *p*=NR **DBP mean relative change, mmHg (multivariate adjusted†):** G1: –1.9 G2: –1.,3 G3: 0 *p*=.05 †adjusted for age, sex, BMI, family history of HTN, basal BP, hypercholesterolemia, caffeine intake, total energy intake, PA and smoking **Incident HTN # of participants / # of incident cases:** G1: 1,143/80 G2: 6,730/359 G3: 1.535/62	NR	**Withdrawals, *n* (%):** 9,190 participants completed 2-yr followup questionnaire 6,428 completed 4-yr followup questionnaire 3,509 completed 6-yr followup questionnaire **Adherence:** NR **Actual nutrient intake:** NR

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
	Fish: Mean (SD) servings/day: G1: 1.0 (0.4) G2: 0.7 (0.4) G3: 0.5 (0.3) **Eggs: Mean (SD) servings/day:** G1: 0.4 (0.2) G2: 0.4 (0.3) G3: 0.4 (0.3) **Dairy products: Mean (SD) servings/day:** G1: 1.0 (0.8) G2: 1.7 (1.3) G3: 2.4 (1.4) **Low-fat dairy products: Mean (SD) servings/day:** G1: 1.7 (1.5) G2: 1.3 (1.4) G3: 0.8 (1.2) **Alcohol intake: Mean (SD) g/day:** G1: 9 (9) G2: 6 (10) G3: 4 (7) **SFA: Mean (SD) % of energy intake:** G1: 10 (2) G2: 13 (3) G3: 15 (3) **MUFA: Mean (SD) % of energy intake:** G1: 15 (4) G2: 16 (4) G3: 16 (3) **CHO: Mean (SD) % of energy intake:** G1: 47 (7) G2: 43 (7) G3: 41 (7) **Protein: Mean (SD) % of energy intake:** G1: 18 (3) G2: 18 (3) G3: 18 (3) **Kcal: Mean (SD):** G1: 2,528 (548) G2: 2,387 (615)		**Incident HTN, HR:*** G1: 1.17 G2: 1.11 G3: 1.00 *p* for trend=.46 *Age- and sex-adjusted **Incident HTN, HR (95% CI), multivariate adjusted*** G1: 1.12 G2: 1.10 G3: 1.00 *p* for trend=.41 *adjusted for age, sex, BMI, family history of HTN, hypercholesterolemia, caffeine intake, sodium intake, total energy intake, physical activity, and smoking		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence Actual Nutrient Intake
	G3: 2,261 (580) **Duration:** **Followup:** median period of 4.2 yr (range, 1.9–7.9) **Intervention delivery:** Dietary habits at baseline assessed using a semi-quantitative food frequency questionnaire with 136 items. After baseline, participants received biennial questionnaires about diet, lifestyle, risk factors, and medical conditions.				

CQ1 Summary Table B–2. DASH Dietary Pattern and DASH Variations

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH Appel et al., 1997[30]; Sacks et al., 1999[31]; Obarzanek et al., 2001[32] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol G1: Diet rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, and 3,000 mg sodium. G2: Diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was and was kept stable by changing calorie level. Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and	Adults ≥22 years; SBP <160 mmHg and a DBP of 80–95 mmHg ***n*:** G1: 151 G2: 154 G3: 154 **Age, mean yr (SD):** G1: 44 (10) G2: 45 (11) G3: 44 (11) **Sex, *n** (%):** Male G1: 74 (49.0) G2: 79 (51.3) G3: 81 (52.6) Female G1: 77 (51.0) G2: 75 (48.7) G3: 73 (47.4) **Race/ethnicity, *n* (%):** Black G1: 93 (61.1) G2: 90 (58.4) G3: 92 (59.7) Non-minority G1: 47 (31.1) G2: 55 (35.7) G3: 54 (35.1) Other Minority G1: 11 (7.3) G2: 9 (5.8) G3: 8 (5.2) **Mean weight, kg:** G1: 83.4 G2: 81.8 G3: 81.5	**At 8 weeks** **Mean change in clinic SBP, mmHg:** G1 vs. G3: –5.5, *p*=S G2 vs. G3: –2.8 *p*=NR **Mean change in clinic DBP, mmHg:** G1 vs. G3: –3.0 *p*=S G2 vs. G3: –1.1 *p*=NR **Mean change in ambulatory SBP, mmHg:** G1 vs. G3: –4.5, *p*=S G2 vs. G3: –3.1 *p*=NR **Mean change in ambulatory DBP, mmHg:** G1 vs. G3: –2.7 *p*=S G2 vs. G3: –2.1 *p*=NR **Mean change in SBP, mmHg (97.5% CI):** G1 vs. G2: –2.7 (–4.6, –0.9) *p*=.001 G1 vs. G3: –5.5 (–7.4, –3.7) *p*<.001 G2 vs. G3:–2.8 (–4.7, –0.9) *p*<.001 **Mean change in SBP, mmHg (97.5% CI):** G1 vs.G2: –1.9 (–3.3, –0.6) *p*=.002	**At 8 weeks** *N*=436* **HDL-C mmol/L, net change (95% CI):** G1 vs. G3: –0.09 (–0.13, –0.06) *p*<.0001 G2 vs. G3: –0.005 (–0.04, 0.030) *p*=NS **LDL-C mmol/L, net change (95% CI):** G1 vs. G3: –0.28 (–0.40, –0.16) *p*<.0001 G2 vs. G3: –0.05 (–0.17, 0.07) *p*=NS *436 participants (95% of the 459) who provided fasting blood samples at baseline and end of the intervention	**Withdrawals, *n* (%):** G1: 2 (1.3) G2: 4 (2.6) G3: 7 (4.5) **Adherence:*** assessed by percent attendance at onsite meals **Onsite meal attendance, %:** G1: 96.1 G2: 95.4 G3: 95.8 Adherence was also assessed by percent of days per person with perfect adherence to study diets. Perfect adherence was defined as all study foods consumed and no nonstudy foods consumed. **Mean % of days with perfect adherence per person:** G1: 93.2 G2: 93.9 G3: 94.6 *Procedures for adherence to the diets were revised after first participant groups completed the program. Data on adherence is for the 362 participants enrolled after the first participant group completed the program.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	participants were required to record their consumption. Three servings of designated nonalcoholic beverages and up to 2 servings of specific alcoholic beverages were allowed. *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal.	**Mean BMI, kg/m^2:** G1: 28.5 G2: 28.2 G3: 28.0 **SBP, mmHg (SD):** G1: 131.2 (10.0) G2: 132.3 (10.5) G3: 132 (10.7) **DBP, mmHg (SD):** G1: 85.1 (3.6) G2: 84.8 (3.9) G3: 85.3 (4.0)	G1 vs. G3: –3.0 (–4.3, –1.6) *p*<.001 G2 vs. G3: –1.1 (–2.4, 0.3) *p*=.07		
DASH-Sodium Sacks et al., 2001[33]; Harsha et al., 2004[34] RCT, crossover design within each diet USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Typical American Diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. Emphasis on fruits, vegetables, and low-fat dairy foods, includes whole grains, poultry, fish, and nuts, and is reduced in fats, red meat, sweets, and sugar-containing beverages. G2: Control diet: 37% fat, 16% SF13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were high (H; 150 mmol/d), intermediate (I; 100 mmol/d), and low (L; 50 mmol/d).All food was provided. Weight was kept stable.	Adults ≥22 years; target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Age, mean yr (SD):** G1: 47 (10) G2: 49 (10) **Sex, *n** (%)** Male G1: 85 (41) G2: 93 (46) Female G1: 123 (59) G2: 111 (54) **n* from Vollmer WM, Sacks FM, Ard J et al., 2001[49] **Race, *n* (%)** Black G1: 118 (57) G2: 114 (56) Non-Hispanic White G1: 83 (40) G2: 81 (40) Asian or other	**At 30 days** **SBP, mmHg (95% CI):** G1 H vs. G2 H: –5.9 (–8.0, –3.7) *p*<.001 G1 I vs. G2 I: –5.0 (–7.6, –2.5) *p*<.001 G1 L vs. G2 L: –2.2 (–4.4, –0.1) *p*<.05 **DBP, mmHg (95% CI):** G1 H vs. G2 H: –2.9 (–4.3, –1.5) *p*<.001 G1 I vs. G2 I: –2.5 (–4.1, –0.8) *p*<.01 G1 L vs. G2 L: –1.0 (–2.5, 0.4) *p*=NS	**At 30 days** **Mean change in LDL-C mmol/L, at 30 days by Na level (95% CI)**:** G1 H vs. G2 H: –0.33 (–0.45, –0.21) *p*<.0001 G1 I vs. G2 I: –0.30 (–0.45, –0.16) *p*<.0001 G1 L vs. G2 L:–0.37 (–0.49, –0.24) *p*<.0001 **Mean change in HDL-C mmol/L, at 30 days by Na level (95% CI)*:** G1 H vs. G2 H: –0.10 (0.14, –0.06) *p*<.0001 G1 I vs. G2 I: –0.09 (–0.14, –0.05) *p*<.0001 G1 L vs. G2 L: –0.08 (–0.11, –0.04) *p*<.0001 **Mean change in TG mmol/L, at 30 days by Na level (95% CI):**** G1 H vs. G2 H: 0.06 (–0.05, 0.18) *p*=.3 G1 I vs. G2 I: –0.02 (–0.16, 0.11) *p*=.7 G1 L vs.G2 L: 0.03 (–0.09, 0.15) *p*=.6 **n*=390 ***n*=379	**Withdrawals, *n* (%):** G1: 10 (95) G2: 12 (94) **Adherence:** NR **Actual nutrient intake:** **Energy kcal/day, mean (SD):** G1: 2576 (511) G2: 2576 (493) **Total Fat, % of energy (SD):** G1: 27.4 (0.2) G2: 38.6 (4.2) **Total CHO, % of energy (SD):** G1: 58.5 (0.3) G2: 49.2 (0.3) **Protein, g:** NR **SF, % of energy (SD):** G1: 6.2 (0.1) G2: 15.0 (0.2) **MUFA, % of energy (SD):** G1: 11.2 (0.1) G2: 12.5 (0.3)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 6 (3) G2: 10 (5) **Weight:** NR **Mean BMI kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Mean SBP, mmHg (SD):** G1: 134 (10) G2: 135 (10) **Mean DBP, mmHg (SD):** G1: 86 (5) G2: 86 (4)			**PUFA, % of energy (SD):** G1: 8.0 (0.2) G2: 7.4 (0.3) **Fiber, g/day, mean (SD):** G1: 35.0 (6.1) G2: 17.3 (18.0) **Cholesterol, mg/day, mean (SD):** G1: 194 (48) G2: 324 (62.7)
DASH-Sodium, Ancillary study Erlinger et al., 2003[35] RCT, crossover USA: outpatient medical center Fair	**Treatment groups:** G1: DASH diet G2: Control diet Run-in: 37% fat, 16% SF,13% MUFA, 8% PUFA, 300 mg/d cholesterol G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration** **Run-in:** 2 weeks Treatment: 14 weeks **Intervention delivery:** Run-in is equivalent to control diet at highest sodium level. All food was provided. Weight was kept stable. There were three 30-day feeding periods, 1 at each of the 3 sodium levels, 150, 100, 50 mmol/d* in a random order. There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. *Sodium levels presented are representative of the diets at the energy level of 2,100 kcal.	Adults ≥22 years of age; SBP of 120–159 mmHg & DBP of 80–95 mmHg ***n*:** G1: 50 G2: 50 **Age, mean yr (SD):** G1: 50 (1.4) G2: 53 (1.3) **Sex female, *n* (%):** Female G1: 31 (62) G2: 21 (42) **Race/ethnicity, *n* (%):** Black G1: 41 (82) G2: 34 (68) **Weight:** NR **BMI, Kg/m^2 (SD):** G1: 29.3 (0.5) G2: 30.1 (0.6) **SBP:**	NR	**At 14 weeks** **Mean change in HDL, mmol/L:** G1 vs. G2:–0.12 *p*<.001 **Mean change in LDL, mmol/L:** G1 vs. G2: –0.29 *p*<.001 **Mean change in TG, mmol/L:** G1 vs. G2: +0.05 *p*=.21	**Withdrawals, *n* (%):** G1: 17 (34) G2: 19 (38) **Adherence:** NR **Actual nutrient Intake:** NR

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
		NR **DBP:** NR			
OmniHeart Appel et al., 2005[40] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH-type diet G2: Protein rich diet G3: Diet rich in unsaturated fat G1: The carbohydrate diet similar to DASH, 58% CHO 27% total fat, 6% SF, 13% MUFA, 8% PUFA, protein 15%, fiber >30g, TC <150 mg/d. G2: The protein rich diet with varied proteins (meat, poultry, egg product substitutes, and dairy products); approximately ½ protein from plant sources like legumes, grains, nuts, and seeds. 48% CHO, 27% fat, 6% SF, 13% MUFA, 8% PUFA, 25% protein, fiber >30 mg/d, cholesterol <150 mg/d G3: The unsaturated fat diet emphasized monounsaturated fats like olive, canola, and safflower oils, and a variety of nuts and seeds. 48% CHO, 37% fat, 6% SF, 21% MUFA, 10% PUFA, 15% protein, fiber >30 mg/d, cholesterol <150 mg/d 5 caloric levels of each diet: 1,600, 2,100, 2,600, 3,100, and 3,600 kcal. The goal was to keep weight within 2% of baseline. *nutrient targets based on 2,100 kcal version of diets **Duration** **Treatment:** 6 weeks for each of the 3 feeding periods **Washout:** 2 to 4 weeks **Intervention delivery:** Participants ate each diet for a total of 3 feeding periods. All food was provided. On each weekday, participants ate their main meal onsite. All other meals were consumed offsite. Washout of 2 to 4 weeks between feeding periods; participants ate their own food during washout.	Adults ≥30 years; BP range included individuals with pre-HTN (SBP 120–139 mmHg or DBP 80–89 mmHg) and stage 1 HTN (SBP 140–159 mmHg or DBP 90–99 mmHg) Baseline population characteristics not reported by treatment group ***n*:** Total: 164 **Age, mean yr (SD):** 53 (10) **Sex, *n** (%)** Male: 92 (56) Female: 73 (44) **Race, *n* (%)** African American: 90 (55) **Weight:** NR **Mean BMI kg/m^2 (SD)*: 30.4 (6.1)** * BMI representative of women sample only **Mean SBP, mmHg (SD):** 131.2 (9.4) **Mean DBP, mmHg (SD):** 77.0 (8.2)	**At 6 weeks** **Mean change in SBP, mmHg:** G1: –8.2 G2: –9.5 G3: –9.3 G1 vs. G2: –1.4; *p*=.002 G1 vs. G3: –1.3 *p*=.005 G2 vs. G3:–0.1 *p*=.90 **Mean change in DBP, mmHg (95% CI):** G1:–4.1 G2:–5.2 G3:–4.8 G1 vs. G2: –1.2 *p*<.001 G1 vs. G3:–0.4 *p*=.20 G2 vs. G3:–0.8 *p*=.02	**At 6 weeks** **Mean change in LDL-C, mg/dL (95% CI):** G1:–11.6 G2:–14.2 G3:–13.1 G1 vs. G2: –3.3 *p*=.01 G1 vs. G3:–1.5 *p*=.24 G2 vs. G3:–0.8 *p*=.02 **Mean change in HDL-C, mg/dL (95% CI):** G1: –1.4 G2: –2.6 G3: –0.3 G1 vs. G2: –1.3 *p*=.02 G1 vs. G3 1.1 *p*=.03 G2 vs. G3: –2.3 *p*<.001 **Mean Non-HDL-C, mg/dL (95% CI):** G1: –11.0 G2: –17.3 G3: –15.1 G1 vs. G2: –6.5 *p*<.001 G1 vs. G3:–2.6 *p*=.054 G2 vs. G3 –4.2 *p*=.002 **Mean change in TG, mg/dL (95% CI):** G1: –0.1 G2: –16.4 G3: –9.3 G1 vs. G2: –15.7	**Withdrawals:** 161 included in analysis of G2 vs. G1 161 included in analysis of G3 vs. G1 160 included in analysis of G3 vs. G2 **Adherence, %:** G1: 96 G2: 95 G3: 96 Adherence defined as % days of perfect adherence. Perfect adherence is self-report of all study food eaten and no nonstudy food eaten expressed as a percentage of person-days of feeding. **Actual nutrient intake:** **Energy intake, mean (SD), kcal/day:** G1: 2599 (578) G2: 2558 (538) G3: 2564 (556)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
				p<.001 G1 vs. G3 –9.6 *p*=.02 G2 vs. G3:–7.1 *p*=.03	

CQ1 Summary Table B–3. DASH Pattern Subgroups: Sex

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH subgroup analysis Appel et al., 1997[30]; Svetkey 1999[45]; Obarzanek et al., 2001[32] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol G1: Diet rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, and 3,000 mg sodium. G2: Diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was kept stable Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and	Adults ≥22 years; SBP <160 mmHg and a DBP of 80–95 mmHg ***n*:** G1: 151 G2: 154 G3: 154 **Sex , *n* (%):** Male G1: 74 (49.0) G2: 79 (51.3) G3: 81 (52.6) Female G1: 77 (51.0) G2: 75 (48.7) G3: 73 (47.4)	**At 8 weeks** Male, *n*=234 Female, *n*=225 **Net change in SBP in females, mmHg:*** G1 F:–6.4 G2 F: –2.2 G3 F: NR **Mean change in SBP in females, mmHg (97.5 CI%)** G1 F vs. G2 F:–3.9 (–6.9, –1.0) *p*=.003 G1 F vs. G3 F: 6.2 (–9.2, –3.3) *p*<.001 G2 F vs. G3 F:–2.3 (–5.3, 0.7) *p*=.08 **Net change in SBP in males, mmHg:*** G1 M: –4.8 G2 M: –3.4 G3 M = NR **Mean change in SBP in males, mmHg (97.5 CI%):** G1 M vs. G2 M:–1.6 (–4.0, 0.8) *p*=.13 G1 M vs. G3 M:–4.9 (–7.3, –2.5) *p*<.001 G2 M vs. G3 M: –3.3 (–5.6, –0.9) *p*=.002 **Net change in DBP in females, mmHg:*** G1 F: –2.9 G2 F: –0.1 G3 F: NR **Mean change in DBP in females,**	**At 8 weeks** *N*=436 **Mean change in HDL-C, mmol/L:** G1 F: –0.09 G1 M: –0.10 G2 F: 0.01 G2 M: –0.03 *p*=NR **Mean change in LDL-C, mmol/L:** G1 F: –0.14 G1 M: –0.43 G2 F: 0.05 G2 M: –0.12 *p*=NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR by subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	participants were required to record their consumption. Three servings of designated nonalcoholic beverages and up to 2 servings of specific alcoholic beverages were allowed.		**mmHg (97.5 CI%):** G1 F vs. G2 F:–2.5 (–4.6, –0.5) *p*=.006 G1 F vs. G3 F: –2.7 (–4.8, –0.7) *p*=.003 G2 F vs. G3 F: –0.2 (–2.3, 1.9) *p*=.83 **Net change in DBP in males, mmHg:*** G1 M: –3.3 G2 M: –2.0 G3 M: NR **Mean change in DBP in males, mmHg:** (97.5 CI%) G1 M vs. G2 M: –1.3 (–3.2, 0.5) *p*=.10 G1 M vs. G3 M: –3.3 (–5.1, –1.5) *p*<.001 G2 M vs. G3 M:–2.0 (–3.7,–0.2) *p*=.01 *adjusted for site and cohort effects		
DASH subgroup analysis Moore et al., 1999[46] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol G1: Diet rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, and 3,000 mg sodium. G2: Diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium	Participants in DASH cohorts 2–5 in which ABP was measured and run-in ABPM was satisfactory ***n*:** G1: 115 G2: 121 G3: 118 **Sex , *n* (%):** Male G1: NR (50) G2: 68 (56) G3: 63 (53) Female G1: NR (50) G2: 53 (44) G3: 55 (47)	**At 8 weeks** **Mean SBP Response (95% CI):** G1 M vs. G3 M:–4.4 (–6.6, –2.1) *p*=.0002 G1 F vs. G3. F:–4.6 (–7.3, –1.9) *p*=.0011 **Mean DBP Response (95% CI):** G1 M vs. G3 M:–2.4 (–4.1, –0.7) *p*=.0050 G1 F vs. G3. F:–3.2 (–5.2, –1.1) *p*=.0025	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR by subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	G3: Control diet typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was kept stable. *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages and up to 2 servings of specific alcoholic beverages were allowed.				
DASH-Sodium subgroup analysis Vollmer et al., 2001[49] RCT, crossover USA, outpatient medical setting Fair	**Treatment groups:** G1: DASH diet G2: Typical American diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. Emphasis on fruits, vegetables, and low-fat dairy foods, includes whole grains, poultry, fish, and nuts, and is reduced in fats, red meat, sweets, and sugar-containing beverages. G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol. **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the	Adults ≥22 years; target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Sex, *n* (%)** Male G1: 85 (41) G2: 93 (46) Female G1: 123 (59) G2: 111 (54)	**Mean change in SBP, mmHg at higher sodium intake level (95% CI):*** G1 F vs. G2 F: –6.6 *p*=NR G1 M vs. G2 M: –5.1 *p*=NR **Mean change in DBP, mmHg at higher sodium intake level (95% CI):*** G1 F vs. G2 F: –3.0 *p*=NR G1 M vs. G2 M: –2.7 *p*=NR *Analyses are unadjusted for other groups. All models included adjustment for baseline BP, study site, feeding cohort, and carryover	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	3 sodium levels (randomly assigned). Levels were high (H; 150 mmol/d), intermediate (I; 100 mmol/d), and low (L; 50 mmol/d). All food was provided. Weight was kept stable. There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was kept stable. *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal.		effects.		

CQ1 Summary Table B–4. DASH Pattern Subgroups: Race/Ethnicity

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH Appel et al., 1997[30]; Sacks et al., 1999[31]; Svetkey et al., 1999[45]; Obarzanek et al., 2001[32] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet G1: DASH. Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol Treatment: rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium G2: Fruits and vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium. G3: Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily	Adults ≥22 years; SBP of <160 mmHg and DBP 80 to 95 mmHg ***n*:** G1: 151 G2: 154 G3: 154 **Race/ethnicity, *n* (%):** Black G1: 92 (61.1) G2: 90 (58.4) G3: 92 (59.7) Non-minority G1: 48 (31.1) G2: 55 (35.7) G3: 54 (35.1) Other Minority G1: 11 (7.3) G2: 9 (5.8) G3: 8 (5.2) Minority, *n*=303 Non-Minority, *n*=156	**At 8 weeks** **Mean Change in SBP, mmHg** G1 AA:–6.9 G1 W:–3.3 *p*=NR **Mean change in DBP, mmHg:** G1 AA: –3.7 G1 W: –2.4 *p*=NR **Mean change in SBP in minority population, mmHg (97.5%):** G1 vs. G2=–3.2 (–5.6, –0.8) *p*=.003 G1 vs. G3= –6.8 (–9.2, –4.4) *p*<.001 G2 vs. G3= –3.6 (–6.1, –1.2) *p*=.001 **Mean change in SBP in non-minority population, mmHg (97.5%):** G1 vs. G2=–1.9 (–4.8, 1.0) *p*=.13 G1 vs. G3= –3.0 (–5.9, –0.1) *p*=.02 G2 vs. G3= –1.1 (–3.9, 1.7) *p*=.38 **Mean change in DBP in minority population, mmHg (97.5%):** G1 vs. G2: –2.1 (–3.8, –0.4) *p*=.007 G1 vs. G3: –3.5 (–5.2, –1.8) *p*<.001 G2 vs. G3: –1.4 (–3.2, 0.3) *p*=.07 **Mean change in SBP in non-minority population, mmHg**	**At 8 weeks** *n*=436 **Mean change in HDL-C mmol/L (95% CI):** G1 AA: –0.09 G1 non AA: –0.10 G2 AA: –0.02 G2 non AA: 0.01 *p*=NR **Mean change in LDL-C mmol/L (95% CI):** G1 AA: –0.29 G1 non AA: –0.28 G2 AA: 0.00 G2 non AA: –0.09 *p*=NR **Mean change in TG mmol/L (95% CI):** G1 AA: 0.02 G1 non AA: 0.05 G2 AA: –0.05 G2 non AA: –0.14 *p*=NR	**Withdrawals:** NR for subgroup **Adherence:** NR for subgroup **Actual nutrient intake:** NR for subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages (coffee, tea, and sugar-free, caffeine free soft drinks) and up to 2 servings of specific alcoholic beverages (beer, white wine, and spirits) were allowed. There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was and was kept stable.		**(97.5%):** G1 vs. G2: –1.6 (–3.8, 0.5) *p*=.09 G1 vs. G3: –2.0 (–4.2, 0.2) *p*=.04 G2 vs. G3: –0.4 (–2.5, 1.7) *p*=.70 **Net change in SBP, mmHg:*** G1 AA: –6.9 G1 W: –3.3 G2 AA: –3.5 G2 W: –0.9 *p*=NR **Net change in DBP, mmHg:*** G1 AA:–3.7 G1 W:–2.4 G2 AA: –1.4 G2 W: –0.3 *p*=NR *adjusted for site and cohort effects **At 8 weeks** **Mean change in SBP in African Americans, mmHg:** G1 H: –13.2 G1 no H: –4.3 G2 H: –8.0 G2 no H: –1.3 **Mean change in SBP in whites, mmHg** G1 H: –6.3 G1 no H: –2.0 G2 H: –5.9 G2 no H: 0.8 **Mean change in DBP in African Americans, mmHg** G1 H: –6.1 G1 no H: –2.6 G2 H: –3.4 G2 no H: –0.3		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
			Mean change in SBP in Whites, mmHg: G1 H: –4.4 G1 no H: –1.2 G2 H: –3.1 G2 no H: 0.4		
DASH Moore et al.,1999[46] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet G1: DASH. Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9g fiber, and 300 mg/d of cholesterol. Treatment: Rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium G2: Fruits and vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks	Participants in DASH cohorts 2–5 in which ABP was measured. Run-in ABPM was satisfactory ***n*:** G1: 115 G2: 121 G3: 118 **Race/ethnicity, *n* (%):** Other [Minority]: G1: 74 (64) G2: 73 (60) G3: 72 (61)	**At 8 weeks** **Mean SBP responses in non-minority population, mmHg (95% CI):** G1 vs. G3: –2.7 (–5.5, 0.2) *p*=.0668 **Mean SBP responses in minority population, mmHg (95% CI):** G1 vs. G3:–5.6 (–7.8, –3.4) *p*=.0001 **Mean DBP responses in non-minority population, mmHg (95% CI):** G1 vs. G3:–1.8 (–3.9, 0.4) *p*=.0998 **Mean DBP responses in minority population, mmHg (95% CI):** G1 vs. G3: –3.4 (–5.0, –1.7) *p*=.0001	NR	**Withdrawals:** NR for subgroup **Adherence:** NR for subgroup **Actual nutrient intake:** NR for subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	Intervention delivery: Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages (coffee, tea, and sugar-free, caffeine free soft drinks) and up to 2 servings of specific alcoholic beverages (beer, white wine, and spirits) were allowed. There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was and was kept stable.				
DASH-Sodium Vollmer et al., 2001[49]; Bray et al., 2004[48] RCT: crossover USA, outpatient medical setting Fair	**Treatment groups:** G1: DASH diet G2: Typical American diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. Emphasis on fruits, vegetables, and low-fat dairy foods, includes whole grains, poultry, fish, and nuts, and is reduced in fats, red meat, sweets, and sugar-sweetened beverages. G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were high (H; 150 mmol/d), intermediate (I; 100 mmol/d), and low (L; 50 mmol/d).All food was provided. Weight was kept stable.	Adults ≥22 years; target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Race, *n* (%)*** African American G1: 119 (57) G2: 115 (56) Total: 234 (57) White G1: NR G2: NR Total: 162 (39) Other G1: NR G2: NR Total: 16 (4) Non-African American G1: 89 (43) G2: 89 (44) Total: 178 (76) ***n*:**	**Mean change in SBP, mmHg at higher sodium intake level (95% CI):*** G1 AA vs. G2 AA: –5.9 *p*=NR G1 Non-AA vs. G2 Non-AA: –5.6 *p*=NR **Mean change in DBP, mmHg at higher sodium intake level (95% CI):*** G1 AA vs. G2 AA: –3.1 *p*=NR G1 Non-AA vs. G2 Non-AA: –2.4 *p*=NR *Analyses are unadjusted for other groups. All models included adjustment for baseline BP, study site, feeding cohort and carryover effects. **At 30 days** **Mean change in SBP, mmHg (higher to lower sodium):*** African American	NR	**Withdrawals:** NR for subgroup **Adherence:** NR for subgroup **Actual Nutrient Intake:** NR

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
		AA H: 56 AA no H: 129 White H: 24 White no H: 77 Baseline characteristics reported for race and reported for HTN but not for both race + HTN	G1 H: –5.7 G1 no H: –2.0 G2 H: –9.4 G2 no H: –6.9 *p*=NR Non-African American G1 H: –3.7 G1 no H: –1.4 G2 H: –6.8 G2 no H: –4.0 *p*=NR **n*=412		

CQ1 Summary Table B–5. DASH Pattern Subgroup: Hypertension Status

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH Appel et al., 1997[30]; Sacks et al., 1999[31]; Svetkey 1999[45] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet G1: DASH. Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9g fiber, and 300 mg/d of cholesterol Treatment: Rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium G2: Fruits and vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily	Adults ≥22 years; SBP of <160 mmHg and DBP 80 to 95 mmHg ***n*:** G1: 151 G2: 154 G3: 154 **HTN, *n* (%):** G1: 37 (25) G2: 49 (32) G3: 47 (31) ***n*/total sample (%):** 133/459 (29)	**At 8 weeks** **Mean change in SBP, mmHg (97.5% CI):** G1 HTN vs.G2 HTN: –4.1 (–8.6, 0.3) *p*=.04 G1 HTN vs. G3 HTN: –11.4 (–15.9, –6.9) *p*<.001 G3 HTN vs. G2 HTN: –7.2 (11.4, 3.0) *p*<.001 G1 no HTN vs. G2 no HTN: –2.7 (–4.5, –0.8) *p*=.001 G1 no HTN vs. G3 no HTN: –3.5 (–5.3, –1.6) *p*<.001 G3 no HTN vs. G2 no HTN: –0.8 (–2.7, 1.1) *p*=.33 **Mean change in DBP, mmHg (97.5% CI):** G1 HTN vs.G2 HTN: –2.6 (–5.4, 0.1) *p*=.03 G1 HTN vs. G3 HTN: –5.5 (–8.2, –2.7) *p*<.001 G3 HTN vs. G2 HTN: –2.8 (–5.4, –0.3) *p*=.01 G1 no HTN vs. G2 no HTN: –1.8 (–3.4, –0.3) *p*=.009 **Mean change in DBP, mmHg (97.5% CI):** G1 no HTN vs. G3 no HTN:	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR by subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages (coffee, tea, and sugar-free, caffeine free soft drinks) and up to 2 servings of specific alcoholic beverages (beer, white wine, and spirits) were allowed. There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was kept stable		–2.1 (–3.6, –0.5) *p*=.003 G3 no HTN vs. G2 no HTN: –0.3 (–1.9, 1.3) *p*=.71 **Net change in SBP, mmHg:*** G1 HTN: –11.6 G1 no HTN: –3.5 *p*≤.008 G2 HTN: –7.1 G2 no HTN: –0.09 *p*=.001 **Net change in DBP, mmHg:*** G1 HTN: –5.3 G1 no HTN: –2.2 *p*≤.008 G2 HTN: –2.8 G2 no HTN: –0.4 *p*=.07 * net change values adjusted for site and cohort effects		
DASH subgroup analysis Moore et al 1999[46] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet G1: DASH, Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol Treatment: Rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium G2: Fruits and vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol,	Participants in DASH cohorts 2–5 in which ABP was measured. Run-in ABPM was satisfactory ***n*:** G1: 115 G2: 121 G3: 118 **HTN, *n* (%):** G1:31 (27) G2:36 (30) G3:36 (31)	**At 8 weeks** **Mean SBP Response (95% CI):** G1 HTN vs. G3 HTN: –10.1 (–13.9,–6.2) *p*=.0001 G1 no HTN vs. G3 no HTN: –2.3 (–4.1,–0.5) *p*=.0121 **Mean DBP Response (95% CI):** G1 HTN vs. G3 HTN: –5.5 (–8.2, –2.7) *p*=.0001 G1 no HTN vs. G3 no HTN: –1.6 (–3.1,–0.2) *p*=.0234	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages (coffee, tea, and sugar-free, caffeine free soft drinks) and up to 2 servings of specific alcoholic beverages (beer, white wine, and spirits) were allowed. There were four calorie levels of 1.600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was and was kept stable.				

