Chapter 2

Nutritional Epidemiology: Application to Cardiovascular Disease

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"*One should eat to live, not live to eat.*"—Benjamin Franklin

Learning Objectives

- Describe the major study designs in nutritional epidemiology.
- Explain implications of study design and population when addressing a study question using nutritional epidemiology studies.
- Describe common methods of diet assessment.
- Describe the factors that contribute to measurement error.
- Explain the significance of cardiovascular disease as a major public health problem and the role of nutritional epidemiology in addressing this problem.
- Describe relationships between dietary intake, including nutrients, foods, diet patterns, and cardiovascular disease.

Case Study: Using Nutritional Epidemiology to Study the Mediterranean Diet and Cardiovascular Disease

Cardiovascular disease (CVD) refers to any of the diseases affecting the heart and blood vessels. They include ischemic heart disease, coronary heart disease (CHD), peripheral artery disease, cerebrovascular disease, or stroke, and **hypertension**. Together, the CVDs are the leading cause of death worldwide, causing 30% of total deaths.[1] Despite their impact, the World Health Organization reports that the majority of CVD is preventable through behaviors such as avoiding tobacco, increasing physical activity, maintaining a healthy weight and eating a more nutritious diet.[2] Westernized diet patterns, characterized by high intakes of sugar, sodium, and saturated fat, are linked to increased risk of CVD. More prudent diet patterns, based on more nutritious, less processed foods, can lower the risk of CVD.

More accurately described as one of several similar dietary patterns than as a single specific diet, the Mediterranean diet is an example of a prudent diet. This type of diet is traditional in Mediterranean nations such as Italy, Greece, and Spain. Compared with Westernized diets, Mediterranean

diets are generally higher in plant-based foods and fish, and lower in red meats, sweets, and saturated and trans fats. Monounsaturated fats from olive oil are the major fat source.

Investigation of Mediterranean Diets and CVD

Mediterranean-style diets are increasingly linked to reduced risk for CVD and improvements in risk factors, such as inflammation, high serum LDL cholesterol, and high blood pressure.[3] Many observational studies suggest the benefits of Mediterranean-style diets.[4] These studies provide important clues about the possible effects of a Mediterranean diet, but experimental trials are considered to be stronger sources of evidence than observational studies.

The PREDIMED Trial

The PREDIMED (Prevención con Dieta Mediterranea) was a groundbreaking multi-site clinical trial conducted in Spain from 2003 to 2008.[5] The 7,447 participants were 55 to 80 years old and had diabetes or at least three risk factors for heart disease. The control group was asked to follow a balanced diet falling within dietary guidelines for percentage of calories from fat, protein, and carbohydrates; the experimental groups were asked to follow a Mediterranean diet and provided with dietary counseling. Both experimental groups were provided either with nuts or with olive oil to supplement their diets. During the follow-up period of nearly five years, individuals in the Mediterranean diet groups experienced fewer cardiovascular events.

Clinical trials such as the PREDIMED trial can provide convincing evidence of links between diet and disease, but more research remains to be done to verify these results and resolve uncertainties. For example, monounsaturated fats are likely to be responsible for at least some of the cardiovascular benefits of a Mediterranean diet,[6] but current evidence is conflicting.[7]

Discussion Questions

- How does a Mediterranean diet differ from a typical Westernized diet? Which characteristics might contribute to its apparent cardioprotective effects?
- What is the role of nutritional epidemiology in combating significant public health nutrition concerns?
- Why can results from a clinical trial, such as the PREDIMED trial, be considered more convincing than results of observational studies? What further research is needed to provide more conclusive evidence on the link between the Mediterranean diet and cardiovascular disease?
- How can appropriate studies be designed to answer specific research questions? What are the strengths and limitations of the major study designs used in nutritional epidemiology?
- How can results from research studies guide the development of public health nutrition policy?

Introduction

Cardiovascular disease is a major public health problem and is the leading cause of death in the United States and the world. Although the mortality rate of CVD has declined over the past 30 years, nearly one-third of adult deaths are from CVD. The high prevalence of hypertension is a significant reason; one in three adults has high blood pressure, which is a modifiable risk factor for CVD. Blood pressure increases with age, and currently 75% of older women and 65% of older men have high blood pressure. Slowing the progression of age-related increase in blood pressure in older adults and reducing blood pressure levels among younger individuals are examples of strategies to ultimately reduce CVD mortality.

