CHAPTER 1

Interpreting Evidence-Based Research: Major Pediatric and Adult Nutrition Studies

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CHAPTER OUTLINE

Reader Objectives

After studying this chapter and reflecting on the contents, you should be able to

1. Discuss the rationale for protection of human subjects in research.
2. Explain specific legal issues relating to research with children, such as the distinction between assent, consent, and permission.
3. Argue for and against giving incentives to study participants or their parents or guardians.
4. Discuss the strengths and weaknesses of different types of epidemiologic studies.
5. Explain the contribution of epidemiologic studies.
6. Explain why longitudinal studies are often referred to as hypothesis-generating studies and intervention studies as hypothesis-testing studies.
7. Discuss examples of health interventions, and how we can assess their impact on the target population.
8. Describe recent changes in the field of nutritional epidemiology and the impact of these changes.
9. Summarize key findings of major epidemiologic studies that have contributed to the research underlying current chronic disease prevention efforts.
10. Describe the strengths, weaknesses, and limitations of these studies, and describe how these studies have contributed to the nutrition guidelines in the United States.

Research Involving Children

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Historically, research involving children has reflected societal views of children (Glantz, 1998; Meaux & Bell, 2001; Kopelman, 2006). Under traditional English common law children were seen as chattel. Early experiments with infectious diseases and vaccines were often conducted on children of slaves or servants or on poor, institutionalized, or mentally challenged children. The latter provided a controlled environment and a "captive subject pool" (Meaux & Bell, 2001). Children were intentionally infected with leprosy, syphilis, gonorrhea, tuberculosis, or yellow fever and then used to study diagnostic tests or vaccines to detect or prevent these diseases. In the 1800s Edward Jenner used his own children before moving on to institutionalized children to test his smallpox vaccine; all children were then challenged with smallpox to determine the efficacy of the vaccine. Other vaccines, such as pertussis (Burns, 2003), were also tested in this manner. These trials constituted a grave risk, and not all were successful. In the 1930s children were used in clinical trials of a live virus polio vaccine; the deaths associated with these trials underscored the necessity of protecting children in research studies. As recently as the 1970s institutionalized mentally challenged children were infected deliberately with hepatitis in an attempt to develop a vaccine. Although "consent" was obtained, it is unclear whether parents actually recognized the risks involved (Jonsen, 1983).

In 1941 this acceptance of using children in research began to change when Francis Payton Rous, the editor of the *Journal of Experimental Medicine*, rejected a manuscript and wrote to the author, "the inoculation of a twelve month old infant with herpes . . . was an abuse of power, an infringement of the rights of an individual, and not excusable because the illness which followed had implications for science. The fact that a child was 'offered as a volunteer'—whatever that may mean—does not palliate the action" (quoted in Glantz, 1998).

It was, however, the public knowledge of the atrocities conducted under the guise of scientific experiments perpetrated by the Nazis that ultimately led to regulations that protected the rights of children in research studies. The 1964 Nuremberg Code clearly mandated the need for "informed, uncoerced, voluntary consent" by all research subjects; however, this effectively excluded the use of children in research because they cannot legally give consent. The Declaration of Helsinki (1964) gave parents the authority to consent for their children; it also stipulated that when minor children were able, they must also provide consent. The Belmont Report—Ethical Principles and Guidelines for the Protection of Human Subjects, or *Common Rule*, underscored the importance of children being able to choose if they wanted to participate in a research project. The Belmont Report established the three fundamental ethical principles that apply to research using human subjects—respect for persons, beneficence, and justice—and provides the philosophical underpinnings for the current federal laws governing human subjects research: Title 45 Code Federal Regulations, Part 46, Protection of Human Subjects (45 CFR Part 46).

Learning Point Before you continue, complete the tutorial, "Human Participant Protections Education for Research Teams," and print out your certificate: http://cme.cancer.gov/c01/intro_02.htm

As researchers strove to protect children from abuses in research, there was increasing concern that children were not benefiting from medical advances, especially important research on drugs. Society continues to view children as vulnerable and in need of protection (Christensen, 1997), but care must be taken not to exclude children from research on new vaccines, pharmaceuticals, and medical devices that would benefit them (Morrow & Richards, 1996). The legal status of children has evolved from that of chattel to persons with limited autonomy (Grodin & Alpert, 1988). Today, the use of children as research participants reflects respect for the child and parents, a balance of risks and benefits, and distributive justice (Nelson, 1998).

Ethics and Regulations Regarding Research with Children

Institutional Review Board

Every organization that conducts biomedical or behavioral research with human subjects is federally mandated to have an institutional review board (IRB). The purpose of the IRB is to review the scientific merits and ethical principles of studies involving human research before the research is conducted.

An IRB must have at least 5 members with varied backgrounds; however, an IRB should include as many members as needed to perform a complete review of research involving human subjects, and membership may include 20 to 30 members. At least

one member must be a "scientist" and at least another, a "nonscientist." One member must be unaffiliated with the institution housing the IRB; this member is considered so important that many IRBs will not review protocols if that person is not present. Diversity in race, gender, cultural heritage, and sensitivity to issues, such as community attitudes, should be considered when considering IRB membership. If the IRB regularly reviews research involving vulnerable subjects, including children or physically or mentally challenged persons, someone who is knowledgeable about and experienced with these subjects should be included in membership. IRB review is guided by The Belmont Report and the Federal Policy for the Protection of Human Subjects.[1] Although federal guidelines are in place, regulations are flexible and there is a broad spectrum of interpretation by different IRBs.

Children have many unique issues with respect to research and the IRB. First, what defines a child needs to be determined. The legal definition is clear, but cognitive abilities of children vary, and a child who has a chronological age of 7 may be unable to understand complexities that a similarly aged child can. Thus, despite individual regulations of the IRB, the individual abilities of the child should also be considered.

Parental Permission and Child Assent

Enrolling children and adolescents in research studies raises ethical concerns because they lack the legal status to provide consent; thus regulations require both parental permission and child assent (Broome & Stieglitz, 1992; Glantz, 1996; Field & Behrman, 2004). Parents provide consent out of beneficence, and assent is obtained from the child to respect his or her autonomy (Rossi, Reynolds, & Nelson, 2003). Generally, if a parent gives permission to participate in a research study but the child does not assent, the child's wishes supersede the parents' (Koren, 2003). Child assent, as defined by federal regulations, means "a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent." Adequate provisions for assent must be provided, unless waived under limited circumstances, for example, if the child is judged incapable of providing assent. Individual IRBs are responsible for setting the exact criteria for assent, but generally the child must (1) demonstrate a developmentally appropriate understanding of the nature of the procedures to be performed, (2) freely choose to undergo the procedure(s), (3) communicate his or her choice unambiguously, and (4) understand that he or she can withdraw at any time without penalty.

Factors affecting the ability of a child to provide assent are divided into two categories: individual factors, such as age, developmental level, and health status, and environmental factors, such as role constraints, family factors, and consent-seeker factors (Weithorn & Scherer, 1994; Meaux & Bell, 2001). The American Academy of Pediatrics (AAP) recommends obtaining assent from children 7 years and older; however, the capacity for assent should be viewed as a continuum as the child matures and as cognitive ability increases. Information for children should be age appropriate. Decision-making ability in children improves with increasing grade level (Lewis, 1998).

Use of Incentives in Pediatric Research Studies

Giving financial or other compensation to research volunteers is a common (Levine, 1979; Vere, 1991; Dickert, Emanuel, & Grady, 2002; Grady, Dickert, Jawetz , Gensler, & Emanuel, 2005) although questionable practice in the United States. Although little empirical data explore the impact of incentives on participation, critics propose that low income populations may be exploited, prospective participants may overlook potential risks associated with the study for financial gain, and altruistic motives may be undermined (Russell, Moralejo, & Burgess, 2000; Dresser, 2001; Kuczewski, 2001; Viens, 2001; Weise, Smith, Maschke, & Copeland, 2002). Giving payment to children and adolescents or their parents is even more debatable (Glantz, 1998; Fernhoff, 2002; Weise et al., 2002; Wendler, Rackoff, & Emanuel, 2002; Field & Behrman, 2004; American Academy of Pediatrics [AAP], 2005). Even seemingly small amounts of money may coerce children and adolescents to overlook the risks associated with a study or may deter them from withdrawing voluntarily. The AAP states that "serious ethical questions arise when payment is offered to adults acting on behalf of minors in return for allowing minors to participate as research subjects" (AAP, 1995). The AAP suggests that any payment be limited to a token gesture and that payment for reimbursement of costs for time or travel should be low enough that it does not become an inducement (AAP, 1995). They further recommend that if the recipient of the payment is a child, the discussion should occur after the completion of the study, not before, as recommended by federal guidelines.