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH Subgroup Analysis Conlin et al., 2000[47] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet G1: DASH, Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol Treatment: rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium. G2: Fruits and Vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks	Participants in DASH with SBP of 140 to 159 mmHg and/or DBP of 90 to 95 mmHg ***n*:** G1: 37 G2: 49 G3: 47 **HTN, *n** (%)** G1: (65) G2 (55) G3: (64)	**At 8 weeks** **Mean between diet differences in SBP, mmHg:*** G1 vs. G3: –11.6 (–15.5, –7.6) *p*<.001 G1 vs. G2: –4.5 (–8.4, –0.7) *p*=.023 G2 vs. G3: –7.0 (–10.7, –3.4) *p*<.001 **Mean between diet differences in DBP, mmHg:*** G1 vs. G3: –5.9 (–8.3, –3.4) *p*<.001 G1 vs. G2: –2.9 (–5.3, –0.5) *p*=.020 G2 vs. G3: –3 (–5.3, –0.7) *p*=.010 *adjusted for Clinical Centers, gender, race, age, ETOH, and baseline SBP		**Withdrawals:** NR **Adherence, %:** G1: 100 G2: 96 G3: 94 **Actual nutrient intake:** NR

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH-Sodium Vollmer et al., 2001[49] RCT: crossover USA, outpatient medical setting Fair	**Treatment groups:** G1: DASH diet G2: Typical American diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. Emphasis on fruits, vegetables, and low-fat dairy foods, includes whole grains, poultry, fish, and nuts, and is reduced in fats, red meat, sweets, and sugar-containing beverages. G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were high (H; 150 mmol/d), intermediate (I; 100 mmol/d), and low (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years; target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **HTN, *n* (%):** G1: 85 (40) G2: 83 (40)	**Mean change in SBP, mmHg at higher sodium intake level (95% CI):*** G1 HTN vs. G2 HTN: –6.6 *p*=NR G1 Non-HTN vs. G2 Non-HTN: –5.4 *p*=NR **Mean change in DBP, mmHg at higher sodium intake level (95% CI):*** G1 HTN vs. G2 HTN: –3.2 *p*=NR G1 Non-HTN vs. G2 Non-HTN: –2.7 *p*=NR *Analyses are unadjusted for other groups. All models included adjustment for baseline BP, study site, feeding cohort, "and carryover effects."	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual Nutrient Intake:** NR

CQ1 Summary Table B–6. DASH Pattern Subgroup: Age

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH subgroup analysis Svetkey et al., 1999 RCT USA, Outpatient Medical Setting Good	**Treatment Groups:** G1. DASH diet G2. Fruits and vegetables diet G3. Control diet G1: DASH, Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol Treatment: rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium G2: Fruits and Vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3. Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal **Duration** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal on site (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium, was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to	Adults ≥22 years of age not taking anti-hypertensive medication; SBP <160 mmHg and a DBP of 80 to 95 mmHg ***n:*** G1: 151 G2: 154 G3: 154 **Mean yr (SD):** G1: 44 (10) G2: 45 (11) G3: 44 (11) **Age ≤45:** G1: 83 G2: 78 G3: 82 **Age >45:** G1: 68 G2: 76 G3: 72	**At 8 weeks** **Net SBP change, mmHg (95% CI):** G1 ≤45:-5.0 G1 >45:-6.8 *p*=NR G2 ≤45:-3.1 G2 >45:-2.5 *p*=NR **Net DBP change, mmHg (95% CI):** G1 ≤45:-3.5 G1 >45:-2.6 *p*=NR G2 ≤45:-1.8 G2 >45:-0.4 *p*=NR	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR by subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	record their consumption. Three servings of designated nonalcoholic beverages (coffee, tea, and sugar-free, caffeine free soft drinks) and up to 2 servings of specific alcoholic beverages (beer, white wine, and spirits) were allowed. There were four calorie levels of 1600, 2100, 2600, or 3100 kcal for each diet. Weight was kept stable.				
DASH subgroup analysis Moore et al., 1999 RCT USA, Outpatient Medical Setting Good	**Treatment Groups:** G1. DASH diet G2. Fruits and vegetables diet G3. Control diet G1: DASH, Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol Treatment: rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium G2: Fruits and Vegetables diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3. Control diet: typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1 700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium *Nutrient values presented for all diets are representative of the diets at the energy level of 2100 kcal **Duration** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:**	Adults ≥22 years of age not taking anti-hypertensive medication; SBP <160 mmHg and a DBP of 80 to 95 mmHg ***n:*** G1: 115 G2: 121 G3: 118 **Mean yr (SD):** G1: 44.9 (9.9) G2: 45.0 (10.5) G3: 45.4 (10.7)	**At 8 weeks** **Mean change in SBP, mmHg:** G1 Y vs. G3 Y:-4.8 (-6.8, -2.7) *p*=.0001 G1 O vs. G3 O:-4.5 (-7.5, -1.5) *p*=.0036 **Mean change in DBP , mmHg:** G1 Y vs. G3:-2.9 (-4.5, -1.2) *p*=.0007 G1 O vs. G3: -2.8(-4.9, -0.8) *p*=.0063 Y=younger O=older	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual nutrient intake:** NR by subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	Participants attended the clinic each weekday to be weighed and to consume one meal on site (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium, was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages (coffee, tea, and sugar-free, caffeine free soft drinks) and up to 2 servings of specific alcoholic beverages (beer, white wine, and spirits) were allowed. There were four calorie levels of 1600, 2100, 2600, or 3100 kcal for each diet. Weight was kept stable.				
DASH-Sodium Vollmer et al., 2001 RCT: crossover USA, Outpatient Medical Setting Fair	**Treatment Groups:** G1. DASH diet G2. Typical American Diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. Emphasis on fruits, vegetables, and low-fat dairy foods, includes whole grains, poultry, fish, and nuts, and is reduced in fats, red meat, sweets, and sugar-containing beverages. G2: Control diet : 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol. **Duration** **Run-in:** 2 weeks **Treatment:** 90 days**,** 30 days per sodium condition **Intervention delivery** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were high (H; 150 mmol/d), intermediate (I; 100 mmol/d), and low (L; 50 mmol/d). All food was provided. Weight was kept stable	Adults ≥ 22 years; target of 50% enrollment of blacks and women ***n:*** G1: 208 G2: 204 **Age, mean yr (SD)*:** G1: 47 (10) G2: 49 (10) * reported in Sacks et al., 2001.[33] **>45 yr/Older, *n* (%):** G1:111 (53) G2:129 (63) **≤45 yr/Younger, *n* (%):** G1: 97 (47) G2: 75 (37)	**Mean Change in SBP, mmHg at higher sodium intake level (95% CI)*:** G1 Y vs. G2 Y: -7.1 *p*=NR G1 O vs. G2 O: -4.3 *p*=NR **Mean Change in DBP, mmHg at higher sodium intake level (95% CI)*:** G1 Y vs. G2 Y: -3.4 *p*=NR G1 O vs. G2 O: -2.2 *p*=NR *Analyses are unadjusted for other groups. All models included adjustment for baseline BP, study site, feeding cohort and carryover effects. Y= younger O= older	NR	**Withdrawals:** NR by subgroup **Adherence:** NR by subgroup **Actual Nutrient Intake:** NR

CQ1 Summary Table B–7. Glycemic Index/Load

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
Canadian Trial of Carbohydrates in Diabetes (CCD) Wolever et al., 2008[29] RCT Canada, multicenter Fair	**Treatment groups:** G1: Low-CHO diet: Low CHO, high monounsaturated-fat G2: Low-GI diet: High-CHO, low glycemic index G3: High-GI diet: High CHO, high glycemic index Run-in for all groups: 55% of energy as CHO, 15% of energy as protein, and 30% of energy as fat and with ≤10% SFAs, ≤10% PUFA and the remainder as MUFA G1: Low-CHO Diet: 1,930 kcal of energy, 34.7 g of fat, 43.6 g of CHO, 19.7 g of protein,11.4 g of SF,14.1 g of MUFA, 6.3 g of PUFA, 22.4 g fiber, 302 mg/d of cholesterol, glycemic index of 59 G2: Low-GI Diet: 1,810 kcal of energy, 31.9 g of fat, 45.9 g of CHO, 20.7 g of protein, 9.8 g of SF,12.9 g MUFA, 6.3 g PUFA, 22.5 g fiber, 268 mg/d of cholesterol, glycemic index of 55 Key foods were olive or canola oils or spreads, nuts, and other foods low in SFAs and high in MUFAs. G3: HI GI Diet: 1,930 kcal of energy, 34.0% of fat, and 43.1% of CHO, 20.2% of proteins, 11.3% of SF, 13.9% MUFA, 6.1% PUFA, 20.3 g fiber, and 323 mg/d of cholesterol; Glycemic index of 59. Key foods were starchy carbohydrates **Duration:** **Treatment:** 1 yr **Intervention delivery:** Participants given list of key foods to consume and specifications how much to consume. Participants were seen by dietician every 2 and 4 weeks after randomization and then every 4 weeks for weighing, review of key-food diaries, and pickup of supplies of key foods.	Adults 35–75, with T2DM ***n*:** G1: 54 G2: 56 G3: 52 **Mean yr (SEM):** G1: 58.6 (1.2) G2: 60.6 (1.0) G3: 60.4 (1.1) **Sex, *n* (%) female:** G1: 54 (47) G2: 56 (66) G3: 52 (50) **Race/ethnicity:** NR **Weight, kg (SEM):** G1: 84.7 (2.6) G2: 81.1 (2.5) G3: 84.4 (2.5) **BMI:** G1: 31.1 (0.6) G2: 31.6 (0.6) G3: 30.1 (0.6) **Mean SBP, mmHg (SEM):** G1: 127 (3) G2: 124 (4) G3: 129 (2) **Mean DBP, mmHg (SEM):** G1: 78 (2) G2: 77 (2) G3: 78 (1) 43% of subjects on at least 1 lipid-lowering medication	**At 1 yr** **SBP, mmHg (SEM):** G1: 128 (1) G2: 129 (1) G3: 127 (1) G1 vs. G3: *p*=NS G1 vs. G2: *p*=NS G2 vs. G3: *p*=NS **DBP, mmHg:** Data NR *p*=NS	**At 1 yr** **Mean change in HDL-C, mmol/L (SEM):** G1: 1.21 (0.03) G2: 1.16 (0.03) G3: 1.19 (0.03) G1 vs. G3: *p*=NS G1 vs. G2:–4%, *p*<.05 G3 vs. G2: *p*=NS **Mean change in LDL-C, mmol/L (SEM):** G1: 2.89 (0.05) G2: 2.92 (0.05) G3: 3.00 (0.08) G1 vs. G3: *p*=NS G1 vs. G2: *p*=NS G2 vs. G3: *p*=NS **Mean change in TC, mmol/L (SEM):** G1: 4.99 (0.08) G2: 5.04 (0.08) G3: 5.04 (0.08) G1 vs. G3: *p*=NS G1 vs. G2: *p*=NS **Mean change in TG, mmHg (SEM):** G1: 1.93 (0.06) G2: 2.17 (0.07) G3: 2.00 (0.07) G1 vs. G3: *p*=NS G1 vs. G2: 12%, *p*<.05 G2 vs. G3: *p*=NS **Mean change in ApoA1, g/L (SEM):** G1: 1.59 (0.01) G2: 1.55 (0.02) G3: 1.60 (0.02) G1 vs. G2: *p*=NS G1 vs. G3: *p*=NS G2 vs. G3: *p*=NS *p*<.05 **Mean change in Apo B100, g/L (SEM):** G1: 1.01 (0.02) G2: 1.04 (0.02)	**Withdrawals, *n* (%):** G1: 10 (5.4) G2: 11 (6.16) G3: 11 (5.72) **Adherence: Reported as % consumed (SD) of amount prescribed:** G1: 106 (3) G2: 81 (3) G3: 85 (3) **Actual nutrient intake:** **Mean SF, % energy (SEM):** G1: 10.8 (0.3) G2: 8.2 (0.4) G3: 10.2 (0.4) **Mean CHO, % energy (SEM):** G1: 39.3 (0.7) G2: 45.9 (0.9) G3: 46.5 (0.9) **Mean energy, kcal (SEM):** G1: 2,020 (57) G2: 1,800 (50) G3: 1,890 (48) **Mean fat, % energy (SEM):** G1: 40.1 (0.6) G2: 26.5 (0.8) G3: 30.8 (0.7) **Mean MUFA, % energy (SEM):** G1: 18.3 (0.3) G2: 10.7 (0.4) G3: 12.3 (0.3) **Mean PUFA, % energy (SEM):** G1: 8.2 (0.2) G2: 5.1 (0.2) G3: 5.5 (0.2) **Mean fiber, % energy (SEM):** G1: 23.0 (0.8)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
				G3: 1.03 (0.02) G1 vs. G3: NR, *p*=NS G2 vs. G3: NR, *p*=NS G1 vs. G2: NR, *p*=NS	G2: 36.3 (1.3) G3: 21.0 (0.8) **Mean protein, % energy (SEM):** G1: 19.1 (0.4) G2: 20.6 (0.4) G3: 20.4 (0.4) **Mean cholesterol, mg (SEM):** G1: 265 (12) G2: 223 (13) G3: 286 (21)
Jenkins et al., 2008[38] RCT Canada, Hospital Good	**Treatment groups:** G1: Low-glycemic index (GI) diet G2: High-cereal fiber diet G1: Participants were advised to eat low-glycemic index breads and breakfast cereals, pasta, parboiled rice, beans, peas, lentils, and nuts were also advised. Participants were instructed to eat temperate fruit (apples, pears, oranges, peaches, cherries, and berries). G1: 1,916 kcal of energy, 36.1% fat, 42.2% CHO, 20.3% protein, 11.2% SF, 14.6% MUFA, 7.4% PUFA, 13.9 g fiber, and 156.4 mg/d of cholesterol G2: Participants were advised to take the whole grain options. Tropical fruit (bananas, mangos, guavas, grapes, raisins, watermelon, cantaloupe) were prescribed. G2: 1,830 kcal of energy, 33.0% fat, 45.4% of CHO, 20.1% of protein,10.3% SF, 13.2% MUFA, 6.7% PUFA, 14.1 g fiber,150.2 mg/d of cholesterol. In both diets, the number of CHO servings prescribed covered 42% to 43% of total calories and 3 servings of fruit and 5 servings of vegetables were encouraged. Participants advised against eating foods recommended in the alternative treatment such as fruit options and starchy items. All participants were specifically advised to avoid foods such as pancakes, muffins, bagels, rolls, cookies, french fries, and chips. **Duration:** **Treatment:** 24 weeks	Men and post-menopausal women with T2DM who take oral medication 85% overweight or obese ***n*:** G1: 106 G2: 104 **Age, mean yr, (SD):** G1: 60 (10) G2: 61 (9) **Sex *n*, (%):** Male G1: 65 (61.3) G2: 63 (60.6) Female G1: 41 (38.7) G2: 41 (39.4) **Race/ethnicity *n*, (%):** European G1: 79 (74.5) G2: 65 (62.5) Indian G1: 14 (13.2) G2: 21 (20.2) Far Eastern G1: 6 (5.7) G2: 6 (5.8)	**At 24 weeks** **SBP, mmHg:** G1: 124.7 G2: 125.8 *p*=NS **DBP, mmHg:** G1: 72.1 G2: 73.5 *p*=NS	**At 24 weeks** **Mean TC, mg/dL:** G1: 168.4 G2: 162.6 *p*=NS **Mean HDL-C, mg/dL:** G1: 42.8 G2: 43.6 *p*=.005 **Mean LDL-C, mg/dL:** G1: 101.3 G2: 95.3 *p*=NS **Mean TG, mg/dL:** G1: 122.2 G2: 124.6 *p*=NS **Mean TC: HDL-C, mg/dL:** G1: 4.06 G2: 3.94 *p*=NS **Mean LDL-C: HDL-C, mg/dL:** G1: 2.45 G2: 2.31 *p*=NS	**Withdrawals, *n* (%):** G1: 19 (19) G2: 23 (23) **Adherence:** NR **Actual nutrient intake at 24 weeks:** *N*=195 **Kcal:** G1: 1,706 G2: 1,690 **Fat,%:** G1: 33.3 G2: 30.5 **CHO, %:** G1: 44.0 G2: 47.5 **Protein, %:** G1: 21.2 G2: 20.7 **SF, %:** G1: 9.6 G2: 9.3 **MUFA, %:** G1: 13.3 G2: 12.2 **PUFA, %:** G1: 6.7

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
	Intervention delivery: Participants received information on either low-glycemic index or high-cereal fiber food options from different categories (breakfast cereals, breads, vegetables, fruit) as approximately 15-g carbohydrate servings. Instruction was provided on evaluating portion size. Participants completed checklists on a daily basis and discussed their 7-day diet records with their dietician when visiting the clinical center at 2 weeks, 4 weeks, and monthly for 6 mo.	African G1: 4 (3.8) G2: 9 (8.7) Hispanic G1: 3 (2.8) G2: 2 (1.9) Native American G1: 0 (0.0) G2: 1 (1.0) **Mean weight, kg (SD):** G1: 87.0 (20.0) G2: 87.8 (19.4) **BMI:** NR **SBP, mmHg (SD):** G1: 127 (16) G2: 128 (14) **DBP, mmHg (SD):** G1: 74 (10) G2: 75 (9)			G2: 6.2 **Fiber, g:** G1: 1 8.7 G2: 15.7 **Cholesterol, mg/d:** G1: 142.9 G2: 142.0
Yusof et al., 2009[44] RCT Malaysia, outpatient clinic Good	**Treatment groups:** G1: Low-glycemic index (GI) diet G2: Conventional carbohydrate exchange (CCE) diet G1: Participants instructed to eat at least one low-GI food from lists and advised to consume carbohydrate foods evenly throughout the day. G2: Participants also advised to spread carbohydrate consumption throughout the day and had a set number of carbohydrate exchanges for each meal Both diets designed to be high in CHO (50–60% of energy), low in fat (25–30% of energy) and rich in low- or high-GI foods depending on the treatment. **Duration:** **Treatment:** 12 weeks **Intervention delivery:** Dietary advice similar for both treatment groups. Dietician gave individual dietary advice to all subjects over 12 weeks.	Overweight Asian adults with type 2 DM ***n*:** G1: 52 G2: 52 **Age, mean yr:** NR **Sex:** NR **Race/ethnicity:** NR **Weight, mean kg (SD):** G1: 69.12 (13.33) G2: 66.83 (11.50) **BMI:** NR **Mean SBP, mmHg (SD):**	**At 4 weeks** **DBP, mmHg (SE):** G1: 76.1 (1.1) G2: 77.3 (1.4) *p*=NR **SBP, mmHg (SE):** G1: 127.5 (2.2) G2: 139.2 (2.7) *p*=NR **At 12 weeks** **Mean change in SBP, mmHg (SE):** G1: 127.5 (2.0) G2: 137.0 (2.3) *p*=NR **Mean change in DBP, mmHg (SE):** G1: 75.2 (1.2)	**At 12 weeks** **Mean change in HDL-C, mmol/(SE):** G1: 1.14 (0.04) G2: 1.21 (0.05) *p*=NR **Mean change in LDL-C, mmol/(SE):** G1: 2.67 (0.11) G2: 2.93 (0.14) *p*=NR **Mean change in TC, mmol/L (SE):** G1: 4.54 (0.12) G2: 4.80 (0.16) *p*=NR **Mean change in TG, mmol/L (SE):** G1: 1.59 (0.10) G2: 1.46 (0.08) *p*=NR	**Withdrawals, *n* (%):** G1: 1 (1.9) G2: 3 (5.8) **Adherence:** NR **Actual nutrient intake:** **At 12 weeks:** **Kcal:** G1: 1,512 G2: 1,526 **Fat, g:** G1: 51.0 G2: 51.0 **CHO, g:** G1: 200 G2: 207 **Protein, g:** G1: 70

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 127.53 (15.39) G2: 139.19 (19.15) **Mean DBP, mmHg (SD):** G1: 76.81 (9.95) G2: 79.31 (8.23)	G2: 79.2 (1.3) *p*=NR	**At 4 weeks** **Mean change in HDL-C, mmol/L (SE):** G1: 1.12 (0.04) G2: 1.21 (0.05) *p*=NR **Mean change in LDL-C, mmol/L (SE):** G1: 2.74 (0.09) G2: 2.77 (0.11) *p*=NR **Mean change in TC, mmol/L (SE):** G1: 4.61 (0.12) G2: 4.57 (0.12) *p*=NR **Mean change in TG, mmol/L (SE):** G1: 1.67 (0.13) G2: 1.29 (0.06) *p*=NR	G2: 66 **Fiber, g:** G1: 24 G2: 11 **Glycemic index, g:** G1: 57 G2: 64 **Glycemic load:** G1: 108 G2: 131

CQ1 Summary Table B–8. Dietary Fat and Cholesterol

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH Appel et al., 1997[30]; Sacks et al., 1999[31]; Obarzanek et al., 2001[32] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet- Refer to the main DASH dietary pattern table G3: Control diet Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol G1: Diet rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, G3: Control diet typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was and was kept stable by changing calorie level. Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal. **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Participants attended the clinic each weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages and up to 2 servings of specific alcoholic beverages were allowed.	Adults ≥22 years; SBP <160 mmHg and a DBP of 80–95 mmHg ***n*:** G1: 151 G3: 154 **Age, mean yr (SD):** G1: 44 (10) G3: 44 (11) **Sex, *n** (%):** Male G1: 74 (49.0) G3: 81 (52.6) Female G1: 77 (51.0) G3: 73 (47.4) **Race/ethnicity, *n* (%):** Black G1: 93 (61.1) G3: 92 (59.7) Non-minority G1: 47 (31.1) G3: 54 (35.1) Other Minority G1: 11 (7.3) G3: 8 (5.2) **Mean weight, kg:** G1: 83.4 G3: 81.5 **Mean BMI, kg/m^2:** G1: 28.5 G3: 28.0		**At 8 weeks** *N*=436* **HDL-C mmol/L, net change (95% CI):** G1 vs. G3: –0.09 (–0.13, –0.06) *p*<.0001 **LDL-C mmol/L, net change (95% CI):** G1 vs. G3: –0.28 (–0.40, –0.16) *p*<.0001 ***436 participants (95% of the 459) who provided fasting blood samples at baseline and end of the intervention**	**Withdrawals, *n* (%):** G1: 2 (1.3) G3: 7 (4.5) **Adherence:*** assessed by percent attendance at onsite meals **Onsite meal attendance, %:** G1: 96.1 G3: 95.8 Adherence was also assessed by percent of days per person with perfect adherence to study diets. Perfect adherence was defined as all study foods consumed and no nonstudy foods consumed. **Mean % of days with perfect adherence per person:** G1: 93.2 G3: 94.6 ***Procedures for adherence to the diets were revised after first participant groups completed the program. Data on adherence is for the 362 participants enrolled after the first participant group completed the program.**

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DASH-Sodium Sacks et al., 2001[33]; Harsha et al., 2004[34] RCT, crossover design within each diet USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Typical American Diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. G2: Control diet: 37% fat, 16% SF13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were high (H; 150 mmol/d), intermediate (I; 100 mmol/d), and low (L; 50 mmol/d).All food was provided. Weight was kept stable.	Adults ≥22 years; target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Age, mean yr (SD):** G1: 47 (10) G2: 49 (10) **Sex, *n** (%)** Male G1: 85 (41) G2: 93 (46) Female G1: 123 (59) G2: 111 (54) **n* from Vollmer WM, Sacks FM, Ard J et al., 2001[49] **Race, *n* (%)** Black G1: 118 (57) G2: 114 (56) Non-Hispanic White G1: 83 (40) G2: 81 (40) Asian or other G1: 6 (3) G2: 10 (5) **Weight:** NR **Mean BMI kg/m^2 (SD):** G1: 29 (5) G2: 30 (5)		**At 30 days** **Mean change in LDL-C mmol/L, at 30 days by Na level (95% CI)**:** G1 H vs. G2 H: –0.33 (–0.45, –0.21) *p*<.0001 G1 I vs. G2 I: –0.30 (–0.45, –0.16) *p*<.0001 G1 L vs. G2 L:–0.37 (–0.49, –0.24) *p*<.0001 **Mean change in HDL-C mmol/L, at 30 days by Na level (95% CI)*:** G1 H vs. G2 H: –0.10 (0.14, –0.06) *p*<.0001 G1 I vs. G2 I: –0.09 (–0.14, –0.05) *p*<.0001 G1 L vs. G2 L: –0.08 (–0.11, –0.04) *p*<.0001 **Mean change in TG mmol/L, at 30 days by Na level (95% CI):**** G1 H vs. G2 H: 0.06 (–0.05, 0.18) *p*=.3 G1 I vs. G2 I: –0.02 (–0.16, 0.11) *p*=.7 G1 L vs.G2 L: 0.03 (–0.09, 0.15) *p*=.6 **n*=390 ***n*=379	**Withdrawals, *n* (%):** G1: 10 (95) G2: 12 (94) **Adherence:** NR **Actual nutrient intake:** **Energy kcal/day, mean (SD):** G1: 2576 (511) G2: 2576 (493) **Total Fat, % of energy (SD):** G1: 27.4 (0.2) G2: 38.6 (4.2) **Total CHO, % of energy (SD):** G1: 58.5 (0.3) G2: 49.2 (0.3) **Protein, g:** NR **SF, % of energy (SD):** G1: 6.2 (0.1) G2: 15.0 (0.2) **MUFA, % of energy (SD):** G1: 11.2 (0.1) G2: 12.5 (0.3) **PUFA, % of energy (SD):** G1: 8.0 (0.2) G2: 7.4 (0.3) **Fiber, g/day, mean (SD):** G1: 35.0 (6.1) G2: 17.3 (18.0) **Cholesterol, mg/day, mean (SD):** G1: 194 (48) G2: 324 (62.7)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
DELTA–1 Ginsberg1998[36] RCT, crossover USA, University research centers Fair	**Treatment groups:** G1: National Cholesterol Education Program (NCEP) Step 1 diet G2: Low-saturated fat diet (low-SFA) G3. Average American diet (AAD) G1: 30% of calories from fat and 9% SFA, 14% MUFA and 7% PUFA, 55% CHO and 15% protein G2: 26% of calories from fat and 5% SFA, 14% MUFA and 7% PUFA, 59% CHO and 15% protein G3: 37% of calories from fat,16% SFA, 14% MUFA, 7% PUFA , 48% CHO, 15% protein **Duration:** **Treatment:** 8 weeks **Washout:** 4–6 weeks **Intervention delivery** Each diet period was consumed for 8 weeks, with a washout of 4 to 6 weeks between each diet period. Food was provided and participants ate 2 meals each weekday onsite. All 3rd meals, snacks, and weekend food were provided (packaged) except for one weekend meal (optional "self-selected "Saturday meal to allow for personal choice). Participants were weighed 2/week adjustments were made in kcal to maintain stable body weight. Compliance assessed by tray checks at meals eaten onsite and by self-report on standardized forms for offsite meals.	Adults ages 22–65 years with normal lipid levels ***n*:** G1: NR G2: NR Total: 103 **Age, mean yr:** Men: 36.0 Women: 39.4 **Sex, *n* (%):** Men: 46 (45) Women: 57 (55) **Race/ethnicity, *n* (%):** Blacks: 26 (25) Non-Blacks:77 **Weight:** NR **BMI:** NR **SBP:** NR **DBP:** NR	NR	**At 8 weeks** **Mean Apo A–1, mg/dL:** G1: 135.4 (2.0) G2: 130.4 (1.9) G3: 142.2 (2.0) G1 vs. G3: *p*<.01 G2 vs. G3: *p*<.01 **Mean Apo B, mg/dL:** G1: 113.6 (2.6) G2: 111.6 (2.6) G3: 116 (2.4) G1 vs. G3: *p*=NR G2 vs. G3: *p*<.01 **Mean HDL-C, mg/dL:** G1: 48.5 (1.1) G2: 46.2 (1.0) G3: 52.2 (1.1) G1 vs. G3: *p*<.01 G2 vs. G3: *p*<.01 **Mean LDL-C mg/dL:** G1: 122.2 (2.6) G2: 116.9 (2.6) G3: 131.4 (2.7) G1 vs. G3: *p*<.01 G2 vs. G3: *p*<.01 **Mean Lp (a), mg/dL:** G1: 17.0 (1.8) G2: 18.2 (1.9) G3: 15.5 (1.8): G1 vs. G3: *p*<.01 G2 vs. G3: *p*<.01 **Mean TG (%), mg/dL** G1: 92.4 (3.7) G2: 93.0 (3.7) G3: 85.1 (3.4) G1 vs. G3: *p*<.01 G2 vs. G3: *p*=NR	**Withdrawals, *n* (%):** G1: NR G2: NR Total: 15 (14.5%) **Adherence:** NR **Actual nutrient intake:*** **Mean fat,% (SEM):** G1: 28.6 (0.2) G2: 25.3 (0.3) G3: 34.3 (0.5) **Mean SFA, % (SEM):** G1: 9.0 (0.1) G2: 6.1 (0.5) G3: 15.0 (0.4) **Mean MUFA, % (SEM):** G1: 12.9 (0.1) G2: 12.4 (0.1) G3: 12.8 (0.1) **Mean PUFA % (SEM):** G1: 6.7 (0.1) G2: 6.7 (0.1) G3: 6.5 (0.1) **Mean cholesterol, mg/d (SEM):** G1: 267 (7.6) G2: 275 (4.0) G3: 285 (3.9) *Mean ± SEM based on 24 complete menu cycles for AAD, 23 cycles for NCEP Step 1 diet, & 22 cycles for low-SFA diet

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
Gardner et al., 2005[37] RCT USA, Clinical Research Center Fair	**Treatment groups:** G1: Low-Fat Plus diet G2: Low-Fat diet G1: Low-Fat diet design with additions consistent with the 2000 American Heart Association revised guidelines. More plant-based, designed to include considerably more vegetables, legumes, whole grains, and fruits. Addition of butter, cheese, and eggs to increase the SF and cholesterol content to match the Low-Fat diet. G2: The Low-Fat diet was relatively typical of a low-fat U.S. diet consistent with former American Heart Association Step I guidelines. Designed to include many reduced-fat prepared-food items (for example, reduced-fat cheeses, low-fat frozen lasagna, and low-fat and low-sugar-rich snack foods). The Low-Fat diet and the Low-Fat Plus diet were designed to be identical in total fat, saturated fat, protein, carbohydrate, and cholesterol content, with ≤30% of energy from total fat and ≤10% of energy or less from SF. **Duration** **Treatment:** 4 weeks **Followup:** mean 28 days **Intervention delivery:** Lunch or dinner eaten onsite, provided with meals, snacks, and beverages on an outpatient basis for 28 days. Weight was held constant.	Hypercholesterolemic adults 30 to 65 years of age ***n:*** G1: 59 G2: 61 **Age, mean yr (SD):** G1: 49 (8) G2: 48 (10) **Sex, *n* (%):** Men: G1: 26 (43) G2: 34 (57) Women: G1: 33 (55) G2: 27 (45) **Race/ethnicity, *n* (%):** Non-Hispanic White G1: 46 (76) G2: 45 (75) **Weight:** NR **BMI, kg/m² (SD):** G1: 26 (3) G2: 27 (3) **SBP:** NR **DBP:** NR	NR	**At 4 weeks** **Mean change in TC, mg/dL (%):** G1: –17.6 (–7.9) G2: –9.2 (–4.1) **Between group difference in TC, mg/dL (95% CI):** G1 vs. G2: –9 (–2, –15) *p*=.014 **Mean change in LDL-C, mg/dL (%):** G1: –13.8 (–9.3) G2: –7 (–4.6%) **Between group difference in LDL-C, mg/dL (95% CI):** G1: –7 (–2, –12) *p*=.016 **Mean change difference in HDL-C, mg/dL:** G1: –3.8 (–7.7%) G2: –2.5 (–5.5) **Between group difference in HDL-C, mg/dL (95% CI):** G1 vs. G2: –2 (0.4, –3) *p*=NS **Mean change difference in TG, mg/dL:** G1: +0.1 (0.1) G2: +1.2 (0.9) **Between group difference in TG, mg/dL (95% CI):** G1 vs. G2: 0.9 (34, –39) *p*=NS	**Withdrawals, *n* (%):** G1: 2 (3.3) G2: 3 (4.9) **Adherence (%):** G1: ≥99 G2: ≥99 Adherence was measured by daily tracking of incomplete consumption of study foods or consumption of any non-study foods. **Actual nutrient intake:** Average of 7 day menus determined by chemical analyses, once for each on-study menu at mean of 28 days **Fat, % of energy:** G1: 31.7 G2: 29.8 **SF, % of energy:** G1: 9.5 G2: 9.5 **CHO, % of energy:** G1: 54.1 G2: 55.6 **Protein, % of energy:** G1: 14.1 G2: 14.6 **Cholesterol, mg:** G1: 200 G2: 187 **MUFA, %:** G1: 9.4 G2: 9.2 **PUFA, %:** G1: 9 G2: 6.4 **Fiber, g:** G1: 40.8 G2: 22.0

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
Women's Health Initiative Dietary Modification Trial Howard et al., 2006[42]; Tinker et al., 2008[43] RCT USA, 40 clinical centers Fair	**Treatment groups:** G1: Intervention group G2: Usual diet group G1: Low-fat diet with total fat as 20% of total energy, 5 fruits and vegetables and ≤6 grains (Intensive behavior modification to reduce total fat intake to 20% of calories and increase vegetables/fruit intake to 5 servings/d and grains to at least 6 servings/d) **Duration:** **Treatment:** Mean of 8.1 yr **Intervention delivery:** G1: Year 1 participated in 18 intensive nutritional and behavioral modification trainings followed by quarterly sessions. Diet was not intended to promote reduced energy intake. G2: Given a copy of the Dietary Guidelines for Americans; not asked to make dietary changes and had no contact with nutritionist	Healthy post-menopausal women ages 50 to 79 years ***n*:** G1: 19,541 G2: 29,294 **Age, mean yr, (SD):** G1: 62.3 (6.9) G2: 62.3 (6.9) **Sex, %:** Female: 100 **Race/ethnicity, *n* (%):** American Indian and Alaskan Native G1: 80 (0.4) G2:105 (0.4) Asian/Pacific Islander G1: 399 (2.2) G2: 618 (2.2) Black or African American G1: 1,841 (10.0) G2: 2,726 (9.9) Native Hawaiian/ Other Pacific Islander G1: 399 (2.2) G2: 618 (2.2) **Race/ethnicity, *n* (%):** White G1: 1,586 (82.3) G2: 22,685 (82.5) Hispanic or Latino G1: 689 (3.7) G2: 1016 (3.7) Other G1: 239 (1.3) G2: 361 (1.3) **Weight, kg (SD):** G1: 76.8 (16.6) G2: 76.7 (16.5)	**At 1 yr** **Mean SBP, mmHg (SD):** G1: 124.4 (17.1) G2: 125.4 (16.8) *p*=NR **Mean DBP, mmHg (SD):** G1: 73.9 (9.2) G2: 74.7 (9.1) *p*=NR **At 3 yr** **Mean change in SBP mmHg (SD):** G1: –2.2 (16.3) G2: –2.1 (16.4) G1 vs. G2 (95% CI):–0.17 (–0.49, 0.15) *p*=NS **Mean change in DBP mmHg (SD):** G1: –2.6 (9.4) G2: –2.3 (9.4) G1 vs. G2 (95% CI):–0.31 (–0.50 , 0.13) *p*<.001 **At 6 yr** **Mean SBP, mmHg (SD):** G1: 124.5 (16.5) G2: 124.6 (16.3) *p*=NR **Mean DBP, mmHg (SD):** G1: 71.7 (9.2) G2: 71.9 (9.2) *p*=NR	**At 3 yr** **Change in LDL-C , mg/dL (SD):** G1: –9.7 (29.3) G2: –6.2 (29.1) G1 vs. G2 (95% CI): –3.55 (–6.58 to –0.52) *p*<.05 **Change in HDL-C, mg/dL (SD)** G1: –0.7 (9.4) G2: –0.3 (10.2) G1 vs. G2 (95% CI): –0.43 (–1.42 to 0.57) *p*=NS **Change in non-HDL-C, mg/dL (SD):** G1: –9.7 (32.0) G2: –6.6 (32.6) G1 vs. G2 (95% CI): –3.08 (–6.37 to 0.22) *p*=NS **Change in TG, mg/dL (SD:)** G1: 1.0 (0.4) G2: 1.0 (0.3) G1 vs. G2 (95% CI): 0.00 (–0.03 to 0.04) *p*=NS	**Withdrawals, *n* (%):** G1: 1867 (9.5) G2: 2617 (8.9) **Adherence:** NR **Actual nutrient intake:** **At 1 yr** **Energy, kcal:** G1: 1502 G2: 1594 **Total fat, %:** G1: 24.2 G2: 35.0 **Saturated fat, %:** G1: 8.0 G2:11.7 ***Trans* fatty acids, %:** G1:1.6 G2: 2.5 **PUFA. %:** G1: 5.2 G2: 7.2 **CHO, %:** G1: 58.5 G2: 48.0 **At 6 yr** **Energy, kcal:** G1: 1435 G2: 1548 **Total fat, %:** G1: 28.6 G2: 35.0 **Saturated fat, %:** G1: 9.5 G2: 12.4 ***Trans* fatty acids, %:**