Dietary intake influences blood pressure levels as well as risk for CVD. Healthy diet patterns lower the risk of developing CVD and its risk factors, such as high blood pressure, high total and LDL cholesterol, triglycerides, and **type 2 diabetes**.

Many associations between dietary intake and CVD are now widely accepted, but they were discovered and confirmed through scientific studies in the field of **nutritional epidemiology**. For example, a number of studies have led to broad acceptance that certain food types, including dairy products, fruit, whole grains, and nuts, are inversely related to the risk of **elevated blood pressure (EBP)** in young African American and Caucasian adults, and consumption of red and processed meat was positively related to higher blood pressure in younger and middle-aged populations. Using nutritional epidemiologic methods will facilitate the elucidation of diet–disease relationships.

Nutritional epidemiology is based on classic methods of epidemiology.[8,9] This chapter discusses research design components in nutritional epidemiology and the application of these concepts in the published literature. The chapter presents the most common types of epidemiologic studies, including experimental trials and observational studies.

Nutritional Epidemiology

Background

Public Health Core Competency 6: Basic Public Health Science Skills 4: Identifies the basic public health sciences (all fields)

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Epidemiology is the study of the distribution and determinants of disease in human populations. The objective of an epidemiologic study is to answer a research question about the relation between an **exposure**, such as dietary intake, and an **outcome**, such as CVD, using an appropriate study design, population, and methods of data collection and analysis.

Epidemiologists use both experimental and observational study designs to investigate hypotheses about etiologic associations between exposures and an outcome. The research question determines the study design and selection criteria of study participants. **Table 2-1** matches a research question about sodium intake and blood pressure to the appropriate study design and population.

Experimental Studies

Experimental studies are designed to manipulate an exposure (sodium intake) to change an outcome (blood pressure) in specific populations. A **randomized clinical trial (RCT)** is the gold standard study design to determine **causality** between an exposure and an outcome. Many RCTs have examined the effectiveness of modified diets to change a clinical measure, such as weight, cholesterol, or blood pressure. Disadvantages include its short duration and expense.

Conducted from 1993 to 1997, the Dietary Approaches to Stop Hypertension (DASH) trial was a multicenter, randomized, outpatient feeding study designed to test the effectiveness of three different dietary patterns on lowering blood pressure among adults with high normal to high blood pressure over eight weeks.[10] The five clinical centers participating in this trial were Johns Hopkins University (Baltimore, Maryland), Duke University Medical Center (Durham, North Carolina), Kaiser Permanente (Portland, Oregon), Brigham and Women's Hospital (Boston, Massachusetts), and Pennington Biomedical Research Center (Baton Rouge, Louisiana).

Table 2-1 Research question matched to the study design and population

Research Question	Study Design	Study Population
Does decreasing dietary sodium lower the risk of developing high blood pressure?	Experimental	Selection is based on study inclusion criteria, including a diastolic blood pressure range between 80 and 85 mm Hg.
Observational Study Designs		
Do adults who have high blood pressure consume a diet higher in sodium than those without high blood pressure?	Cross-sectional	Select adults from a *defined population*. Selection is not based on blood pressure or diet criteria.
Did adults who had high blood pressure consume a diet higher in sodium than those without high blood pressure?	Case-control	Cases: Adults who have high blood pressure Controls: Adults without high blood pressure
Do those who typically consume a high-sodium diet have a higher incidence of high blood pressure than those who typically consume a diet lower in sodium over 15 years of follow-up?	Cohort	Adults who do not have high blood pressure at baseline and who also reported dietary intake at baseline and have both diet and blood pressure measures during follow-up

Over 8,800 adults were screened for eligibility. Eligibility criteria included age 22 years or older, systolic blood pressure less than 160 mm Hg, and diastolic blood pressure 80 to 95 mm Hg.[11] Exclusionary criteria included poorly controlled diabetes mellitus, hyperlipidemia, a cardiovascular event within the previous six months, chronic diseases that might interfere with participation, pregnancy or lactation, **body mass index (BMI)** over 35, the use of medications that affect blood pressure, unwillingness to stop taking vitamin and mineral supplements or antacids containing magnesium or calcium, renal insufficiency, and an alcoholic beverage intake of more than 14 drinks per week.[12] The final study population consisted of 459 Caucasian and African American healthy men and women average age 46 years with high normal blood pressure to mild hypertension at enrollment.