Table 1.1 provides Internet resources on legal and ethical issues concerning children in research. **Table 1.2**

1. http://www.cdc.gov/nchs/nhanes.htm

TABLE 1.1 Internet Resources for Ethics and Human Research

American Society for Bioethics and Humanities http://www.asbh.org
Belmont Report http://www.cdc.gov/od/ads/ethcodes/belm-eng.pdf
Bioethics Databases http://www.nlm.nih.gov/pubs/cbm/hum_exp.html#300
Bioethics Resources on the Web http://www.nih.gov/sigs/bioethics
Center for Cancer Research Institutional Review Board: The Process of Informed Consent http://home.ccr.cancer.gov/irb/informed.html
Council for International Organizations of Medical Sciences http://www.cioms.ch
Declaration of Helsinki http://www.wma.net/e/policy/b3.htm
Food and Drug Administration http://www.fda.gov
Health Insurance Portability and Accountability Act (HIPAA) http://www.hhs.gov/ocr/hipaa
HIPAA Privacy Rule http://privacyruleandresearch.nih.gov
Information about National Institutes of Health (NIH)/National Cancer Institute cancer research studies http://cancertrials.nci.nih.gov
International Guidelines for Ethical Review of Epidemiologic Studies http://www.cdc.gov/od/ads/intlgui3.htm
National Bioethics Advisory Commission http://www.georgetown.edu/research/nrcbl/nbac
NIH Ethics Program http://ethics.od.nih.gov
NIH Infosheets, Forms, Checklists http://ohsr.od.nih.gov/info
NIH Office of Extramural Research http://grants.nih.gov/grants/oer.htm
NIH Office of Human Subjects Research http://ohsr.od.nih.gov
National Library of Medicine Bibliography—Ethical Issues in Research Involving Human Participants http://www.nlm.nih.gov/pubs/cbm/hum_exp.html
Nuremberg Code http://ohsr.od.nih.gov/guidelines/nuremberg.html http://www.fda.gov
Office for Human Research Protections (OHRP) http://www.hhs.gov/ohrp
OHRP Guidance Topics by Subject http://www.hhs.gov/ohrp/policy/topics.html
President's Council on Bioethics http://www.bioethics.gov
Public Responsibility in Medicine and Research http://www.primr.org

provides information on the requirement under the U.S. Department of Health and Human Services Regulations 45 CFR 46, Subpart D based on the risks and benefits to children who participate in research.

Nuturition Monitoring of Infants, Children, and Adolescents

The Centers for Disease Control and Prevention (CDC) has several health monitoring studies of infants, children, and adolescents. The best known is the National Health and Nutrition Examination Survey[2] (NHANES), which is part of the National Center for Health Statistics (NCHS).[3] Other important studies are the Pediatric Nutrition Surveillance System (PedNSS)[4] and the Pregnancy Surveillance System (Table 1.3). NHANES I and II and the PedNSS were initiated in the 1970s. In 1990 the National Nutrition Monitoring and Related Research Program (PL 101-445) established a comprehensive coordinated program for nutrition monitoring and related research to improve health and nutrition assessment in U.S. populations. The National Nutrition Monitoring and Related Research Program requires a program to coordinate federal nutrition monitoring efforts and assists states and local governments in participating in a nutrition monitoring network to create an interagency board to develop and implement the program, to create a nine-member advisory council to provide scientific and technical advice, and to evaluate program effectiveness.

Learning Point NHANES data are available to researchers to help them understand the data set and how to work with it. The CDC has a tutorial that can be found at http://www.cdc.gov/nchs/tutorials/index.htm. Why not take the tutorial to see how NHANES data can help you with your research?

NHANES

The NHANES cohort is selected to comprise a nationally representative sample. The current NHANES has a special accent on adolescents and the elderly; accordingly, these groups are oversampled. The emphasis for adolescents is nutrition and fitness. New measures of physical fitness can improve our understanding of the impact that physical activity has on health. African-Americans and

2. http://www.cdc.gov/nchs/nhanes.htm
3. http://www.cdc.gov/nchs/Default.htm
4. http://www.cdc.gov/pednss/index.htm

TABLE 1.2 Requirements Under the U.S. Department of Health and Human Services (DHHS) Regulations 45 CFR 46, Subpart D Based on the Risks and Benefits to Children Who Participate in Research

Types of Research	Requirements	Examples
§46.404 Research not involving greater than minimal risk	Assent of child and permission of at least one parent. **Note:** An advantage to this type of research is that it enables investigators to obtain expedited review, modify or waive consent, and allow vulnerable populations, like children, to be enrolled in studies (Kopelman, 2004).	Surveys, blood drawing, x-rays, chart reviews, educational interventions, growth and development studies
§46.405 Research with greater than minimal risk but with the prospect of direct benefit to the individual subjects	Assent of child and permission of at least one parent Anticipated benefit justifies the risk AND Anticipated benefit is at least as favorable as that of alternative approaches	Randomized clinical trials; comparison of the efficacy and safety of standard treatments of asthma
§46.406 Research with greater than minimal risk and no prospect of direct benefit to the individual subjects but likely to yield generalizable knowledge about the subject's condition or disease	Assent of child and permission of both parents Only a minor increase over minimal risk Likely to yield generalizable knowledge about the child's disorder or condition that is of vital importance for the understanding or amelioration of the disorder or condition AND The intervention or procedure presents experiences to the child that are reasonably commensurate with those in the child's actual or expected medical, dental, psychological, social, or educational situations.	Bone marrow aspiration, lumbar puncture, skin punch biopsy—all with suitable pain control
§46.407 Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children	Assent of child and permission of both parents IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children AND The Secretary of DHHS, after consultation with a panel of experts in pertinent disciplines (e.g., science, medicine, education, ethics, law) and following publication and public comment, determines the research will be conducted in accordance with sound ethical principles. **Note:** The United States alone has a provision for this type of research on children (Kopelman and Murphy, 2004).	

From http://grants.nih.gov/grants/guide/notice-files/not98-024.html Accessed May 19, 2006.

TABLE 1.3 Other Epidemiologic Studies Looking at Health and Nutrition of Infants, Children, and Adolescents

Study	Population	Purpose	Comments/Important Findings
Gerber Feeding Infants and Toddlers Study (FITS)	3,000 4- to 24-month-old children	To investigate infant and toddler eating habits and nutrient intakes, to determine whether IOM recommendations are being met, and to examine the relationship between food intake and self-feeding	Collaboration among researchers in diet and food, statisticians, and the food industry. Results can be found in the January 2006 supplement of the *Journal of the American Dietetic Association*.
Northern Ireland Young Hearts Project (YH 1990) (1989–1990)	~2,000 boys and girls 12–15 years of age	To identify major modifiable coronary risk factors with a randomly selected cohort of adolescents in Northern Ireland	Risk factors for cardiovascular disease tend to cluster (Twisk et al., 1999). Ttracking of nutrients in adolescents was inconsistent (Robson et al., 2000). Although socioeconomic status is defined, it is not yet lined with cardiovascular risk factors (Van Lenthe et al., 2001).
Northern Ireland Young Hearts Project (YH 2000) (1999–2000)	~2,000 boys and girls 12–15 years of age	To identify the prevalence of risk factors for cardiovascular disease present in this population and to identify modifiable life-style factors associated with bone mineral density in the participants To be able to examine secular trends in these factors by comparing data to YH 1990	Decreases in blood pressure between the studies (Watkins et al., 2004); high intake of fruit is associated with increased bone health in girls (McGartland et al., 2004), whereas carbonated beverage intake is associated with lower bone health (McGartland et al., 2003).
Growing up in Australia	Cohort 1: 5,000 infants aged less than 12 months in 2003–2004 followed until 6–7 years old Cohort 2: 5,000 children aged 4 years followed until 10–11 years old	To determine critical periods to provide social and welfare support and to determine individual, family, and broader social impacts on children's development and change	There are a limited number of published papers available at this time, but some include descriptions of the study (Nicholson and Sanson, 2003; Harrison and Ungerer, 2005).
Amsterdam Growth and Health Longitudinal Study—initiated in 1977	500 healthy 13-year-old boys and girls	Until ~age 17 annual assessments included anthropometrics, physiologic and psychological parameters, life-style characteristics (activity, diet, smoking), and health parameters (Kemper et al., 1997). Subsequent testing was done at ages 21, 27, 32, and 36, allowing investigators to track health and life-style variables from early adolescence into young adulthood.	No differences were observed for high and mid-level calcium intake at a threshold of approximately 800 mg/day above which calcium intake has no additional beneficial effect (Boon et al., 2005). A 14-year follow-up showed both stability coefficients and tracking for subjects at risk for life-style risk factors were low (except for smoking), indicating low predictability of early measurements for values later in life. For cardiopulmonary fitness and blood pressure tracking was also low, whereas for the lipoproteins and body fatness tracking was much better, indicating good predictability (Twisk et al., 1997).
PNSS	Convenience sample of low-income high-risk pregnant women	To assess the demographics, pregravid weight and maternal weight gain, anemia, behavioral risk factors, birth weight, and formula-feeding data as risk factors for the mother and infant. PNSS provides surveillance reports to help with	Begun in 1973 and continuing