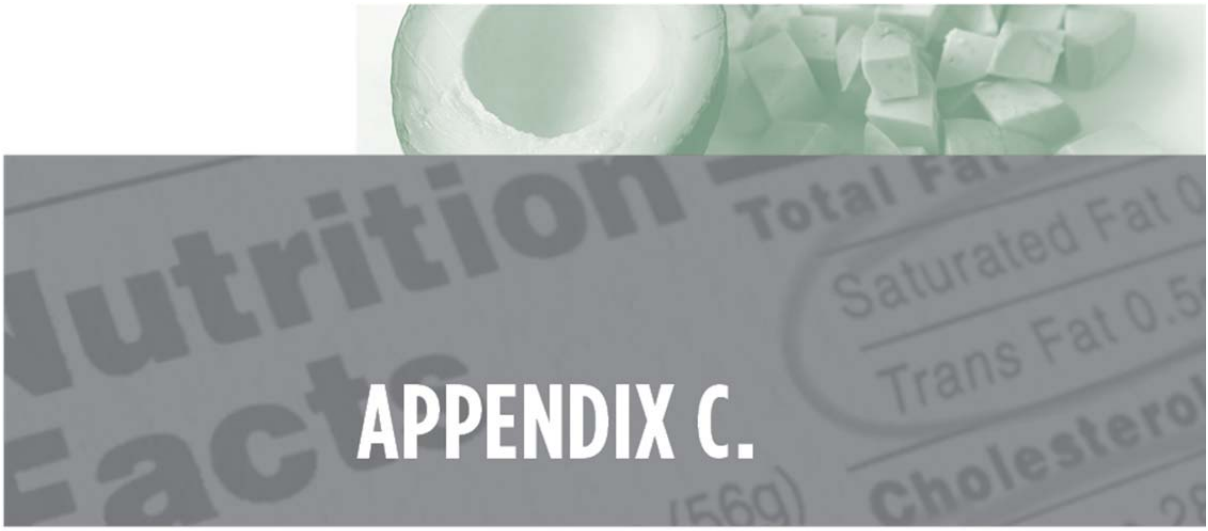
Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Lipid Outcomes	Attrition Adherence/Compliance Actual Nutrient Intake
		Mean BMI (SD): G1: 29.1 (5.9) G2: 29.1 (5.9) **Mean SBP, mmHg (SD):** G1: 127.5 (17.2) G2: 127.9 (17.2) **Mean DBP, mmHg (SD):** G1: 75.9 (9.1) G2: 76.0 (9.1)			G1: 1.8 G2: 2.3 **PUFA, %:** G1: 6.0 G2: 7.5 **CHO, %:** G1: 54.1 G2: 45.9

Table B–9. Critical Question 1 Studies Rated as Poor, With Rationale

Study	Design	Primary Reasons for Poor Quality Rating
Ammerman et al., 2003[145]	RCT	High LTF; no ITT analysis; no information on power calculations or adherence.
Appleby et al., 1999[146]	Observational cohort	No information on LTF or confounding factors.
Aquilani et al., 1999[147]	RCT	No information on blinding procedures, power, or differential LTF rates.
Asztalos et al., 2000[148]	RCT	Poorly described randomization process; high LTF; low adherence; and information on differential LTF rates and power analysis was not reported.
Bo et al., 2008[149]	RCT	Inadequately powered, LTF, and subgroups were not prespecified.
Chrysohoou et al., 2004[150]	RCT	No information on randomization procedure, LTF, or ITT analysis.
Clarke et al., 1997[52]	Meta-analysis	Study details not provided.
de Lorgeril et al., 1999[151]	Observational cohort	High LTF, unclear description of intervention, no information on sample size justification or power, and no statistical testing was reported for risk factors.
Furtado et al., 2008[152]	RCT	High LTF; no ITT analysis.
Gardner et al., 1995[153]	Meta-analysis	Lack of quality rating of included studies.
Garg 1998[154]	Meta-analysis	Methodology not described in detail. No indication that the study was conducted by more than one individual.
Griffin et al., 2006[155]	RCT	No ITT analysis; inadequate randomization and power.
Hjerkinn et al., 2004[156]	RCT	No ITT analysis, LTF, or information on power analysis.
Hopkins 1992[51]	Meta-analysis	Lacks important description of study methods.
Hu et al., 2002[157]	Review	Review not performed in a systematic way to determine whether study selection, data entry, and analysis were free from various biases.
Hunninghake et al., 2000[158]	RCT	High LTF; no information on randomization procedure and power analysis.
Kolovou et al., 2003[159]	Observational cohort	No information on LTF or sample size justification.
Kuller et al., 2001[160]	RCT	No information on sample size justification, power analysis, LTF, or ITT analysis.
Lagström et al., 1999[161]	RCT	No ITT analysis, LTF, or information on blinding procedures, sample size calculation or power analysis.
Morgan et al., 2009[162]	RCT	High LTF; no ITT analysis or power calculation.
Rasmussen et al., 2006[163]	RCT	No information on randomization procedure or power analysis.
Søndergaard et al., 2003[164]	RCT	Inadequate randomization and blinding procedures; no information on LTF or power analysis; no ITT analysis.

Study	Design	Primary Reasons for Poor Quality Rating
Stefanick et al., 1998[165]	RCT	No ITT analysis; no information on LTF, power analysis, or adherence.
Toobert et al., 2003[166]	RCT	Inadequate randomization procedure; no information on blinding procedure or power analysis.
Witana et al., 2005[167]	Observational cohort	No information on power analysis, sample size justification; unclear definition of exposure measure.
Xiao et al., 2003[168]	RCT	No ITT analysis; no information on LTF or power analysis.
Yu-Poth et al., 1999[169]	Meta-analysis	Details on study methods were not reported.

Note: ITT = intent-to-treat; LTF = lost to followup; RCT = randomized controlled trial.



APPENDIX C.

Critical Question 2 Methods

Appendix C. Critical Question 2 Methods

i. Search Strategy

Among adults, what is the effect of dietary intake of sodium and potassium on CVD risk factors and outcomes, when compared to no treatment or to other types of interventions?a. Study type query

Study types eligible for this question: RCTs, systematic reviews or meta-analyses of RCTs or controlled clinical trials, observational or epidemiologic studies with time difference between interventions/exposures and outcomes (e.g., cohort studies, case-control studies).

- (RCT) OR (Systematic Review) OR
- genre= (Controlled Clinical Trial) OR
- (subject= ("Controlled Clinical Trials as Topic") **and** (subject,abstract,title= (random?) or systematic? or critical or (study selection) or (predetermined or inclusion and criteri?) or exclusion criteri? or "main outcome measures" or "standard of care" or "standards of care")) OR
- (subject,title,abstract= (Case-Control Stud? or Retrospective Stud? or Cohort Stud? or Followup Stud? or Longitudinal Stud? or Prospective Stud? or Observational Stud?))

b. Boolean search

- (publicationYear >1997)
- **AND** subject,title,abstract,qualifier= (diet? or food? or fruit? or vegetable? or life style or lifestyle or ((sodium or potassium) intake?))
- **AND** (MeSHSubjectPhrase= ("Sodium" or "Sodium, Dietary" or "Diet, Sodium-Restricted" or "Sodium Chloride, Dietary" or "Potassium" or "Potassium, Dietary" or "Calcium, Dietary" or "Calcium" or)
  - OR "dietary sodium" or "dietary potassium" or
  - OR (subject,abstract,title= (sodium or potassium or calcium or salt) and (electrolyte? or mineral? or subject,abstract,title=micronutrient? or nutrient? or intake?))
  - OR (subject,abstract,title= (fruit? or vegetable?) and (electrolyte? or mineral? or subject,abstract,title=micronutrient?)))
- **AND** (subject,qualifier,title,abstract=mortality or death? or died or fatal? or subject= ("Cause of Death" or "Fatal Outcome" or "Survival Rate")
- or subject,title,abstract= ("Acute Coronary Syndrome" or "Myocardial Infarction" or "Shock Cardiogenic" or "Myocardial Stunning" or "No Reflow Phenomenon" or "Heart Arrest" or "Death Sudden Cardiac" or "Angina, Unstable" or "Heart Attack" or "Heart Failure") or STEMI or NSTEMI or myocardial infarctions or unstable angina? or acute coronary syndromes
- or subject,abstract,title= ("Stroke" or "Brain Infarction" or "Brain Stem Infarctions" or "Lateral Medullary Syndrome" or "Cerebral Infarction" or "Dementia, Multi-Infarct" or "Infarction Anterior Cerebral Artery" or "Infarction Middle Cerebral Artery" or "Infarction Posterior Cerebral Artery")
- or ((CVD or CHD or HF or CHF or cardiovascular or coronary or heart failure or cardiac) and (subject,abstract,title= (hospitalization) or hospitalization? or rehospitalization? or subject,abstract,title= (inciden? or morbidity or prevalence)))
- or ((subject= (Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders)) with (qualifier=complications))

- or subject,title,abstract= (Angioplasty or Revascularization or Coronary Artery Bypass or Coronary Angiography or Stents or Endarterectomy) or CABG
- or subject= ("Kidney Failure, Chronic" or "Renal Insufficiency, Chronic") or Chronic Kidney Failure or CKD or Chronic Kidney Disease or End Stage Renal or ESRD or ((kidney or renal) %5 stage? %5 (3 or 4 or 5 or III or IV or V))
- or (composite %5 (index or score or outcome?))
- **or ((**
  - ((subject= (Triglycerides or "Cholesterol" or "Apolipoproteins B" or Apolipoprotein B? or "Apolipoprotein A-I" or "Apolipoproteins A" or Apolipoproteins or "Lipoprotein (a)" or "Apoprotein (a)")) with (qualifier= (blood or metabolism))) or Triglyceride? or HDL Cholesterol or HDL-C or Apolipoprotein B? or apoB or Apolipoprotein A? or apoA–1 or Lp (a) or "Lipoprotein (a)" or "Apoprotein (a)" or total cholesterol or LDL particle number or LDL-P or (LDL and subject,abstract,title="Particle Size") or lipid goal? or lipid level?
  - or ((subject= (Hypertension or Cholesterol)) with (qualifier= (blood or diagnosis or prevention)))
  - or subject,title,abstract= ("Blood pressure" and (systol? or diastol?)) or BP or SBP or DPB or hypertensive or non-hypertensive or blood pressure goal?
  - or (urin? %2 (albumin or sodium or potassium))
  - or subject,title,abstract= ("Glomerular Filtration Rate" or "Albuminuria") or GFR or eGFR or estGFR
  - or (change %3 (medication or dose or dosage))
  - **)**
  - **and (** subject,title,abstract= (risk? or factor? or marker? or biomarker? or indicator? or level? or concentration? or end point? or endpoint? or Treatment Outcome or response) **))**
)
-)
- **NOT** majorSubject= ("Digestive System Surgical Procedures" or "Bariatric Surgery" or "Gastric Bypass" or "Gastric Balloon" or Laparoscopy or Gastroplasty or Coronary Artery Bypass or Gastrectomy or "Biliopancreatic Diversion")
- **NOT** (((subject= ("Digestive System Surgical Procedures" or "Bariatric Surgery" or "Gastric Bypass" or "Gastric Balloon" or Laparoscopy or Gastroplasty or Coronary Artery Bypass or Gastrectomy or Biliopancreatic Diversion)) with (qualifier= (instrumentation or methods or adverse effects or economics or standards or statistics))))
- **NOT** subject= ("Postoperative Complications" or Reoperation or "Postoperative Period" or "Length of Stay" or "Reconstructive Surgical Procedures" or "Equipment and Supplies" or "Preoperative Care" or "Postoperative Care" or "Prenatal Care" or "Weight Gain and Pregnancy" or "Pregnancy Complications")
- **NOT** subject= ("Equipment Design" or "Advertising as Topic")
- **NOT** subject= (Heel or Foot diseases or Cosmetic techniques or Hair Removal or Hirsutism)
- **NOT** subject= (Practice Guidelines as Topic or Pilot Projects or Cross Sectional Studies)
- **NOT** majorSubject= ("Research Design")
- **NOT** subject= (Animals or Venoms)
- **NOT** title,abstract,subject=flax?
- **NOT** ((?dialysis %5 patients) or subject= (renal dialysis) or hemodialysis)
- **NOT** title= (Alcohol or red wine or Coffee or Case study or "design and baseline characteristics" or "Summaries for patients")
- **NOT** subject,title= (pregnan?)

- **NOT** (recordStatus=delete)

c. Boolean filter

The Boolean filter in the Lifestyle 2 search strategy implements an extension of the search period for sodium and hard outcomes from 2010 to April 2012.

- (publicationYear >1997 and publicationYear<2010) **OR** (
- (publicationYear >2009)

  - **AND** (MeSHSubjectPhrase= ("Sodium" or "Sodium, Dietary" or "Diet, Sodium-Restricted" or "Sodium Chloride, Dietary") OR "dietary sodium" OR (subject,abstract,title= (sodium or salt) and (electrolyte? or mineral? or subject,abstract,title=micronutrient? or nutrient? or intake)))
  - **AND** (
    subject,qualifier,title,abstract=mortality or death? or died or fatal? or
    subject= ("Cause of Death" or "Fatal Outcome" or "Survival Rate") or
    subject,title,abstract= ("Acute Coronary Syndrome" or "Myocardial Infarction" or "Shock Cardiogenic" or "Myocardial Stunning" or "No Reflow Phenomenon" or "Heart Arrest" or "Death Sudden Cardiac" or "Angina, Unstable" or "Heart Attack" or "Heart Failure") or
    STEMI or NSTEMI or myocardial infarctions or unstable angina? or acute coronary syndromes or
    subject,abstract,title= ("Stroke" or "Brain Infarction" or "Brain Stem Infarctions" or "Lateral Medullary Syndrome" or "Cerebral Infarction" or "Dementia, Multi-Infarct" or "Infarction Anterior Cerebral Artery" or "Infarction Middle Cerebral Artery" or "Infarction Posterior Cerebral Artery") or
    ((CVD or CHD or HF or CHF or cardiovascular or coronary or heart failure or cardiac) and (subject,abstract,title= (hospitalization) or hospitalization? or rehospitalization? or subject,abstract,title= (inciden? or morbidity or prevalence))) or
    ((subject= (Cardiovascular Diseases or Coronary Disease or Coronary Artery Disease or Myocardial Infarction or Heart Failure or Cerebrovascular Disorders)) with (qualifier=complications)) or
    subject,title,abstract= (Angioplasty or Revascularization or Coronary Artery Bypass or Coronary Angiography or Stents or Endarterectomy) or CABG or
    subject= ("Kidney Failure, Chronic" or "Renal Insufficiency, Chronic") or
    Chronic Kidney Failure or CKD or Chronic Kidney Disease or End Stage Renal or ESRD or ((kidney or renal) %5 stage? %5 (3 or 4 or 5 or III or IV or V)) or
    (composite %5 (index or score or outcome?))
)
)

ii. Search Strategy Results, PRISMA Diagram, and CQ2 Summary Tables

The databases listed below were searched for RCTs, controlled clinical trials, observational or epidemiologic studies with a time difference between interventions/exposures and outcomes (i.e., cohort studies, case-control studies), and systematic reviews and meta-analyses of these study designs to answer Question 2. Observational and epidemiologic studies or systematic reviews of such studies were eligible for hard health outcomes only.

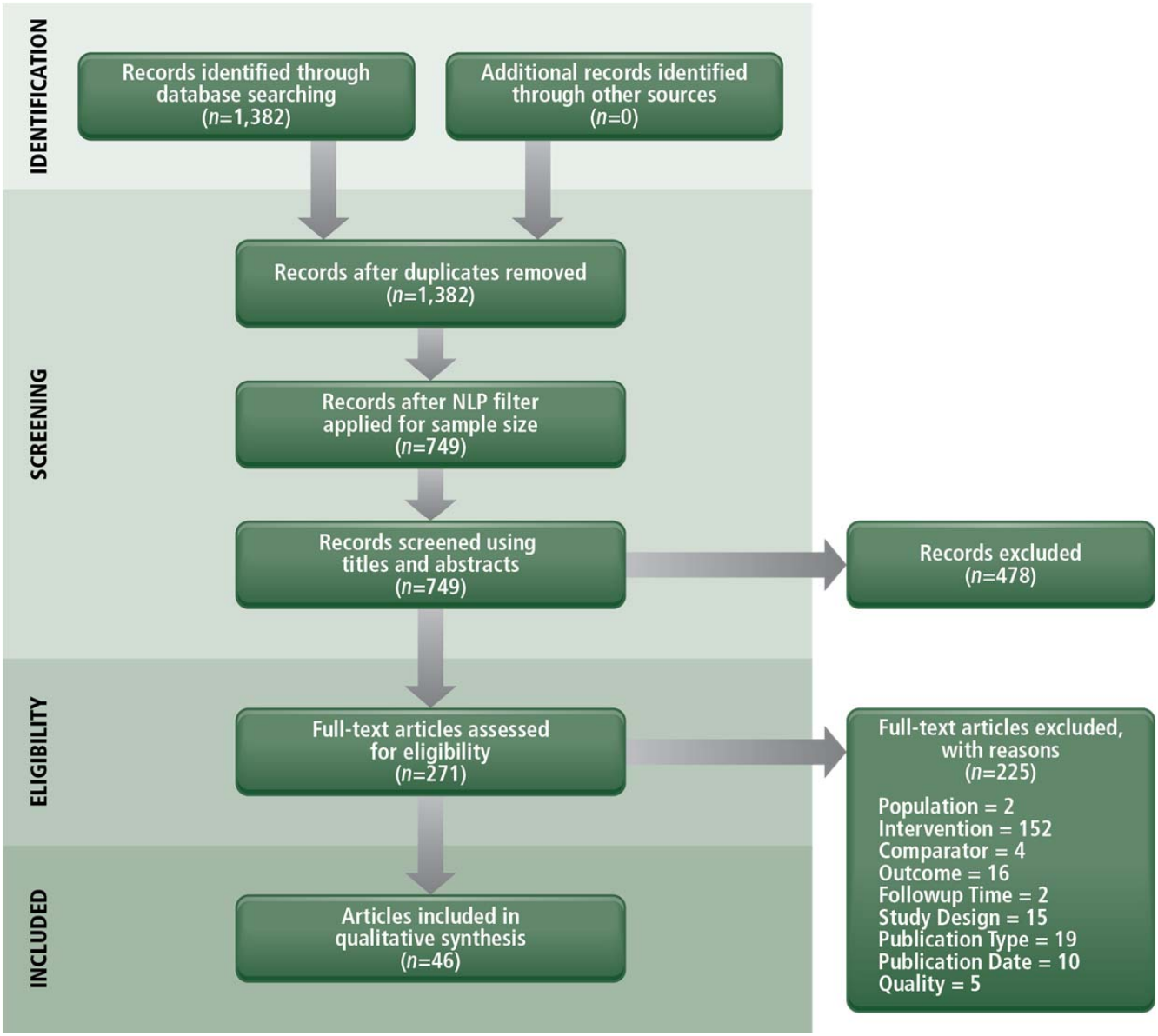
- PubMed from January 1998 to April 2012
- CINAHL from January 1998 to July 2008
- EMBASE from January 1998 to July 2008
- PsycINFO from January 1998 to July 2008
- EBM (Evidence-Based Medicine) Cochrane Libraries from January 1998 to July 2008

- Biological Abstracts from January 2004 to July 2008
- Wilson Social Sciences Abstracts from January 1998 to July 2008

Duplicate citations which arise from the same citation being found in more than one database were removed from the Central Repository before screening. The search produced 1,382 citations. This number of citations includes results from a supplemental search of PubMed focused on sodium and hard health outcomes, which publication dates that were extended through April 2012.

A natural language processing filter was used to identify studies with sample sizes less than 500 for studies reporting hard health outcomes, and for sample sizes less than 50 for biomarker assessment and risk factor studies. The natural language processing filter was executed against titles and abstracts. Six hundred and thirty-three publications were automatically excluded using the natural language processing filter because they were studies with less than the required sample size. The titles and abstracts of the 749 remaining publications were screened against I/E criteria independently by two reviewers, which resulted in the retrieval of 271 full-text papers. These papers were independently screened by two reviewers. Per figure C–1 and summary tables C–1 through C–8, 46 articles were included in the evidence base for Question 2—16 RCTs, 25 cohort studies, 1 case-control study, and 4 systematic reviews or meta-analyses—and 225 publications were excluded on one or more I/E criteria. An additional 5 publications (all RCTs) were excluded because they were rated as poor quality (table C–9).

Figure C–1. PRISMA Diagram Showing Selection of Articles for Lifestyle Critical Question 2



Note: NLP = natural language processing.

A note about the unit of measure presented for dietary and urinary sodium: Sodium is presented in studies in mmol, grams, and milligrams (mg). The Work Group chose to convert the sodium results to milligrams for the evidence statements, recommendations, and rationales so that the data from different studies would be displayed in a consistent unit. Also, U.S. dietary recommendations and the Nutrition Facts Label display sodium in milligrams, and this unit (mg) will be clearer to health care providers. Urinary and dietary sodium are portrayed in the original units from each published study in the summary tables.

CQ2 Summary Table C–1. Overall Sodium and Blood Pressure Outcomes

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
Cappuccio et al., 2006[65] Community-based cluster RCT 12 villages (6 rural, 6 semi-urban) Ashanti region of Central Ghana Fair	**Treatment groups:** G1: Specific salt-reduction education G2: Control: general health education **Duration:** **Treatment:** 6 mo **Intervention delivery:** Group intervention G1 & G2: Intensive health education program carried out by community health workers; educational and health promotion sessions open to all villagers, regardless of trial participation. Meetings held daily for 1st week of trial, then once a week. Sessions lasted ≈1 h (both for intervention and control). No mention was made of any possible dietary prevention of hypertension. G1 only: In the intervention villages, additional advice was given not to add salt to food and in cooking, to limit the amount of salted fish, salted pigs' feet, and salted beef and to soak the items in water overnight before eating them.	Adult males and females, ≈40 to 75 years of age ***n:*** G1: 522 G2: 491 **Age, mean yr (SD):** G1: 54 (11) G2: 55 (11) **Sex, *n* (%):** Female G1: 324 (62) G2: 304 (62) **Race/ethnicity *n*, (%):** African: 100% **Weight, kg (SD):** G1: 54 (11) G2: 54 (11) **BMI, kg/m^2 (SD):** G1: 21 (4) G2: 21 (4) **Mean SBP, mmHg (SD):** G1: 129 (25) G2: 127 (27) **Mean DBP, mmHg (SD):** G1: 77 (13) G2: 76 (13) **Hypertension, *n* (%):** G1: 154 (30) G2: 137 (28) **Urinary sodium, mmol/day**	**At 3 mo** ***n***: G1: 444 G2: 450 **SBP, mmHg (SD):** G1: 124.6 (26.6) G2: 123.8 (26.0) **DBP, mmHg (SD)** G1: 74.2 (13.7) G2: 74.0 (14.1) **At 6 mo** ***n***: G1: 399 G2: 402 **SBP, mmHg (SD):** G1: 127.9 (27.7) G2: 127.4 (26.0) **DBP, mmHg (SD):** G1: 76.0 (14.2) G2: 78.7 (14.3) **Effect of intervention (control – intervention) on reduction in BP (adjusted for time of day)** **At 3 mo** **SBP, mmHg (95% CI):** –0.48 (–5.45, 4.50) **DBP, mmHg (95% CI):** –1.02 (–3.95, 1.91) **At 6 mo**	**At 3 mo** ***n:*** G1: 444 G2: 450 **Urinary Na, mmol/24 h (SD):** G1: 94.0 (44.5) G2: 97.5 (42.3) **At 6 mo** ***n***: G1: 399 G2: 402 **Urinary Na, mmol/24 h (SD):** G1: 91.8 (41.8) G2: 89.8 (39.1) **Effect of intervention (control—intervention) on reduction in urinary sodium excretion** **At 3 mo** **Urinary Na, mmol/24 h (95% CI):** –0.5 (–12.3, 11.3) **At 6 mo** **Urinary Na, mmol/24 h (95% CI):** 6.0 (–4.1, 16.1)	**Withdrawals, *n* (%):** **3 mo** G1: 78 (14.9) G2: 41 (8.4) **6 mo** G1: 123 (23.6) G2: 89 (18.1) **Adherence:** NR **Nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
		(SD) G1: 99.9 (44.7) G2: 102.5 (45.3)	**SBP, mmHg (95% CI):** –2.54 (–6.54, 1.45) **DBP, mmHg (95% CI):** –3.95 (–7.11, –0.78) *p*=.015		
DASH-Sodium Sacks et al., 2001[33] RCT, crossover USA, outpatient medical centers Good	**Treatment groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Age, mean yr (SD):** G1: 47 (10) G2: 49 (10) **Sex, *n* (%)** Female G1: 123 (59) G2: 111 (54) **Race/ethnicity, *n* (%)** Black G1: 118 (57) G2: 114 (56) **Race/ethnicity, *n* (%)** Non-Hispanic White G1: 83 (40) G2: 81 (40) Asian or other G1: 6 (3) G2: 10 (5) **Weight:** NR **Mean BMI, kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Mean SBP, mmHg (SD):** G1: 134 (10) G2: 135 (10)	**After 30 days of intervention** **SBP mean change, mmHg (95% CI):** G1 I vs. G1 H: –1.3 (–2.6, 0.0) *p*<.05 G1 L vs. G1 I: –1.7 (–3.0, –0.4) *p*<.01 G2 H vs. G2 L: –6.7 (–5.4, –8.0) *p*<.001 G2 I vs. G2 H: –2.1 (–3.4, –0.8) *p*<.001 G2 L vs. G2 I: –4.6 (–5.9, –3.2) *p*<.001 G2 H vs. G2 L: –3.0 (–1.7, –4.3) *p*<.001 G1 H vs. G2 H: –5.9 (–8.0, –3.7) *p*<.001 G1 I vs. G2 I: –5.0 (–7.6, –2.5) *p*<.001 G1 L vs. G2 L: –2.2 (–4.4, –0.1) *p*<.05 G1 L vs. G2 H: –8.9 (–6.7, –11.1); *p*<.001 **DBP mean change, mmHg (95% CI):** G1 I vs. G1 H: –0.6 (–1.5, 0.2) *p*=NS G1 L vs. G1 I: –1.0 (–1.9, –0.1) *p*<.01 G1 H vs. G1 L: –1.6 (–0.8, –2.5) *p*<.001 G2 I vs. G2 H: –1.1 (–1.9, –0.2) *p*<.01 G2 L vs. G2 I: –2.4 (–3.3, –1.5) *p*<.001 G2 H vs. G2 L: –3.5 (–2.6, –4.3) *p*<.001	**After 30 days of intervention** **Urinary Na, mmol/day (SD):** G1 H: 144 (58) G1 I: 107 (52) G1 L: 67 (46) G2 H: 141 (55) G2 I: 106 (44) G2 L: 64 (37) **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L: 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, *n* (%):** G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables, dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Actual nutrient Intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
		Mean DBP, mmHg (SD): G1: 86 (5) G2: 86 (4) **Urinary sodium, mmol/day (SD):** G1: 158 (79) G2: 152 (72)	G1 H vs. G2 H: –2.9 (–4.3, –1.5) *p*<.001 G1 I vs. G2 I: –2.5 (–4.1, –0.8) *p*<.01 G1 L vs. G2 L: –1.0 (–2.5, 0.4) *p*=NS G1L vs. G2 H: –4.5 (–3.1, –5.9) *p*<.001		
Ancillary DASH-Sodium followup at one center Ard et al., 2004[64] Longitudinal observational study USA, single clinical center Fair	**Treatment groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Followup:** 12 mo **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable. Ancillary study: followup 12 mo after completion of intervention.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** G1: 29 G2: 27 **Age, mean yr (SD):** G1: 46.62 (11.20) G2: 51.59 (9.75) **Sex, % female:** G1: 66 G2: 78 **Race/ethnicity, % non-White:** G1: 31 G2: 48 **Weight, kg (SD):** NR **BMI, kg/m^2 (SD):** G1: 27.79 (4.87) G2: 29.54 (4.30) **Mean SBP, mmHg (SD):** G1: 132.17 (10.21) G2: 139.54 (9.70) **Mean DBP, mmHg (SD):** G1: 84.08 (5.10) G2: 86.00 (4.53) **Hypertension, *n* (%):** G1: 27.6 G2: 63.0	Change from end of intervention treatment to 12-mo followup, mean (95% CI) **SBP, mmHg:** G1: 4.46 (–0.22, 9.14) G2: 1.82 (–4.19, 7.82) *p*=.48 G1 H: 0.09 (–11.15, 11.32) G2 H: 5.58 (–18.44, 13.55) *p*=.37 G1 I: 4.90 (–2.25, 12.05) G2 I: 2.97 (–10.14, 16.09) *p*=.76 G1 L: 8.83 (0.44, 17.21) G2 L: 3.25 (–10.54, 10.08) *p*=.09 **DBP, mmHg:** G1: 0.11 (–3.32, 3.55) G2: 0.79 (–2.40, 3.98) *p*=.77 G1 H: –1.82 (–9.85, 6.20) G2 H: 2.50 (–0.94, 5.94) *p*=.29 G1 I: 0.50 (–4.91, 5.91) G2 I: 1.51 (–6.15, 9.18) *p*=.81 G1 L: 1.80 (–5.38, 8.98) G2 L: 1.73 (–8.35, 4.90) *p*=.41	Change from end of intervention treatment to 12-mo followup, mean (95% CI) **Urinary Na, mmol/day:** G1: 7.12 (–11.89, 26.11) G2: 11.42 (–28.47, 51.31) *p*=.84 G1 H: –10.91 (–40.44, 18.62) G2 H: –23.61 (–154.73, 107.51) *p*=.82 G1 I: –4.92 (–37.37, 27.54) G2 I: 6.75 (–34.21, 47.70) *p*=.61 G1 L: 43.91 (6.08, 81.73) G2 L: 51.70 (26.76, 76.63) *p*=.69	**Withdrawals:** Upon completion of trial, 56 of 113 entered 12 mo observational followup study. 52 of 56 had 12-mo followup visit **Adherence:** NA **Actual nutrient intake at 12-mo followup:** Sodium, mg (SD) G1: 2599.68 (1110.06) G2: 2214.69 (735.98)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
TOHP II The Trials of Hypertension Prevention Collaborative Research Group, 1997[54]; Kumanyika et al., 2005[58]; Cook et al., 2005[59] 2 X 2 factorial RCT USA, 9 academic medical centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration** **Treatment:** 36–48 mo **Additional Followup after Treatment:** None **Intervention delivery:** Individual and group counseling through in-person, telephone, and mail contact **Intensive phase:** Groups of 11 to 34, counseled weekly for 10 weeks; primary goal was to provide core knowledge and behavioral skills to make and maintain reductions in Na intake. **Transitional phase:** 4 monthly sessions; designed to prevent relapse and ease transition to less frequent contact **Final extended phase:** 1 or 2 monthly contacts; 3 to 6 refresher sessions were offered; goal: maintain participants' behavior changes **Goal for G1:** Reduction in sodium intake of 80 mmol per day, or less.	Adults 30–54 years, not taking antihypertensive drugs, SBP<140 mmHg, DBP 83 to 89 mmHg, BMI representing 110% to 165% of desirable body weight ***n***: G1: 594 G2: 596 **Age:** G1: 44.2 (6.1) G2: 43.2 (6.1) **Sex, % male:** G1: 64.8 G2: 68.3 **Race/ethnicity:** White, % G1: 81.1 G2: 79.5 Black, % G1: 16.8 G2: 17.3 **Weight, kg (SD):** G1: 94.0 (14.3) G2: 93.6 (13.5) **BMI:** NR **Mean SBP, mmHg (SD):** G1: 127.7 (6.6) G2: 127.3 (6.4) **Mean DBP, mmHg (SD):** G1: 86.1 (1.9) G2: 85.8 (1.9) **Urinary sodium, mmol/d (SD):** G1: 186.1 (80.7) G2: 188.0 (80.9)	**6 mo** **SBP mean change, mmHg (SD):** G1: –5.1 (8.6) G2: –2.2 (8.1) **SBP net change, mmHg (SE):** G1 vs. G2: –2.9 (0.5) *p*<.001 **DBP mean change, mmHg (SD):** G1: –4.4 (6.7) G2: –2.8 (6.1) **DBP net change, mmHg (SDE):** G1 vs. G2: –1.6 (0.4) *p*<.001 **18 mo** **SBP mean change, mmHg (SD):** G1: –3.8 (8.2) G2: –1.8 (7.0) **SBP net change, mmHg (SE):** G1 vs. G2: –2.0 (0.5) *p*<.001 **DBP mean change, mmHg (SD):** G1: –4.4 (6.5) G2: –3.2 (5.8) **DBP net change, mmHg (SE):** G1 vs. G2: –1.2 (0.4) *p*=.002 **36 mo** **SBP mean change, mmHg (SD):** G1: –0.7 (9.0) G2: +0.6 (8.5) **SBP net change, mmHg (SE):** G1 vs. G2: –1.2 (0.5) *p*=.02	**6 mo** ***n***: G1: 147 G2: 126 **24-h urinary Na mean change, mmol/d (SD):** G1: –75.5 (81.5) G2: –24.5 (10.38) **24-h urinary Na net difference, mmol/d 95% CI):** G1 vs. G2: –51.0 (28.9, 73.0) **18 mo** ***n***: G1: 450 G2: 467 **24-h urinary Na mean change, mmol/d (SD):** G1: –59.5 (91.7) G2: –16.8 (94.8) **24-h urinary Na net difference, mmol/d 95% CI):** G1 vs. G2: –42.7 (30.6, 54.8) **36 mo** ***n***: G1: 470 G2: 482 **24-h urinary Na mean change, mmol/d (SD):** G1: –50.9 (86.3) G2: –10.5 (88.5) **24-h urinary Na net difference, mmol/d 95% CI):** G1 vs. G2: –40.4 (29.3, 51.5)	**Withdrawals:** Proportion of participants with BP readings at all 3 scheduled visits at or after 36 mo ranged from 88.9% to 91.6% Completion of sodium excretion data at 36 mo ranged from 79.1% to 80.9% **Adherence:** Adherence measures such as food diaries and overnight urine samples were not used as study outcome data. **Actual nutrient intake:** 24-h dietary recall and 3-day food record information was obtained at 18- and 36-mo for randomly selected samples.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
			DBP mean change, mmHg (SD): G1: –3.0 (6.5) G2: –2.4 (7.0) **DBP net change, mmHg (SDE):** G1 vs. G2: –0.7 (0.4) *p*=.10		
TONE Whelton et al., 1998[53]; Appel et al., 2001[55]; Espeland et al., 2002[56] RCT USA, 4 academic health centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:** Mean of 27.8 mo (range 15.6 to 35.9 mo) after randomization **Intervention delivery:** In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 4-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. **Goal for sodium reduction:** Achieving and maintaining a 24-h dietary sodium intake of 80 mmol (1,800 mg) or less G2 received no study-related counseling in lifestyle change; were invited to meetings on topics unrelated to trial goals.	Adults 60 to 80 years; had baseline BP <145/85 mmHg while on a single antihypertensive medication ***n:*** G1: 340 G2: 341 **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:** 47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR **SBP on medication, mean mmHg (SD):** 128.0 (9.4) **DBP on medication, mean mmHg (SD):** 71.3 (7.3) **Urinary sodium, mean mmol/day (SD):** G1: 144 (53) G2: 145 (55)	**Mean interval, 3.5 mo (baseline to visit prior to medication withdrawal)** **SBP change, mean mmHg (SD):** G1: –4.6 (11.3) G2: –0.4 (10.5) **SBP between-group difference, mean mmHg (95% CI):** –4.3 (–6.0, –2.5) *p*<.001 **DBP change, mean mmHg (SD):** G1: –2.2 (8.0) G2: –0.2 (7.0) **DBP between-group difference, mean mmHg (95% CI):** –2.0 (–3.2, –0.8) *p*=.001 **30 mo** **Proportion without an end point, %:** G1: 36 G2: 21 **Relative HR (95% CI) for end points associated with assignment G1 vs. G2:** 0.68 (0.56, 0.82) *p*<.001	**30 mo** **24-h urinary Na change, mean mmol (SD):** G1: –45 (55.8) G2: –5 (50.0) **24-h urinary Na change between-group difference, mean mmol (95% CI):** –40 (–48, –32) *p*<.001	**Withdrawals:** Attended final study visit (15–37 mo) G1: 91% G2: 92% **Adherence:** NR **Daily nutrient intake:** Mean between-group difference (95% CI) **Total energy, kcal:** –119 (–197, –41) **Total fat, g:** –5.8 (–10.1, –1.5) **Monounsaturated fat, g:** –2.2 (–4.0, –0.4) **Polyunsaturated fat, g:** –1.1 (–2.3, 0.1) **Protein, g:** –1.3 (–5.0, 2.4) **CHO, g:** –0.2 (–11.6, 11.2) **Potassium, mg:** 160 (25, 295)