The two experimental diets were a diet pattern rich in fruit and vegetables and low in dairy products, and the DASH diet pattern, which is rich in low-fat dairy products, fruits, vegetables, and fish, and low in meat, sugar-sweetened beverages, saturated fats, and added sugars. Effects of these diets were compared with those of the control diet, or typical American diet. Adults who consumed the DASH diet had lower blood pressure after eight weeks than those who consumed the other two diets.[13]

Observational Studies

The most common observational study designs include (1) cross-sectional, (2) case-control, and (3) cohort.

Cross-Sectional Studies

The cross-sectional study is based on observing a group of individuals on a single occasion, or "snapshot" of time, to estimate the **prevalence** of a condition. In addition, the study findings may be used for hypothesis-generating. Surveillance studies, which are population surveys, use a cross-sectional study design, usually designed to determine the prevalence of a condition (high blood pressure) or a behavior (sodium consumption) in a **probability sample**. Cross-sectional studies cannot determine the sequence of events, or whether the exposure or outcome occurred first.

The **National Health and Nutrition Examination Study (NHANES)** is a surveillance study conducted annually and designed to monitor the health of the U.S. population. NHANES investigators select a probability sample of U.S. noninstitutionalized children and adults to participate in this survey. The survey combines interviews and physical examinations to gather data on the health of children and adults. Researchers can then use cross-sectional techniques to examine the data.

For example, Welch et al. studied the cross-sectional relation between added sugar intake and CVD risk factors in U.S. adolescents.[14] Using NHANES data collected from 1999 to 2004, investigators identified 2,157 adolescents eligible for this study and observed that over 21% of total daily energy intake came from added sugars. Further, added sugar intake was inversely related to **high-density lipoprotein (HDL) cholesterol** and positively related to **low-density lipoprotein (LDL) cholesterol** and **triglyceride** levels.

Case-Control Studies

In a case-control study, the exposure is compared between a group of study participants who have a disease or condition (cases) and another group who do not have the disease/condition (controls). Since cases are selected based on their case status, the case-control study is more efficient in studying a rare disease than using a cohort study design. Another benefit of case-control studies is that they can be conducted quickly, since the disease of interest has already developed by the time the study period begins.

A disadvantage of case-control studies is that they are more prone to **recall bias** and **selection bias** than other study designs. For example, in a case-control study examining the relation between coffee intake and pancreatic cancer, recall bias may occur when the cases inaccurately recall their dietary (coffee) intake prior to their diagnosis of disease. Further, selection bias can occur in a case-control study, when the selection of controls is related to the exposure-of-interest (coffee). For example, when the controls are recruited from a pool of patients with gastrointestinal (GI) conditions, these GI patient controls are not likely to drink coffee. Thus, the **measure of association** between the exposure (coffee consumption) and outcome (pancreatic cancer) will be over- or underestimated due to recall bias and/or selection bias. Another limitation of case-control studies is that the disease may influence the exposure rather than vice versa. For example, upon diagnosis of diabetes, saturated fat consumption may decrease as patients follow medical nutrition therapy recommendations. Finally, the measure of association between the exposure and outcome or odds ratio is an estimate of the relative risk, which is a measure of association in a cohort study.

One example of a population-based case-control study evaluated the relationship between alcohol intake and the risk of having a venous thromboembolism (VTE) event.[15]

Patients, or cases, attending one of six anticoagulation clinics in the Netherlands were asked to enroll in this study if they had had an incident or first VTE between March 1999 and September 2004. The control population included partners/spouses of patients and adults who were randomly selected from the same community as the cases. Cases (n = 4,423) and controls (n = 5,235) completed a standardized questionnaire about demographic characteristics, alcohol intake, and physical activity, and a blood sample was collected. The investigators found that alcohol consumption of two to four drinks per day compared with no alcohol was associated with a lower risk of VTE. However, lower fibrinogen levels in those who consumed alcohol may partly explain this association between alcohol intake and VTE.