TABLE 1.3 Other Epidemiologic Studies Looking at Health and Nutrition of Infants, Children, and Adolescents *(continued)*

Study	Population	Purpose	Comments/Important Findings
		priority setting, planning, implementing, and evaluating public health policy.	
Early Childhood Longitudinal Study	Two overlapping cohorts—birth (n = 10, 688 born in 2001) to be followed to kindergarten and kindergarten (n = 22,000 from 1,000 programs) to be followed to the eighth grade	Provides national data on children's status from birth on children's transitions to nonparental care, early education programs, and school and children's experiences and growth through the eighth grade. Data are also provided to test hypotheses about a wide range of family, school, community, and individual variables on children's development, early learning, and school performance.	http://nces.ed.gov/ecls/index.asp is the best way to learn about this study. One recent article using these data showed that WIC mothers are less likely to breast-feed than noneligible participants (Jacknowitz et al., 2007).

IOM, Institute of Medicine; PNSS, Pregnancy Surveillance System: WIC, Special Supplemental Nutrition Program for Women, Infants, and Children.

Mexican-Americans are also over-sampled to get a more representative cohort.

Data are collection for NHANES at three levels: a brief household screener interview, an in-depth household survey interview, and a medical examination. Because detailed interviews and clinical, laboratory, and radiologic examinations are conducted, participants' response burden is significant. For the years 1999–2000 and 2001–2002 the interview sample size was 21,004, and the Mobile Examination Center sample size was 19,759.

Data from the NCHS was used to establish the CDC pediatric growth charts[5] in 1977; when these growth charts were revised in 2000 most of the data came from NHANES. The most obvious change in the growth charts is the substitution of body mass index (BMI) for weight for height measures. These charts can be used when the child is 2 years old and a standing height can be obtained. Other changes involved infants, including revision of head circumference standards; NHANES provided the national data needed for these charts. These charts have been adapted and adopted for worldwide use. Another major effect on the health of children is the monitoring of blood lead levels. Early NHANES studies documented a high percentage (77.8%) of children aged 1 to 5 years with high blood lead levels. This information was instrumental in using legislation to remove the lead from gasoline and food and soft drink cans. NHANES 1991/1994 showed a steep decline in the percentage (4.4%) of children with blood lead levels of at least 10 μg/dL (Centers for Disease Control and Prevention [CDC], 2005). Information from NHANES can be used to monitor the impact that fortification of foods has on nutrient intake of children, which in turn can lead to policy change.

It is difficult to quantify the tremendous impact that NHANES and related surveys have had on health policy and health research in the United States (Woteki, 2003). A recent PubMed search using NHANES with the key words "English," "Human," and "All Children" produced 3,780 articles. Research as diverse as late bottle weaning and obesity, alcohol consumption

GROUP Project

NHANES is an ongoing survey, and new questions can be added if investigators need the information; for example, dietary supplement use was recently added to the surveys. Look at the survey contents (http://www.cdc.gov/nchs/about/major/nhanes/nhanes2003-2004/questexam03_04.htm) and at the proposal guidelines for new survey content (the deadline is past, but there will be another; http://www.cdc.gov/nchs/about/major/nhanes/research_proposal_guidelines.htm). What would you add to the NHANES survey and why? Include in your answer the knowledge gap your new question(s) is designed to fill and how you will use the information. It may help you to understand the power of NHANES if you review some of the literature and explore the website before completing this project.

5. http://www.cdc.gov/growthcharts

and periodontal disease, and blood pressure trends in children and adolescents was found. NHANES also showed ethnic differences in dietary intake (Ford & Ballew, 1998; Arab, Carriquiry, Steck-Scott, & Gaudet, 2003), food sources for different nutrients are different in separate ethnic groups (Looker, Loria, Carroll, McDowell, & Johnson, 1993), cardiovascular risk factors cluster according to socioeconomic status (Sharma, Malarcher, Giles, & Myers, 2004), and hypertension varies according to geographic region (Hicks, Fairchild, Cook, & Ayanian, 2003). These findings demonstrate that data cannot be generalized for state or local areas without considering age, gender, ethnicity, or socioeconomic status in the particular area and that these data have important implications for public policy and intervention strategies. The findings underscore the importance of looking at nationally representative data.

Youth Risk Behavior Surveillance System

Initiated in 1990 by the CDC, the Youth Risk Behavior Surveillance System (YRBSS) is a large-scale biennial survey of 9th through 12th grade students at national, state, and local levels that studies behaviors linked to the leading causes of morbidity and mortality—chronic disease and unintentional injury. This self-reported survey looks at tobacco use, unhealthy dietary behaviors, and physical activity levels. Purposes include determining the prevalence of risk-taking behaviors, providing national and state data, monitoring levels of risk-taking behavior, and assessing progress toward the goals outlined in *Healthy People 2010*. The most recent survey assessed the national data, 40 state surveys, and 21 local surveys throughout the period from October 2004 to January 2006. That survey used sampling strategies to over-sample African-American and Hispanic youth. The full report is available online,[6] but, briefly, 79.9% had not eaten five or more servings of fruits and vegetables per day in the 7 days preceding the survey, 16.2% consumed three or more glasses of milk per day, 67% did not attend daily physical activity classes, and 13.1% were overweight. These data clearly indicate that most adolescents are not meeting current recommendations for diet and physical activity.

A Middle School RBSS was initiated by the CDC to assess health risk behaviors in students in sixth to eighth grade. The 2003 report is also available online.[7]

The advantages of the YRBSS are that the study is anonymous, encouraging youth to be truthful in their answers, and the large sample size—data generated for the 2005 report were from 13,953 surveys and the national representation. Limitations are that the survey only reaches those in school and the data are self-reported. Although test/retest reliability is good, BMI may be underreported.

PedNSS

The PedNSS is a child-based public health monitoring system that describes the nutritional status of low income children in federally funded maternal and child health and nutrition programs, including Special Supplemental Nutrition Program for Women, Infants, and Children; Early and Periodic Screening, Diagnosis, and Treatment Program; and Title V Maternal and Child Health Program. The goal of PedNSS is to provide data on the prevalence and trends of nutrition-related indicators and to disseminate information that would help establish policy.

CRITICAL Thinking

You may have participated in the YRBSS when you were in high school. If not, you can see what this study is about. The 2007 survey (http://www.cdc.gov/HealthyYouth/yrbs/pdf/questionnaire/2007HighSchool.pdf) and the Middle School Behavioral Risk Survey (http://www.cdc.gov/HealthyYouth/yrbs/pdf/questionnaire/2007MiddleSchool.pdf) are available online. How can these new data be used?