CQ2 Summary Table C–2. Different Levels of Sodium

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
DASH-Sodium Sacks et al., 2001[33]; Svetkey et al., 2004[57]; Bray et al., 2004[48]; Vollmer et al., 2001[49] RCT, crossover USA, outpatient medical centers Good	**Treatment groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Age, mean yr (SD):** G1: 47 (10) G2: 49 (10) **Sex, *n* (%):** Female G1: 123 (59) G2: 111 (54) **Race/ethnicity, *n** (%):** Black G1: 118 (57) G2: 114 (56) Non-Hispanic White G1: 83 (40) G2: 81 (40) Asian or other G1: 6 (3) G2: 10 (5) **Weight:** NR **Mean BMI, kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Mean SBP, mmHg (SD):** G1: 134 (10) G2: 135 (10) **Mean DBP, mmHg (SD):** G1: 86 (5) G2: 86 (4)	**After 30 days of treatment** **SBP mean change, mmHg (95% CI):** G1 I vs. G1 H: –1.3 (–2.6, 0.0) *p*<.05 G1 L vs. G1 I: –1.7 (–3.0, –0.4) *p*<.01 G2 H vs. G2 L: –6.7 (–5.4, –8.0) *p*<.001 G2 I vs. G2 H: –2.1 (–3.4, –0.8) *p*<.001 **SBP mean change, mmHg (95% CI):** G2 L vs. G2 I: –4.6 (–5.9, –3.2) *p*<.001 G2 H vs. G2 L: –3.0 (–1.7, –4.3) *p*<.001 G1 H vs. G2 H: –5.9 (–8.0, –3.7) *P*<.001 G1 I vs. G2 I: –5.0 (–7.6, –2.5) *p*<.001 G1 L vs. G2 L: –2.2 (–4.4, –0.1) *p*<.05 G1 L vs. G2 H: –8.9 (–6.7, –11.1) *p*<.001 **DBP mean change, mmHg (95% CI):** G1 I vs. G1 H: –0.6 (–1.5, 0.2) *p*=NS G1 L vs. G1 I: –1.0 (–1.9, –0.1) *p*<.01 G1 H vs. G1 L: –1.6 (–0.8, –2.5) *p*<.001 G2 I vs. G2 H: –1.1 (–1.9, –0.2) *p*<.01 G2 L vs. G2 I: –2.4 (–3.3, –1.5) *p*<.001	**After 30 days of treatment** **Urinary Na, mmol/day (SD):** G1 H: 144 (58) G1 I: 107 (52) G1 L: 67 (46) G2 H: 141 (55) G2 I: 106 (44) G2 L: 64 (37) **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, *n* (%):** G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables, dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Nutrient intake:** Actual nutrient intake for sodium is reported as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		Urinary sodium mmol/day (SD): G1: 158 (79) G2: 152 (72)	G2 H vs. G2 L: –3.5 (–2.6, –4.3) *p*<.001 G1 H vs. G2 H: –2.9 (–4.3, –1.5) *p*<.001 G1 I vs. G2 I: –2.5 (–4.1, –0.8) *p*<.01 G1 L vs. G2 L: –1.0 (–2.5, 0.4) *p*=NS **DBP mean change, mmHg (95% CI):** G1L vs. G2 H: –4.5 (–3.1, –5.9) *p*<.001 For changes in subgroups, see Summary Tables on subpopulations (i.e., race, sex, hypertension status)		

CQ2 Summary Table C–3. Sodium and Other Dietary Changes

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Actual Nutrient Intake
Charlton et al., 2008[62] RCT South Africa, Cape Town township Good	**Treatment groups:** G1: Food-based intervention G2: Control G1: Intervention comprised 5 commonly consumed food items (brown bread, margarine, stock cubes, soup mixes, and Aromat) modified in Na, K, Mg and Ca content plus a salt replacement and 500 ml of maas (fermented milk) G2: Control diet provided the same foods but of standard commercial composition, as well as artificially sweetened cold drink instead of maas. Based on laboratory-determined chemical food analyses, compared to control foods, the intervention foods were planned to provide 41% less Na (100.3 vs. 170.3 mmol/d), 826% more K (70.9 vs. 8.6 mmol/d), 388% more Ca (857 vs. 221 mg/d) and 368% more Mg (13.8 v. 3.7 mmol/d) **Duration:** **Run-in:** 3 weeks **Treatment:** 8 weeks **Intervention delivery:** Subjects were instructed to consume their usual amounts of food and sufficient food was provided for the whole family. A single dietitian was responsible for food-packing and all food was locked and sealed in large shopping bags, labeled only with participants' names and contact details. A driver delivered the food three times a week.	Black residents of a Cape Town township, 50 to 75 years of age, with drug-treated mild-to-moderate hypertension (SBP ≤160 mmHg, DBP ≤95 mmHg) ***n***: G1: 47 G2: 45 **Age, mean yr (SD):** G1: 61.8 (6.6) G2: 60.4 (7.4) **Sex, male, *n*:** G1: 7 G2: 6 **Sex, female, *n*:** G1: 33 G2: 34 **Race, % Black:** G1: 100 G2: 100 **Weight, mean kg (SD):** G1: 83.3 (13.7) G2: 88.8 (15.5) **BMI, kg/m² (SD):** G1: 32.9 (5.8) G2: 35.3 (6.0) **Mean SBP, mmHg (SD):** G1: 133.9 (14.6) G2: 135.4 (16.7) **Mean DBP, mmHg (SD):** G1: 79.8 (8.6) G2: 82.3 (7.5)	**Mean net difference (G1–G2), mmHg (95% CI)** **SBP, Office:** –6.194 (–11.442, –0.945) *p*=.021 **DBP, Office:** –0.595 (–3.019, 1.829) **24-h ABPM, Avg SBP:** –4.527 (–9.047, –0.006) *p*=.050 **24-h ABPM, Avg DBP:** –2.494 (–5.160, 0.173) *p*=.066	**Mean within group change from baseline** **Urinary Na, mmol/24h (SD):** G1: –14.6 (54.4) G2: –5.9 (54.3) **Urinary K, mmol/24h (SD):** G1: 20.0 (22.7) G2: –4.6 (14.8) **Urinary Mg, mmol/24h (SD):** G1: +0.88 (1.20) G2: +0.19 (0.81) **Urinary Ca, mmol/24h (SD):** G1: +0.27 (1.00) G2: +0.32 (1.11) **Mean between group difference (G1–G2)** **Urinary Na, mmol/24h (SD):** –8.7 (46.9) **Urinary K, mmol/24h (SD):** +24.6 (16.5) *p*<.001 **Urinary Mg, mmol/24h (SD):** +0.68 (0.88) *p*<.05 **Urinary Ca, mmol/24h (SD):** –0.05 (0.91)	**Withdrawals, *n* (%):** G1: 7 (14.9) G2: 5 (11.1) **Adherence:** Dietary compliance was monitored using data from 24-h recalls and 24-h urinary electrolyte concentrations; returned salt and Aromat shakers were weighed weekly. **Reported daily dietary intake: mean difference (G1–G2)** **Na, mg (SD):** –1167 (1532) *p*<.01 **K, mg (SD):** 867 (890) *p*<.0001 **Mg, (SD):** 71 (89) *p*<.001 **Ca, mg (SD):** 310 (392) *p*<.001

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Actual Nutrient Intake
China Salt Substitute Study China Salt Study Collaborative Group, 2007[61] RCT China, 39 sites distributed between 6 regional coordinating centers Good	**Treatment groups:** G1: Salt substitute G2: Normal salt G1: Salt substitute was 65% Na Cl, 25% K Cl and 10% Mg sulphate G2: normal salt was 100% Na Cl **Duration** **Run-in:** 4 week run-in on salt substitute **Treatment:** 12 mo **Additional followup time after treatment:** none **Characteristics of treatment delivery:** Participants were instructed to use study salt for all food preparation throughout the study duration; existing salt and foods previously pickled in salt were not removed from participants' households. Salt (substitute & normal) was delivered in identical 1 kg bags; up to 3 kg/mo available to each randomized participant to cover all household uses.	Adult males and females, living in rural China, at elevated risk of future vascular disease ***n*:** G1: 306 G2: 302 **Age, mean yr (SD):** G1: 59 (10.0) G2: 61 (9.7) **Sex, female, *n* (%):** G1:166 (52) G2:174 (58) **Race/ethnicity:** All were "rural Chinese" **Weight:** NR **BMI, mean kg/m² (SD):** G1: 26 (3.6) G2: 25 (3.9) **Mean SBP, mmHg (SD):** G1: 159 (25) G2: 159 (26) **Mean DBP, mmHg (SD):** G1: 93 (14) G2: 93 (14) **Urinary sodium, mean mmol/day (IQR):** G1: 151 (92–201) G2: 154 (94–200)	**SBP:** SBP lower in G1 vs. G2 at 6, 9, and 12 mo visits; (data reported in figure) *p*<.002) Maximum net reduction achieved at 12 mo: 5.4 (2.3, 8.5) **Over 12 mo:** **SBP mean difference, mmHg (95% CI):** G1 vs. G2: 3.7 (1.6, 5.9) *p*<.001 **DBP:** No differences between groups at any time (*p*>.20)	No significant differences between groups in first morning urine sodium concentrations at 6 mo or 12 mo G1 had significantly higher first morning urine concentrations of potassium at 6 mo and 12 mo **At 6 mo:** G1 vs. G2: 8.6 mmol/L 95% CI: (-1.1, 18.2) **At 12 mo:** G1 vs. G2: 8.0 mmol/L 95% CI: (-3.3, 19.2)	**Withdrawals, *n* (%):** G1: 14 (4.6) G2: 9 (3) **Nutrient intake:** Concentrations of sodium and potassium were measured.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Actual Nutrient Intake
China Salt Substitute Study Subgroup Analysis Hu et al., 2009[60] Subgroup analysis of RCT China, 2 sites (overall RCT conducted in 39 sites distributed among 6 regional coordinating centers) Fair	**Treatment groups:** G1: Salt substitute G2: Normal salt G1: Salt substitute was 65% Na Cl, 25% K Cl and 10% Mg sulphate G2: normal salt was 100% Na Cl **Duration:** **Run-in:** 4 week run-in on salt substitute **Treatment:** 12 mo **Additional followup time after treatment:** none **Characteristics of treatment delivery:** Participants were instructed to use study salt for all food preparation throughout the study duration; existing salt and foods previously pickled in salt were not removed from participants' households	Adult males and females, living in rural China, at elevated risk of future vascular disease ***n*:** G1: 95 G2: 97 **Age, mean yr (SD):** G1: 59 (10.0) G2: 59 (9.1) **Sex, male, *n* (%):** G1: 43 (46) G2: 33 (35) **Race/ethnicity:** All were "rural Chinese" **Weight:** NR **BMI, mean kg/m² (SD):** G1: 27 (3.9) G2: 26 (3.8) **Mean SBP, mmHg (SD):** G1: 149.4 (22.3) G2: 150 24.2) **Mean DBP, mmHg (SD):** G1: 91.0 (12.8) G2: 91.8 (13.3) **Urinary sodium, mean mmol/day:** NR	**At 12 mo** **Change in peripheral SBP, mmHg (SD):** G1: –0.2 (18.1) G2: 6.9 (23.0) *p*=.23 **Change in peripheral DBP, mmHg (SD):** G1: 0.1 (10.6) G2: 2.1 (11.4) *p*=.227 **Change in central SBP, mmHg (SD):** G1: 1.1 (17.4) G2: 7.4 (21.9) *p*=.032 **Change in central DBP, mmHg (SD):** G1: 0.2 (10.8) G2: 2.3 (11.8) *p*=.210	NR	**Withdrawals, *n* (%):** G1: 2 (2.1) G2: 3 (31) **Adherence:** NR **Nutrient intake:** Concentrations of sodium and potassium were measured.
DASH-Sodium Sacks et al., 2001[33] RCT, crossover USA, outpatient medical centers Good	**Treatment groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration** **Run-in:** 2 weeks	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** G1: 208 G2: 204 **Age, mean yr (SD):**	**After 30 days of intervention** **SBP mean change, mmHg (95% CI):** G1 I vs. G1 H: –1.3 (–2.6, 0.0) *p*<.05 G1 L vs. G1 I: –1.7 (–3.0, –0.4) *p*<.01 G2 H vs. G2 L: –6.7 (–5.4, –8.0) *p*<.001	**After 30 days of intervention** **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, *n* (%):** G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables,

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Actual Nutrient Intake
	Treatment: 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	G1: 47 (10) G2: 49 (10) **Sex, *n* (%)** Female G1: 123 (59) G2: 111 (54) **Race/ethnicity, *n* (%)** Black G1: 118 (57) G2: 114 (56) Non-Hispanic White G1: 83 (40) G2: 81 (40) Asian or other G1: 6 (3) G2: 10 (5) **Weight:** NR **Mean BMI, kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Mean SBP, mmHg (SD):** G1: 134 (10) G2: 135 (10) **Mean DBP, mmHg (SD):** G1: 86 (5) G2: 86 (4) **Urinary sodium mmol/day (SD):** G1: 158 (79) G2: 152 (72)	G2 I vs. G2 H: –2.1 (–3.4, –0.8) *p*<.001 G2 L vs. G2 I: –4.6 (–5.9, –3.2) *p*<.001 G2 H vs. G2 L: –3.0 (–1.7, –4.3) *p*<.001 G1 H vs. G2 H: –5.9 (–8.0, –3.7) *p*<.001 **SBP mean change, mmHg (95% CI):** G1 I vs. G2 I: –5.0 (–7.6, –2.5) *p*<.001 G1 L vs. G2 L: –2.2 (–4.4, –0.1) *p*<.05 G1 L vs. G2 H: –8.9 (–6.7, –11.1) *p*<.001 **DBP mean change, mmHg (95% CI):** G1 I vs. G1 H: –0.6 (–1.5, 0.2) *p*=NS G1 L vs. G1 I: –1.0 (–1.9, –0.1) *p*<.01 G1 H vs. G1 L: –1.6 (–0.8, –2.5) *p*<.001 G2 I vs. G2 H: –1.1 (–1.9, –0.2) *p*<.01 G2 L vs. G2 I: –2.4 (–3.3, –1.5) *p*<.001 G2 H vs. G2 L: –3.5 (–2.6, –4.3) *p*<.001 G1 H vs. G2 H: –2.9 (–4.3, –1.5) *p*<.001 G1 I vs. G2 I: –2.5 (–4.1, –0.8) *p*<.01 G1 L vs. G2 L: –1.0 (–2.5, 0.4) *p*=NS G1L vs. G2 H: –4.5 (–3.1, –5.9) *p*<.001		dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.
TONE Whelton et al., 1998[53];	**Treatment groups:** G1: Sodium reduction	Adults 60 to 80 years; had baseline BP <145/85 mmHg	**Mean interval, 3.5 mo (baseline to visit prior to medication**	**30 mo** **24-h urinary Na change, mean mmol**	**Withdrawals:** Attended final study visit (15–37

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Actual Nutrient Intake
Appel et al., 2001[55]; Espeland et al., 2002[56] RCT USA, 4 academic health centers Good	G2: Usual care **Duration** Mean of 27.8 mo (range 15.6 to 35.9 mo) after randomization **Intervention delivery:** In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 4-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. Goal for sodium reduction: achieving and maintaining a 24-h dietary sodium intake of 80 mmol (1,800 mg) or less G2 received no study-related counseling in lifestyle change; were invited to meetings on topics unrelated to trial goals	while on a single antihypertensive medication. ***n*:** G1: 340 G2: 341 **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:** 47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR **SBP on medication, mean mmHg (SD):** 128.0 (9.4) **DBP on medication, mean mmHg (SD):** 71.3 (7.3) **Urinary sodium, mean mmol/day (SD):** G1: 144 (53) G2: 145 (55)	**withdrawal)** **SBP change, mean mmHg (SD):** G1: –4.6 (11.3) G2: –0.4 (10.5) **SBP between-group difference, mean mmHg (95% CI):** –4.3 (–6.0, –2.5) *p*<.001 **DBP change, mean mmHg (SD):** G1: –2.2 (8.0) G2: –0.2 (7.0) **DBP between-group difference, mean mmHg (95% CI):** –2.0 (–3.2, –0.8) *p*=.001 **30 mo** **Proportion without an end point, %:** G1: 36 G2: 21 **Relative HR (95% CI) for end points associated with assignment G1 vs. G2:** 0.68 (0.56, 0.82) *p*<.001	**(SD):** G1: –45 (55.8) G2: –5 (50.0) **24-h urinary Na change between-group difference, mean mmol (95% CI):** –40 (–48, –32) *p*<.001	mo) G1: 91% G2: 92% **Daily nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

CQ2 Summary Table C–4a. Sodium and Subpopulation: Sex

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
DASH-Sodium Subgroup analysis Sacks et al., 2001[33]; Bray et al., 2004[48]; Vollmer et al., 2001[49] RCT, crossover USA, outpatient medical centers Fair	**Treatment Groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** Men G1: 85 G2: 93 Women G1: 123 G2: 111 **Mean SBP, mmHg (SD):** Men G1 H: 125 (11) G1 I: 124 (11) G1 L: 123 (10) G2 H: 131 (11) G2 I: 127 (10) G2 L: 125 (9) Women G1 H: 128 (11) G1 I: 127 (13) G1 L: 124 (11) G2 H: 135 (12) G2 I: 133 (13) G2 L: 127 (11) **Mean DBP, mmHg (SD):** Men G1 H: 81 (7) G1 I: 81 (7) G1 L: 80 (6) G2 H: 84 (7) G2 I: 82 (6) G2 L: 81 (6) **Mean DBP, mmHg (SD):** Women	**Men** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.7 (–3.4, 0.0) *p*<.10 G1 L vs. G1 I: –0.7 *p*=NR (NS) G1 I vs. G1 H: –0.9 *p*=NR (NS) G2 L vs. G2 H: –5.7 (–7.3, –4.1) *p*<.01 G2 L vs. G2 I: –3.1 *p*<.01 G2 I vs. G2 H: –2.6 *p*<.01 G1 H vs. G2 H: –5.1 (–7.7, –2.6) G1 L vs. G2 H: –6.8 (–9.3, –4.3) **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.6 *p*<.01 G1 L vs. G1 I: –0.7 *p*=NR (NS) G1 I vs. G1 H: –0.5 *p*=NR (NS) G2 L vs. G2 H: –3.2 *p*<.01 G2 L vs. G2 I: –1.9 *p*<.01 G2 I vs. G2 H: –1.4 *p*<.05 G1 H vs. G2 H: –2.7 (–4.4, –1.0) G1 L vs. G2 H: –4.2 (–5.9, –2.6) **Women** **Mean change (95% CI)* in SBP**	Not reported by subgroup **Overall:** **After 30 days of intervention** **Urinary Na, mmol/day (SD):** G1 H: 144 (58) G1 I: 107 (52) G1 L: 67 (46) G2 H: 141 (55) G2 I: 106 (44) G2 L: 64 (37) **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L: 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, *n* (%):** Not reported by subgroup Overall: G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables, dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion, which was not reported by subgroup.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		G1 H: 81 (7) G1 I: 80 (7) G1 L: 79 (7) G2 H: 83 (7) G2 I: 82 (7) G2 L: 80 (6) **Other baseline characteristics not reported by males or females separately.** **Overall sample characteristics:** Age, mean yr (SD): G1: 47 (10) G2: 49 (10) **Sex, *n* (%):** Female G1: 123 G2: 111 **Race/ethnicity, *n* (%):** Black G1: 118 (57) G2: 114 (56) **Non-Hispanic White** G1: 83 (40) G2: 81 (40) **Asian or other** G1: 6 (3) G2: 10 (5) **Mean BMI kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Urinary sodium mmol/day (SD):** G1: 158 (79) G2: 152 (72)	**by diet group + sodium reduction level:** G1 L vs. G1 H: –4.0 (–5.4, –2.5) *p*<.05 G1 L vs. G1 I: –2.4 *p*<.01 G1 I vs. G1 H: –1.6 *p*<.05 G2 L vs. G2 H: –7.5 (–9.0, –6.0) *p*<.01 G2 L vs. G2 I: –5.8 *p*<.01 G2 I vs. G2 H: –1.7 *p*<.05 G1 H vs. G2 H: –6.6 (–8.8, –4.3) G1 L vs. G2 H: –10.5 (–12.8, –8.2) *p*<.05 **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.7 (–2.6, –0.8) *p*<.01 G1 L vs. G1 I: –1.2 *p*<.05 G1 I vs. G1 H: –0.5 *p*=NR (NS) G2 L vs. G2 H: –3.7 (–4.7, –2.7) *p*<.01 G2 L vs. G2 I: –2.8 *p*<.01 **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G2 I vs. G2 H: –0.8 *p*<.10 G1 H vs. G2 H: –3.0 (–4.5, –1.5) G1 L vs. G2 H: –4.7 (–6.2, –3.2) 95% CI not reported for all comparisons		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
TOHP II The Trials of Hypertension Prevention Collaborative Research Group, 1997[54]; Kumanyika et al., 2005[58] 2 X 2 factorial RCT USA, 9 academic medical centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:** **Treatment:** 36–48 mo **Additional Followup after Treatment:** none **Intervention delivery:** Individual and group counseling through in-person, telephone, and mail contact **Intensive phase:** Groups of 11 to 34, counseled weekly for 10 weeks; primary goal was to provide core knowledge and behavioral skills to make and maintain reductions in Na intake. **Transitional phase:** 4 monthly sessions; designed to prevent relapse and ease transition to less frequent contact **Final extended phase:** 1 or 2 monthly contacts; 3 to 6 refresher sessions were offered; goal: maintain participants' behavior changes Goal for G1: reduction in sodium intake of 80 mmol per day or less	Adults 30–54 years, not taking antihypertensive drugs, SBP<140 mmHg, DBP 83 to 89 mmHg, BMI representing 110% to 165% of desirable body weight **Urinary sodium, mmol/d (SD):** Men G1: 203.8 (84.2) G2: 201.7 (84.1) Women G1: 153.4 (61.9) G2: 158.0 (64.1) Other baseline characteristics not reported by intervention group + males or females separately. **Overall sample characteristics:** ***n*:** G1: 594 G2: 596 **Overall sample characteristics:** **Age:** G1: 44.2 (6.1) G2: 43.2 (6.1) **Sex, % male:** G1: 64.8 G2: 68.3 **Race/ethnicity:** White, % G1: 81.1 G2: 79.5 Black, % G1: 16.8 G2: 17.3 **Weight, kg (SD):**	**6 Mo** **Black Men** **SBP mean change, mmHg (SD):** G1: –4.3 (9.1) G2: 0.5 (7.8) **SBP difference, mmHg (95% CI):** –4.8 (–8.6, –1.0) **DBP mean change, mmHg (SD):** G1: –3.4 (7.0) G2: –1.3 (7.2) **DBP difference, mmHg (95% CI):** –2.1 (–5.3, 1.1) **White Men** **SBP mean change, mmHg (SD):** G1: –4.6 (8.5) G2: –2.4 (7.8) **SBP difference, mmHg (95% CI):** –2.2 (–3.5, –0.9) **DBP mean change, mmHg (SD):** G1: –4.0 (6.6) G2: –3.2 (6.0) **DBP difference, mmHg (95% CI):** –0.9 (–1.9, 0.1) **Black Women** **SBP mean change, mmHg (SD):** G1: –5.9 (7.6) G2: –1.3 (9.5) **SBP difference, mmHg (95% CI):** –4.6 (–8.1, –1.1) **DBP mean change, mmHg**	**6 Mo** **Men** **24-h urinary Na mean change, mmol/D (SD):** G1: –82.1 (85.0) G2: –26.3 (116.5) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 55.8 (26.3, 85.2) **Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –62.5 (73.5) G2: –20.4 (–68.6) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 42.0 (11.8, 72.4) **18 Mo** **Men** **24-h urinary Na mean change, mmol/D (SD):** G1: –68.7 (99.7) G2: –15.0 (102.6) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 53.6 (37.7, 69.6) **Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –41.8 (70.8) G2: –20.8 (74.4) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 21.0 (4.4, 37.6) **36 mo** **Men** **24-h urinary Na mean change, mmol/D (SD):** G1: –60.1 (91.3) G2: –8.8 (95.2) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 51.3 (36.8, 65.8)	**Withdrawals:** Proportion of participants with BP readings at all 3 scheduled visits at or after 36 mo ranged from 88.9% to 91.6% Completion of sodium excretion data at 36 mo ranged from 79.1% to 80.9% **Adherence:** Adherence measures such as food diaries and overnight urine samples were not used as study outcome data. **Nutrient intake:** 24-h dietary recall and 3-day food record information was obtained at 18- and 36-mo for randomly selected samples.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 94.0 (14.3) G2: 93.6 (13.5) **BMI:** NR **Mean SBP, mmHg (SD):** G1: 127.7 (6.6) G2: 127.3 (6.4) **Mean DBP, mmHg (SD):** G1: 86.1 (1.9) G2: 85.8 (1.9)	**(SD):** G1: –5.4 (6.5) G2: –2.8 (7.2) **DBP difference, mmHg (95% CI):** –2.5 (–5.3, 0.2) **White Women** **SBP mean change, mmHg (SD):** G1: –6.3 (9.2) G2: –3.3 (8.3) **SBP difference, mmHg (95% CI):** –3.0 (–5.2, –0.8) **DBP mean change, mmHg (SD):** G1: –5.1 (6.9) G2: –2.7 (5.6) **DBP difference, mmHg (95% CI):** –2.3 (–3.9, –0.7) **18 Mo** **Black Men** **SBP mean change, mmHg (SD):** G1: –2.7 (11.1) G2: –1.3 (7.5) **SBP difference, mmHg (95% CI):** –1.4 (–5.9, 3.1) **DBP mean change, mmHg (SD):** G1: –4.5 (8.3) G2: –3.4 (6.4) **DBP difference, mmHg (95% CI):** –1.1 (–4.5, 2.4)	**Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –34.4 (73.8) G2: –14.6 (70.4) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 19.8 (3.6, 35.9)	

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			White Men **SBP mean change, mmHg (SD):** G1: –3.7 (7.9) G2: –2.2 (6.5) **SBP difference, mmHg (95% CI):** –1.5 (–2.7, –0.4) **DBP mean change, mmHg (SD):** G1: –4.0 (6.3) G2: –3.4 (5.8) **DBP difference, mmHg (95% CI):** –0.6 (–1.6, 0.4) **Black Women** **SBP mean change, mmHg (SD):** G1: –5.0 (8.6) G2: 0.2 (8.4) **SBP difference, mmHg (95% CI):** –5.2 (–8.7, –1.7) **DBP mean change, mmHg (SD):** G1: –5.6 (6.7) G2: –1.3 (7.1) **DBP difference, mmHg (95% CI):** –4.2 (–7.0, –1.4) **White Women** **SBP mean change, mmHg (SD):** G1: –4.1 (8.1) G2: –2.4 (7.4) **SBP difference, mmHg (95% CI):** –1.8 (–3.8, 0.2) **DBP mean change, mmHg**		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			(SD): G1: –4.9 (6.1) G2: –3.3 (5.3) **DBP difference, mmHg (95% CI):** –1.6 (–3.1, –0.1) **36 Mo** **Black Men** **SBP mean change, mmHg (SD):** G1: 2.2 (10.3) G2: 1.7 (7.4) **SBP difference, mmHg (95% CI):** 0.5 (–3.8, 4.9) **DBP mean change, mmHg (SD):** G1: –0.6 (8.1) G2: –1.9 (7.0) **DBP difference, mmHg (95% CI):** 1.4 (–2.2, 4.9) **White Men** **SBP mean change, mmHg (SD):** G1: –1.3 (8.5) G2: –0.3 (7.8) **SBP difference, mmHg (95% CI):** –1.1 (–2.4, 0.2) **DBP mean change, mmHg (SD):** G1: –3.0 (6.2) G2: –2.7 (7.1) **DBP difference, mmHg (95% CI):** –0.3 (–1.4, 0.8)		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			Black Women **SBP mean change, mmHg (SD):** G1: –1.0 (11.1) G2: 2.0 (9.2) **SBP difference, mmHg (95% CI):** –3.0 (–7.2 (1.3) **DBP mean change, mmHg (SD):** G1: –4.0 (8.2) G2: –1.6 (7.5) **DBP difference, mmHg (95% CI):** –2.4 (–5.7, 0.8) **White Women** **SBP mean change, mmHg (SD):** G1: 0.5 (8.9) G2: 2.1 (10.4) **SBP difference, mmHg (95% CI):** –1.5 (–4.0, 0.9) **DBP mean change, mmHg (SD):** G1: –3.4 (5.8) G2: –1.9 (6.8) **DBP difference, mmHg (95% CI):** –1.4 (–3.1, 0.2)		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
TONE Whelton et al., 1998[53]; Appel et al., 2001[55]; Espeland et al., 2002[56] RCT USA, 4 academic health centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:** **Treatment:** Average of 27.6 mo (range 15.6 to 35.9 mo) after randomization **Followup:** NR **Intervention delivery:** In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 3-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. Goal for sodium reduction: achieving and maintaining a 24-h dietary sodium intake of 80 mmol (1,800 mg) or less	Adults 60 to 80 years; had baseline BP <145/85 mmHg while on a single antihypertensive medication ***n*:** G1: 340 G2: 341 **Mean SBP, mmHg (SD):** Men G1: 129.0 (9.0) G2: 126.9 (9.7) Women G1: 127.7 (9.5) G2: 127.7 (8.9) **Mean DBP, mmHg (SD):** Men G1: 72.7 (6.6) G2: 72.2 (7.0) Women G1: 70.0 (8.1) G2: 70.4 (7.2) **Urinary sodium, mean mmol/day (SD):** Men G1: 162 (53) G2: 159 (55) Women G1: 125 (45) G2: 128 (48) Other baseline characteristics not reported by sex grouping. **Overall sample characteristics:** **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:**	**Mean interval, 3.5 mo** **Men** **SBP change, mean mmHg (SD):** G1: –5.6 (11.3) G2: –0.4 (9.5) **SBP between-group difference, mean mmHg (95% CI):** –5.2 (–7.5, –2.9) *p*<.001 **DBP change, mean mmHg (SD):** G1: –2.7 (7.7) G2: –0.1 (7.0) **DBP between-group difference, mean mmHg (95% CI):** –2.6 (–4.2, –1.0) *p*=.002 **Women** **SBP change, mean mmHg (SD):** G1: –3.7 G2: –0.4 **SBP between-group difference, mean mmHg (95% CI):** –3.4 (–6.0, –0.6) *p*=.02 **DBP change, mean mmHg (SD):** G1: –1.6 (8.2) G2: –0.3 (7.0) **DBP between-group difference, mean mmHg (95% CI):** –1.3 (–3.1, 0.4) *p*=.14	**30 mo** **Men** **24-h urinary Na change, mean mmol/L (SD):** G1: –59 (53.0) G2: –7 (53.6) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –53 (–64, –41) *p*<.001 **Women** **24-h urinary Na change, mean mmol/L (SD):** G1: –30 (55) G2: –3 (45) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –27 (–39, –16) *p*<.001	**Withdrawals, %:** Not reported by subgroup **Overall:** Attended final study visit (15–37 mo) G1: 91% G2: 92% **Adherence:** Not reported by subgroup **Daily nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR			