Cohort Studies

The cohort study observes a group of participants over time, and can evaluate a range of effects related to one exposure. Unlike cross-sectional studies, which can measure only prevalence, cohort studies can estimate incidence of a disease or condition. Measurement of exposure is less likely to be affected by recall bias than in a case-control study because it occurs prior to development of the outcome. However, cohort studies are usually more expensive and time consuming than case-control studies.

As an example of a cohort study, a 15-year prospective cohort study examined the relationship between consumption of a plant-based diet and EBP among young African American and Caucasian adults.[16] The study population included young adult men and women enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Exclusion criteria included reporting consumption of extreme caloric intakes at baseline and at exam 7 (less than 800 or more than 8,000 kcal/day for men and less than 600 or more than 6,000 kcal/day for women) (n = 119), lactating or pregnant at baseline (n = 54) or year 7 exam (n = 134), EBP (n = 443) or diabetes (n = 34) at baseline, or lack of fasting blood sample (n = 147). The remaining sample size was 4,304, consisting of 883 black men, 1,249 black women, 989 white men, and 1,183 white women. Standardized questionnaires were administered to obtain information about demographics, physical activity, smoking, and medical history. Trained staff measured blood pressure, weight, height, and waist circumference, and trained diet interviewers assessed dietary intake, using the CARDIA Diet History method, at baseline and at the year 7 exam. To assess the relation between plant-based food intake and EBP, investigators created food groups of meat, fish/seafood, dairy products, whole grains, refined grains, fruit, vegetables, legumes, and nuts. Individual food groups, including fruit, whole grains, nuts, and dairy, were inversely related to the risk of developing EBP over 15 years of follow-up, while meat intake was positively related to developing EBP.

Readers are referred to epidemiology textbooks for more details about epidemiologic methods and concepts.[17]

Data Collection Methods in Nutritional Epidemiology: Assessment of Dietary Intake

Part of designing a study is deciding which methods will be used. The following are common methods for assessing dietary intake.

24-Hour Diet Recall Interview Method

The objective of the **24-hour recall** is to obtain information about food and beverage intake during the previous 24 hours. It may be interviewer-administered in person or over the telephone. The multiple-pass interview is a standard 24-hour recall technique to (1) obtain a list of reported foods and beverages consumed, (2) review the list, (3) collect details about each food and beverage, and (4) review the details.[18] Dietary supplement use within the recall period, including use of antacids, may also be assessed. Food models, household measures, and pictures facilitate portion size estimation during in-person interviews, while for telephone interviews a two-dimensional booklet is mailed to participants prior to the telephone interview for use in estimating food and beverage amounts.[19]

In many cases, 24-hour dietary recalls can provide the least-biased dietary data.[20] In a **validation study** using **doubly-labeled water** to calculate **total energy expenditure**, energy intake estimated by the 24-hour recall was underreported by a relatively small 12–14% in men and 16–20% among women.[21] However, 24-hour recalls are expensive and impractical for large studies because multiple recalls per participant would be necessary to gather usual diet intake data, such as that required for predicting disease outcomes. The method can be useful for assessing the usual intake of populations.

Food Records

A **food record** or food diary is a detailed description of all foods and beverages consumed over a period of three to seven days. Staff sometimes train participants on food recording procedures; often, participants meet later with

staff to review and document their records' accuracy. Then study staff can enter the data into a food and nutrient data entry system. Little difference is apparent between the quality of the food records from participants trained on techniques versus not trained.[22,23] This suggests that the use of undocumented food records is feasible for use in large cohort studies.

In validation studies, usual energy intake by seven-day food records has been underreported by 20% when compared with doubly-labeled water estimated energy expenditure in women.[24]

Direct Diet Data Entry and Analysis Systems

Available data entry and analysis systems for direct data entry of reported 24-hour recalls or food and beverage records or diaries include the Nutrition Data System for Research (NDSR; University of Minnesota Nutrition Coordinating Center), the Automated Self-Administered 24-hour recall (ASA24; National Cancer Institute), and the Food Intake Analysis System (University of Texas, Houston). NDSR and ASA24 use multiple-pass 24-hour recalls. These systems generally use the Food and Nutrient Databases produced by the U.S. Department of Agriculture (USDA); however, the NDSR system periodically supplements its nutrient and food database with food items and their nutrient values from food manufacturers. In addition, the NDSR has a Dietary Supplement Assessment Module (DSAM)[25] with a database of more than 2,000 dietary supplements and antacids. Direct data entry is more efficient and less costly than data entry of participants' completed paper forms by research staff. However, a disadvantage is the time gap when new foods become available in the marketplace and when the food and nutrient values are entered into the USDA food and nutrient database.