Epidemiologic Surveys of Children and Adolescents

In addition to the NCHS data, a number of long-term, primarily government-funded, epidemiologic studies on children and adolescents have provided critical information used to guide the nation's health policies. The Bogalusa Heart Study (BHS) and the National Longitudinal Study of Adolescent Health are leading examples, as is the new National Children's Study.

Most governments, either autonomously or through universities, track the health and nutrition status of their population. Many of the studies listed below, such as the Young Finns Study and the Amsterdam Growth and Health Longitudinal Study, were not done in the United States. As global health problems, notably obesity and its recognized comorbid conditions, invade not only developed countries but also undeveloped

6. http://www.cdc.gov/mmwr/PDF/SS/SS5505.pdf

7. http://www.cdc.gov/healthyyouth/yrbs/middleschool2003/pdf/fullreport.pdf

ones, it is important to understand more fully the universality that diet, physical activity, and other life-style factors have on the development of chronic disease.

BHS

The BHS was designed initially to examine the early natural history of coronary heart disease and essential hypertension in a biracial (African-American and white) pediatric population (Berenson et al., 1980; Berenson, Wattigney, Bao, Srinivasan, & Radhakrishnamurthy, 1995; Berenson, 1986). Today, the BHS population consists of approximately 5,000 individuals studied at various growth phases and followed for as long as 15 years. The mixed epidemiologic design of the study included **cross-sectional** and longitudinal surveys to provide information on three questions:

Cross-sectional surveys: Look at individuals with respect to both exposure and disease at a point in time. Because both exposure and disease are assessed at the same time, it can be difficult to determine whether exposure predated disease.

1. What is the distribution and prevalence of cardiovascular disease risk factors in a defined pediatric population, and how are abnormal serum lipid levels, blood pressure, and other risk factors defined?
2. Do cardiovascular risk factors track and change over time?
3. What is the interrelationship among these risk factors?

Other questions—notably, what is the interaction of genetics and the environment—were also posed.

Data from the BHS have contributed significantly to our knowledge and understanding of cardiovascular risk factors in children. More than 800 publications have been generated from this study. Information on children, adolescents, and young adults from birth to 31 years of age has provided the framework to establish desirable cholesterol levels in children and has led investigators to recommend screening of cardiovascular risk factors for all children, not only those with a parental history of cardiovascular disease, beginning at preschool age. Data have also suggested that risk factors for cardiovascular disease "track," that is, they remain in a rank relative to peers. For example, children with elevated serum total cholesterol or low-density lipoprotein (LDL) cholesterol levels are likely to become adults with dyslipidemia. Recently it was shown that children with BMIs in the 99th percentile may be at risk for biochemical anomalies and severe adult obesity (Freedman, Kettel-Khan, Srinivasan, & Berenson, 2000).

BHS data have been used to characterize children's diets and secular trends in children's diets for more than 20 years (Nicklas et al., 2004) and were used by the AAP as part of the rationale for its recommendation that the Dietary Guidelines for Americans could apply to healthy children aged 2 years and older. Data were also used to develop the American Dietetic Association's position paper on dietary guidance for healthy children aged 2 to 11 years (Nicklas & Johnson, 2004). This rich data set has also provided the opportunity to examine the link between cardiovascular risk factors and genotypes in individuals who had been evaluated from 2 to 12 times (Hallman, Srinivasan, Chen, Boerwinkle, & Berenson, 2004; Chen, Li, Srinivasan, Boerwinkle, & Berenson, 2005).

Another major accomplishment of the BHS comes not from the epidemiologic data per se but from autopsy studies of participants (Berenson et al., 1992), usually children and adolescents killed in accidents. BHS data confirmed and extended earlier studies (Strong & McGill, 1962) that showed fatty streaks in the aorta are evident in the first decade of life and that the extensiveness of these lesions is highly correlated with serum total cholesterol and LDL cholesterol levels.

The strengths of the BHS include its length, which allowed children to be followed into young adulthood; a large well-characterized biracial cohort; and excellent relations with the community that allowed ancillary studies, such as the autopsy study described above. Early in the BHS study it was demonstrated that BHS dietary data were similar to national data (Nicklas, 1995; Nicklas, Johnson, Myers, Webber, & Berenson, 1995). Limitations of the BHS are that data were collected from a restricted semirural geographic area and may not be representative of the country as a whole; although a biracial (African-American and white) population was studied, African-Americans were underrepresented in some surveys and no other ethnic groups were considered. Many of the dietary studies are based on a single dietary recall. Because the BHS has a mixed study design, many of the publications present cross-sectional data only; thus cause and effect relationships cannot be determined. Finally, physical activity data were not collected on the children.

The Framingham Children's Study

The Framingham Children's Study is a longitudinal study looking at diet and physical activity patterns in childhood. In 1987, 106 two-parent families who were third- or fourth-generation offspring of the orig-

inal Framingham Heart Study[8] cohort with a healthy biological child between 3 and 5 years of age (mean age, 4.0) were enrolled. Diet was assessed using a 3-day food diary. This study showed that tracking of nutrient intake begins in children as young as 3 years of age (Singer, Moore, Garrahie, & Ellison, 1995). Further, children ($n = 95$) who consumed four or more servings of fruit and vegetables or two or more servings of dairy had smaller yearly increases in systolic blood pressure than those who did not (Moore et al., 2005).

The Framingham Children's Study examined the relationship of life-style factors to measures of adiposity in children and underscored the contribution of physical activity to weight in children. Preschool children who were not physically active gained more subcutaneous fat than those who were not (Moore, Nguyen, Rothman, Cupples, & Ellison, 1995). Moore et al. (2003) also showed that higher levels of physical activity in early childhood ($n = 103$) led to lower levels of body fat in early adolescence. By age 11 ($n = 106$), children who watched 3 or more hours of television a day had a higher mean sum of five skinfold measurements than those who did not. The effect of television viewing was greater in children who were sedentary and had a high-fat diet (Proctor et al., 2003). Further, parents displaying high levels of disinhibited eating, especially when coupled with high dietary restraint, fostered the development of excess body fat in their children ($n = 92$) (Hood et al., 2000). Together, these studies suggest that obesity in children is multifactorial and that when planning intervention studies a multidisciplinary approach should be taken.

Advantages of the Framingham Children's Study are that this is a longitudinal study and there has been a high retention rate, possibly because this is such a well-studied population. However, a major limitation is its small sample size; thus all data should be interpreted with caution.

Healthy Passages

Healthy Passages is a 10-year study, begun in 2004, that looks at individual, family, peer, and community influences on health risk factors of preteens and teens (Windle et al., 2004). Although the primary focus is to examine influences on substance abuse, mental health, sexual behaviors, and school achievement, the study also looks at factors that contribute to diet and physical activity and how race, ethnicity, gender, family income, and parental behavior affect behaviors and health. This multicenter study enrolled 5,250 fifth-grade students and will collect data every other year from the children and their parents. Participants are from 75 schools in Houston, Texas, Birmingham, Alabama, and Los Angeles, California, and the population is approximately divided among white, African-American, and Hispanic children. Although this study has barely begun, investigators are designing a follow-up study to continue monitoring the population. The strengths of this study are that it is multicentered and has a large and ethnically diverse sample. Healthy Passages has the potential to provide the basis for adolescent health recommendations and interventions.

If you want to know more about adolescent health, the monograph "Reducing the Risk: Connections That Make a Difference in the Lives of Youth" is available online (http://allaboutkids.umn.edu/cfahad/Reducing_the_risk.pdf).

National Longitudinal Study of Adolescent Health

The National Longitudinal Study of Adolescent Health[9] is the largest and most comprehensive survey of adolescents ever undertaken. It was created in response to a federal mandate as part of the National Institutes of Health Revitalization Act of 1993 (Public Law 103-43, Title X, Subtitle D, Section 1031). Initiated in 1994, this study explores the causes of health-related behaviors of adolescents in grades 7 through 12 and their outcomes in young adulthood. The impact of three potential influences on adverse health—social environment, behaviors, and "strengths and vulnerabilities"—are being studied. Information collected includes diet, physical activity, sexual practices, substance use, and suicidal thoughts. Complementary information collected includes height, weight, physical development, mental status, and any chronic health conditions.