CQ2 Summary Table C–4b. Sodium and Subpopulation: Race/Ethnicity

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
DASH-Sodium Sacks et al., 2001[33]; Vollmer et al., 2001[49]; Bray et al., 2004[48] RCT, crossover USA, outpatient medical centers Fair	**Treatment groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** African American G1: 119 G2: 115 Non-African American G1: 89 G2: 89 **Mean SBP, mmHg (SD):** African American G1 H: 128 (11) G1 I: 127 (12) G1 L: 125 (11) G2 H: 134 (12) G2 I: 131 (12) G2 L: 126 (10) Non-African American G1 H: 125 (11) G1 I: 124 (11) G1 L: 123 (10) G2 H: 131 (11) G2 I: 129 (12) G2 L: 127 (10) **Mean DBP, mmHg (SD):** African American G1 H: 82 (7) G1 I: 81 (8) G1 L: 80 (6) G2 H: 84 (7) G2 I: 82 (6) G2 L: 80 (6) Non-African American G1 H: 80 (7)	**African American** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 L vs. G1 H: –3.6 (–5.1, –2.2) *p*<.01 G1 L vs. G1 I: –2.1 *p*<.01 G1 I vs. G1 H: –1.5 *p*<.05 G2 L vs. G2 H: –8.0 (–9.4, –6.5) *p*<.01 G2 L vs. G2 I: –5.7 *p*<.01 G2 I vs. G2 H: –2.2 *p*<.01 G1 H vs. G2 H: –59. (–8.2, –3.6) G1 L vs. G2 H: –9.6 (–11.8, –7.3) *p*=NR (NS) **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.9 (–2.9, –1.0) *p*<.01 G1 L vs. G1 I: –1.0 *p*<.05 G1 I vs. G1 H: –0.9 *p*<.10 G2 L vs. G2 H: –4.5 (–5.5, –3.6) *p*<.01 G2 L vs. G2 I: –3.0 *p*<.01 G2 I vs. G2 H: –1.5 *p*<.01 G1 H vs. G2 H: –3.1 (–4.6, –1.6) G1 L vs. G2 H: –5.0 (–6.5, –3.6)	Not reported by subgroup **Overall:** **After 30 days of intervention** **Urinary Na, mmol/day (SD):** G1 H: 144 (58) G1 I: 107 (52) G1 L: 67 (46) G2 H: 141 (55) G2 I: 106 (44) G2 L: 64 (37) **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, *n* (%):** Not reported by subgroup **Overall:** G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables, dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Nutrient intake:** Nutrient intake for sodium is reflected as urinary sodium excretion, which was not reported by subgroup.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		G1 I: 80 (7) G1 L: 79 (6) G2 H: 83 (7) G2 I: 82 (6) G2 L: 81 (6) **Other baseline characteristics not reported by race/ethnicity subgroup.** **Overall sample characteristics:** **Age, mean yr (SD):** G1: 47 (10) G2: 49 (10) **Sex, *n* (%)** Female G1: 123 (59) G2: 111 (54) **Race/ethnicity, *n** (%)** Black G1: 118 (57) G2: 114 (56) Non-Hispanic white G1: 83 (40) G2: 81 (40) Asian or other G1: 6 (3) G2: 10 (5) **Weight:** NR **Mean BMI, kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Urinary sodium mmol/day (SD):** G1: 158 (79) G2: 152 (72)	*p*=NR (NS) **Non-African American** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 L vs. G1 H: –2.2 (–3.8, –0.5) *p*<.01 G1 L vs. G1 I: –1.3 *p*=NR (NS) **Non-African American** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 I vs. G1 H: –0.9 *p*=NR (NS) G2 L vs. G2 H: –5.1 (–6.7, –3.4) *p*<.01 G2 L vs. G2 I: –3.0 *p*<.01 G2 I vs. G2 H: –2.1 *p*<.05 G1 H vs. G2 H: –5.6 (–8.1, –3.0) G1 L vs. G2 H: –7.8 (–10.3, –5.2) *p*=NR (NS) **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.3 (–2.4, –0.2) *p*<.05 G1 L vs. G1 I: –1.0 *p*<.10 G1 I vs. G1 H: –0.3 *p*=NR (NS) G2 L vs. G2 H: –2.2 (–3.2, –1.1) *p*<.01 G2 L vs. G2 I: –1.6 *p*<.01 G2 I vs. G2 H: –0.6 *p*=NR (NS) G1 H vs. G2 H: –2.4 (–4.1, –0.8)		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			G1 L vs. G2 H: –3.7 (–5.4, –2.0) *p*=NR (NS)		
TOHP II Kumanyika et al., 2005[58] RCT, 2 X 2 factorial USA, 9 academic medical centers Fair	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:** **Treatment:** 36–48 mo **Additional Followup after Treatment:** none **Intervention delivery:** Individual and group counseling through in-person, telephone, and mail contact. **Intensive phase:** Groups of 11 to 34, counseled weekly for 10 weeks; primary goal was to provide core knowledge and behavioral skills to make and maintain reductions in Na intake. **Transitional phase:** 4 monthly sessions; designed to prevent relapse and ease transition to less frequent contact **Final extended phase:** 1 or 2 monthly contacts; 3 to 6 refresher sessions were offered; goal: maintain participants' behavior changes **Goal for G1:** Reduction in sodium intake of 80 mmol per day or less	Adults 30–54 years, not taking antihypertensive drugs, SBP<140 mmHg, DBP 83 to 89 mmHg, BMI representing 110% to 165% of desirable body weight **Baseline characteristics not reported by intervention group + race/ethnicity separately.** **Overall sample characteristics:** ***n*:** G1: 594 G2: 596 **Age:** G1: 44.2 (6.1) G2: 43.2 (6.1) **Sex, % male:** G1: 64.8 G2: 68.3 **Race/ethnicity:** White, % G1: 81.1 G2: 79.5 Black, % G1: 16.8 G2: 17.3 **Weight, kg (SD):** G1: 94.0 (14.3) G2: 93.6 (13.5) **BMI:** NR **Mean SBP, mmHg (SD):** G1: 127.7 (6.6) G2: 127.3 (6.4)	**6 Mo** **Black Men** **SBP mean change, mmHg (SD):** G1: –4.3 (9.1) G2: 0.5 (7.8) **SBP difference, mmHg (95% CI):** –4.8 (–8.6, –1.0) **DBP mean change, mmHg (SD):** G1: –3.4 (7.0) G2: –1.3 (7.2) **DBP difference, mmHg (95% CI):** –2.1 (–5.3, 1.1) **White Men** **SBP mean change, mmHg (SD):** G1: –4.6 (8.5) G2: –2.4 (7.8) **SBP difference, mmHg (95% CI):** –2.2 (–3.5, –0.9) **DBP mean change, mmHg (SD):** G1: –4.0 (6.6) G2: –3.2 (6.0) **DBP difference, mmHg (95% CI):** –0.9 (–1.9, 0.1) **Black Women** **SBP mean change, mmHg (SD):** G1: –5.9 (7.6)	**6 Mo** **Black Men** **24-h urinary Na mean change, mmol/D (SD):** G1: –82.8 (101.8) G2: –50.9 (198.2) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 31.9 (–117.4, 181.3) **White Men** **24-h urinary Na mean change, mmol/d (SD):** G1: –82.0 (84.6) G2: –21.1 (96.9) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 60.9 (32.1, 89.7) **Black Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –29.4 (67.5) G2: –7.0 (82.5) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 22.4 (–43.4, 88.3) **White Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –71.9 (73.9) G2: –27.9 (60.1) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 44.0 (8.7, 79.3) **18 Mo** **Black Men** **24-h urinary Na mean change, mmol/D (SD):** G1: –58.1 (72.9) G2: –8.2 (145.5)	**Withdrawals:** Proportion of participants with BP readings at all 3 scheduled visits at or after 36 mo ranged from 88.9% to 91.6% Completion of sodium excretion data at 36 mo ranged from 79.1% to 80.9% **Adherence:** Adherence measures such as food diaries were not used as study outcome data. **Nutrient intake:** The primary measure of sodium intake was sodium excretion in 24-h urine samples.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		Mean DBP, mmHg (SD): G1: 86.1 (1.9) G2: 85.8 (1.9) **Urinary sodium:** G1: 186.1 (80.7) G2: 188.0 (80.9)	G2: –1.3 (9.5) **SBP difference, mmHg (95% CI):** –4.6 (–8.1, –1.1) **DBP mean change, mmHg (SD):** G1: –5.4 (6.5) G2: –2.8 (7.2) **DBP difference, mmHg (95% CI):** –2.5 (–5.3, 0.2) **White Women** **SBP mean change, mmHg (SD):** G1: –6.3 (9.2) G2: –3.3 (8.3) **SBP difference, mmHg (95% CI):** –3.0 (–5.2, –0.8) **DBP mean change, mmHg (SD):** G1: –5.1 (6.9) G2: –2.7 (5.6) **DBP difference, mmHg (95% CI):** –2.3 (–3.9, –0.7) **18 Mo** **Black Men** **SBP mean change, mmHg (SD):** G1: –2.7 (11.1) G2: –1.3 (7.5) **SBP difference, mmHg (95% CI):** –1.4 (–5.9, 3.1) **DBP mean change, mmHg (SD):** G1: –4.5 (8.3)	**24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 49.9 (–11.4, 111.2) **White Men** **24-h urinary Na mean change, mmol/d (SD):** G1: –71.1 (101.9) G2: –14.9 (97.1) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 56.1 (39.2, 73.0) **Black Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –35.9 (74.2) G2: –20.9 (51.3) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 15.0 (–14.6, 44.6) **White Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –43.2 (69.5) G2: –22.8 (80.8) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 20.4 (0.2, 40.7) **36 Mo** **Black Men** **24-h urinary Na mean change, mmol/D (SD):** G1: –49.4 (92.1) G2: 25.2 (76.3) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 74.6 (–37.0, 69.0) **White Men** **24-h urinary Na mean change, mmol/d (SD):** G1: –61.5 (91.8) G2: –13.4 (97.2) **24-h urinary Na net difference, mmol/d (95%**	

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			G2: –3.4 (6.4) **DBP difference, mmHg (95% CI):** –1.1 (–4.5, 2.4) **White Men** **SBP mean change, mmHg (SD):** G1: –3.7 (7.9) G2: –2.2 (6.5) **SBP difference, mmHg (95% CI):** –1.5 (–2.7, –0.4) **DBP mean change, mmHg (SD):** G1: –4.0 (6.3) G2: –3.4 (5.8) **DBP difference, mmHg (95% CI):** –0.6 (–1.6, 0.4) **Black Women** **SBP mean change, mmHg (SD):** G1: –5.0 (8.6) G2: 0.2 (8.4) **SBP difference, mmHg (95% CI):** –5.2 (–8.7, –1.7) **DBP mean change, mmHg (SD):** G1: –5.6 (6.7) G2: –1.3 (7.1) **DBP difference, mmHg (95% CI):** –4.2 (–7.0, –1.4) **White Women** **SBP mean change, mmHg (SD):** G1: –4.1 (8.1)	**CI):** G1 vs. G2: 48.0 (32.4, 64.0) **Black Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –26.7 (86.0) G2: –5.5 (73.9) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 21.3 (–14.0, 56.5) **White Women** **24-h urinary Na mean change, mmol/D (SD):** G1: –37.0 (69.0) G2: –18.6 (70.0) **24-h urinary Na net difference, mmol/d (95% CI):** G1 vs. G2: 18.4 (0.0, 36.8)	

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			G2: –2.4 (7.4) **SBP difference, mmHg (95% CI):** –1.8 (–3.8, 0.2) **DBP mean change, mmHg (SD):** G1: –4.9 (6.1) G2: –3.3 (5.3) **DBP difference, mmHg (95% CI):** –1.6 (–3.1, –0.1) **36 Mo** **Black Men** **SBP mean change, mmHg (SD):** G1: 2.2 (10.3) G2: 1.7 (7.4) **SBP difference, mmHg (95% CI):** 0.5 (–3.8, 4.9) **DBP mean change, mmHg (SD):** G1: –0.6 (8.1) G2: –1.9 (7.0) **DBP difference, mmHg (95% CI):** 1.4 (–2.2, 4.9) **White Men** **SBP mean change, mmHg (SD):** G1: –1.3 (8.5) G2: –0.3 (7.8) **SBP difference, mmHg (95% CI):** –1.1 (–2.4, 0.2) **DBP mean change, mmHg (SD):** G1: –3.0 (6.2)		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			G2: –2.7 (7.1) **DBP difference, mmHg (95% CI):** –0.3 (–1.4, 0.8) **Black Women** **SBP mean change, mmHg (SD):** G1: –1.0 (11.1) G2: 2.0 (9.2) **SBP difference, mmHg (95% CI):** –3.0 (–7.2 (1.3) **DBP mean change, mmHg (SD):** G1: –4.0 (8.2) G2: –1.6 (7.5) **DBP difference, mmHg (95% CI):** –2.4 (–5.7, 0.8) **White Women** **SBP mean change, mmHg (SD):** G1: 0.5 (8.9) G2: 2.1 (10.4) **SBP difference, mmHg (95% CI):** –1.5 (–4.0, 0.9) **DBP mean change, mmHg (SD):** G1: –3.4 (5.8) G2: –1.9 (6.8) **DBP difference, mmHg (95% CI):** –1.4 (–3.1, 0.2)		
TONE Whelton et al., 1998[53]; Appel et al., 2001[55]	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:**	Adults 60 to 80 years; had baseline BP<145/85 mmHg while on a single antihypertensive	**Mean interval, 3.5 mo** **African American** **SBP change, mean mmHg**	Not reported by race/ethnicity grouping alone **30 mo** **African American Men**	**Withdrawals, %:** Not reported by subgroup Overall: Attended final study visit

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
RCT USA, 4 clinical centers Fair	**Treatment:** Average of 27.6 mo (range 15.6 to 35.9 mo) after randomization **Followup:** NR **Intervention delivery:** In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 3-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. **Goal for sodium reduction:** Achieving and maintaining a 24-h dietary sodium intake of 80 mmol (1,800 mg) or less	medication ***n*:** G1: 340 G2: 341 **Mean SBP, mmHg (SD):** African American G1: 125.6 (7.6) G2: 127.3 (8.4) Non-African American G1: 129.2 (9.5) G2: 127.2 (9.7) **Mean DBP, mmHg (SD):** African American G1: 71.6 (6.7) G2: 70.2 (7.5) Non-African American G1: 71.3 (7.7) G2: 71.8 (7.0) **Urinary sodium, mean mmol/day (SD):** Other baseline characteristics not reported by race/ethnicity grouping. **Overall sample characteristics:** **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:** 47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR **SBP on medication, mean mmHg (SD):**	**(SD):** G1: –3.8 (10.1) G2: 1.1 (10.7) **SBP between-group difference, mean mmHg (95% CI):** –5.0 (–8.4, –1.6) *p*=.005 **DBP change, mean mmHg (SD):** G1: –2.7 (7.1) G2: 0.3 (7.4) **DBP between-group difference, mean mmHg (95% CI):** –2.9 (–5.3, –0.5) *p*=.02 **Non-African American** **SBP change, mean mmHg (SD):** G1: –4.9 (11.6) G2: –0.9 (10.4) **SBP between-group difference, mean mmHg (95% CI):** –4.0 (–5.9, –2.0) *p*<.001 **DBP change, mean mmHg (SD):** G1: –2.0 (8.2) G2: –0.4 (6.8) **DBP between-group difference, mean mmHg (95% CI):** –1.7 (–3.0, –0.3) *p*=.01	**24-h urinary Na change, mean mmol/L (SD):** G1: –55 (44) G2: –14 (48) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –41 (–69, –13) *p*=.007 **Non-African American Men** **24-h urinary Na change, mean mmol/L (SD):** G1: –60 (54) G2: –6 (54) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –54 (–67, –42) *p*<.001 **African American Women** **24-h urinary Na change, mean mmol/L (SD):** G1: –26 (64) G2: –1 (48) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –25 (–47, –3) *p*=.03 **Non-African American Women** **24-h urinary Na change, mean mmol/L (SD):** G1: –32 (51) G2: –4 (43) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –25 (–41, –15) *p*<.001	(15–37 mo) G1: 91% G2: 92% **Adherence:** Not reported by subgroup **Daily nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		128.0 (9.4) **DBP on medication, mean mmHg (SD):** 71.3 (7.3) **Urinary sodium, mean mmol/day (SD):** G1: 144 (53) G2: 145 (55)			

CQ2 Summary Table C–4c. Sodium and Subpopulation: Age

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
DASH-Sodium Subgroup analysis Bray et al., 2004[48]; Vollmer et al., 2001[49] RCT, crossover USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Control G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women ***n*:** ≤45 yr G1: 97 G2: 75 >45 years G1: 111 G2: 129 **Mean SBP, mmHg (SD):** Age ≤45 yr G1 H: 125 (11) G1 I: 124 (11) G1 L: 124 (10) G2 H: 128 (10) G2 I: 126 (9) G2 L: 123 (7) Age >45 yr G1 H: 129 (12) G1 I: 127 (12) G1 L: 124 (11) G2 H: 136 (12) G2 I: 133 (13) G2 L: 128 (11) **Mean DBP, mmHg (SD):** Age ≤45 yr G1 H: 81 (7) G1 I: 81 (7) G1 L: 81 (7) G2 H: 83 (7) G2 I: 83 (6) G2 L: 80 (6) **Mean DBP, mmHg (SD):** Age >45 yr	**Age ≤45 yr** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.4 (–2.9, 0.2) *p*<.10 (NS) G1 L vs. G1 I: –0.1 *p*=NR (NS) G1 I vs. G1 H: –1.3 *p*=NR (NS) G2 L vs. G2 H: –5.3 (–7.0, –3.5) *p*<.01 G2 L vs. G2 I: –3.9 *p*<.01 G2 I vs. G2 H: –1.4 *p*=NR (NS) G1 H vs. G2 H: –4.3 (–6.9, –1.7) G1 L vs. G2 H: –5.6 (–8.2, –3.1) **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.1 (–2.1, 0.0) *p*<.05 G1 L vs. G1 I: –0.6 *p*=NR (NS) G1 I vs. G1 H: –0.5 *p*=NR (NS) G2 L vs. G2 H: –2.8 (–4.0, –1.7) *p*<.01 G2 L vs. G2 I: –2.6 *p*<.01 G2 I vs. G2 H: –0.2 *p*=NR (NS) G1 H vs. G2 H: –2.2 (–3.9, –0.6) G1 L vs. G2 H: –3.3 (–5.0, –1.6) **Age >45 yr** **Mean change (95% CI)* in SBP by diet group + sodium**	Not reported by age subgroup **Overall:** **After 30 days of intervention** **Urinary Na, mmol/day (SD):** G1 H: 144 (58) G1 I: 107 (52) G1 L: 67 (46) G2 H: 141 (55) G2 I: 106 (44) G2 L: 64 (37) **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, *n* (%):** Not reported by age subgroup **Overall:** G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables, dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Nutrient intake:** Actual nutrient Intake for sodium is reflected as urinary sodium excretion, which was not reported by age subgroup

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
		G1 H: 80 (7) G1 I: 80 (7) G1 L: 79 (6) G2 H: 84 (7) G2 I: 82 (7) G2 L: 80 (6) **Other baseline characteristics not reported by age grouping.** **Overall sample characteristics:** **Age, mean yr (SD):** G1: 47 (10) G2: 49 (10) **Sex, *n* (%):** Female G1: 123 G2: 111 **Race/ethnicity, *n* (%):** Black G1: 118 (57) G2: 114 (56) Non-Hispanic white G1: 83 (40) G2: 81 (40) Asian or other G1: 6 (3) G2: 10 (5) **Mean BMI kg/m^2 (SD):** G1: 29 (5) G2: 30 (5) **Urinary sodium, mmol/day (SD):** G1: 158 (79) G2: 152 (72)	**reduction level:** G1 L vs. G1 H: –4.5 (–6.0, –3.0) *p*<.01 G1 L vs. G1 I: –3.2 *p*<.01 G1 I vs. G1 H: –1.3 *p*<.10 (NS) G2 L vs. G2 H: –7.5 (–8.9, –6.1) *p*<.01 G2 L vs. G2 I: –5.0 *p*<.01 G2 I vs. G2 H: –1.3 *p*<.10 (NS) G1 H vs. G2 H: –7.1 (–9.4, –4.9) G1 L vs. G2 H: –11.6 (–13.9, –9.4) *p*<.01 **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –2.2 (–3.1, –1.2) *p*<.01 G1 L vs. G1 I: –1.3 *p*<.01 G1 I vs. G1 H: –0.8 *p*<.10 (NS) G2 L vs. G2 H: –3.8 (–4.8, –2.9) *p*<.01 G2 L vs. G2 I: –2.3 *p*<.01 **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G2 I vs. G2 H: –1.6 *p*<.01 G1 H vs. G2 H: –3.4 (–4.8, –1.9) G1 L vs. G2 H: –5.5 (–7.0, –4.0) *p*<.05 **95% CI not reported for all comparisons**		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
TONE Whelton et al., 1998[53]; Appel et al., 2001[55]; Espeland et al., 2002[56] RCT USA, 4 academic health centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:** **Treatment:** Average of 27.8 mo (range 15.6 to 35.9 mo) after randomization **Intervention delivery:** In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 3-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. **Goal for sodium reduction:** Achieving and maintaining a 24-h dietary sodium intake of 80 mmol (1,800 mg) or less G2 received no study-related counseling in lifestyle change; were invited to meetings on topics unrelated to trial goals	Adults 60 to 80 years; had baseline BP <145/85 mmHg while on a single antihypertensive medication ***n*:** G1: 340 G2: 341 **Mean SBP, mmHg (SD):** 60–69 yr age group G1: 128.2 (9.2) G2: 126.8 (9.6) 70–80 yr age group G1: 129.2 (9.4) G2: 128.7 (8.6) **Mean DBP, mmHg (SD):** 60–69 yr age group G1: 72.1 (7.4) G2: 72.3 (6.4) 70–80 yr age group G1: 68.8 (7.2) G2: 68.2 (8.8) **Urinary sodium, mean mmol/day (SD):** 60–69 yr age group G1: 144 (54) G2: 151 (66) 70–80 yr age group G1: 142 (48) G2: 124 (39) **Other baseline characteristics not reported by age grouping.** **Overall sample characteristics:** **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:**	**Mean interval, 3.5 mo** **60–69 yr age group** **SBP change, mean mmHg (SD):** G1: –5.2 (11.1) G2: –0.2 (10.3) **SBP between-group difference, mean mmHg (95% CI):** –5.0 (–6.9, –3.1) *p*<.001 **DBP change, mean mmHg (SD):** G1: –2.3 (8.1) G2: –0.2 (7.0) **DBP between-group difference, mean mmHg (95% CI):** –2.1 (–3.5, –0.8) *p*=.002 **70–80 yr age group** **SBP change, mean mmHg (SD):** G1: –2.6 (11.8) G2: –1.1 (11.2) **SBP between-group difference, mean mmHg (95% CI):** –1.5 (–5.4, 2.4) *p*=.46 **DBP change, mean mmHg (SD):** G1: –1.6 (7.5) G2: –0.2 (6.8) **DBP between-group difference, mean mmHg (95% CI):** –1.4 (–3.9, 1.0) *p*=.25	**60–69 yr age group** **24-h urinary Na change, mean mmol/L (SD):** G1: –46 (57) G2: –8 (52) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –38 (–48, –29) *p*<.001 **70–80 yr age group** **24-h urinary Na change, mean mmol/L (SD):** G1: –41 (52) G2: 5 (42) **24-h urinary Na change between-group difference, mean mmol/L (95% CI):** –46 (–62, –30) *p*<.001	**Withdrawals, %:** Not reported by age group **Overall:** Attended final study visit (15–37 mo) G1: 91% G2: 92% **Adherence:** Not reported by age group **Daily nutrient intake** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Nutrient Intake
		47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR			

CQ2 Summary Table C–4d. Sodium and Subpopulation: Hypertension Status

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
DASH-Sodium Svetkey et al., 2004[57]; Bray et al., 2004[48]; Vollmer et al., 2001[49] RCT, crossover USA, outpatient medical settings Fair	**Treatment groups:** G1: DASH diet G2: Typical American diet Run-in: Control diet + high sodium level, 50 mmol/d G1: 27% of calories from total fat; 6% from SF, 13% MUFA, and 8% PUFA and 151 mg/d of cholesterol. Emphasis on fruits, vegetables, and low-fat dairy foods, includes whole grains, poultry, fish, and nuts, and is reduced in fats, red meat, sweets, and sugar-sweetened beverages. G2: Control diet: 37% fat, 16% SF, 13% MUFA, 8% PUFA, 300 mg/d cholesterol. **Duration:** **Run-in:** 2 weeks **Treatment:** 90 days, 30 days per sodium condition **Intervention delivery:** There were three 30-day feeding periods, 1 at each of the 3 sodium levels (randomly assigned). Levels were higher (H; 150 mmol/d), intermediate (I; 100 mmol/d), and lower (L; 50 mmol/d). All food was provided. Weight was kept stable.	Adults ≥22 years of age, SBP of 120–159 mmHg, DBP of 80–95 mmHg, target of 50% enrollment of Blacks and women **Hypertensive, n (%):** G1: 85 (40.9) G2: 83 (40.7) **Nonhypertensive, n (%):** G1: 123 (59.1) G2: 121 (59.3) **Hypertensive** **Mean SBP, mmHg (SD):** G1 H: 134 (11) G1 I: 133 (12) G1 L: 129 (11) G2 H: 141 (11) G2 I: 139 (12) G2 L: 133 (11) **Mean DBP, mmHg (SD):** G1 H: 84 (7) G1 I: 84 (7) G1 L: 82 (6) G2 H: 86 (7) G2 I: 85 (6) G2 L: 82 (6) **Nonhypertensive** **Mean SBP, mmHg (SD):** G1 H: 122 (9) G1 I: 121 (9) G1 L: 120 (9) G2 H: 122 (9) G2 I: 125 (7) G2 L: 122 (6) **Mean DBP, mmHg (SD):** G1 H: 79 (6) G1 I: 78 (7)	**Hypertensive** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 L vs. G1 H: 4.9 (–6.6, –3.3) *p*<.01 G1 L vs. G1 I: –3.3 *p*<.01 G1 I vs. G1 H: –1.6 *p*<.10 G2 L vs. G2 H: –-8.3 (–10.0, –6.6) *p*<.01 G2 L vs. G2 I: –6.2 *p*<.01 G2 I vs. G2 H: –2.1 *p*<.5 G1 H vs. G2 H: –6.6 (–9.1, –4.0) G1 L vs. G2 H: –11.5 (–14.1, –8.9) *p*<.01 **Mean change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H:–2.5 (–3.6, –1.4) *p*<.05 G1 L vs. G1 I: –2.0 *p*<.01 G1 I vs. G1 H: –0.5 *p*=NR (NS) G1 H vs. G2 H: –3.2 (–4.8, –1.5) G1 L vs. G2 H: –5.7 (–7.4, –4.0) **Nonhypertensive** **Mean change (95% CI)* in SBP by diet group + sodium reduction level:** G1 L vs. G H: –1.7 (–3.1, –0.3)	Not reported by hypertensive & nonhypertensive subgroups **Overall:** **After 30 days of intervention** **Urinary Na, g/day (SD):** G1 H: 303 (1.3) G1 I: 2.5 (1.2) G1 L: 1.5 (1.0) G2 H: 3.3 (1.3) G2 I: 2.4 (1.0) G2 L: 1.5 (0.8)	**Withdrawals, n (%):** Not reported by subgroup **Overall:** G1: 10 (4.8) G2: 12 (5.9) **Adherence:** Reported as 24-h urinary excretion: The levels of urinary potassium, phosphorus, and urea nitrogen (reflective of the intake of fruit and vegetables, dairy products, and protein, respectively) were higher in the DASH-diet group than in the control-diet group, and were nearly identical for all three sodium levels. **Nutrient Intake:** Nutrient intake for sodium is reflected as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		G1 L: 78 (6) G2 H: 81 (6) G2 I: 81 (6) G2 L: 79 (6) Subgroup analyses from Svetkey et al., 2004[57] **Stage I Hypertensives** ***n*:** G1: 79 G2: 76 **Age, yr (SD):** G1: 49.4 (10.8) G2: 52.0 (10.3) **Sex, women:** G1: 63.3% G2: 60.5% **Race/ethnicity, %** Non-Hispanic white G1: 38.0 G2: 35.5 African American G1: 60.8 G2: 59.2 Other G1: 1.3 G2: 5.3 **SBP, mmHg:** G1: 142.0 (8.0) G2: 144.1 (7.2) **DBP, mmHg:** G1: 88.6 (4.9) G2: 88.1 (4.1) **BMI:** G1: 28.3 (5.0) G2: 29.5 (5.0) **Urinary sodium, mmol/24-h:** G1: 157.5 (79.7)	*p*<.05 G1 L vs. G1 I: –0.6 *p*=NR (NS) G1 I vs. G1 H: –1.1 *p*=NR (NS) G2 L vs. G2 H: –5.6 (–7.0, –4.1) *p*<.01 G2 L vs. G2 I: –3.4 *p*<.01 G2 I vs. G2 H: –2.2 *p*<.01 G1 H vs. G2 H: –5.4 (–7.7, –3.2) G1 L vs. G2 H: –7.1 (–9.4, –4.9) **Mean Change (95% CI)* in DBP by diet group + sodium reduction level:** G1 L vs. G1 H: –1.1 (–2.0, –0.1) *p*<.05 G1 L vs. G1 I: –0.3 *p*=NR (NS) G1 I vs. G1 H: –0.8 *p*=NR (NS) G2 L vs. G2 H: –2.8 (–3.8, –1.9) *p*<.01 G2 L vs. G2 I: –2.0 *p*<.01 G2 I vs. G2 H: –0.8 *p*<.10 G1 H vs. G2 H: –2.7 (–4.1, –1.2) G1 L vs. G2 H: –3.7 (–5.2, –2.3) **Mean Change (95% CI)* in DBP by diet group + sodium reduction level:** *CI not reported for all comparisons Subgroup analyses from Svetkey et al., 2004[57] **Hypertensive** **End-of-feeding BP control rates, %:** G1 H: 63		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		G2: 153.4 (73.1) **Isolated Systolic Hypertension (ISH):** ***n:*** G1: 37 G2: 40 **Age, yr (SD):** G1: 54.8 (10.9) G2: 53.7 (11.1) **Sex, women:** G1: 73.0% G2: 60.0% **Race/ethnicity, %:** Non-Hispanic White G1: 37.8 G2: 40.0 African American G1: 59.5 G2: 57.5 Other G1: 2.7 G2: 2.5 **SBP, mmHg:** G1: 146.6 (5.0) G2: 145.7 (4.7) **DBP, mmHg:** G1: 84.2 (3.4) G2: 84.9 (2.9) **BMI:** G1: 28.6 (5.5) G2: 30.0 (4.6) **Urinary sodium, mmol/24-h:** G1: 150.1 (72.5) G2: 154.3 (68.5) **High-normal BP:** ***n***:	G2 H: 32 G1 I: 65 G2 I: 51 G1 L: 84 G2 L: 74 G1 H vs. G2 H: *p*<.01 G2 I vs. G2 H: *p*<.01 G1 I vs. G2 H: *p*<.01 G2 L vs. G2 H: *p*<.01 G1 L vs. G2 H: *p*<.01 G1 L vs. G1 H: *p*<.05 **ISH** **End-of-feeding BP control rates, %:** G1 H: 57 G2 H: 43 G1 I: 62 G2 I: 53 G1 L: 78 G2 L: 75 G1 H vs. G2 H: *p*=NS G2 I vs. G2 H: *p*=NS G1 I vs. G2 H: *p*=NS G2 L vs. G2 H: *p*<.01 G1 L vs. G2 H: *p*<.01 G1 L vs. G1 H: *p*<.05		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 63 G2: 68 **Age, yr (SD):** G1: 48.1 (8.6) G2: 48.1 (10.3) **Sex, women:** G1: 57.1% G2: 55.8% **Race/ethnicity, %:** Non-Hispanic White G1: 38.1 G2: 35.3 African American G1: 58.7 G2: 60.3 **Race/ethnicity, %:** Other G1: 3.2 G2: 4.4 **SBP, mmHg:** G1: 132.0 (4.2) G2: 132.4 (4.5) **DBP, mmHg:** G1: 84.9 (3.2) G2: 85.3 (2.9) **BMI:** G1: 29.9 (4.8) G2: 29.6 (5.3) **Urinary sodium, mmol/24-h:** G1: 155.3 (78.5) G2: 149.6 (75.6)			