Each data entry and analysis system has advantages and disadvantages. Systems should be selected based on study objectives and budget constraints.

Food Frequency Questionnaires

The **food frequency questionnaire (FFQ)** consists of a structured list of food items. Participants indicate frequency of food intake, such as number of times per day, week, or month, and often the portion size, which is generally a standard serving size, such as one-half cup of vegetables, a slice of bread, or one cup of cereal. Serving sizes may also be estimated, using categories such as small, medium, and large. An open-ended question is available to report any other food consumed that was not listed on the FFQ. The time period representing usual intake is often one month to a year.

The nutrient and food databases for FFQs typically use USDA Food and Nutrient Databases and can also include nutrition data reported by food manufacturers. However, the nutrients for each food on the FFQ food list are fixed; that is, the listed food item is generic as brand name information is not coded. In addition, food preparation is usually not taken into account. Data entry methods for FFQs may be direct entry by trained staff or by the participant, or electronic scanning of completed paper questionnaires.

The FFQ may be more economical to administer, since it can be self- or interviewer-administered. Nurses and health professionals have successfully completed self-administered questionnaires and mailed them back to the investigators.[26] An FFQ can also be used to screen for adherence to certain diet patterns. For example, in Spain, individuals who scored high on a Mediterranean Diet Adherence screener, a short FFQ, were categorized as adhering to a Mediterranean diet pattern.[27] The screener included 14 yes-no questions regarding frequency of consumption or use of various food types, such as fruits, vegetable, red meat and olive oil, and submissions with at least 7 "yes" responses indicated adherence. Other food frequency screeners might be used to identify individuals who meet dietary guidelines, or to divide individuals into percentiles.

A drawback of FFQs is that children, adolescents, and less-educated adults may require help completing the FFQ because of low literacy. Interviewer-administered FFQs are better for these populations. Another limitation is that FFQs rely on memory.

Validation studies show the FFQ to have substantial measurement error. One European study of more than 3,000 adults found that 33% of the study population underestimated usual energy intake from an FFQ compared with doubly-labeled water estimation of total energy expenditure.[28] In a recent study of U.S. adults, the self-reported FFQ energy intake compared with doubly-labeled water total energy expenditure underestimated energy intake by 31–36% in men and 34–38% in women. Self-reported protein intake was also underreported in both men and women compared with the gold standard urinary nitrogen biomarker.[29] Validation of the FFQs against multiple 24-hour recalls have yielded low to moderate correlations for nutrients and moderate correlations for reported food intake.[30,31]

Diet History

A **diet history (DH)** is a structured interview to gather data on usual dietary intake over a selected period of time, such as a month or year. Participants provide a list of food items, frequency of consumption, and portion size. Participants are also asked to report brand names or nutrient-modified food items, as well as additions to foods and beverages, such as sauces, condiments, butter, or margarine. Portion sizes are estimated by use of food models, household measures, or pictures. The DH may ask about food preparation and cooking fats, type or brand name of additions to foods at the table, and brand names of study foods-of-interest, such as ready-to-eat cereals with the information used to categorize the item as a whole or refined grain. Traditionally, the DH is followed by a 3-day food record or 24-hour recall interview; however, this component is sometimes omitted. Data entry may be direct or from a paper DH form.[32] The nutrient and food database for a DH uses the USDA Food and Nutrient Database and may also include food manufacturer nutrient values.