There were 80 high schools and 52 middle schools in the core study, and in wave I (1994–1995) 12,105 adolescents were interviewed as part of the core sample. The cohort had an oversampling of certain ethnic/socioeconomic status groups: 1,038 African-Americans with at least one parent with a college education, 334 Chinese, 450 Cubans, 437 Puerto Ricans, and 1,500 Mexican-Americans, and other Hispanics and Asians. Further, 589 students described themselves as disabled. This provides an ethnically diverse data set that is lacking in many

8. http://www.nhlbi.nih.gov/about/framingham

9. http://www.cpc.unc.edu/projects/addhealth

of the other cohorts, and, not surprisingly, this study has provided a rich data set for study. Wave II (1996) interviewed nearly 15,000 of the original cohort. Wave III (2001 and 2002) interviewed the original participants and their partners and collected saliva and urine to test for sexually transmitted diseases and the human immunodeficiency virus. Wave IV has been funded through 2010 and will study developmental and health trajectories across adolescents into young adulthood.

More than 1,700 publications and dissertations have used data generated from this study, and the list is available online.[10] Virtually every aspect of adolescent life is covered in these publications, including but certainly not limited to clustering of behavior problems (Bartlett, Holditch-Davis, & Belyea, 2005), perceptions of weight management (Kilpatrick, Ohanessian, & Bartholomew, 1999), and the accuracy of teen reporting of BMI (Goodman et al., 2000).

Cardiovascular Risk in Young Finns Study

The purpose of this multicenter study[11] was to determine the effects that childhood life-style as well as biological and psychological measures have on the risk of cardiovascular diseases in adulthood. Begun in 1980, the original cohort of 3,596 (83.2% of those invited to participate) children and adolescents aged 3, 6, 9, 12, 15, and 18 years were followed at 3-year intervals. Risk factor assessment included laboratory measures of serum lipoproteins, insulin, markers of inflammation (e.g., C-reactive protein), and homocysteine; adiposity measures; blood pressure; life-style factors, including diet, physical activity, smoking status, and alcohol use; psychological factors, such as depressive symptoms; and socioeconomic status. Genetic studies were also conducted. In 2001 the 21-year follow-up was conducted on over 2,283 (63.5% of the original cohort) young adults (aged 24 to 30 years). In addition to the risk factors mentioned, noninvasive ultrasound examinations were performed to assess carotid artery intima-media thickness, carotid artery elasticity, and brachial artery flow-mediated endothelium-dependent dilatation.

The Young Finns Study confirmed and extended data on the tracking of risk factors for cardiovascular disease generated by the BHS. For example, the study showed that systolic blood pressure tracks into adulthood but also demonstrated that low socioeconomic status in early life influences blood pressure later in life, in part due to its effect on blood pressure in childhood (Kivimaki et al., 2006a, 2006b). This study demonstrated that the diet of young Finns has improved over time but that it fell short of recommendations (Mikkilä, Räsänen, Raitakari, Pietinen, Viikari, 2004). Other diet intake studies used pattern analysis to show changes over time and identified two food patterns—a traditional one and a health-conscious pattern, which was associated with other healthy behaviors (Mikkilä, Räsänen, Raitakari, Pietinen, & Viikari, 2005). The studies with ultrasound at the 21-year follow-up provide important information on the relationship of subclinical atherosclerosis and other risk factors. The study suggested that endothelial dysfunction is an early event in atherosclerosis, and systemic endothelial function may modify the association between risk factors and atherosclerosis (Juonala et al., 2004). Moreover, there were geographic differences in greater carotid intima-media thickness and lower brachial flow-mediated dilation, suggesting genetic influences (Juonala et al., 2005).

The strengths of the Young Finns Study include the long follow-up period, large sample size (it is one of the largest longitudinal studies of children, adolescents, and young adults), inclusion of physical activity, use of a 48-hour recall to assess diet, and innovative approach with ultrasound to detect early changes associated with atherosclerosis. To date, there are over 200 publications from data collected during this study. Study limitations are that the sample was all white and all limited to a single group. Further, a high percentage of the cohort was lost to follow-up.

Avon Longitudinal Study of Parents and Children

The Avon Longitudinal Study of Parents and Children was initiated in 1990 (Golding, 1990). It is the largest longitudinal study of childhood in the world, aiming to reveal how physical and social environment interact with genetic inheritance to affect all aspects of a child's health and development. This birth study has the advantage of long-term follow-up. The core sample consisted of 14,541 pregnancies (1991–1992), with 14,062 live births (13,971 alive at 12 months). There are comprehensive data on nearly 10,000 children and their parents, from early pregnancy to ages 8 and 9. These data appear very comparable with national United Kingdom data, increasing the generalization of the

10. http://www.cpc.unc.edu/projects/addhealth/pubs?func=viewandwid=1257andfolderId=1009

11. http://vanha.med.utu.fi/cardio/youngfinnsstudy

findings. The goal of the study is to continue to collect detailed data on the children as they go through puberty, noting in particular changes in anthropometry, attitudes and behavior, fitness and other cardiovascular risk factors, bone mineralization, allergic symptoms, and mental health.

There are several important findings from the Avon Longitudinal Study of Parents and Children: childhood bone mass is related to maternal diet in pregnancy (Tobias et al., 2005), breast-feeding is associated with lower blood pressure in children born at term (Martin et al., 2004), and habitual physical activity was associated with improved bone size and bone mineral density (Tobias, Steer, Mattocks, Riddoch, & Ness, 2007). It is obvious that this rich data set will continue to be assessed and other important publications will be forthcoming; to date, more than 270 peer-reviewed journal articles have appeared.

This study is presented because it is an example of a birth study—newborns and their parents can be followed over time, providing insight into the development of physical, physiologic, and psychosocial changes and their relationship to chronic disease. The large sample size adds statistical power to the variety of studies performed. Limitations include a limited racial/ethnic diversity and a small geographic area from which subjects were recruited.

The German Dortmund Nutritional and Anthropometric Longitudinally Designed Study

The Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) study is an observational longitudinal open **cohort study** began in 1985 that examines diet, metabolism, growth, and development from healthy subjects between infancy and adulthood (Kroke et al., 2004). This study has approximately 1,000 children, 1,000 mothers, and 1,000 fathers participating. Approximately 40 to 50 healthy infants are enrolled yearly. Participants are studied every 3 months in year 1, twice in year 2, and once a year thereafter. A 3-day diet record kept either by the parents or by older children is used to assess dietary intake. Urine sampling and urinalysis, anthropometry, and physical examinations are also conducted. Participants are interviewed using age-specific questions on sleeping habits, dejection, sports activities, and use of medical preventative services. One of the unique aspects of the DONALD study is attention to dietary supplementation. The DONALD study has shown that on average German children meet nutritional recommendations without supplements, with the exception of folate and vitamin D (Sichert-Hellert, Kersting, Alexy, & Manz, 2000). The study also showed that 56% of fortified foods consumed had added sugar. However, the positive effect of food fortification was stronger than the negative effect of added dietary sugars, suggesting that fortification of foods masks nutrient dilution (Alexy, Sichert-Hellert, & Kersting, 2002). Other diet studies suggest that an energy-based approach should be used when setting dietary recommendations for children (Alexy, Kersting, & Sichert-Hellert, 2006). Findings like these are important in setting nutrition policy with regard to food fortification and dietary recommendations for individual countries.

Cohort studies: Classify participants based on the presence or absence of exposure and follow them over time to assess disease development. An example of this type of study is the Nurses Health Study. In a *retrospective cohort study,* the disease of interest has already occurred at the time the study begins; in a *prospective cohort study,* the disease has not yet occurred.

The DONALD study also defined adequate intake of water (Manz, Wentz, & Sichert-Hellert, 2000) and the role of nutritional status in the regulation of adrenarche (Remer & Manz, 1999). Subsets of the population have participated in the Euro Growth Study (van't Hof, Haschke, & the Euro-Growth Group, 2000) and a study to determine the circadian rhythms of urine osmolality and renal excretion rates (Ballauff, Rascher, Tolle, Wember, & Manz, 1991). Studies like these suggest the flexibility of the data set.