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
TOHP II The Trials of Hypertension Prevention Collaborative Research Group, 1997[54]; Kumanyika et al., 2005[58]; Cook et al., 2005[59] RCT, 2 X 2 factorial USA, 9 academic medical centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual care **Duration:** **Treatment:** 36–48 mo **Additional followup after treatment:** none **Intervention delivery:** Individual and group counseling through in-person, telephone, and mail contact. **Intensive phase:** Groups of 11 to 34, counseled weekly for 10 weeks; primary goal was to provide core knowledge and behavioral skills to make and maintain reductions in Na intake. **Transitional phase:** 4 monthly sessions; designed to prevent relapse and ease transition to less frequent contact **Final extended phase:** 1 or 2 monthly contacts; 3 to 6 refresher sessions were offered; goal: maintain participants' behavior changes Goal for G1: reduction in sodium intake of 80 mmol per day or less.	Adults 30–54 years, not taking antihypertensive drugs, SBP<140 mmHg, DBP 83 to 89 mmHg, BMI representing 110% to 165% of desirable body weight ***n***: G1: 594 G2: 596 **Age:** G1: 44.2 (6.1) G2: 43.2 (6.1) **Sex, % male:** G1: 64.8 G2: 68.3 **Race/ethnicity:** White, % G1: 81.1 G2: 79.5 Black, % G1: 16.8 G2: 17.3 **Weight, kg (SD):** G1: 94.0 (14.3) G2: 93.6 (13.5) **BMI:** NR **Mean SBP, mmHg (SD):** G1: 127.7 (6.6) G2: 127.3 (6.4) **Mean DBP, mmHg (SD):** G1: 86.1 (1.9) G2: 85.8 (1.9) **Urinary sodium, mmol/d (SD):** G1: 186.1 (80.7) G2: 188.0 (80.9)	**6 mo** **SBP mean change, mmHg (SD):** G1: –5.1 (8.6) G2: –2.2 (8.1) **SBP net change, mmHg (SE):** G1 vs. G2: –2.9 (0.5) *p*<.001 **DBP mean change, mmHg (SD):** G1: –4.4 (6.7) G2: –2.8 (6.1) **DBP net change, mmHg (SDE):** G1 vs. G2: –1.6 (0.4) *p*<.001 **18 mo** **SBP mean change, mmHg (SD):** G1: –3.8 (8.2) G2: –1.8 (7.0) **SBP net change, mmHg (SE):** G1 vs. G2: –2.0 (0.5) *p*<.001 **DBP mean change, mmHg (SD):** G1: –4.4 (6.5) G2: –3.2 (5.8) **DBP net change, mmHg (SE):** G1 vs. G2: –1.2 (0.4) *p*=.002 **36 mo** **SBP mean change, mmHg (SD):** G1: –0.7 (9.0) G2: +0.6 (8.5) **SBP net change, mmHg (SE):** G1 vs. G2: –1.2 (0.5) *p*=.02 **DBP mean change, mmHg**	**6 mo** ***n***: G1: 147 G2: 126 **24-h urinary Na mean change, mmol/d (SD):** G1: –75.5 (81.5) G2: –24.5 (10.38) **24-h urinary Na net difference, mmol/d 95% CI):** G1 vs. G2: –51.0 (28.9, 73.0) **18 mo** ***n***: G1: 450 G2: 467 **24-h urinary Na mean change, mmol/d (SD):** G1: –59.5 (91.7) G2: –16.8 (94.8) **24-h urinary Na net difference, mmol/d 95% CI):** G1 vs. G2: –42.7 (30.6, 54.8) **36 mo** ***n***: G1: 470 G2: 482 **24-h urinary Na mean change, mmol/d (SD):** G1: –50.9 (86.3) G2: –10.5 (88.5) **24-h urinary Na net difference, mmol/d 95% CI):** G1 vs. G2: –40.4 (29.3, 51.5)	**Withdrawals:** Proportion of participants with BP readings at all 3 scheduled visits at or after 36 mo ranged from 88.9% to 91.6% Completion of sodium excretion data at 36 mo ranged from 79.1% to 80.9% **Adherence:** Adherence measures such as food diaries and overnight urine samples were not used as study outcome data. **Nutrient intake:** 24-h dietary recall and 3-day food record information was obtained at 18- and 36-mo for randomly selected samples.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Sodium	Attrition Adherence/Compliance Actual Nutrient Intake
			(SD): G1: –3.0 (6.5) G2: –2.4 (7.0) **DBP net change, mmHg (SDE):** G1 vs. G2: –0.7 (0.4) *p*=.10		
TONE Whelton et al., 1998[53]; Appel et al., 2001[55] RCT USA, 4 academic health centers Good	**Treatment Groups:** G1: Sodium reduction G2: Usual care **Duration** Mean of 27.8 mo (range 15.6 to 35.9 mo) after randomization **Intervention delivery:** In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 4-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. **Goal for sodium reduction:** Achieving and maintaining a 24-r dietary sodium intake of 80 mmol (1,800 mg) or less G2 received no study-related counseling in lifestyle change; were invited to meetings on topics unrelated to trial goals	Adults 60 to 80 years; had baseline BP <145/85 mmHg while on a single antihypertensive medication. ***n*:** G1: 340 G2: 341 **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:** 47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR **SBP on medication, mean mmHg (SD):** 128.0 (9.4) **DBP on medication, mean mmHg (SD):** 71.3 (7.3) **Urinary sodium, mean mmol/day (SD):** G1: 144 (53) G2: 145 (55)	**Mean interval, 3.5 mo (baseline to visit prior to medication withdrawal)** **SBP change, mean mmHg (SD):** G1: –4.6 (11.3) G2: –0.4 (10.5) **SBP between-group difference, mean mmHg (95% CI):** –4.3 (–6.0, –2.5) *p*<.001 **DBP change, mean mmHg (SD):** G1: –2.2 (8.0) G2: –0.2 (7.0) **DBP between-group difference, mean mmHg (95% CI):** –2.0 (–3.2, –0.8) *p*=.001 **30 mo** **Proportion without an end point, %:** G1: 36 G2: 21 **Relative HR (95% CI) for end points associated with Assignment G1 vs. G2:** 0.68 (0.56, 0.82) *p*<.001	**30 mo** **24-h urinary Na change, mean mmol (SD):** G1: –45 (55.8) G2: –5 (50.0) **24-h urinary Na change between-group difference, mean mmol (95% CI):** –40 (–48, –32) *p*<.001	**Withdrawals:** Attended final study visit (15–37 mo) G1: 91% G2: 92% **Daily nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

CQ2 Summary Table C–5. Sodium and CVD Outcomes: Trials or Observational Followup of Trials

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	CVD Events	Attrition Adherence/Compliance Actual Nutrient Intake
TOHP I and II long-term followup for CVD Cook 2007[66], 2009[68] Observational followup study Fair	**Treatment groups:** G1: Sodium reduction intervention G2: Control **Duration of treatment in the trials:** TOHP I 18 mo TOHP II 36 mo **Followup study for CVD*** TOHP I Began ≈ 10 yr after end of trial TOHP II Began ≈ 5 yr after end of trial *In this analysis, the weight loss arms of TOHP II were included. Followup began 5 yr after the end of the randomized trial.	Adults 30–54 years, DBP 80 to 89 mmHg without antihypertensive drugs **Baseline characteristics, at the start of the randomized trials:** ***n*:** TOHP I G1: 327 G2: 417 TOHP II G1: 1191 G2: 1191 **Age:** TOHP I G1: 43.4 (6.6) G2: 42.6 (6.5) TOHP II G1: 43.9 (6.2) G2: 43.3 (6.1) **Sex, % male:** TOHP I G1: 232 (71.0) G2: 299 (71.7) TOHP II G1: 784 (65.8) G2: 782 (65.7) **Race/ethnicity, *n* (%):** White TOHP I G1: 255 (78.0) G2: 319 (76.5) TOHP II G1: 950 (79.8) G2: 938 (78.8) Black TOHP I G1: 64 (19.6) G2: 87 (20.9) TOHP II	**Cardiovascular disease,* Hazard ratio (95% CI)** **Overall:** 0.75 (0.57, 0.99) *p*=.044 **Cardiovascular disease,* Hazard ratio† (95% CI)** **Overall:** 0.70 (0.53, 0.94) *p*=.018 TOHP I: 0.48 (0.25, 0.92) *p*=.027 TOHP II: 0.79 (0.57, 1.09) *p*=.16 **Cardiovascular disease,* Crude rate, %** **Overall:** G1: 7.5 G2: 9.0 *p*=.19 *p* stratified by trial=0.21 TOHP I G1: 7.4 G2: 10.3 *p*=.24 TOHP II G1: 7.6 G2:8.6 *p*=.43 *MI, stroke, revascularization, or death due to cardiovascular cause † HR additionally adjusted for baseline weight and sodium excretion	**Followup response:** **Overall** G1: 77% G2: 77.5% **OR‡ (95% CI):** 0.93 (0.78, 1.11) *p*=.42 ‡ Adjusted for trial, clinic, age, race, sex, and weight loss intervention **Adherence:** Not applicable for CVD followup study

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	CVD Events	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 212 (17.8) G2: 209 (17.6) Other TOHP I G1: 8 (2.4) G2: 11 (2.6) TOHP II G1: 29 (2.4) G2: 44 (3.7) **Weight, kg (SD):** TOHP I G1: 82.7 (14.3) G2: 82.8 (13.9) TOHP II G1: 93.8 (14.3) G2:93.5 (13.8) **BMI, kg/m^2 (SD):** TOHP I G1: 27.1 (3.8) G2: 27.1 (3.6) TOHP II G1: 30.9 (3.1) G2: 30.9 (3.1) **Mean SBP, mmHg (SD):** TOHP I G1: 124.8 (8.5) G2: 125.1 (8.1) TOHP II G1: 127.5 (6.6) G2: 127.4 (6.2) **Mean DBP, mmHg (SD):** TOHP I G1: 83.7 (2.7) G2: 83.9 (2.8) TOHP II G1: 86.0 (1.9) G2:85.9 (1.9) **Sodium excretion, mmol/24 h (SD):** TOHP I		

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	CVD Events	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 154.6 (59.9) G2: 156.4 (60.5) TOHP II G1: 182.9 (78.4) G2: 184.5 (76.8) **Change to end of randomized trials:** **Weight change, kg (SD):** TOHP I G1: –0.2 (3.8) G2: 0.2 (3.9) TOHP II G1: 0.7 (5.5) G2: 0.8 (5.7) **Sodium excretion change, mmol/24 h (SD):** TOHP I G1: –55.2 (76.9) G2: –11.3 (77.7) TOHP II G1: –42.5 (89.0) G2: –9.8 (87.7)		
Chang et al., 2006[67] RCT (randomized 5 kitchens) Taiwan, Veteran's retirement home Fair	**Treatment groups:** G1: Potassium-enriched salt G2: Regular salt G1: Composition of potassium-enriched salt: 49% sodium chloride, 49% potassium chloride, 2% other additives G2: Composition of regular salt: 99.6% sodium chloride, 0.4% other additives. **Duration:** **Average followup period:** ≈31 mo **Intervention delivery:** G1: Potassium-enriched salt gradually replaced regular salt in the kitchens in a gradual manner; it was mixed with regular salt in a 1 to 3 ratio for 1st week, ratio increased to 1:1 in 2nd week, 3:1 in 3rd week; at 4th week the cooks used only potassium-enriched salt. G2: The kitchens used regular salt at all times.	Male veterans ***n*:** G1: 768 (Kitchens 2 & 3) G2: 1213 (Kitchens 1, 4 & 5) **Age, mean yr (SD):** G1 Kitchen 2: 75.6 (7.7) Kitchen 3: 74.8 (7.0) G2 Kitchen 1: 74.8 (7.3) Kitchen 4: 74.6 (6.7) Kitchen 5: 74.6 (6.1) **Sex, male %:** 100 **Race/ethnicity, %:** All Taiwanese **Weight, kg (SD):**	**Cause-specific incidence of death per 100,000 person yr in G1 and G2** **Absolute risk reduction (95% CI)** CVD: –828.7 (–1424, –232.9) G1 vs. G2: p<.05 Ischemic heart disease: –256.3 (–600.3, 87.7) G1 vs. G2: p=NR (NS) Hypertensive disease: 64.8 (164.5, 294.1) G1 vs. G2: p=NR (NS) Heart failure: –227.3 (–389.5, –65.1) G1 vs. G2: p<.05 Cerebrovascular disease: –389.8 (–741.1, –65.5)	**Withdrawals:** All were included in survival analysis **Nutrient intake:** G1: Avg. amount of potassium-enriched salt used per day per kitchen: ≈1–2 kg: 1.41 (0.22) Each kitchen served ≈400 persons per meal. Salt was the major source of sodium added in the cooking process, whereas other sauces accounted for ≈30% of total sodium.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	CVD Events	Attrition Adherence/Compliance Actual Nutrient Intake
		G1: 60.7 (10.8) 60.3 (9.8) **BMI, kg/m^2 (SD):** G1: 23.3 (3.5) G2: 23.0 (3.3) **SBP, mean mmHg (SD):** G1: 131.3 (19.7) G2: 130.7 (20.4) **DBP on medication, mean mmHg (SD):** G1: 71.2 (10.8) G2: 71.4 (10.8) **Urinary sodium, mean mmol/day (SD):** NR	G1 vs. G2: *p*<.05 **Relative risk reduction*** CVD: –38.8% Ischemic heart disease: –32.5% Hypertensive disease: 49.9% Heart failure: –70.0% Cerebrovascular disease: –50.0% *Calculated as (rate of experimental – rate of control)/(rate of control) X 100	
TONE Appel et al., 2001[55] RCT USA, 4 academic health centers Good	**Treatment groups:** G1: Sodium reduction G2: Usual :care **Duration:** **Treatment:** Average of 27.6 mo (range 15.6 to 35.9 mo) after randomization Intervention delivery: In the reduced sodium group, each person had an introductory individual session. The TONE interventions consisted of a 4-mo "intensive" phase with weekly meetings, a 3-mo "extended" phase with biweekly meetings, and a maintenance phase. The interventionist typically was a registered dietitian. The meetings were conducted as group sessions (9–12 participants) with individual sessions at every fourth contact. **Goal for sodium reduction:** Achieving and maintaining a 24-h dietary sodium intake of 80 mmol (1,800 mg) or less G2 received no study-related counseling in lifestyle change; were invited to meetings on topics unrelated to trial goals	Adults 60 to 80 years; had baseline BP <145/85 mmHg while on a single antihypertensive medication. ***n*:** G1: 340 G2: 341 **Age, mean yr (SD):** 65.8 (4.6) **Sex, female %:** 47 **Race/ethnicity, %:** African American: 23 **Overweight, %:** 43 **BMI:** NR **SBP on medication, mean mmHg (SD):** 128.0 (9.4) **DBP on medication, mean mmHg (SD):** 71.3 (7.3) **Urinary sodium, mean mmol/day (SD):** G1: 144 (53) G2: 145 (55)	**Reported Cardiovascular events, *n* of individuals (n of events)** **Any cardiovascular event:** G1: 36 (44) G2: 46 (57) *p*=.24 **Stroke:** G1: 1 (1) G2: 2 (2) *p*>.99 **Transient ischemic attack:** G1: 7 (8) G2: 7 (8) *p*>.99 **MI:** G1: 2 (2) G2: 4 (4) *p*=.69 **Arrhythmia:** G1: 6 (6) G2: 3 (4) *p*=.34 **Congestive heart failure:**	**Withdrawals:** Attended final study visit (15–37 mo) G1: 91% G2: 92% **Daily nutrient intake:** Actual nutrient intake for sodium is reflected as urinary sodium excretion.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	CVD Events	Attrition Adherence/Compliance Actual Nutrient Intake
			G1: 2 (4) G2: 1 (1) *p*>.99 **Angina:** G1: 9 (10) G2: 17 (19) *p*=.16 **Other:** G1: 12 (13) G2: 19 (19) *p*=.27	

CQ2 Summary Table C–6. Sodium and CVD Outcomes: Observational Data

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
Ekinci et al., 2011[83] Prospective cohort study Melbourne, Australia; University diabetes clinic Good	**Study groups** Determined by level of 24-h urinary sodium excretion G1: <150 mmol G2: 150–208 mmol G3: >208 mmol **Duration:** Followup time: 9.9 yr (median) **Other study characteristics:** Patients were given general dietary advice as part of their routine care at an initial assessment by a dietitian. However, detailed assessment of dietary salt intake was not performed. During followup, all patients continued to have standard medical care including antihypertensive, lipid-lowering, and anti-diabetic medications according to recommended guidelines.	Type 2 diabetics, in long-term followup ***n*:** NR by group Total *N*=638 *N*=638 **Age, mean yr (SD):** G1: 67 (12) G2: 64 (11) G3: 61 (12) **Sex, male %:** G1: 42 G2: 56 G3: 70 **Race/ethnicity, %:** NR **Overweight, %:** NR **Obese (BMI >30kg/m^2), %:** G1: 41 G2: 45 G3: 55 **SBP, mean mmHg (SD):** G1: 141 (17) G2: 140 (17) G3: 140 (16) **DBP, mean mmHg (SD):** G1: 77 (10) G2: 80 (9) G3: 78 (10)	**Cardiovascular mortality by baseline parameter, sub-HR (95% CI)** **24-h urinary sodium excretion:** 0.65 (0.44, 0.95) *p*=.017 **SBP:** 0.97 (0.96–0.99) *p*<.001 **Preexisting CVD:** 1.88 (1.14, 3.11) *p*=.014	**Loss to followup:** Overall *N* (%): 18 (2.8) **Other methodological details:** High participation rate (96% of eligible sample) Long-term followup Small % LTF Multiple 24-h urine collections to estimate Na intake

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
Gardener et al., 2012[82] Population-based cohort study (using the Northern Manhattan Study cohort) USA, Manhattan Fair	**Study groups** Determined by sodium intake (based on self-reported food consumption) G1: ≤1,500 mg/d G2+G3: 1,501–3,999 mg/d G4: ≥4,000 mg/d **Duration:** Mean followup: 10 yr **Other study characteristics:** Participants completed modified Block National Cancer Institute food frequency questionnaire at baseline. Questionnaire was modified to include items commonly eaten among Hispanics. Sodium intake calculated based on self-reported food consumption using DIETSYS software.	Adults >40 years of age, stroke free, residing in northern Manhattan for ≥3 mo ***n*:** G1: 320 G2: 1,779 G3: 558 **Age, mean (SD):** G1: 70 (10) G2: 69 (10) G3: 68 (9) **Sex, male *n* (%):** G1: 68 (21) G2: 622 (35) G3: 275 (49) **Race/ethnicity, *n*:** Black or African American G1: 104 G2: 418 G3: 115 White G1: 49 G2: 397 G3: 106 Hispanic or Latino G1: 160 G2: 952 G3: 322 **BMI mean kg/m^2 (SD):** G1: 28 (5) G2: 28 (5) G3: 29 (6) **Weight, mean kg (SD):** NR **SBP, mean mmHg (SD):** G1: 144 (20) G2: 143 (21) G3: 144 (21) **DBP, mean mmHg (SD):** G1: 83 (11)	**Stroke risk per daily dietary sodium at 10 yr followup, HR* (95% CI)** Per 500 mg/d sodium increase 1.17 (1.07, 1.27) 1,501–2,300 mg/d dietary sodium 1.38 (0.84–2.27) 2,301–3,999 mg/d dietary sodium 1.32 (0.78, 2.23) 4,000–10,000 mg/d dietary sodium 2.59 (1.27, 5.28) *Adjusted for demographics + behavioral risk factors + vascular risk factors **Stroke, MI or vascular death per daily dietary sodium at 10 yr followup, HR† (95% CI)** Per 500 mg/d sodium increase 1.05 (0.99, 1.11) 1,501–2,300 mg/d dietary sodium 1.35 (1.00, 1.82) 2,301–3,999 mg/d dietary sodium 1.21 (0.87, 1.67) 4,000–10,000 mg/d dietary sodium (1.06, 2.67) *Adjusted for demographics + behavioral risk factors + vascular risk factors	**Loss to followup:** NR Person-time of followup accrued from baseline to end of followup (March 2011), the time of outcome event, time of death, or loss to followup. **Other methodological details:** Sodium intake (exposure) assessed by self-report of food consumption Significant baseline differences *N*s included in models not clearly reported

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
		G2: 83 (11) G3: 84 (11)		
Liang et al., 2011[81] Retrospective case-control study Guangdong Province, China Fair	**Study groups** G1: Hospital inpatients w/ ischemic stroke (cases) G2: Hospital-based control patients **Duration** N/A (45 minute interview) **Other study characteristics:** Information on typical food consumption collected using structured questionnaire developed for southern Chinese population.	Inpatients from Chinese hospitals with first ever ischemic stroke and outpatient controls with no history of stroke ***n*:** G1: 374 G2: 464 G1 Men: 226 G1 Women: 148 G2 Men: 248 G2 Women: 216 **Age, mean yr (SD):** G1 Men: 69.6 (8.0) G1 Women: 69.1 (9.2) G2 Men: 68.7 (7.0) G2 Women: 69.0 (9.0) **Sex, female %:** G1: 39.6 G2: 46.6 **Race/ethnicity, %:** NR **Overweight, %:** NR **BMI mean kg/m^2 (SD):** G1 Men: 22.9 (2.7) G1 Women: 21.5 (3.6) G2 Men: 23.1 (3.0) G2 Women: 22.8 (3.6) **SBP, mean mmHg (SD):** NR **DBP, mean mmHg (SD):** NR **Hypertension, *n* (%):** G1 Men: 119 (52.7) G1 Women: 76 (51.4) G2 Men: 71 (28.6) G2 Women: 60 (27.8)	**Ischemic stroke risk by weekly dietary sodium intake, adjusted* OR (95% CI)** ≤3,726 mg/week: 1.0 [Reference] 3,727, 5,565 mg/week: 1.34 (0.83, 2.18) 5,566, 8,073 mg/week: 1.82 (1.09, 3.06) ≥8,074 mg/week: 1.30 (0.73, 2.32) *Adjusted for weekly intake of iron, sodium, potassium, calcium, and magnesium; weekly energy intake; sex, age, BMI, education level, lifelong physical activity involvement, smoking status, cumulative smoking, alcohol drinking status, and presence of hypertension, hyperlipidemia, or diabetes **Risk of ischemic stroke risk by sodium intake, adjusted* OR (95% CI)** Low: 1 [Reference] Normal: 2.47 (1.47, 4.19) High: 2.33 (1.34, 4.09) *Adjusted for weekly energy intake, sex, age, BMI, education level, lifelong physical activity involvement, smoking status, cumulative smoking, alcohol drinking status, and presence of hypertension, hyperlipidemia, or diabetes	**Loss to followup:** 6 (0.01%) **Other methodological details:** Sodium intake based on questionnaire; reference recall period set at 1 yr before interview Sodium consumption from salt and soy sauce added to foods was difficult to quantify so excluded in calculation of Na intake

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
		Urinary sodium, mean mmol/day (SD): NR **Mean sodium intake, mg/week (SD):** G1 Men: 7319 (5540) G1 Women: 5973 (5303) G2 Men: 7270 (5271) G2 Women: 6055 (3910)		
Marniemi et al., 2005[79] Case-control study Finland, population-based health survey Fair	**Study groups** G1: AMI cases G2: AMI controls G3: Stroke cases G4: Stroke controls **Duration:** Followup for up to 10 yr **Other study characteristics:** Food consumption information obtained from dietary history interview	Elderly men and women, 65 to 99 years of age ***n*:** G1: 130 G2: 559 G3: 70 G4: 590 **Age, mean yr (SD):** NR **Sex, female %:** NR **Race/ethnicity, %:** NR **Overweight, %:** NR **BMI:** NR **SBP, mean mmHg (SD):** NR **DBP, mean mmHg (SD):** NR **Urinary sodium, mean mmol/day (SD):** NR	**Daily sodium, mean mg (SD):** G1: 2,190 (953) G2: 2,280 (1210) G3: 2,350 (1250) G4: 2,330 (1770) **Serum concentration of sodium, mean mmol/L (SD):** G1: 142 (3) G2: 142 (3) G3: 141 (3) G4: 142 (3) **Adjusted* RR (95% CI) of AMI and stroke between tertiles of sodium intake:** Middle tertile vs. lowest tertile AMI: 0.862 (0.55, 1.36) Stroke: 0.617 (0.33, 1.15) Highest tertile vs. lowest tertile AMI: 1.42 (0.81, 2.47) Stroke: 0.617 (0.33, 1.15) *Adjusted in Cox proportional hazards model for age, gender, smoking, functional capacity and weight adjusted energy intake **Adjusted* RR (95% CI) of AMI and stroke between tertiles of serum concentration of sodium:** Middle tertile vs. lowest tertile AMI: 1.02 (0.38, 1.55) Stroke: 1.01 (0.54, 1.88) Highest tertile vs. lowest tertile AMI: 0.866 (0.52, 1.44) Stroke: 0.968 (0.54, 1.72) *Adjusted for age, gender, smoking, and functional	**Loss to followup:** 484 subjects died during 10-yr followup **Other methodological details:** Sodium intake based on questionnaire LTF unclearly reported

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
			capacity	
NHANES I Alderman et al., 1998[72] Prospective cohort study Fair	**Study groups** Full model involved three dietary measures of sodium intake, total calorie intake, and sodium/calorie ratio. S1–S8 represent sodium intake quartiles for men and women SC1–SC8 represent sodium/calorie ratio quartiles for men and women S1: First (lowest) quartile of sodium intake for men S2: Second quartile of sodium intake for men S3: Third quartile of sodium intake for men S4: Fourth (highest) quartile of sodium intake for men S5: First (lowest) quartile of sodium intake for women S6: Second quartile of sodium intake for women S7: Third quartile of sodium intake for women S8: Fourth (highest) quartile of sodium intake for women SC1: First (lowest) quartile of sodium/calorie ratio for men SC2: Second quartile of sodium/calorie ratio for men SC3: Third quartile of sodium/calorie ratio for men SC4: Fourth (highest) quartile of sodium/calorie ratio for men SC5: First (lowest) quartile of sodium/calorie ratio for women SC6: Second quartile of sodium/calorie ratio for women SC7: Third quartile of sodium/calorie ratio for women SC8: Fourth (highest) quartile of sodium/calorie ratio for women	Individuals 25–75 years of age at time of NHANES I survey **Age, mean yr, (SD):** S1: 56.9 (14.3) S2: 54.4 (15.5) S3: 51.7 (15.5) S4: 48.6 (15.1) S5: 49.8 (16.0) S6: 49.2 (16.0) S7: 47.8 (15.9) S8: 43.9 (14.9) SC1: 50.3 (15.9) SC2: 52.9 (15.3) SC3: 54.0 (15.2) SC4: 54.5 (15.0) SC5: 46.1 (15.5) SC6: 48.1 (16.0) SC7: 48.7 (16.0) SC8: 47.9 (15.9) **Sex, %:** S1, SC1: Male: 100 S2, SC2: Male: 100 S3, SC3: Male: 100 S4, SC4: Male: 100 S5, SC5: Female: 100 S6, SC6: Female: 100 S7, SC7: Female: 100 S8, SC8: Female: 100 **Race/ethnicity, Black, %:** S1: 24.4 S2: 17.0 S3: 13.3 S4: 8.8 S5: 26.0 S6: 18.3 S7: 15.4 S8: 11.5 SC1: 20.1 SC2: 14.8 SC3: 17.0	**Risk of CVD mortality: Associated variables based on full model, HR (95% CI)** **Sodium (per 1313 mg):** 0.89 (0.77, 1.02) *p*=.0864 **Calories (per 849 kcal):** 0.98 (0.87, 1.11) *p*=.7394 **Sodium/calories (per 0.5787 mg/kcal):** 1.13 (1.04, 1.24) *p*=.0056 **Male:** 1.89 (1.71, 2.09) *p*<.0001 **Black race:** 1.05 (0.93, 1.18) *p*=0.4347 **History of CVD:** 1.63 (1.46, 1.80) *p*<.0001 **History of hypertension:** 1.09 (0.97, 1.22) *p*=.1668 **Age (per 15.9 yr)** 4.33 (3.98, 4.71) *p*<.0001 **BMI (per 5.15 kg/m^2)** 1.04 (0.99, 1.10) *p*=.1000 **SBP (per 24.98 mmHg)** 1.29 (1.23, 1.36) *p*<.0001 **Table salt use (always)** 0.99 (0.86, 1.13) *p*=.8510 **Table salt use (never)** 1.00 (0.89, 1.12)	**Loss to followup:** Data on sodium intake missing for 2 participants who were therefore excluded **Other methodological details:** This study was not included in Strazzullo et al.,[85] SR/MA because authors determined that it focuses on the same cohort as He et al., 1999[75] which used more stringent criteria Included participants with existing CVD Sodium intake based on 24-h dietary recall

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
		SC4: 11.6 SC5: 23.2 SC6: 17.4 SC7: 16.8 SC8: 13.8 **Weight, mean kg, (SD):** S1: 76.0 (14.5) S2: 76.4 (13.4) S3: 76.4 (14.2) S4: 77.7 (13.7) S5: 68.4 (16.3) S6: 66.3 (15.2) S7: 65.6 (14.3) S8: 64.3 (14.9) SC1: 77.7 (14.3) SC2: 76.4 (13.7) SC3: 76.0 (14.1) SC4: 76.2 (13.7) SC5: 66.4 (15.9) SC6: 66.2 (14.9) SC7: 65.7 (15.5) SC8: 66.1 (14.7) **BMI, mean kg/m² (SD):** S1: 25.7 (4.3) S2: 25.4 (4.0) S3: 25.2 (4.2) S4: 25.5 (4.1) S5: 26.6 (6.0) S6: 25.6 (5.7) S7: 25.3 (5.5) S8: 24.6 (5.5) SC1: 25.7 (4.2) SC2: 25.4 (4.1) SC3: 25.2 (4.2) SC4: 25.4 (4.1) SC5: 25.6 (5.9) SC6: 25.5 (5.5) SC7: 25.4 (5.9) SC8: 25.6 (5.6) **SBP mean mmHg (SD):** S1: 142.4 (24.9) S2: 138.8 (33.2)	*p*=.9825	

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
		S3: 136.0 (22.3) S4: 134.4 (20.6) S5: 136.7 (26.8) S6: 134.9 (26.1) S7: 133.7 (26.2) S8: 129.5 (24.5) SC1: 137.0 (22.8) SC2: 137.0 (22.9) SC3: 138.8 (22.6) SC4: 138.8 (23.7) SC5: 131.6 (25.5) SC6: 133.7 (25.8) SC7: 134.9 (26.4) SC8: 134.5 (26.4) **DBP, mean mmHg (SD):** S1: 87.3 (14.0) S2: 85.8 (13.0) S3: 84.5 (12.1) S4: 84.6 (11.8) S5: 83.5 (13.7) S6: 82.6 (13.8) S7: 81.8 (13.1) S8: 80.2 (12.8) SC1: 85.7 (12.8) SC2: 85.1 (12.8) SC3: 85.9 (12.8) SC4: 85.6 (12.9) SC1: 81.7 (13.7) SC2: 82.1 (13.3) SC3: 82.3 (13.1) SC4: 82.0 (13.4)		

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
NHANES Epidemiologic followup study He et al., 2002[76] Prospective cohort study Fair	**Study groups** G1: Overweight participants G2: Nonoverweight participants Dietary sodium and other nutrient intake estimates obtained by 24-h dietary recall baseline exam conducted from 1971 to 1975; incidence of CHF assessed using medical records and death certificates obtained in 1982 to 1984, 1986, 1987, and 1992 **Duration:** **Average followup:** 19 yr **Other study characteristics:** Dietary sodium and other nutrient intake estimates obtained by 24-h dietary recall; incidence of CHF assessed using medical records and death certificates	Men and women, 25 to 74 years of age, without a history of CHF ***n*:** G1: 5,129 G2: 5,233 **Age, mean yr (SD):** G1: 52.2 (15.2) G2: 48.2 (16.1) **Sex, male %:** G1: 44 G2: 36 **Race/ethnicity, %:** African American G1: 19 G2: 13 **Hypertension, %:** G1: 38 G2: 20 **SBP on medication, mean mmHg (SD):** G1: 141.0 (24.7) G2: 129.2 (23.4) **DBP on medication, mean mmHg (SD):** NR **Sodium intake, mean mmol/day (SD):** G1: 86.8 (58.2) G2: 91.1 (56.2)	**Number of cases of CHF by quartile of dietary sodium intake (mmol/d)** Quartile 0–50.2 G1: 208 G2: 110 Quartile >50.2–76.2 G1: 177 G2: 125 Quartile >76.2–113.6 G1: 146 G2: 91 Quartile >113.6 G1: 148 G2: 87 **RR* (95% CI) of CHF by quartile of dietary sodium intake (mmol/d):** Quartile 0–50.2 G1: 1.00 G2: 1.00 Quartile >50.2–76.2 G1: 1.04 (0.87, 1.24) G2: 0.88 (0.71, 1.09) Quartile >76.2–113.6 G1: 1.00 (0.79, 1.26) G2: 0.79 (0.63, 1.01) Quartile >113.6 G1: 1.40 (1.08, 1.81) G2: 0.84 (0.59, 1.20) **Multivariate relative risk* (95% CI) of CHF associated with a 100-mmol increase in dietary sodium intake:** G1: 1.25 (1.02, –1.54) G2: 0.97 (0.73, 1.30) *p*=.15 *adjusted for baseline age, sex, race, and total calorie (energy intake)	**Loss to followup:** 4% of eligible participants were lost to followup **Other methodological details:** Sodium intake based on 24-h dietary recall Low % LTF This study was not included in Strazzullo et al.,[85] meta-analysis because CHF was not an outcome of interest

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
NHANES III Yang et al., 2011[77] Prospective cohort study Fair	**Study groups** **Mean usual sodium intake mg/d (SE):** Men: 4,323 (21) Women: 2,918 (17) **Duration:** **Mean followup:** 14.8 yr **Other study characteristics:** Dietary information obtained from in person 24-h dietary recall; method developed at NCI to estimate usual intakes of sodium, potassium and total energy (since only 7% of participants provided a reliable second sample)	Nationally representative sample of U.S. adults ≥20 years of age **Age yr, *n* (%):** <60 Men: 4,444 (85.2) Women: 4,904 (85.1) ≥60 Men: 1,455 (14.8) Women: 1,464 (18.5) **Sex, female *n* (%):** 6368 (52) **Race/ethnicity, %:** Non-Hispanic White Men: 76.1 Women: 76.6 Non-Hispanic Black Men: 9.8 Women: 10.6 Mexican American Men: 6.1 Women: 4.7 **Weight:** NR **BMI, %:** <25 Men: 43.3 Women:54.4 25–30 Men: 40.2 Women: 24.7 >30 Men: 16.6 Women: 20.9 **Hypertension, %:** Men: 20.6 Women: 18.6 **G2:** **SBP, %:** <125 mmHg	**CVD Mortality by Estimated Usual Sodium Intake, mg (range 839–8555), HR* (95% CI):** Q1: 1.00 [reference] Q2: 0.95 (0.71, 1.27) Q3: 0.90 (0.51, 1.60) Q4: 0.83 (0.31, 2.28) Total: 0.94 (0.67, 1.32) **IHD Mortality by Estimated Usual Sodium Intake, mg (range 839–8555), HR* (95% CI):** Q1: 1.0 Q2: 1.17 (0.84, 1.62) Q3: 1.36 (0.71, 2.58) Q4: 1.70 (0.55, 5.27) Total: 1.20 (0.81, 1.77) **CVD Mortality by Sodium-Potassium Ratio, (range 0.46–2.98), HR* (95% CI):** Q1: 1.0 Q2: 1.13 (1.03, 1.23) Q3: 1.25 (1.07, 1.47) Q4: 1.46 (1.11, 1.92) Total: 1.90 (1.20, 3.03) * Adjusted for sex, race/ethnicity, educational attainment, BMI, smoking status, alcohol intake, total cholesterol, high-density lipoprotein cholesterol, physical activity, family history of CVD, and total calorie intake	**Loss to followup:** All MEC participants provided 24-h dietary recall; among 12,267 NHANES III participants who were eligible for this analysis, 912 (7.4%) provided reliable second 24-h dietary recalls. **Other methodological details:** Sodium intake based on a single 24-h dietary recall Repeated exposure measurement only performed on 7% of participants