The DH method was developed by Bertha Burke in 1947[33,34] and later used in the Western Electric Study,[35] the CARDIA study,[36] and in several European studies.[37,38] In one study among children and adolescents, reported energy intake from a DH was overestimated compared with doubly-labeled water energy expenditure estimates.[39]

Measurement Error

Incorporating quality assurance (QA) and quality control (QC) activities into the study design can assure quality data and reduced **measurement error**, which occurs when random or systematic error is present (**Table 2-2**). QA activities before data collection consist of standardized study procedures and tools or instruments available to the diet interviewers as well as training and certification of the diet interviewers in study procedures prior to the start of data collection. QC activities during data collection consist of recording a proportion of the diet interviews to review interviewer performance, reviewing the data for irregularities, implementing automated software edits, and conducting analytic processing.

Table 2-2 Types of measurement error

Type of Error	Problem	Solution
Systematic error (bias) influences the validity of the measure		
Observer bias	When the interviewer is not accurate in measuring or reporting the participant's response	Implement quality control measures; retraining
Instrument bias	Inaccurate measurement due to a questionnaire or device that is not calibrated	Calibrate the instrument; pilot test the questionnaire
Subject or recall bias	A distortion in the subject's response; e.g., underreporting or overreporting dietary intake by certain groups	Neutral probing; review the questions and check the response
Random error is a wrong result occurring by chance that influences precision		
Observer variability	Possibly due to lack of training and certification	Training, certification
Instrument variability	Due to environmental factors (age of device, temperature, different assay lots, etc.)	Calibrate the device; buy the same device model across studies; regularly check the room temperature; order the same assay lot for all blood samples
Subject variability	Due to intrinsic variability of the individual, such as mood swings, illness, etc.	Reschedule the study exam; record the subject characteristic

Differential Reporting

A concern about the accuracy of self-reported dietary intake is the differential underreporting of food intake between groups, such as overweight versus normal-weight individuals. Differential reporting obscures associations between diet exposures and disease outcomes.[40,41] For example, diet–CHD relations were null before calibration, but the study found significant positive relations of calibrated-energy intake with CHD and inverse relations of percent energy from calibrated-protein intake with CHD risk in older, mostly white women.[42]

Objective biomarkers, such as doubly-labeled water, are accurate but expensive methods to calibrate and improve the accuracy of self-reported data. Another objective biomarker is urinary nitrogen to calibrate self-reported protein intake. Electrolytes help calibrate noncaloric sodium and potassium. Findings from the use of doubly-labeled water include decreasing energy expenditure with age and higher total energy expenditure among men than women for both whites[43] and African Americans.[44] Underreporting of energy expenditure is more likely among overweight or obese adults than normal weight,[45] younger versus older women and African Americans compared with whites.[46,47] Although energy and protein intakes may be calibrated, foods that have been underreported or omitted from the diet interview are still unknown; therefore, other nutrients may be misrepresented. Commonly underreported foods include cakes, pies, regular soft drinks, savory snacks, cheese, fat-type spreads, meats, and condiments, or items high in energy, sugar, sodium, and/or fat.[48,49]

Diet, Nutrition, and Cardiovascular Disease

HP 2020 Objectives

HDS-1 (Developmental): Increase overall cardiovascular health in the U.S. population

HDS-2: Reduce coronary heart disease deaths

HDS-3: Reduce stroke deaths

HDS-5: Reduce the proportion of persons in the population with hypertension

ED/AU: okay that this is HDS-5 and not HDS-4?

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Cardiovascular Disease Is a Public Health Problem

Public Health Core Competency 1: Analytical/Assessment Skills 2: Describes the characteristics of a population-based health problem

Cardiovascular disease is the leading cause of death in the United States, while stroke follows in third place.[50] Ischemic heart disease is the top cause of death worldwide, along with stroke and other cerebrovascular diseases. Despite its impact, however, CVD is largely affected by modifiable risk factors, such as high blood pressure, high cholesterol, cigarette smoking, diabetes, poor diet, physical inactivity, obesity, and **metabolic syndrome**.[51] Epidemiological studies have exposed relationships between nutrients, food groups or diet patterns, and CVD.[52] This section highlights some of these studies.