Advantages of the DONALD study are that the food consumed was recorded for 3 days, leading to greater accuracy in estimating intake, and special care was taken to collect information on fortified food and supplements. Disadvantages are its use of a convenience sample and that no blood was collected, so the relationship of diet or obesity cannot be related to genetic or other biomarkers of chronic disease. Another limitation is the study's relatively small sample size, with a limited ethnic variety residing in a limited geographic area.

Intervention Studies

Large-scale long-term diet or physical activity **intervention studies** are relatively uncommon in healthy children. The two discussed in this chapter were chosen because they illustrate interventions at different times in the life cycle—infancy

Intervention studies: A type of prospective cohort study where the exposure is controlled by the investigator. These studies can be considered therapeutic (secondary prevention) or preventative. Dietary Approaches to Stop Hypertension (DASH) and DASH-sodium are intervention studies.

Think about it. What elements of an intervention study are needed to make it successful? What can be done to maintain the population over time?

(Special Turku Coronary Risk Factor Intervention Project for Babies) (Lapinleimu et al., 1995; Simell et al., 2000) and childhood and adolescence (Child and Adolescent Trial for Cardiovascular Health [CATCH]).

Special Turku Coronary Risk Factor Intervention Project for Babies

This study was designed to test the effect of a low saturated fat, low cholesterol diet on infants. The argument for doing this was that atherosclerotic mechanisms, including foam cells in the arterial intima (Strong, Malcom, Newman, & Oalmann, 1992), are already active in children; lesion development depends in part on serum cholesterol levels (Newman et al., 1986) in childhood. Studies also show that if earlier cholesterol levels can be lowered, the prognosis is better (Law, Wald, & Thompson, 1994). The argument against an intervention like this is that altering dietary fat in the diets of children would interfere with growth and development (Lifshitz & Moses, 1989; AAP, 1992).

CRITICAL Thinking

The Special Turku Coronary Risk Factor Intervention Project for Babies study is a well-conceived and carefully controlled intervention. Do you believe the results from this study should be used to make policy changes in dietary recommendations for infants and young children? Why or why not? Do additional studies need to be performed? If so, what kind of studies should be done?

Originally, 1,062 seven-month-old infants in Turku, Finland were recruited and randomly assigned to a low saturated fat, low cholesterol diet ($n = 540$) to meet the Nordic dietary recommendations for individuals 3 years and older or to a control group ($n = 522$). Twice yearly, the intervention group received intensive health education aimed at reducing risk of atherosclerosis and individual dietary counseling from a physician and a dietitian; after weaning of the infants, families kept food records for 4 consecutive days, including a weekend day. The control group received standard health education given to well babies at clinics, but they did not receive individual dietary counseling. Serum lipids, lipoproteins, and apolipoproteins were measured, as were weight and length or standing height (depending on the age of the child). There was no difference in baseline parameters between the two groups.

At 36 months of age, 426 children (79%) remained in the intervention group and 417 children (80%) remained in the control group (Simell et al., 2000). At that time total serum and high-density lipoprotein (HDL) cholesterol levels were lower in the intervention group than in the control group; further, there was no evidence of delayed growth, and height and weight increases were comparable with Finnish standards (Simell et al., 2000). At 5 years of age the children in the intervention group consumed less saturated fat, had lower total and LDL cholesterol levels (Salo et al., 1999), and had no delays in neurodevelopment (Rask-Nissila et al., 2002). The conclusion of this study was that there were no ill effects of the low saturated fat, low cholesterol diet in these children.

CATCH (1987–2000)

CATCH was a National Heart Lung and Blood Institute funded multicenter randomized trial of a school-wide intervention to improve cardiovascular disease–related behaviors, including diet, physical activity, and smoking, of elementary schoolchildren. CATCH provides an excellent example of how information from a natural history study like the BHS, that identified risk factors for cardiovascular disease present in childhood, can be used as the basis for an intervention study. CATCH was the largest and one of the most comprehensive school-based intervention studies and included an educational curriculum along with a behavioral component, modification of the school environment—including modifying school meals and family-oriented interventions (Perry et al., 1990). The overarching goal was to reduce dietary fat and sodium, increase physical activity, and prevent smoking in children. Initially, 5,100 racial and ethnically diverse third- to fifth-grade students attending 96 elementary schools in California, Louisiana, Minnesota, and Texas constituted the cohort; schools were randomized to intervention ($n = 56$) or control ($n = 40$) schools. Follow-up surveys were conducted in 1996–1997 (Osganian et al., 1999) and in 2000–2001 (Osganian et al., 2003a), when students were in grades 8 and 12, respectively.

CATCH participants provided information about diet and health behaviors; BMI and serum lipid levels were determined. CATCH demonstrated the following: cardiovascular risk factors in children varied by gender and ethnicity (Webber et al., 1995); physiologic variables, including serum lipid levels, tracked into the eighth grade, and tracking was stronger in

boys and in African-Americans (Kelder et al., 2002); a school food service–based intervention could modify school lunch, health behaviors, and physical activity programs (Luepker et al., 1996); and changes resulting from the intervention could be maintained (Nader et al., 1999).

The success of CATCH as an intervention study can be seen by its widespread adoption in school systems. For example, by autumn 2000, 728 elementary schools in Texas had adopted CATCH materials (Hoelscher et al., 2001), and it is clear that the program has been successful (Hoelscher et al., 2004). What makes an intervention program successful and adaptable to other school systems is not clear. Because CATCH was adopted by so many other schools, it was important to use this program as a model of a program that can be institutionalized—the CATCH-ON study was designed to do this (Osganian, Parcel, & Stone, 2003b). The physical activity component appeared to have the highest level of institutionalization (Lytle, Ward, Nader, Pedersen, & Williston, 2003), whereas the educational curriculum and the family components had the lowest level. Factors that facilitated maintenance of the CATCH Eat Smart Program (the school food service component of CATCH) included satisfaction of school food service personnel and perceived student satisfaction with the program (McCullum-Gomez, Barroso, Hoelscher, Ward, & Kelder, 2006). Identification of barriers to and enablers for program institutionalization are key elements of a successful program.

Comment on Epidemiologic Studies in Children and Adolescents

Many of these studies have followed children from birth into young adulthood and, in some cases, into middle adulthood. This provides a smooth transition through the life cycle and allows us to understand more fully the changes that occur in chronic disease risk factors and the occurrence of chronic disease throughout the life cycle. Over time, studies have become more complex. As more biological risk factors for disease have been identified and the understanding of risk factors for chronic diseases has improved, investigators have been able to include additional questionnaires or laboratory tests to garner still more information.

Study results can be compared and trends can be identified and targeted for intervention. NHANES data have allowed us to follow the pediatric obesity epidemic. Using 1999–2002 data, 23% of children aged 2 to 5 years were overweight or at risk of becoming overweight (BMI $\geq$ 85th percentile) and 10.3% were overweight (BMI $\geq$ 95th percentile). The percentage of children who were overweight increased compared with data from NHANES III (1988–1994), which showed 7.2% of children aged 2 to 5 years were overweight. These data were confirmed by the YRBSS and by longitudinal studies from all over the world. Additional studies confirmed risk factors that are amenable to modification through intervention, so clearly the universality of these data clear the way for policy change and intervention studies.

A number of challenges had to be met when conducting research with children. The first, as discussed above, revolved around issues of informed consent. Although these issues have not been fully resolved, solutions have been found for individual studies to allow research to go forward. Other challenges include how to collect information on children because, for instance, young children cannot complete a 24-hour recall or fill out a food frequency questionnaire (FFQ). Investigators in pioneering studies, like BHS, painstakingly worked to develop methods to obtain diet information on children (Frank, Berenson, Schilling, & Moore, 1977). BHS set the standard for working with children in longitudinal studies: Their quality controls included a standardized protocol for the collection, calculation, and editing of 24-hour dietary recalls (from the BHS nutrition staff: "In-house Dietary Studies Methodology" [editions 1–8], 1978–1988); graduated food models for quantification of amounts of foods and beverages consumed (Moore, Judlin, & Kennemur, 1967); a product identification notebook for snack probing; a school lunch (Nicklas, Forcier, Webber, & Berenson, 1991); and a family recipe collection of actual food preparation, recipes, brand names of foods, and actual serving sizes of school meal food items served.