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
		Men: 62.6 Women: 74.6 ≥125 mmHg Men: 37.4 Women:25.4 **DBP, %:** <85 mmHg Men: 83.1 Women:93.1 ≥85 Men: 16.9 Women: 6.9		
O'Donnell et al., 2011[78] Retrospective cohort study [retrospective observational analysis combining populations of 2 RCTs] Fair	**Study groups** Defined by sodium excretion, g/d G1: <2 G2: 2–2.99 G3: 3–3.99 G4: 4–5.99 G5: 6–6.99 G6: 7–8 G7: >8 **Duration** Median followup: 58 mo **Other study characteristics:** Populations from two RCTs: ONTARGET and TRANSCEND ONTARGET: rampiril 10 mg/d vs. telmisartan 80 mg/d vs. their combination in 25,620 patients. TRANSCEND: telmisartan 80 mg/d vs. placebo in 5,926 ACE-inhibitor intolerant participants This analysis combined the 2 cohorts to assess the association between urinary sodium and potassium and CV events. Morning fasting urine sample obtained prior to run-in period of the RCTs	High-risk patients with coronary, peripheral, or cerebrovascular disease or diabetes with end-organ damage ***n*:** G1: 818 G2 + G3: 8,353 G4: 14,156 G5 + G6: 4,706 G7: 847 **Age, mean yr (SD):** G1: 67.61 (7.62) G2 + G3: 67.04 (7.42) G4: 66.46 (7.15) G5 + G6: 65.79 (6.95) G7: 65.37 (6.75) **Sex, female *n* (%):** G1: 438 (53.5) G2 + G3: 3172 (38.0) G4: 3764 (26.6) G5 + G6: 952 (20.2) G7: 178 (21.0) **Race/ethnicity, *n* (%):** White/European G1: 521 (63.7) G2 + G3: 5851 (70.0) G4: 10249 (72.4) G5 + G6: 3387 (72.0)	**Association between estimated 24-h urinary Na excretion and CV events and mortality multivariate analysis, HR (95% CI):** Composite Outcome: CV mortality, MI, Stroke, and Hospitalization for CHF: G1: 1.21 (1.03, 1.43) G2: 1.16 (1.04, 1.28) G3: 1.06 (0.98, 1.14) G4: 1 [reference] G5: 1.09 (0.99, 1.20) G6: 1.15 (1.00, 1.32) G7: 1.49 (1.28, 1.75) **Association between estimated 24-h urinary Na excretion and CV events and mortality multivariate analysis, HR (95% CI):** CV death: G1: 1.37 (1.09, 1.73) G2: 1.19 (1.02, 1.39) G3: 1.09 (0.96, 1.23) G4: 1 [reference] G5: 1.11 (0.96, 1.29) G6: 1.53 (1.26, 1.86) G7: 1.66 (1.31, 2.10) MI: G1: 1.10 (0.80, 1.53) G2: 1.04 (0.85, 1.27) G3: 1.11 (0.96, 1.28) G4: 1 [reference]	**Loss to followup:** 0.2% **Other methodological details:** Used 1st morning void rather than 24-h Equation used to estimate total sodium excretion was developed for an Asian population Key potential confounders not addressed adequately Numerous significant differences between groups at baseline High participation rate (91.6% of those enrolled in the RCTs) Low % LTF

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
		G7: 620 (73.2) **BMI, mean kg/m² (SD):** G1: 27.32 (4.63) G2 + G3: 27.48 (4.51) G4: 28.05 (4.38) G5 + G6: 29.13 (4.70) G7: 30.17 (4.70) **Weight, mean kg (SD):** NR **Hypertension, *n* (%):** G1: 640 (78.2) G2 + G3: 5761 (69.0) G4: 9616 (67.9) G5 + G6: 3488 (74.1) G7: 695 (82.1) **SBP, mean mmHg (SD):** G1: 138.61 (17.63) G2 + G3: 140.81 (17.32) G4: 141.96 (17.39) G5 + G6: 142.95 (16.80) G7: 142.93 (17.01) **DBP, mean mmHg (SD):** NR **Urinary sodium, mean g/day (SD):** G1: 1.55 (0.35) G2 + G3: 3.24 (0.53) G4: 4.93 (0.56) G5 + G6: 6.71 (0.53) G7: 9.40 (1.81)	G5: 1.21 (1.03, 1.43) G6: 1.11 (0.85, 1.44) G7: 1.48 (1.11, 1.98) Stroke G1: 1.06 (0.76, 1.46) G2: 1.05 (0.89, 1.28) G3: 0.97 (0.83, 1.13) G4: 1 [reference] G5: 0.95 (0.79, 1.15) G6: 1.06 (0.81, 1.40) G7: 1.48 (1.09, 2.01)	

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
Stolarz-Skrzpek et al., 2011[84] Prospective cohort study following participants from 2 population-based cohorts FLEMENGHO set in Northern Belgium, EPOGH set in Europe Fair	**Study groups** G1: Outcome cohort G2: Hypertension cohort G3: Blood pressure cohort **Duration:** **Median followup:** G1: 7.93 yr G2: 6.48 yr G3: 6.14 yr **Other study characteristics:** Experienced observers measured blood pressure at baseline and followup; sodium and potassium excretion measured; outcomes adjudicated against source documents in each country.	Adults without CVD ***n*:** G1: 3681 G2: 2096 G3: 1499 **Age, mean yr (SD):** G1: 40.9 (16.3) G2: 38.6 (14.6) G3: 38.3 (14.2) **Sex, female %:** G1: 52.7 G2: 54.1 G3: 52.4 **Race/ethnicity, %:** NR **Overweight, %:** NR **BMI:** G1: 25.2 (4.6) G2: 24.5 (4.0) G3: 24.6 (4.0) **Hypertension, %:** G1: 25.8 G2: 0 G3: 9.9 **SBP, mean mmHg (SD):** G1: 124.7 (17.1) G2: 118.7 (10.4) G3: 120.9 (12.8) **DBP, mean mmHg (SD):** G1: 76.3 (10.6) G2: 73.3 (8.0) G3: 74.6 (8.9) **Urinary sodium, mean mmol/day (SD):** G1: 178.0 (74.8) G2: 174.2 (74.1) G3:172.7 (62.5)	**Outcomes by tertile of 24-h urinary sodium excretion (tertiles: low, medium, high) adjusted HR (95% CI):** Cardiovascular mortality: Low: 1.56 (1.02–2.36) Medium: 1.05 (0.72–1.53) High: 0.95 (0.66–1.38) All CV events (fatal and nonfatal) Low: 1.13 (0.90–1.42) Medium: 1.11 (0.90–1.36) High: 0.90 (0.73–1.11) Coronary events (fatal and nonfatal) Low: 1.42 (0.99–2.04) Medium: 1.17 (0.89–1.54) High: 0.86 (0.55–1.13) Stroke (fatal and nonfatal) Low: 1.07 (0.57–2.00) Medium: 1.29 (0.75–2.20) High: 0.78 (0.45–1.33)	**Loss to followup:** During followup, 219 participants died, 16 became seriously ill, and 259 moved out of the study areas, potentially leaving 3,187 participants, 2,856 (89.6%) of whom agreed to take part in examinations. **Other methodological details:** Used 24-h urine excretion. Reference group is entire study population rather than group with highest or lowest sodium excretion. Considerable amount of missing data but no sensitivity analyses
Takachi et al., 2010[80]	**Study groups**	Japanese adults, ages 40 to 59 years (cohort I), ages	**CVD by sodium consumption, HR (95% CI):**	**Loss to followup:**

Study Cited Design Setting Quality Rating	Study Groups and Details Duration	Sample Characteristics	Results	Loss to followup Methodological details
Prospective cohort study Japan, 11 public health centers Fair	G1: Lowest Quintile of Sodium intake G2: Second Quintile of Sodium intake G3: Third Quintile of Sodium intake G4: Fourth Quintile of Sodium intake G5: Highest Quintile of Sodium intake **Duration:** Followup: 7 to 9 yr **Other study characteristics:** Examination of associations between sodium and salted food consumption and CVD risk using validated food frequency questionnaires.	40 to 69 years (cohort II) **Age, mean yr (SD):** G1: 56.1 (8.0) G2: 56.4 (7.8) G3: 56.7 (7.7) G4: 57.1 (7.6) G5: 57.9 (7.6) **Sex, female *n:*** G1: 5930 G2: 7450 G3: 8371 G4: 9468 G5: 10551 **Race/ethnicity, %:** NR **Overweight, %:** NR **BMI, mean kg/m^2:** G1: 28.2 G2: 28.0 G3: 28.7 G4: 29.8 G5: 31.1 **SBP, mean mmHg (SD):** NR **DBP, mean mmHg (SD):** NR **Urinary sodium, mean mmol/day (SD):** NR **Mean sodium consumption, mg:** G1: 3084 G2: 4005 G3: 4709 G4: 5503 G5: 6844	G1: 1.00 (reference) G2: 1.11 (0.96, 1.29) G3: 1.02 (0.87, 1.19) G4: 1.10 (0.94, 1.29) G5: 1.19 (1.01, 1.40) *p*=.06 for trend **Stroke by sodium consumption, HR (95% CI):** G1: 1.00 (reference) G2: 1.05 (0.90, 1.24) G3: 0.97 (0.82, 1.14) G4: 1.08 (0.92, 1.28) G5: 1.21 (1.01, 1.43) *p*=.03 for trend	**Other methodological details:** Questionnaire not sensitive for sodium intake

CQ2 Summary Table C–7. Potassium and Blood Pressure and CVD Outcomes

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Nutrient Intake
Charlton et al., 2008[62] RCT South Africa, Cape Town township Good	**Treatment groups:** G1: Food-based intervention G2: Control G1: Intervention comprised 5 commonly consumed food items (brown bread, margarine, stock cubes, soup mixes, and Aromat) modified in Na, K, Mg and Ca content plus a salt replacement and 500 ml of maas (fermented milk). G2: Control diet provided the same foods but of standard commercial composition, as well as artificially sweetened cold drink instead of maas. Based on laboratory-determined chemical food analyses, compared to control foods, the intervention foods were planned to provide 41% less Na (100.3 vs. 170.3 mmol/d), 826% more K (70.9 vs. 8.6 mmol/d), 388% more Ca (857 vs. 221 mg/d) and 368% more Mg (13.8 v. 3.7 mmol/d.) **Duration:** **Run-in:** 3 weeks Treatment: 8 weeks **Intervention delivery:** Subjects were instructed to consume their usual amounts of food and sufficient food was provided for the whole family. A single dietitian was responsible for food-packing and all food was locked and sealed in large shopping bags, labeled only with participants' names and contact details. A driver delivered the food three times a week.	Black residents of a Cape Town township, 50 to 75 years of age, with drug-treated mild-to-moderate hypertension (SBP≤160 mmHg, DBP≤95 mmHg) ***n*:** G1: 47 G2: 45 **Age, mean yr (SD):** G1: 61.8 (6.6) G2: 60.4 (7.4) **Sex, male, *n*:** G1: 7 G2: 6 **Sex, female, *n*:** G1: 33 G2: 34 **Race, % Black:** G1: 100 G2: 100 **Weight, mean kg (SD):** G1: 83.3 (13.7) G2: 88.8 (15.5) **BMI, kg/m² (SD):** G1: 32.9 (5.8) G2: 35.3 (6.0) **Mean SBP, mmHg (SD):** G1: 133.9 (14.6) G2: 135.4 (16.7) **Mean DBP, mmHg (SD):** G1: 79.8 (8.6) G2: 82.3 (7.5)	**Mean net difference (G1–G2), mmHg (95% CI)** **SBP, Office:** –6.194 (–11.442, –0.945) *p*=.021 **DBP, Office:** –0.595 (–3.019, 1.829) **24-h ABPM, Avg SBP:** –4.527 (–9.047, –0.006) *p*=.050 **24-h ABPM, Avg DBP:** –2.494 (–5.160, 0.173) *p*=.066	**Mean within group change from baseline** **Urinary Na, mmol/24h (SD):** G1: –14.6 (54.4) G2: –5.9 (54.3) **Urinary K, mmol/24h (SD):** G1: 20.0 (22.7) G2: –4.6 (14.8) **Urinary Mg, mmol/24h (SD):** G1: +0.88 (1.20) G2: +0.19 (0.81) **Urinary Ca, mmol/24h (SD):** G1: +0.27 (1.00) G2: +0.32 (1.11) **Mean between group difference (G1–G2)** **Urinary Na, mmol/24h (SD):** –8.7 (46.9) **Urinary K, mmol/24h (SD):** +24.6 (16.5) *p*<.001 **Urinary Mg, mmol/24h (SD):** +0.68 (0.88) *p*<.05 **Urinary Ca, mmol/24h (SD):** –0.05 (0.91)	**Withdrawals, *n* (%):** G1: 7 (14.9) G2: 5 (11.1) **Adherence:** Dietary compliance was monitored using data from 24-h recalls and 24-h urinary electrolyte concentrations; returned salt and Aromat shakers were weighed weekly. **Reported daily dietary intake: mean difference (G1–G2)** Na, mg (SD) –1,167 (1532) *p*<.01 K, mg (SD) 867 (890) *p*<.0001 Mg, (SD) 71 (89) *p*<.001 Ca, mg (SD) 310 (392) *p*<.001

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Nutrient Intake
China Salt Substitute Study China Salt Study Collaborative Group, 2007[61]; Hu et al., 2009[60] RCT China, 39 sites distributed between 6 regional coordinating centers Good	**Treatment groups:** G1: Salt substitute G2: Normal salt G1: Salt substitute was 65% Na Cl, 25% K Cl, and 10% Mg sulphate G2: normal salt was 100% Na Cl **Duration:** **Run-in:** 4 week run-in on salt substitute Treatment: 12 mo **Characteristics of treatment delivery:** Participants were instructed to use study salt for all food preparation throughout the study duration; existing salt and foods previously pickled in salt were not removed from participants' households. Salt (substitute & normal) was delivered in identical 1 kg bags; up to 3 kg/mo available to each randomized participant to cover all household uses.	Adult males and females, living in rural China, at elevated risk of future vascular disease ***n*:** G1: 306 G2: 302 **Age, mean yr (SD):** G1: 59 (10.0) G2: 61 (9.7) **Sex, female, *n* (%):** G1:166 (52) G2:174 (58) **Race/ethnicity:** All were "rural Chinese" **Weight:** NR **BMI, mean kg/m² (SD):** G1: 26 (3.6) G2: 25 (3.9) **Mean SBP, mmHg (SD):** G1: 159 (25) G2: 159 (26) **Mean DBP, mmHg (SD):** G1: 93 (14) G2: 93 (14) **Urinary sodium, mean mmol/day (IQR):** G1: 151 (92–201) G2: 154 (94–200)	**SBP** **SBP lower in G1 vs. G2 at 6, 9 and 12 mo visits; (data reported in figure)** *p*<.002) **Maximum net reduction achieved at 12 mo:** 5.4 (2.3, 8.5) **Over 12 mo:** **SBP mean difference, mmHg (95% CI):** G1 vs. G2: 3.7 (1.6, 5.9) *p*<.001 **DBP** No differences between groups at any time (*p*>.20)	No significant differences between groups in first morning urine sodium concentrations at 6 mo or 12 mo. G1 had significantly higher first morning urine concentrations of potassium at 6 mo and 12 mo. **6 mo, mmol/L (IQR)** 6.8 (1.8, 11.8) **12 mo, mmol/L (IQR):** 7.2 (2.2, 12.3)	**Withdrawals, *n* (%):** G1: 14 (4.6) G2: 9 (3) **Nutrient intake:** Concentrations of sodium and potassium were measured.

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Nutrient Intake
DASH Appel et al., 1997[30]; Sacks et al., 1999[31]; Obarzanek et al., 2001[32] RCT USA, outpatient medical setting Good	**Treatment groups:** G1: DASH diet G2: Fruits and vegetables diet G3: Control diet Run-in: 37% fat, 48% CHO, 15% protein, 16% SF, 9 g fiber, and 300 mg/d of cholesterol G1: Diet rich in fruits, vegetables, and low-fat dairy foods; reduced in saturated fat, total fat, and cholesterol; and modestly increased in protein. Diet was designed to provide 27% kcal from fat, 55% CHO, 18% protein, 6% SF, 13% MUFA, 8% PUFA, 31 g fiber, 150 mg/d of cholesterol, 4,700 mg potassium, 500 mg magnesium, 1,240 mg calcium, 3,000 mg sodium. G2: Diet rich in fruits and vegetables otherwise similar to control. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 31 g fiber, 300 mg/d of cholesterol, 4,770 mg potassium, 500 mg magnesium, 450 mg calcium, 3,000 mg sodium G3: Control diet typical of that consumed by Americans. 37% fat, 48% CHO, 15% protein, 16% SF, 13% MUFA, 8% PUFA, 9 g fiber, 300 mg/d of cholesterol, 1,700 mg potassium, 165 mg magnesium, 450 mg calcium, 3,000 mg sodium There were four calorie levels of 1,600, 2,100, 2,600, or 3,100 kcal for each diet. Weight was and was kept stable by changing calorie level. Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal **Duration** Run-in: 3 weeks Treatment: 8 weeks **Intervention delivery** Participants attended the clinic each	Adults ≥22 years; SBP <160 mmHg and a DBP of 80–95 mmHg ***n*:** G1: 151 G2: 154 G3: 154 **Age, mean yr (SD):** G1: 44 (10) G2: 45 (11) G3: 44 (11) **Sex, *n* (%):** Male G1: 74 (49.0) G2: 79 (51.3) G3: 81 (52.6) Female G1: 77 (51.0) G2: 75 (48.7) G3: 73 (47.4) **Race/ethnicity, *n** (%):** Black G1: 93 (61.1) G2: 90 (58.4) G3: 92 (59.7) Non-minority G1: 47 (31.1) G2: 55 (35.7) G3: 54 (35.1) Other Minority G1: 11 (7.3) G2: 9 (5.8) G3: 8 (5.2) **Mean Weight, kg:** G1: 83.4 G2: 81.8 G3: 81.5 **Mean BMI, kg/m^2*:** G1: 28.5 G2: 28.2	**At 8 weeks** **Mean change in SBP, mmHg (97.5% CI)** G1 vs. G2: –2.7 (–4.6, –0.9) *p*=.001 G1 vs. G3: –5.5 (–7.4, –3.7) *p*<.001 G2 vs. G3:–2.8 (–4.7, –0.9) *p*<.001 **Mean change in DBP, mmHg (97.5% CI)** G1 vs.G2: –1.9 (–3.3, –0.6) *p*=.002 G1 vs. G3: –3.0 (–4.3, –1.6) *p*<.001 G2 vs. G3: –1.1 (–2.4, 0.3) *p*=.07	NR	**Withdrawals, *n* (%):*:** G1: 2 (1.3) G2: 4 (2.6) G3: 7 (4.5)

Study Cited Design Setting Quality Rating	Intervention Groups and Details Duration	Sample Characteristics	Blood Pressure Outcomes	Urinary Excretion	Attrition Adherence/Compliance Nutrient Intake
	weekday to be weighed and to consume one meal onsite (lunch or dinner). All other food was provided, including weekend meals. 0.2 g of sodium was provided daily for discretionary use. Beverages and salt were discretionary items and participants were required to record their consumption. Three servings of designated nonalcoholic beverages and up to 2 servings of specific alcoholic beverages were allowed. *Nutrient values presented for all diets are representative of the diets at the energy level of 2,100 kcal	G3: 28.0 **SBP, mmHg (SD):** G1: 131.2 (10.0) G2: 132.3 (10.5) G3: 132 (10.7) **DBP, mmHg (SD):** G1: 85.1 (3.6) G2: 84.8 (3.9) G3: 85.3 (4.0)			

CQ2 Summary Table C–8. Potassium and CVD Outcomes

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
CVD-FACTS (CardioVascular Disease risk FACtor Two-township study) Weng et al., 2008[92] Prospective cohort study Fair	**Study groups:** G1: Nonevent Group G2: Ischemic Event Group **Duration** Followup: 10.6 yr Potassium intake obtained from food frequency questionnaire. Nutrient intakes were calorie-adjusted by residual method.	Adults >40 years of age who were stroke and cancer free at baseline from CVD-FACTS ***n*:** G1: 1640 G2: 132 **Age, mean yr (SD):** G1: 56.1 (9.8) G2: 62.2 (8.1) **Sex, male (%):** G1:43.7 G2:49.2 **Race/ethnicity:** NR **Weight:** NR **BMI, mean kg/m² (SD):** G1: 24.4 (3.3) G2: 25.3 (3.4) **SBP:** NR **DBP:** NR	**Quartiles of potassium intake, mg:** Q4 + Q3 High: >3,150 Q2: 2,556–3,150 Q1 Low: <2,555 **Hazard ratios for incident IS by quartiles of potassium intake HR* (95% CI):** Q4 + Q3: 1 Q2: 1.20 (0.77, 1.86) Q1: 1.69 (1.12, 2.56) *p* for trend =0.017 *Adjusted for age, sex, hypertension, use of antihypertensive drugs, DM, area (township), central obesity, alcohol consumption habits, smoking habit, sex-smoking habit interaction, BMI, self-report heart disease hypercholesterolemia, hypertriglyceridemia, physical activity, fibrinogen, apolipoprotein B, and plasminogen
Green et al., 2002[91] Prospective cohort study Fair	**Study groups:** By quintile based on serum potassium and by quintile based on dietary potassium **Serum potassium, mEq/L:** G1: 2.6–3.8 G2: 3.81–4.0 G3: 4.01–4.2 G4: 4.21–4.4 G5: 4.41–5.8 **Dietary Potassium, g/d:** G6: ≤2.34 G7: 2.35–2.92 G8: 2.93–3.47 G9: 3.48–4.16	Adult men and women >65 years of age who were stroke-free at baseline **Age, yr:** G1: G2: 72.4 G3: G5: 72.9 G6: 72.7 G7: G10: 72.8 **Sex, female, *n* (%):** G1: G2: 1340 (68) G3: G5: 1894 (53) G6: 601 (60) G7: G10: 2268 (57) **Race, African American, *N* (%):** G1: G2: 398 (20)	**Relative risk* (95% CI) for stroke for serum potassium:** Nondiuretic user: 1.01 (0.88, 1.15); *p*=NS Diuretic user: 1.38 (1.20, 1.59); *p*<.0001 *p* for interaction <.005 **Relative risk* (95% CI) for stroke for dietary potassium:** Nondiuretic user: 1.18 (1.04, 1.33); *p*<.01 Diuretic user: 0.89 (0.77, 1.03); *p*=NS *p* for interaction <.005 *Cox models included age, sex, history of DM, HTN, CAD, CHF, AF, SBP, serum creatinine, potassium supplement use, and serum potassium in the dietary potassium model RR are for one SD decrease **Relationship of serum potassium levels in quintiles to stroke risk by diuretic use, RR† (95% CI):**

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
	G10: ≥4.17 **Duration:** **Followup:** 4 to 8 yr Dietary potassium intake determined by food frequency questionnaire administered at single time. Baseline testing included potassium level	G3: G5: 419 (12) G6: 52 (5) G7: G10: 177 (4) **Weight:** NR **SBP, mean mmHg:** G1; G2: 138 G3: G5: 135 G6: 137 G7: G10: 135 **DBP, mean mmHg:** G1: G2: 72 G3: G5: 70 G6: 71 G7: G10: 70	Nonusers of diuretics G1: 1.07 (0.68, 1.69) G2: 0.94 (0.63, 1.4) G3: 1.07 (0.77, 1.49) G4: 1.10 (0.8, 1.53) G5: 1.0 *p*=.96 Users of diuretics G1: 2.37 (1.33, 4.23) G2: 2.21 (1.21, 4.03) G3: 0.77 (0.37, 1.59) G4: 1.06 (0.53, 2.14) G5: 1.0 *p*<.001 †Cox models included age, sex, history of DM, HTN, CAD, CHF, AF, SBP, serum creatinine, and potassium supplement use. **Relationship of dietary potassium levels in quintiles to stroke risk by diuretic use, RR‡ (95% CI):** Nonusers of diuretics G6: 1.76 (1.21, 2.57) G7: 1.22 (0.81, 1.83) G8: 1.11 (0.73, 1.67) G9: 1.37 (0.93, 2.04) G10: 1.0 *p*<.025 Users of diuretics G6: 0.87 (0.54, 1.40) G7: 0.66 (0.40, 1.11) G8: 0.66 (0.40, 1.10) G9: 1.09 (0.69, 1.73) G10: 1.0 *p*=NS ‡Cox models included age, sex, history of DM, HTN, CAD, CHF, AF, SBP, serum creatinine, serum potassium and potassium supplement use

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
Health Professionals Followup Study Al-Delaimy et al., 2004[89] Prospective cohort study Fair	**Study groups:** By quintile based on median potassium intake, mg/d G1: 2,632 G2: 3,042 G3: 3,341 G4: 3,672 G5: 4,250 **Duration:** **Followup:** 12 yr Food frequency questionnaire administered in 1986 and updated in 1990 and 1994.	Health professionals 40 to 75 years of age who completed a food frequency questionnaire for the Health Professionals Followup Study, had a daily caloric intake of 800 to 4,200 kcal, and had <70 blanks on the food item questionnaire, did not have MI or CVD at baseline, and had no diagnosis of cancer at baseline Baseline characteristics were reported by magnesium quintile and not by potassium quintile so not reported here. Total sample was predominantly white ***N:*** Total: 39,633 NR by potassium group	**Number of CHD cases:** G1: 268 G2: 248 G3: 296 G4: 283 G5: 354 **Adjusted relative risk of developing CHD by potassium quintile:** Age-adjusted RR (95% CI) G1: 1.00 G2: 0.87 (0.74, 1.04) G3: 1.01 (0.86, 1.20) G4: 0.89 (0.75, 1.05) G5: 0.99 (0.84, 1.16) Multivariate* RR (95% CI) G1: 1.00 G2: 0.92 (0.77, 1.10) G3: 1.06 (0.90, 1.26) G4: 0.95 (0.80, 1.12) G5: 1.01 (0.86, 1.20) *p*=.83 Multi-nutrient† RR (95% CI) G1: 1.00 G2: 0.99 (0.82, 1.19) G3: 1.18 (0.97, 1.43) G4: 1.10 (0.89, 1.32) G5: 1.27 (1.01, 1.58) *p*=.03 *Covariates: age, time period, energy intake, history of diabetes, history of high cholesterol, family history of MI, smoking history, aspirin intake, BMI, alcohol intake, physical activity, vitamin E intake †The above covariates plus nutrient variables: *trans* fatty acid, total protein intake, cereal fiber, folate, omega-3 fatty acid, magnesium

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
Health Professionals Followup Study Ascherio et al., 1998[90] Prospective cohort study Fair	**Study groups:** By quintile based on median potassium intake, mg/d G1: 2632 G2: 3042 G3: 3341 G4: 3672 G5: 4250 **Duration:** **Followup:** 8 yr Food frequency questionnaire administered in 1986 and updated in 1990 and 1994.	Health professionals 40 to 75 years of age who completed a food frequency questionnaire for the Health Professionals Followup Study, had a daily caloric intake of 800 to 4,200 kcal, and had <70 blanks on the food item questionnaire. ***n*:** Total: 43,738 **Age, mean yr (SD):** NR **Sex, male %:** 100 **Race/ethnicity, %:** NR **Weight:** NR **BMI:** NR **SBP, mean mmHg:** G1: 131 G5: 129 **DBP, mean mmHg:** G1: 82 G5: 81	**Stroke, number of cases:** G1: 76 G2: 65 G3: 62 G4: 64 G5: 61 **Adjusted relative risk of stroke by potassium intake:** Age-adjusted RR G1: 1.0 G2: 0.80 G3: 0.71 G4: 0.68 G5: 0.59 *p*=.004 Multivariate* RR (95% CI) G1: 1.0 G2: 0.85 (0.61, 1.18) G3: 0.78 (0.55, 1.10) G4: 0.76 (0.54, 1.07) G5: 0.62 (0.43, 0.88) *p*=.007 Further Adjusted† RR (95% CI) G1: 1.0 G2: 0.86 (0.61, 1.23) G3: 0.82 (0.56, 1.20) G4: 0.83 (0.56, 1.24) G5: 0.69 (0.45, 1.07) *p*=.110 *Model includes age, total energy intake, smoking, alcohol consumption, history of hypertension, history of hypercholesterolemia, parental history of MI before age 65, profession, and quintiles of BMI and physical activity † Above model plus fiber and magnesium intake

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
Japan Collaborative Cohort Study for Evaluation of Cancer Risks Umesawa et al., 2008[71] Prospective cohort study Fair	Divided into quintiles (low to high) based on potassium intake **Study groups, median mmol/d (SD):** G1: 35 (6) G2: 44 (2) G3: 51 (2) G4: 58 (2) G5:68 (6) **Duration:** **Average followup: 12.7 yr** Potassium intake obtained from food frequency questionnaire	Adults, 40 to 79 years of age, who provided valid responses to dietary questionnaires, no medical history of stroke, CHD, or cancer ***n*:** G1: 11,746 G2: 11,746 G3: 11,746 G4: 11,746 G5: 11,746 **Age, yr (SD):** G1: 55 (10) G2: 56 (10) G3: 56 (10) G4: 57 (10) G5: 58 (10) **Sex, % male:** G1: 67 G2: 44 G3: 35 G4: 29 G5: 23 **Race/ethnicity:** NR **Weight:** NR **BMI*, mean kg/m^2:** G1: 22.8 G2: 22.8 G3: 22.8 G4: 22.9 G5: 22.9 *Age- and sex-adjusted **SBP:** NR **DBP:** NR **Calibrated* potassium intake, median mmol/d (SD):** G1: 44 (8) G2: 56 (3) G3: 65 (2) G4: 73 (3) G5: 86 (8)	**Hazard ratios of mortality from stroke:** Age- and sex-adjusted HR (95% CI): G1: 1.00 G2: 0.88 (0.72, 1.08) G3: 0.84 (0.69, 1.03) G4: 0.88 (0.72, 1.07) G5:0.77 (0.63, 0.94) *p* for trend = .021 **Multivariable HR* (95% CI):** G1: 1.00 G2: 0.93 (0.71, 1.17) G3: 0.91 (0.70, 1.19) G4: 1.01 (0.77, 1.34) G5: 0.96 (0.70, 1.31) *p* for trend = .967 **Multivariable HR† (95% CI):** G1: 1.00 G2: 0.89 (0.71, 1.13) G3: 0.84 (0.65, 1.10) G4: 0.91 (0.69, 1.22) G5: 0.83 (0.60, 1.14) *p* for trend = 0.355 **Hazard ratios of mortality from CHD:** Age- and sex-adjusted HR (95% CI): G1: 1.00 G2: 0.79 (0.59, 1.05) G3: 0.72 (0.54, 0.97) G4: 0.65 (0.48, 0.88) G5: 0.57 (0.42, 0.77) *p* for trend <.001 **Multivariable HR* (95% CI):** G1: 1.00 G2: 0.81 (0.58, 1.13) G3: 0.74 (0.51, 1.09) G4: 0.69 (0.45, 1.06) G5: 0.69 (0.43, 1.12) *p* for trend = .127 **Multivariable HR† (95% CI):** G1: 1.00 G2: 0.80 (0.57, 1.11) G3: 0.72 (0.49, 1.07) G4: 0.66 (0.43, 1.03)

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
		*from a validation study	G5: 0.65 (0.39, 1.06) *p* for trend = .083 **Hazard ratio of mortality from total CVD:** Age- and sex-adjusted HR (95% CI): G1: 1.00 G2: 0.84 (0.73, 0.96) G3: 0.82 (0.72, 0.94) G4: 0.84 (0.73, 0.96) G5: 0.71 (0.62, 0.81) *p* for trend <.001 **Multivariable HR* (95% CI):** G1: 1.00 G2: 0.88 (0.75, 1.02) G3: 0.86 (0.72, 1.03) G4: 0.91 (0.75, 1.10) G5: 0.82 (0.66, 1.02) *p* for trend = .153 **Multivariable HR† (95% CI):** G1: 1.00 G2: 0.84 (0.72, 0.99) G3: 0.81 (0.67, 0.97) G4: 0.84 (0.69, 1.02) G5: 0.73 (0.59, 0.92) *p* for trend = .018 *Cox proportional hazard models adjusted further for BMI, smoking status, ethanol intake, history of HTN, history of diabetes, menopause, HRT, time spent on sports activity, walking time, educational status, perceived mental stress, and calcium intake †Cox proportional hazard models adjusted further for sodium intake

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
Marniemi et al., 2005[79] Case-control study Finland, population-based health survey Fair	**Study groups:** G1: AMI cases G2: AMI controls G3: Stroke cases G4: Stroke controls **Duration:** Followup for up to 10 yr Food consumption information obtained from dietary history interview	Elderly men and women, 65 to 99 years of age ***n*:** G1: 130 G2: 559 G3: 70 G4: 590 **Age, mean yr (SD):** NR **Sex, female %:** NR **Race/ethnicity, %:** NR **Overweight, %:** NR **BMI:** NR **SBP, mean mmHg (SD):** NR **DBP, mean mmHg (SD):** NR	**Daily potassium, mean mg (SD):** G1: 3,900 (1250) G2: 4,090 (1350) G3: 4,110 (1430) G4: 4,140 (1330) **Serum concentration of potassium, mean mmol/L (SD):** G1: 4.25 (0.34) G2: 4.22 (0.35) G3: 4.25 (0.37) G4: 4.23 (0.37) **Adjusted* RR (95% CI) of AMI and stroke between tertiles of potassium intake:** Middle tertile vs. lowest tertile AMI: 0.821 (0.53, 1.27) Stroke: 1.21 (0.68, 2.14) Highest tertile vs. lowest tertile AMI: 0.847 (0.50, 1.43) Stroke: 0.751 (0.35, 1.60) *Adjusted in Cox proportional hazards model for age, gender, smoking, functional capacity and weight adjusted energy intake **Adjusted* RR (95% CI) of AMI and stroke between tertiles of serum concentration of potassium:** Middle tertile vs. lowest tertile AMI: 1.27 (0.82, 1.98) Stroke: 1.39 (0.74, 2.60) Highest tertile vs. lowest tertile AMI: 1.12 (0.72, 1.76) Stroke: 1.40 (0.75, 2.60) *Adjusted for age, gender, smoking, and functional capacity

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
NHANES Bazzano et al., 2001[88] Prospective cohort study Fair	Participants were divided into quartile groupings based on their potassium intake, mmol/24h **Study groups:** G1: <34.6 G2: 34.6–49.8 G3: 49.8–68.4 G4: >68.4 **Duration:** **Average followup:** 19 yr	NHANES I participants who were ages 25 to 74 at their baseline examinations between 1971 and 1975 ***n:*** G1: 2,452 G2: 2,451 G3: 2,450 G4: 2,452 **Age yr, mean (SD):** G1: 50.1 (15.9) G2: 50.7 (15.8) G3: 49.3 (15.5) G4: 46.6 (14.8) **Sex, male, %:** G1: 23.0 G2: 31.0 G3: 39.6 G4: 60.0 **Race/ethnicity, %:** White: G1: 68.5 G2: 84.9 G3: 89.6 G4: 92.0 **Weight:** NR **BMI, kg/m² mean (SD):** G1: 26.4 (5.8) G2: 25.8 (5.2) G3: 25.2 (4.8) G4: 25.1 (4.6) **SBP mmHg mean (SD):** G1: 137.8 (26.6) G2: 135.4 (24.8) G3: 133.5 (24.3) G4: 130.6 (20.4) **DBP mmHg mean (SD):** G1: 84.5 (13.8) G2: 83.1 (13.2) G3: 82.8 (13.0)	**Stroke incidence, events:** G1: 287 G2: 230 G3: 235 G4: 175 **Stroke HR (95% CI), adjusted for age, race, sex, energy:** G1: 1.0 G2: 0.76 (0.65, 0.88) G3: 0.84 (0.72, 0.99) G4: 0.76 (0.60, 0.97) *p* for trend = .07 **Stroke HR (95% CI) multivariate:*** G1: 1.0 G2: 0.75 (0.63, 0.88) G3: 0.85 (0.71, 1.01) G4: 0.76 (0.58, 1.01) *p* for trend = .14 **CHD Incidence, events:** G1: 456 G2: 504 G3: 456 G4: 431 **CHD HR (95% CI), adjusted for age, race, sex, energy:** G1: 1.0 G2: 1.00 (0.86, 1.15) G3: 0.90 (0.77, 1.06) G4: 0.97 (0.79, 1.19) *p* for trend = .57 **CHD HR (95% CI) multivariate:*** G1: 1.0 G2: 10.4 (0.89, 1.20) G3: 0.95 (0.78, 1.17) G4: 1.01 (0.78, 1.33) *p* for trend = .93 **Stroke incidence associated with low dietary potassium intake, HR (95% CI):** Age, energy adjusted: 1.37 (1.20, 1.54); *p*<.0001 Age, race, sex, energy adjusted: 1.26 (1.11, 1.45); *p*=.0007 Multivariate*: 1.28 (1.11, 1.47); *p*=.0001 **CHD incidence associated with low dietary potassium intake, HR (95% CI):**