Public Health Core Competency 1: Analytical/Assessment Skills 1: Identifies the health status of populations and their related determinants of health and illness

Public Health Core Competency 6: Public Health Science Skills 5: Describes the scientific evidence related to a public health issue, concern, or intervention

Nutrient Intake and Hypertension

Higher sodium intake is related to higher blood pressure and risk for developing hypertension, but other nutrients may prevent high blood pressure. One cross-sectional study that assessed diet intake using four 24-hour recall in-person interviews found that dietary phosphorous, calcium, and magnesium were inversely associated with blood pressure among 4,680 men and women ages 40 to 59 from Japan, China, the United Kingdom, and the United States.[53] Calcium and magnesium were significantly correlated with phosphorus. A diet pattern rich in food sources of these nutrients, or dairy products, fruits and vegetables, and fish, is likely related to lower blood pressure. A meta-analysis of eight RCTs found substantially lower systolic blood pressure but smaller reductions in diastolic blood pressure with higher flavonoid intake; however, the optimal dose is still unknown.[54] A separate meta-analysis demonstrated marginally lower systolic and diastolic blood pressure with

vitamin D supplementation among adults with hypertension,[55] although no effect of supplementation on blood pressure in individuals with normal blood pressure.

Food Groups and Hypertension

In the Atherosclerosis Risk in Communities (ARIC) study of middle-aged adults, higher consumption of low-fat milk, assessed by FFQ at baseline and six years later, was associated with smaller increases in blood pressure in whites but not in African Americans over nine years of follow-up.[56] In the same population, consumption of more full-fat or reduced-fat dairy products was associated with lower risk of developing high blood pressure.[57] In the CARDIA study, which included whites and African Americans aged 18–30 years at baseline, dietary intake was assessed with a diet history questionnaire at baseline and seven years later. Steffen et al. examined the relation between consumption from major food groups, defined as fruit, vegetables, legumes, nuts, meat, dairy, refined grains, whole grains; intakes; and the risk of developing EBP over 15 years of follow-up.[58] Greater intakes of plant foods and dairy products were associated with 31% and 15% lower risks, respectively, of developing EBP, while risk of EBP was increased by 50% with greater consumption of red and processed meat. In subgroup analysis of plant foods, whole-grain products, fruit, and nuts were each significantly and inversely related to EBP.

Investigations of Diet Patterns and CVD Risk Factors

As earlier described, DASH was a randomized clinical trial that demonstrated lower blood pressure among middle-aged adults with high normal or high blood pressure who were randomized to the DASH diet pattern compared with those randomized to the fruit and vegetable or control groups.[59] A different nutrient-rich diet pattern, the Mediterranean diet, was found to lower blood pressure, according to a meta-analysis of 14 clinical trials conducted in the United States, Europe, and Australia.[60] The diet is rich in fruit, vegetables, fish, nuts, and monounsaturated fat from olive oil. Multiple observational studies have demonstrated that healthy diet patterns, including the Mediterranean diet,[61] healthy diet score,[62] and a prudent diet pattern,[63] were related to lower risk of developing high blood pressure. In contrast, a cross-sectional study found higher blood pressure among Japanese adults who consumed a "Western" diet pattern, characterized by higher meat and lower vegetable intake.

Application of Research Findings to Public Health Policy

The DASH trial and other research studies have helped shape nutrition policies, including the Dietary Guidelines, to educate the general population in making changes in their eating habits. The 2010 Dietary Guidelines for Americans, for example, recommend choosing whole-grain products, reduced-fat dairy products, and a variety of protein foods, including lean meat, poultry, seafood, legumes, nuts and seeds, and increasing intake of fruit and vegetables.[64] However, despite consistent epidemiologic evidence relating greater red and processed meat consumption to higher risk of hypertension and other chronic diseases, these foods remain in the list of recommended foods.

Dietary Intake and CVD

The Seven Countries study, an **ecologic study** conducted in 1980 by Ancel Keys and colleagues, linked CHD incidence to greater intake of dietary saturated fat.[65] Based on this landmark study and other studies about dietary fat, subsequent versions of the U.S. Dietary Guidelines for Americans recommended consumption of a lower intake of total and saturated fat.[66] Since then, epidemiologic evidence has been accumulating regarding other diet–disease relationships.