A major limitation of many of these studies described herein is that most examined white children and adolescents only. This is also true of the international studies. Even in studies where children of other racial and ethnic groups were included, they were often underrepresented, making it difficult to statistically factor race or ethnicity into any analysis—especially in small studies. It is critical that studies look at the impact that life-style factors have on different races and ethnicities. The BHS study showed

clear differences with regard to weight, especially in African-American girls (Freedman et al., 2000); with regard to physiologic parameters such as birth weight and blood pressure (Cruickshank et al., 2005); and with regard to diet (Demory-Luce et al., 2004) of African-American children when compared with white children. It is clear that when Asian and Hispanic children and adolescents were studied, there were differences in health behaviors (Allen et al., 2007), suggesting a need for different intervention strategies.

Many of the studies are regional with comparatively small sample sizes. These studies have provided important information on diet and other life-style behaviors, health parameters such as blood pressure, and biomarkers of disease such as serum lipid levels. Multiple studies demonstrated that these risk factors track into adulthood and suggest that early intervention is important to reduce the risk of childhood and adult disease. It is important to replicate these findings in nationally representative samples.

Finally, when assessing these and other studies, it is vital to evaluate the strength of the body of scientific evidence, by taking the following into account:

1. The quality of the studies, including the extent to which bias was minimized
2. The quantity of the studies, including the magnitude of effect, the number of studies, and the *sample size* and *statistical power* of the study
3. The consistency of results (i.e., do similar studies produce similar results)
4. The study design (i.e., what type of study was used to produce the test results and the relevance to the disease under study)

TABLE 1.4 National Heart, Lung, and Blood Institute's Evidence Categories

Category	Sources of Evidence	Definition
A	Randomized controlled) trials (rich body of data	Well-designed randomized clinical trials that provide a consistent pattern of findings in the population for which the recommendation is made. Category A requires substantial numbers of studies involving substantial numbers of participants.
B	Randomized controlled trials (limited body of data)	Limited randomized trials or interventions, post-hoc subgroup analyses, or meta-analyses of randomized clinical trials are used when there are a limited number of existing trials, study populations are small or provide inconsistent results, or when the trials were undertaken in a population that differs from the target population.
C	Observational or nonrandomized studies	Evidence is from outcomes of uncontrolled or nonrandomized trials or from observational studies.
D	Panel consensus judgment	Expert judgment is based on the panel's synthesis of evidence from experimental research described in the literature or derived from the consensus of panel members based on clinical experience or knowledge that does not meet the criteria described in the above categories. This category is used only where the provision of some guidance was deemed valuable but an adequately compelling clinical literature addressing the subject of the recommendation was deemed insufficient to place in one of the other categories.

Source: Adapted from the National Heart, Lung, and Blood Institute, available at http://www.nhlbi.nih.gov/guidelines/obesity/ob_gdlns.pdf

The National Heart, Lung, and Blood Institute uses a four-point scale to grade the scientific evidence from different study types (Table 1.4). Other types of evidence may also be available, but they are weaker and should be considered less definitive.

Cooper and Zlotkin (2003) outlined a six-step framework by which nutrition guidelines can be developed. Their method is similar to that of the National Heart, Lung, and Blood Institute but emphasizes nutrition information. The Agency for Healthcare Research and Quality[12] provides additional information about evidence-based practice, outcomes and other types of research, technology assessment, and clinical practice guidelines to professionals and to the public. A review of systems to rate the strength of sci-

12. http://www.ahrq.gov

Sample Size and Study Power

The smaller a sample, the greater the variability; thus it is important to be sure the *sample size* of a study is adequate. Standard formulas are available to determine the values of the probabilities of the type I and type II errors, the proportion of the baseline population exposed to the factor of interest (case-control studies) **or to the disease under study (cohort or intervention studies), and the magnitude of the expected effect. The latter is sometimes determined from a pilot study. The formula you choose is determined by the study design, the research question, and the type of data to be collected.**

Case-control studies: A case series of individuals who have the disease of interest and a group of similar individuals who do not have the disease—exposure comparisons are made.

The *power* of a study is the probability that the test will reject a false null hypothesis, not make a type II error. As power increases, the chance of making a type II error decreases. The probability of a type II error is referred to as β, and power is equal to 1−β. Power analyses can be done before (a priori) or after (post hoc) data are collected. An a priori power analyses is conducted before conducting the research and is generally used to determine the sample size of the population that will give adequate power. There are no formal standards for power; however, many scientists use 0.80 as the standard.

entific evidence is also available from the National Library of Medicine.[13]

Future of Epidemiologic Studies in Children

National Children's Study

Perhaps the most exciting epidemiologic study of children is one that has not yet begun—the National Children's Study.[14] Authorized by Congress as part of the Children's Health Act of 2000,[15] this study will examine the environmental influences on health and development on a nationally representative cohort of 100,000 children from before birth to age 21.

Priority health and disease outcomes are pregnancy outcomes, neurodevelopment and behavior, childhood injury, asthma, obesity, and physical development. "Environment" is broadly defined and will include natural and man-made environmental factors, biological and chemical factors, physical surroundings, social factors, behavioral influences and outcomes, genetics, cultural and family influences, and differences among geographic locations. This study is predicted to be one of the richest information sources available on children's health and should form the basis for interventions, policy, training future researchers, and a "comprehensive blueprint for disease prevention in children" (Trasande et al., 2006; Landrigan et al., 2006).

In 2005 contracts were awarded to seven Vanguard Centers in universities, hospitals, and health departments located in Orange County, California; New York City (Queens); Duplin County, North Carolina; Montgomery County, Pennsylvania; Brookings County, South Dakota; Lincoln, Pipestone, and Yellow Medicine Counties, Minnesota (cluster site); Salt Lake City, Utah; and Waukesha County, Wisconsin. The lead federal agencies involved (the U.S. Department of Health and Human Services, the Environmental Protection Agency, the CDC, and the National Institute for Environmental Health Sciences) anticipate 30 to 40 study sites that will involve 105 sites, of which 79 are metropolitan counties and 26 are rural nonmetropolitan areas, as defined by the U.S. Census Bureau. The 79 metropolitan sites include populous counties and smaller urban and suburban areas. Each site has the goal of enrolling at least 250 newborns each year for 5 years. Initial enrollment is planned for 2008.

The National Children's Study will be the first to evaluate environmental exposures before and early in pregnancy and to then track participants into adulthood. Pregnant women and their partners, couples planning pregnancy, and women who are of childbearing age but are not planning a pregnancy will constitute the initial cohort. Although other studies have assessed prenatal exposures on children, they have either started in the first trimester of pregnancy or stopped tracking at birth.

Centers for Children's Environmental Health and Disease Prevention Research

Two of the lead federal agencies for the National Children's Study are the Environmental Protection Agency and the National Institute for Environmental Health Sciences, who funded the Centers for Children's Environmental Health and Disease Prevention Research (Children's Centers).[16] Recently, a mini-monograph about the Children's Centers was published that was intended to serve as a "primer" for the National Children's Study (Kimmel, Collman, Fields, & Eskenazi, 2005), including topics on methodology on conducting birth cohort studies (Eskenazi et al., 2005) and community participatory research (Israel et al., 2005) as well as issues in studying air pollution (Gilliland et al., 2005), pesticide exposure (Fenske, Bradman, Whyatt, Wolff, & Barr,

13. http://www.nlm.nih.gov/nichsr/hta101/ta10107.html
14. http://www.nationalchildrensstudy.gov/index.cfm
15. http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=106_cong_billsanddocid=f:h4365enr.txt
16. http://www.niehs.nih.gov/translat/children/children.htm

2005), asthma (Eggleston et al., 2005), and neurobehavioral toxicity (Dietrich et al., 2005). In *Life of Reason* (1905, p. 284) George Santayana says, "Progress, far from consisting in change, depends on retentiveness. Those who cannot remember the past are condemned to repeat it." This "lessons learned" philosophy should also be applied to research, and these authors should be applauded for sharing this information.