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
		G4: 82.4 (12.0)	Age, energy adjusted: 1.04 (0.92, 1.18); *p*=.54 Age, race, sex, energy adjusted: 1.04 (0.91, 1.19); *p*=.53 Multivariate*:1.00 (0.86, 1.15); *p*=.95 *Additionally adjusted for SBP, serum cholesterol, BMI, history of diabetes, physical activity, education level, regular alcohol consumption, current cigarette smoking, vitamin supplement use, sat fat intake, cholesterol intake, sodium intake, calcium intake, dietary fiber, vitamin C intake and vitamin A intake
NHANES I Epidemiological followup study Fang et al., 2000[87] Prospective cohort study Fair	**Study groups:** G1: Men, White, Tertile I: Potassium <2,003 mg/d G2: Men, White, Tertile II: Potassium 2,003–2,879 mg/d G3: Men, White, Tertile III: Potassium >2,879 mg/d G4: Men, Black, Tertile I: Potassium <1,260 mg/d G5: Men, Black, Tertile II: Potassium 1,260–2206 mg/d G6: Men, Black, Tertile III: Potassium >2,206 mg/d G7: Women, White, Tertile I: Potassium <1,508 mg/d G8: Women, White, Tertile II: Potassium 1,508–2,207 mg/d G9: Women, White, Tertile III: Potassium >2,207 mg/d G10: Women, Black, Tertile I: Potassium <1,017 mg/d G11: Women, Black, Tertile II: Potassium 1,017–1,641 mg/d G12: Women, Black, Tertile III: Potassium >1,641 mg/d **Duration:** **Mean followup:** 16.7 yr Data on nutrient intake were available from a single 24-h dietary recall	NHANES I survey examined adults, 25 to 74 years of age ***n*:** G1: 1056 G2: 1057 G3: 1056 G4: 198 G5: 199 G6: 198 G7: 1691 G8: 1690 G9: 1692 G10: 343 G11: 343 G12: 343 **Age, mean yr (SD):** G1: 55.4 G2: 52.5 G3: 47.9 G4: 58.3 G5: 56.0 G6: 48.2 G7: 48.5 G8: 48.9 G9: 45.3 G10: 46.8 G11: 48.9 G12: 45.8 **Sex, female %:** 61.8 **Race/ethnicity, %:** White: 83.5 **BMI:** G1: 25.5	**Age-adjusted stroke mortality, rates per 1,000 person-yr (deaths):** G1: 1.94 (37) G2: 2.28 (39) G3: 1.17 (17) G3 vs. G1: *p*=.042 RR (95% CI): 1.66 (1.32, 2.14) G4: 5.08 (14) G5: 3.40 (11) G6: 1.19 (3) G6 vs. G4: *p*=.0016 RR (95% CI): 4.27 (1.88, 9.19) G7: 1.61 (50) G8: 1.52 (49) G9: 1.43 (37) G9 vs. G7: *p*=.53 RR (95% CI): 1.13 (0.84, 1.66) **Age-adjusted stroke mortality, rates per 1,000 person-yr (deaths):** G10: 2.46 (14) G11: 2.74 (17) G12: 3.04 (16) G12 vs. G10: *p*=.5425 RR (95% CI): 0.80 (0.21, 2.01) **Age/race-adjusted stroke mortality by sex and HTN status:** Hypertensive Men Tertile I: 6.02 (19) Tertile II: 4.63 (17) Tertile III: 2.82 (9) III vs. I: *p*=.0242 RR (95% CI): 2.13 (1.09, 6.78) Hypertensive women Tertile I: 4.43 (36) Tertile II: 3.34 (30) Tertile III: 3.80 (27)

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
		G2: 25.6 G3: 25.4 G4: 24.5 G5: 26.0 G6: 25.6 G7: 25.9 G8: 25.0 G9: 24.1 G10: 27.5 G11: 27.5 G12: 27.5 **SBP, mean mmHg (SD):** G1: 139.2 G2: 136.2 G3: 132.7 **SBP, mean mmHg (SD):** G4: 149.4 G5: 144.1 G6: 139.9 G7: 134.4 G8: 132.6 G9: 128.5 G10: 140.5 G11: 141.1 G12: 138.6 **DBP, mean mmHg (SD):** G1: 85.5 G2: 85.0 G3: 83.8 G4: 91.3 G5: 88.6 G6: 88.8 G7: 82.1 G8: 81.1 G9: 79.6 G10: 86.1 G11: 86.6 G12: 86.3 **Potassium intake, mg/d:** G1: 1492.6 G2: 2432.6 G3: 3745.8	III vs. I: *p*=.746 RR (95% CI): 1.16 (0.86, 3.59) Nonhypertensive men Tertile I: 1.66 (30) Tertile II: 1.42 (24) Tertile III: 1.34 (22) III vs. I: 0.458 RR (95% CI): 1.23 (0.84, 3.89) Nonhypertensive women Tertile I: 1.19 (35) Tertile II: 1.17 (33) Tertile III: 1.07 (22) III vs. I: 0.415 RR (95% CI):1.11 (0.85, 3.54)

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
		G4: 866.4 G5: 1672.8 G6: 2993.6 G7: 1094 G8: 1841 G9: 2889 G10: 716 G11: 1309 G12: 2383	
Nurse's Health Study Iso et al., 1999[94] Prospective cohort study Fair	**Study groups:** Participants divided into quintiles (lowest to highest) based on potassium intake, median mg/d: G1: 2,017 (Lowest) G2: 2,412 G3: 2,708 (Intermediate) G4: 3,030 G5: 3,555 (Highest) **Duration:** **Followup:** 14 yr Potassium intake determined by food frequency questionnaire	Women who returned the 1980 dietary questionnaire and left <10 items blank, had no history of cancer, angina, MI, stroke, or other CVD; predominantly White ***n*:** Total: 86,368 NR by quintile **Age, mean yr:** G1: 44.9 G2: NR G3: 46.1 G4: NR G5: 47.3 **Sex, % female:** 100 **Race/ethnicity:** NR **Weight:** NR **BMI ≥29 kg/m^2:** G1: 15.9 G2: NR G3: 12.9 G4: NR G5: 13.4 **SBP:** NR **DBP:** NR	**All Stroke** **Cases, *n*:** G1: 147 G2: 117 G3: 146 G4: 134 G5: 146 **Relative risk (95% CI):** G1: 1.0 G2: 0.75 (0.59, 0.95) G3: 0.90 (0.72, 1.14) G4: 0.80 (0.63, 1.01) G5: 0.83 (0.66, 1.04) *p* for trend = .34 **Multivariate relative risk of ischemic stroke:** Adjusted RR* (95% CI) G1: 1.0 G2: 0.69 (0.49, 0.97) G3: 0.85 (0.62, 1.16) G4: 0.71 (0.52, 0.99) G5: 0.69 (0.50, 0.95) *p* for trend = .04 *Adjusted for age, smoking status, time interval, and history of HTN Adjusted RR† (95% CI) G1: 1.0 G2: 0.72 (0.51, 1.01) G3: 0.90 (0.66, 1.25) G4: 0.75 (0.54, 1.05) G5: 0.72 (0.51, 1.01) *p* for trend = .10 †Adjusted for * plus BMI, alcohol intake, menopausal status and post-menopausal hormone use, vigorous exercise, usual aspirin use, multivitamin use, vitamin E use, omega-3 fatty acid intake, and

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
			histories of diabetes and high cholesterol levels **Multivariate relative risk of ischemic stroke:** Adjusted RR‡ (95% CI) G1: 1.0 G2: 0.78 (0.55, 1.10) G3: 1.03 (0.73, 1.44) G4: 0.89 (0.62, 1.27) G5: 0.87 (0.58, 1.30) *p* for trend = .67 ‡ Adjusted for † plus calcium intake
Rotterdam Study Geleijnse et al., 2007[93] Case-cohort study Good	**Study groups:** G1: Random sample G2: Cases of incident MI G3: Cases of incident stroke G4: Cases of CVD mortality G5: Cases of all-cause mortality **Duration:** Median followup: 5.5 yr	Adult men and women, ≥55 years of age ***n*:** G1: 1,448 G2: 206 G3: 181 G4: 217 G5: 795 **Age mean yr (SD):** G1: 69.2 (8.7) G2: 71.0 (8.0) G3: 74.0 (8.5) G4: 76.8 (8.4) G5: 76.9 (8.9) **Sex, male (%):** G1: 41 G2: 62 G3: 45 G4: 51 G5: 49 **Race/ethnicity:** NR **Weight:** NR **BMI, mean kg/m² (SD):** G1: 26.4 (3.8) G2: 26.3 (3.4) G3: 26.0 (3.3) G4: 26.2 (3.8) G5: 25.7 (3.8) **SBP, mean mmHg (SD):**	**Incident MI, all subjects:** RR (95% CI), model 1* Urinary potassium excretion: 1.10 (0.89, 1.35) Dietary potassium intake: 0.98 (0.85, 1.13) RR (95% CI), model 2† Urinary potassium excretion: 1.16 (0.94, 1.43) Dietary potassium intake: 0.94 (0.81, 1.09) RR (95% CI), model 3‡ Urinary potassium excretion: 1.11 (0.87, 1.43) Dietary potassium intake: 0.90 (0.65, 1.24) **Incident stroke, all subjects:** RR (95% CI), model 1* Urinary potassium excretion: 1.09 (0.87, 1.36) Dietary potassium intake: 0.99 (0.84, 1.17) RR (95% CI), model 2† Urinary potassium excretion: 1.12 (0.89, 1.42) Dietary potassium intake: 0.99 (0.84, 1.16) RR (95% CI), model 3‡ Urinary potassium excretion: 1.17 (0.86, 1.58) Dietary potassium intake: 1.02 (0.71, 1.46) **CVD mortality, all subjects:** RR (95% CI), model 1* Urinary potassium excretion: 1.13 (0.90, 1.41) Dietary potassium intake: 0.97 (0.82, 1.14) RR (95% CI), model 2† Urinary potassium excretion:1.14 (0.92, 1.42) Dietary potassium intake: 0.95 (0.81, 1.12) RR (95% CI), model 3‡ Urinary potassium excretion: 1.23 (0.94, 1.60)

Study Cited Design Setting	Study Groups and Details Duration	Sample Characteristics	Results
		G1: 140 (22) G2: 145 (23) G3: 149 (24) G4: 146 (25) G5: 145 (25) **DBP, mean mmHg (SD):** G1: 74 (11) G2: 74 (12) G3: 75 (13) G4: 73 (13) G5: 73 (14) **Urinary potassium excretion, mean mmol/24 h:** G1: 45 (22) G2: 47 (22) G3: 45 (23) G4: 44 (24) G5: 44 (22) Based on one timed overnight urine sample **Potassium dietary intake, mean g/d (SD):** G1: 3.6 (0.8) G2: 3.7 (0.8) G3: 3.6 (0.8) G4: 3.6 (0.9) G5: 3.6 (0.9)	Dietary potassium intake: 0.97 (0.72, 1.31) * Adjusted for age, sex and (for urinary potassium) 24-h urinary creatinine excretion † Adjusted for * plus FMI, smoking status, diabetes, use of diuretics, and highest completed education ‡ Adjusted for † plus daily intake of total energy, alcohol, calcium, sat fat, and 24-h urinary sodium excretion

Table C–9. Critical Question 2 Studies Rated as Poor, With Rationale

Study	Design	Primary Reason for Poor Quality Rating
Forrester et al., 2005[170]	RCT	Sample size justification, power analysis, and LTF not reported
He et al., 2005[171]	RCT	Post hoc analysis; small sample size; no power, sample size justification, adherence, or LTF reported
Manios et al., 2006[172]	RCT	Information on randomization procedures, blinding, differential dropout rates, and power not reported
Roberts 2006[173]	RCT	Small sample size; information on randomization procedures, differential dropout rate, and adherence not reported
Takahashi et al., 2006[174]	RCT	No ITT analysis; high LTF
Tuekpe et al., 2006[175]	RCT	No ITT analysis; high LTF

Note: ITT = intent-to-treat; LTF = lost to followup; RCT = randomized controlled trial.

APPENDIX D.

Critical Question 3 Methods

Appendix D. Critical Question 3 Methods

i. Search Strategy

Among adults, what is the effect of physical activity on hypertension and cholesterol when compared to no treatment, or to other types of interventions?

a. Study type query

Study types eligible for this question: Systematic reviews and meta-analyses

- (Systematic Review)

b. Boolean search

(

- (publicationYear>2000)
- AND (subject,title,abstract= ("Physical Fitness" OR "Motor Activity" or "Exercise Tolerance" OR "Metabolic Equivalent" OR "Exercise Test" or Life Style or Lifestyle) OR subject= (Exercise or Training or Walking) OR VO2? OR "maximal MET" OR (METs not "metabolic syndrome mets") OR physical activity or "maximal metabolic" OR metabolic equivalent? or graded exercise test? OR GXT)
- AND (subject,title,abstract= (?cholesterol? or ?lipid? or lipoprotein? or triglyceride? or LDL-cholesterol or HDL-cholesterol or HDL-C or LDL-C or non-HDL-cholesterol or ApoB or Lp (a) or LDL-P or Apo A–1 or anticholesterol? or blood pressure or systol? or diastol? or hypertension or antihypertens? or hypertensive or non-hypertensive or metabolic syndrome or Risk Factors or Biological Markers or ((cardiovascular or CVD or coronary or CHD or stroke or myocardial infarction or cerebrovascular or heart disease?) and (risk? or confound? or predict? or marker? or incidence))))

)

NOT subject= ((child or adolescent or infant) not (adult or aged))
NOT recordStatus=delete

c. Boolean filter

None

ii. Search Strategy Results, PRISMA Diagram, and CQ3 Summary Tables

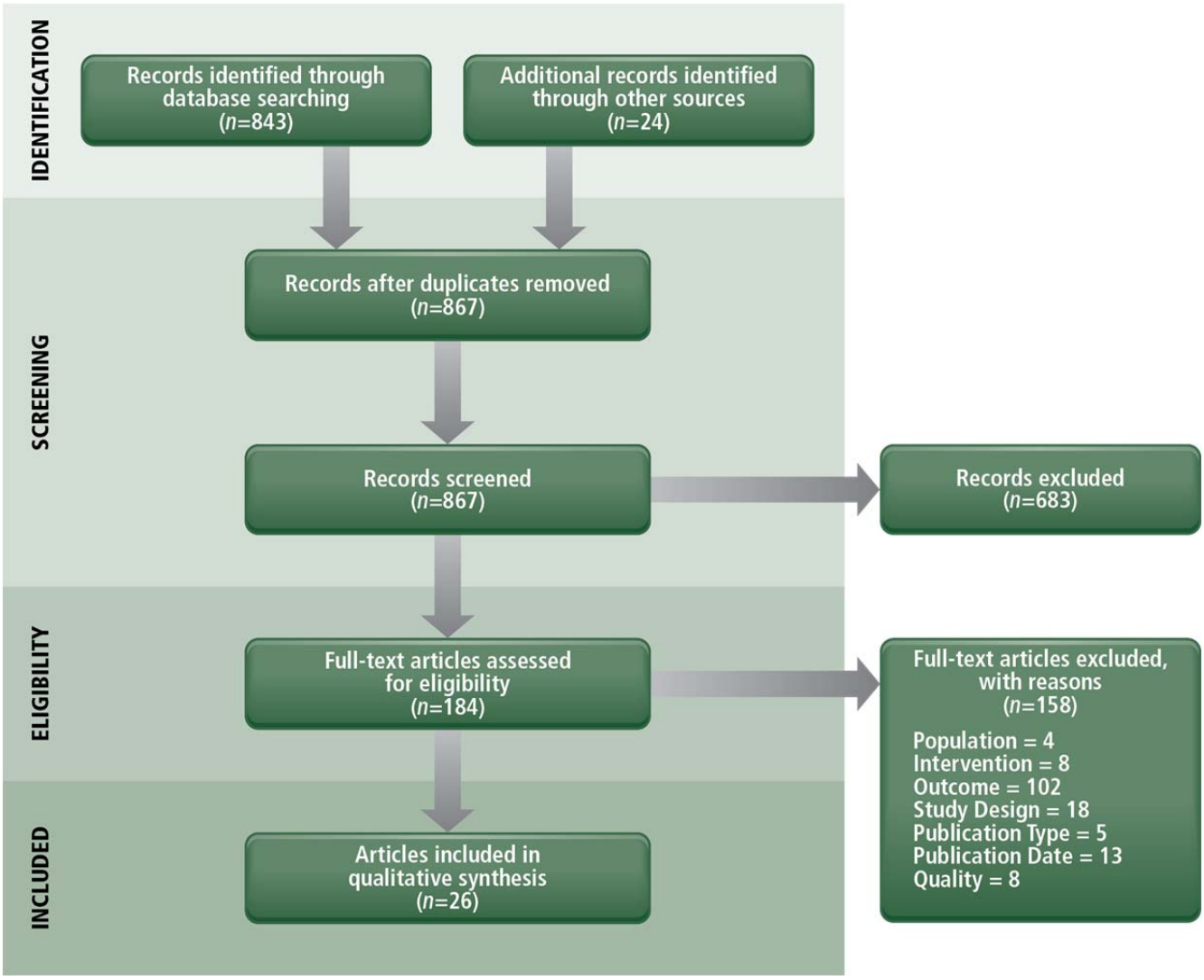
Lifestyle Question 3 was restricted to systematic reviews and meta-analyses. The following databases were searched for evidence to answer Question 3:

- PubMed from January 2001 to January 2010
- CINAHL from January 2001 to July 2008
- EMBASE from January 2001 to July 2008
- PsycINFO from January 2001 to July 2008
- EBM (Evidence-Based Medicine) Cochrane Libraries from January 2001 to July 2008
- Biological Abstracts from January 2001 to July 2008
- Wilson Social Sciences Abstracts from January 2001 to July 2008

Duplicate citations which arise from the same citation being found in more than one database were removed from the Central Repository before screening. The search produced 843 systematic reviews and meta-analyses. An additional 24 citations published between January 2010 and May 2010 were retrieved from PubMed for review.

The titles and abstracts of these 867 publications were screened against I/E criteria independently by two reviewers, which resulted in the retrieval of 184 full-text papers. These papers were independently screened by two reviewers. Per figure D–1 and summary tables D–1 through D–6, 26 systematic reviews and meta-analyses were included—25 were published between January 2001 and May 2010, and 1 was published in December 2010[131]—and 158 were excluded on one or more I/E criteria. The majority of full-text articles that were excluded were excluded because the outcomes did not meet those specified in the criteria. An additional 8 publications were excluded because they were rated as poor quality (table D–7).

Figure D–1. PRISMA Diagram Showing Selection of Articles for Lifestyle Critical Question 3



CQ3 Summary Table D–1. Aerobic Exercise and LDL-C

Cite	Type	LDL Cholesterol	Duration (Weeks)	Sessions per Week	Minutes per Session	Intensity	Increase in Steps per Day
Kelley et al., 2005, Int J. Obes. [118]	Meta-analysis	Nonsignificant decrease of –3.0 mg/dL	19.8±10.2 weeks	3.9±1.0	41.5±13.5	63.9±10.8% VO2max	
Kelley et al., 2005, Preventive Cardiology[112]	Meta-analysis		22.5±17.8 weeks	4.9±2.6	38.4±16.4	64.9±9.3% VO2max	
Kelley et al., 2005, Preventive Cardiology[111] (older adults)	Meta-analysis	Significant decrease of –3.9 mg/dL (–2.5%)	35.3±31.8 weeks	3.5±1.0	42.4±12.1	67.8±9.8% VO2max	
Kelley et al., 2004[109]	Meta-analysis	Significant decrease of –5.5 mg/dL	23.19±17.7 weeks	4.75±2.5	38.4±15.6	64.2±9.4% VO2max	
Kelley et al., 2004, Journal of Women's Health[110] (Women Only)	Meta-analysis	Significant decrease of –4.4 mg/dL	21.8±19.5 weeks	3.7±1.1	36.3±13.2	69.2±10.1% VO2max	
Kelley and Kelley, 2007, Public Health[113] (type 2 diabetes)	Meta-analysis	Significant decrease of –6.4 mg/dL	15.1±5.5 weeks	4.2±1.8	47.1±14.4	68.3±3.0% VO2max	
Kelley and Kelley, 2006, Atherosclerosis[176]	Meta-analysis		24.4±22.4 weeks	4.0±1.1	40.6±12.7	68.3±11.3% VO2max	
Bravata et al., 2007, JAMA[115]	Systematic review	Significant decrease of –0.06 mmol/L					+2492 (1098–3885)
Kodama et al., 2007. Arch Int Med[114]	Meta-analysis		27.0 weeks	3.7	40.5	64.8% VO2max (5.3 METS)	
Taylor et al., 2004, Am J. Med.[119] (pts with CVD)	Systematic review and meta-analysis	Nonsignificant decrease of 7.7 mg/dL					
Leon and Sanchez 2001, Med Sci Sports Exerc[117]	Systematic review	Inconsistent improvement					
Durstine et al., 2001, Sports Medicine[116]	Systematic review	Infrequent improvement					
Physical Activity Guidelines 2008[102]		Inconsistent evidence of improvement					

CQ3 Summary Table D–2. Resistance Exercise and LDL-C

Cite	Type	LDL Cholesterol	Duration (Weeks)	Sessions per Week	Minutes per Session	Intensity	Other Details
Kelley and Kelley 2009 (Preventive Medicine)	Meta-analysis	Significant decrease of –6.1 mg/dL	24.0±19.0 weeks	2.9±0.4	47.7±11.5	70.3±10.4% 1RM	2.6±1.1 sets 11.5±6.6 reps 9.2±3.1 exercises
Gordon et al., 2009, Diabetes Research and Clinical Practice[121]	Systematic review	Generally showed improvement	4–6 weeks to 12 mo	Typically 3 days per week		Varied	Varied

CQ3 Summary Table D–3. Aerobic Exercise and HDL-C

Cite	Type	HDL Cholesterol	Duration (Weeks)	Sessions per Week	Minutes per Session	Intensity	Increase in Steps per Day
Kelley et al., 2005, Int J. Obes[118]	Meta-analysis	Nonsignificant increase of 1.6 mg/dL	19.8±10.2 weeks	3.9±1.0	41.5±13.5	63.9±10.8% VO2max	
Kelley et al., 2005, Preventive Cardiology[112]	Meta-analysis	Nonsignificant increase of 1.4 mg/dL (3%)	22.5±17.8 weeks	4.9±2.6	38.4±16.4	64.9±9.3% VO2max	
Kelley et al., 2005, Preventive Cardiology[111] (older adults)	Meta-analysis	Significant increase of 2.5 mg/dL (5.6%)	35.3±31.8 weeks	3.5±1.0	42.4±12.1	67.8±9.8% VO2max	
Kelley et al., 2004[109]	Meta-analysis	Nonsignificant increase of 1.2 mg/dL	23.19±17.7 weeks	4.75±2.5	38.4±15.6	64.2±9.4% VO2max	
Kelley et al., 2004. Journal of Women's Health[110] (Women Only)	Meta-analysis	Significant increase of 1.8 mg/dL	21.8±19.5 weeks	3.7±1.1	36.3±13.2	69.2±10.1% VO2max	
Kelley and Kelley, 2007, Public Health[113] (type 2 diabetes)	Meta-analysis	Nonsignificant increase of 0.9 mg/dL	15.1±5.5 weeks	4.2±1.8	47.1±14.4	68.3±3.0% VO2max	
Kelley and Kelley, 2006, Atherosclerosis[176]	Meta-analysis	Significant increase of 2.6 mg/dL	24.4±22.4 weeks	4.0±1.1	40.6±12.7	68.3±11.3% VO2max	
Bravata et al., 2007, JAMA[115]	Systematic review	Nonsignificant increase of 0.06 mmol/L					+2492 (1098–3885)
Kodama et al., 2007, Arch Int Med[114]	Meta-analysis	Significant increase of 2.63 mg/dL	27.0 weeks	3.7	40.5	64.8% VO2max (5.3 METS)	
Taylor et al., Am J. Med. 2004[119] (pts with CVD)	Systematic review and meta-analysis	Nonsignificant decrease of –1.9 mg/dL					
Leon and Sanchez. Med Sci Sports Exerc, 2001[117]	Systematic review	More consistent improvement					
Durstine et al., Sports Medicine 2001[116]	Systematic review	More consistent improvement					
Physical Activity Guidelines 2008[102]		Favorable improvement					

CQ3 Summary Table D–4. Resistance Exercise and HDL-C

Cite	Type	HDL Cholesterol	Duration (Weeks)	Sessions per Week	Minutes per Session	Intensity	Other Details
Kelley and Kelley 2009 (Preventive Medicine)	Meta-analysis	Nonsignificant increase of 0.7 mg/dL	24.0±19.0 weeks	2.9±0.4	47.7±11.5	70.3±10.4% 1RM	2.6±1.1 sets 11.5±6.6 reps 9.2±3.1 exercises
Gordon et al., Diabetes Research and Clinical Practice, 2009[121]	Systematic review	Generally showed improvement	4–6 weeks to 12 mo	Typically 3 days per week		Varied	Varied

CQ3 Summary Table D–5. Aerobic Exercise and Blood Pressure

Reference (quality)	Subject Characteristics	SBP	DBP	Duration (Weeks)	Sessions per Week	Min per Session	Intensity
Cornelissen 2005[136] (poor)	72 trials ≥4 weeks aerobic exercise (*n*=3936; 46.6 yr)	Normotensive: Sig decrease 2.4 mmHg Pre-HTN: Sig decrease 1.7 mmHg HTN: Sig decrease 6.9 mmHg	Normotensive: Sig decrease 1.6 mmHg Pre-HTN: Sig decrease 1.7 mmHg HTN: Sig decrease 4.9 mmHg	16	3	40	65% HR_{res}
Whelton 2002[135] (fair)	54 trials ≥2 weeks aerobic exercise (*n*=2419; mean ages 21–79 yr)	Normotensive: Sig decrease 4.0 mmHg HTN: Sig decrease 4.9 mmHg	Normotensive: Sig decrease 2.3 mmHg HTN: Sig decrease 3.7 mmHg	N/A	N/A	N/A	N/A
Kelley et al., 2001[127] (fair)	16 trials ≥4 weeks walking (*n*=650; 84% female; mean age 58 yr)	Sig decrease 3 mmHg	Sig decrease 1 mmHg	25	4	42	63% VO_2 max
Murphy 2007[132] (fair)	24 trials ≥4 weeks walking (*n*=1128; 83% female; mean age 52 yr) BP data only from 9 trials, *n*=356	Nonsig decrease 1 mmHg	Sig decrease 2 mmHg	35	4	38	56% VO_2 max
Guo 2008[124] (fair)	9 trials of qigong (*n*=908) (age mainly 40s and 50s)	Vs. drug (*n*=278): Nonsig decrease 1 mmHg Vs. aerobic ex (*n*=157): Nonsig increase 2 mmHg Vs. no treatment (*n*=130) Nonsig increase17 mmHg	Vs. drug (*n*=333): Non-sig increase2 mmHg Vs. aerobic ex (*n*=157): Non-sig decrease 2 mmHg Vs. no treatment (*n*=130) Non-sig increase10 mmHg	N/A	N/A	N/A	N/A
Lee 2007[130] (good)	12 trials of qigong (*n*=1218) (age mainly 40–70 yr)	Vs. no treatment (*n*=94) Sig decrease 19 mmHg Vs. aerobic ex (*n*=172): Nonsig increase 1 mmHg	Vs. no treatment N/A Vs. aerobic ex (*n*=172): Nonsig increase 2 mmHg	N/A	N/A	N/A	N/A

Reference (quality)	Subject Characteristics	SBP	DBP	Duration (Weeks)	Sessions per Week	Min per Session	Intensity
Kelley 2001[128] (good)	7 trials of aerobic exercise in ≥50 yr (*n*=802; mean age 68.5 yr)	Sig decrease 2 mmHg	Nonsig decrease 1 mmHg	35	3	40	63% VO_2 max
Asikainen 2004[123] (fair)	7 trials of post-menopausal women Qualitative review	1 of 5 walking studies in normotensives showed sig decrease in BP 1 aerobic + resistance exercise study in HTN and overweight showed sig decrease in BP	1 aerobic exercise + diet study did not show any effect on BP	N/A	N/A	N/A	N/A
Taylor 2004[119] (good)	Trials ≥6 mo of CHD patients; 8 trials (*n*=774) for SBP, 5 trials (482) for DBP (mean age 55 yr)	Sig decrease 3.19 mmHg	Nonsig decrease 1.18 mmHg	N/A	4	53	76% VO_2 max
Jolly 2006[126] (fair)	5 trials of CHD patients (*n*=574; age N/A)	Sig decrease 4.2 mmHg	N/A	N/A	N/A	N/A	N/A
Thomas 2006[134] (good)	Trials ≥8 weeks of T2D patients; 4 trials (*n*=127) for SBP, 3 trials (*n*=78) for DBP	Nonsig decrease 4.16 mmHg	Nonsig decrease 0.13 mmHg	N/A	N/A	N/A	N/A

CQ3 Summary Table D–6. Resistance Exercise and Blood Pressure

Reference (Quality)	Subject Characteristics	SBP	DBP	Duration (Weeks)	Sessions per Week	Min per Session	Intensity
Cornelissen 2005[137] (poor) (PAGAC)	9 trials resistance training; 9 included normotensive, 3 HTN (*n*=341; mean ages 18–72 yr)	Nonsig decrease 3.2 mmHg	Sig decrease 3.5 mmHg	16	3	10 exerc, 2 sets, 1–25 reps	61% 1RM
Gordon 2009[121] (fair)	10 trials resistance training (*n* N/A; age N/A) Qualitative review	3 of 10 “beneficial” changes in SBP”	“improvements in DBP were less frequently observed”	N/A	N/A	N/A	N/A

Table D–7. Critical Question 3 Studies Rated as Poor, With Rationale

Study	Design	Primary Reason for Poor Quality Rating
Bartlo et al., 2007[177]	Systematic review/ meta-analysis	Unclear if review of citations and quality of component citations were completed by two independent reviewers; search strings not well described
Cornelissen et al., 2005[136]	Systematic review/ meta-analysis	Results based on search of one electronic database; Unable to determine if dual review or assessment of internal validity was completed
Cornelissen et al., 2005[137]	Systematic review/ meta-analysis	Unclear if review of citations and quality of component citations were completed by two independent reviewers
Fagard 2001[178]	Systematic review/ meta-analysis	No quality assessment of component studies, heterogeneity testing, or sensitivity analyses was performed
Haennel et al., 2002[179]	Systematic review/ meta-analysis	Results based on search of one electronic database; Unable to determine if dual review or assessment of internal validity was completed
Hamer et al., 2006[180]	Systematic review/ meta-analysis	No quality assessment of component studies, heterogeneity testing, or sensitivity analyses was performed
Tambalis et al., 2009[181]	Systematic review/ meta-analysis	Results based on search of one electronic database (PubMed); Unable to determine if dual review or quality assessment of component studies was performed
Yang 2007[182]	Systematic review/ meta-analysis	No dual review; unclear assessment of quality of component studies

APPENDIX E.

Abbreviations and Acronyms

Appendix E. Abbreviations and Acronyms

AAD	average American diet
ADA	American Dietetic Association
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
APO	apolipoprotein
ApoA	apolipoprotein A
ApoA–1	apolipoprotein A–1
ApoB	apolipoprotein B
BMI	body mass index
BP	blood pressure
CABG	coronary artery bypass grafting
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
CKD	chronic kidney disease
CQ	critical question
CRP	C-reactive protein
CVD	cardiovascular disease
DASH	Dietary Approaches to Stop Hypertension
DBP	diastolic blood pressure
DELTA	Dietary Effects on Lipoproteins and Thrombogenic Activity
EBM	evidence-based medicine
eGFR	estimated glomerular filtration rate
ES	evidence statement
ESRD	end-stage renal disease
estGFR	estimated glomerular filtration rate

FFQ	food frequency questionnaire
GFR	glomerular filtration rate
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	heart failure
high-CHO	high-carbohydrate
HOMA	homeostatic model assessment
HR	hazard ratio
Hs-CRP	high-sensitivity C-reactive protein
I/E	inclusion/exclusion
IMT	intima-media wall thickness
IOM	Institute of Medicine
ITT	intent-to-treat
IVGTT	intravenous glucose tolerance test
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LDL-P	low-density lipoprotein particle number
low-CHO	low-carbohydrate
Lp (a)	lipoprotein (a)
LTF	lost to followup
MED	Mediterranean-style
MeSH	Medical Subject Headings
MET	metabolic equivalent task
MUFA	monounsaturated fatty acid
NA	Not applicable
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey

NHLBI	National Heart, Lung, and Blood Institute
NLP	natural language processing
NR	not reported
NSTEMI	non-ST-segment elevation myocardial infarction
OGTT	oral glucose tolerance test
OmniHeart	Optimal Macronutrient Intake Strategies Against Heart Disease
PICO	population, intervention/exposure, comparison group, outcome
PICOTS	population, intervention/exposure, comparison group, outcome, time, and setting
PREDIMED	Prevención con Dieta Mediterránea
PUFA	polyunsaturated fatty acid
RCT	randomized controlled trial
SBP	systolic blood pressure
SFA	saturated fatty acid
STEMI	ST-segment elevation myocardial infarction
TG	triglycerides
TOHP II	Trials of Hypertension Prevention II
TONE	Trial of Nonpharmacologic Interventions in the Elderly
USPSTF	U.S. Preventive Services Task Force
VCW	virtual collaborative workspace

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