Nutrient Intake and CVD

Few studies have shown a positive relation between total energy relative and risk of developing CHD, possibly due to underestimation of total energy intake due to underreporting of consumption of high-calorie snack foods, such as salty snacks, crackers, cake, cookies, pastries, candy, sugar-sweetened beverages, and alcohol.[67,68,69] Foods consumed at main meals tend to be more accurately reported than foods consumed between meals; thus the resulting micronutrient intake may be sufficiently accurate to predict diet–disease relations if it can be assumed that the majority of micronutrients are contributed by foods eaten at meals. Evidence reported from observational studies is inconsistent for the associations of the dietary antioxidants vitamin C and beta-carotene with CHD,[70] although a protective effect of vitamin E on CHD is consistent in observational studies. However, RCTs have not reproduced these results. Findings have been similarly inconsistent for supplemental vitamin C and beta-carotene.[71] It appears that one supplemental

antioxidant is not protective against CHD. However, numerous observational studies have reported significant and inverse associations of dietary **omega-3** fatty acids with CHD, congestive heart failure, and stroke.[72] In these studies, dietary intake was measured using 24-hour recall interviews, FFQ, or diet history questionnaires.

Food Groups and CVD

Numerous studies have examined the relation of single food groups relative to CVD. The evidence is consistent for whole-grain products and red and processed meat, but not for refined grains, dairy, or fruit and vegetable intakes. For example, in a prospective cohort study among over 15,000 white and African American middle-aged adults where dietary intake was assessed by FFQ, whole-grain products protected against the development of coronary artery disease (CAD) over 11 years of follow-up.[73] Fruit and vegetable intake was also protective only among African American adults. Refined grain products were not related to CAD in the whole group, and in subgroup analysis, refined grains were positively related to CAD in African Americans. It is not clear why these food groups were predictive in African Americans and not whites in the ARIC study.

Findings from a meta-analysis of 13 cohort studies with an average of 11 years of follow-up showed a 17% lower risk of CHD for adults consuming more than five servings of fruit and vegetables per day compared with those consuming less than three servings per day.[74] For red and processed meat, the risk of ischemic stroke increased by 13% with each 100g increase for red meat, and the risk increased by 11% for each 50g increase in processed meat intake according to a meta-analysis of five cohort studies.[75] Similar results have been reported for CHD in single studies using an FFQ to assess dietary intake. Finally, consumption of fish has been consistently related to lower CVD mortality, including fatal heart attack and sudden death.[76] Mechanisms that explain lower CVD with greater fish intake have been proposed.[77] In contrast, although the majority of evidence for whole grains and red and processed meats is consistent for CVD, the causal mechanisms have yet to be elucidated.

Diet Patterns and CVD

Numerous epidemiologic studies have examined the relations between diet patterns and risk of CVD. Diet patterns or scores have created **a priori** (based on an established concept) or generated **a posteriori** (data driven).[78,79] Data-driven-derived "prudent" diet patterns, a priori–derived healthy diet scores, the DASH diet pattern, and the Mediterranean diet pattern have been inversely related to mortality from all causes and CHD in several populations.[80,81,82,83,84] These diet patterns or scores have some common characteristics. The Mediterranean and DASH diet patterns are rich in fruits, vegetables, and nuts, while the Mediterranean diet pattern is rich in olive oil and the DASH diet pattern is higher in low-fat dairy products. A Norwegian healthy food score was rich in fruit, vegetables, and high-fat fish.[85] All three of these diet patterns were low in red and processed meat. In a Danish study, the prudent diet pattern, rich in fruits, vegetables, and whole-meal bread, was inversely related to all-cause and CVD mortality in men and women, after adjusting for relevant confounding factors; however, the Western diet, represented by greater meat, potatoes, white bread, and butter, was not significantly related to mortality.[86]

Conclusion

Although single nutrients, but not all, have been significantly related to CVD and its risk factors, such as high blood pressure, it is evident that combinations of nutrients and compounds in foods as well as the combination of foods in diet patterns work synergistically and, therefore, have greater health benefits or risks than individual nutrients or foods.[87] However, to understand the mechanisms underlying these relations, further nutrition research is warranted. Recent research in the field of nutritional metabolomics has focused on correlations between diet patterns and biomarkers.[88] These correlations may vary between individuals, with more pronounced differences between healthy individuals and those with heart disease, diabetes, and hypertension.[89,90,91] As nutritional epidemiology continues to provide new knowledge, public health nutritionists can work to improve diets through multilevel interventions.

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