The impact that the National Children's Study and other future studies will have on the understanding of health and disease is extraordinary, and it is questionable whether they could have been attempted previously. There has been a growing public concern over the link between health, genetics, and environmental exposures (Israel et al., 2005) because of the mounting evidence of increasing morbidity and mortality in children from health problems, including those from environmental exposures, including asthma (Akinbami & Schoendorf, 2002), neuropsychological and developmental disorders (Hertz-Picciotto et al., 2006), and cancer (Daniels, Olshan, & Savitz, 1997). The rising prevalence of pediatric overweight and obesity, coupled with the appearance of adult comorbidities, such as type 2 diabetes, metabolic syndrome, and nonalcoholic fatty liver disease, in pediatric populations (Cruz et al., 2005) has fueled public interest in children's health. From a scientific standpoint these adult disease risk factors include health behaviors such as diet (Mikkilä et al., 2005; Lake, Mathers, Rugg-Gunn, & Adamson, 2006) and physical activity (Telama et al., 2005); anthropometric markers, notably weight (Deshmukh-Taskar et al., 2006); and health measures such as plasma lipid (Webber, Srinivasan, Wattigney, & Berenson, 1991; Bao, Srinivasan, Wattigney, & Berenson, 1994), C-reactive protein levels (Juonala et al., 2006), insulin levels (Bao et al., 1994), and blood pressure (Bao, Threefoot, Srinivasan, & Berenson, 1995).

Thus strong public interest in health research coupled with technologic advances, including sequencing the human genome, public health genomics, and the creation of the Human Genome Epidemiology Network[17]; advances in assessing biomarkers, including markers of human environmental exposures; public health informatics; statistical advances in data modeling; and improved communications have led to the conceptualization of such ambitious projects. This is not to say that these studies will be without problems. The diversity of the population and growing health disparities in the United States are major challenges (Gupta, Carrion-Carire, & Weiss, 2006; Selden, 2006). Medical–legal issues, such as those revolving around the use of vulnerable populations, including children and adolescents (Diaz et al., 2004; Summers et al., 2006), and the financial support of investigators, are becoming more complex (Davidoff et al., 2001). Finally, research standards have risen, and the way research studies are evaluated has changed.

17. http://www.cdc.gov/genomics/hugenet/default.htm

Research Involving Adults

Elizabeth Metallinos-Katsaras, PhD, RD and Sari Kalin, MS

The purpose of this section is to provide an overview of some of the major adult epidemiologic studies that have contributed to the research-based underlying prevention efforts and the development of nutrition guidelines. The following major nutrition-related adult studies are summarized and, where applicable, links are made to dietary recommendations:

- Framingham Heart Study, original and offspring cohorts
- Nurses Health Study I
- Nurses Health Study II
- Health Professionals Follow-Up Study
- Physicians' Health Study I
- Physicians' Health Study II
- Iowa Women's Health Study
- Dietary Approaches to Stop Hypertension (DASH) and DASH-sodium
- Women's Health Initiative
- OmniHeart

Each study is reviewed regarding the following aspects:

1. History and original purpose
2. Sample characteristics
3. Types of data collected (nutrition related)
4. Example of a major contribution
5. Study strengths and limitations

Studies are classified according to design, emphasizing how the selected design elucidated the association between nutrition and the development of chronic diseases.

Prospective Cohort Studies

A cohort study is a type of observational study in which the researcher defines two or more groups of people who are disease free and differ with respect

to their degree of exposure to a possible cause of the disease in question (Rothman & Greenland, 1998). Prospective cohort studies are those in which the subjects are free of the disease at the initiation of the study and the relevant exposure may or may not have occurred (Hennekens & Buring, 1987). This design is rigorous and is second only to the randomized controlled trial. A major strength of this study design is that exposure data are collected before disease diagnosis. Thus the presence of the disease does not bias the reporting of the exposure data. Limitations of this design are that it is not good for studying rare diseases and there is significant potential for confounding bias because subjects have self-selected their exposure.

Framingham Heart Study

The Framingham Heart Study, one of the longest running prospective cohort studies, started in 1948 with the goal of understanding the causes of heart disease. The original cohort of 5,209 men and women, ranging from ages 30 to 62 years, was randomly selected from the adult population of Framingham, Massachusetts (Framingham Heart Study, 2005). Every 2 years since the study's inception participants received a thorough physical examination (including medical history interviews and laboratory tests) (Framingham Heart Study, 2005). The study has grown into a multigenerational enterprise, one that is now using molecular techniques to yield information about the genetic underpinnings of chronic disease. In 1971 study investigators began the Framingham Offspring Cohort, which includes 5,124 sons and daughters of the original cohort participants who are examined approximately every 4 years (Millen et al., 1996; Framingham Heart Study, 2005). Moreover, in 2005 investigators launched the Generation III Cohort with 4,095 third-generation descendants of the original study participants; by September of that year 299 of the 472 surviving original participants received their 28th medical examinations (Framingham Heart Study, 2005).

One critique of the Framingham study is that the original and offspring cohorts are predominantly white, reflecting the homogenous demographic makeup of the Framingham community at the study's launch. Framingham has since become a more diverse community, and study investigators began the multiethnic Omni Cohort in 1994, with 506 men and women (Framingham Heart Study, 2005). At baseline, Omni cohort members were between the ages of 40 and 74, and they received a thorough physical and laboratory examination identical to that of the Framingham Offspring Cohort (Quan et al., 1997).

Framingham's nutritional assessment methods have evolved throughout the decades. Some of the earliest inquiries, in the early 1960s, used Burke-style hour-long interviews (Mann, Pearson, Gordon, & Dawber, 1962). Single 24-hour recalls were collected at various time points (e.g., in 1966–1969 from the original cohort and in 1984–1988 from the offspring cohort), as were 3-day diet records, yielding insights on the relationship between diet and heart disease (Gordon et al., 1981; Millen et al., 1996). Framingham investigators also developed a 145-item FFQ (a modified version of the Willett semiquantitative FFQ) and validated it with the offspring cohort (Posner et al., 1992). Cluster analysis of the offspring cohort's FFQ data has been used to identify distinct dietary patterns (e.g., the "heart healthy" and "empty calorie" patterns in women) and relate these patterns to overweight, metabolic syndrome, and chronic disease outcomes (Millen et al., 2001, 2002, 2005a, 2005b; Sonnenberg et al., 2005). This type of pattern analysis could be useful for target health promotion messages to prevent chronic disease.

Credited with coining the term "risk factor," the Framingham Heart Study is best known for providing decades of evidence that smoking, high blood cholesterol, high blood pressure, sedentary life-styles, obesity, and diabetes dramatically increase the risk of heart disease (Framingham Heart Study, 2005). Doctors now use the Framingham Point Score prediction algorithm to predict patients' 10-year risk of coronary heart disease; this risk prediction helps guide clinical decision making on LDL targets and management (National Cholesterol Education Program, 2001). Over the years the Framingham cohorts have yielded insights on nutrition and life-style relationships for other disease end points, including cancer (Radimer et al., 2004), osteoporosis (Tucker et al., 2006), and Alzheimer's disease (Seshadri et al., 2002).

Nurses Health Studies

There are two prospective cohort studies based solely on female registered nurses. These are, in chronological order, the Nurses Health Study (NHS) and the NHS II. The first NHS was initiated in 1976 with the express purpose of studying the long-term consequences of oral contraceptive use (Nurses Health Study [NHS] I, n.d.). The NHS I was begun by Dr. Frank Speizer and was designed to study oral con-

traceptives and also to investigate diet and life-style risk factors in the population (Nurses Health Study [NHS] II, n.d.).

Originally, registered nurses were selected as the target population because their degree of education would facilitate accurate responses to technically worded health-related questions (NHS I, n.d.). Moreover, it was anticipated that they would be more motivated than the average person in the population to participate over the long term. This was substantiated in relatively high response rates reported, 71% for the 1976 questionnaire (Meyers et al., 1987) and 90% for each 2-year period thereafter (NHS I, n.d.).

NHS originally included 121,700 female nurses who were between the ages of 30 and 55 in 1976. They were sampled from the most populous states whose nursing boards agreed to supply the member's names and addresses; this yielded a representation from 11 states (NHS I, n.d.). The original cohort was 96.8% white (G. Chase, Data Manager, NHS, personal communication, August 16, 2006). Dietary assessment for the NHS was conducted in 1980, 1984, and 1986 and every 4 years thereafter, using a semiquantitative FFQ developed for the study (HFFQ). Three different versions of the HFFQ were developed ranging from the inclusion of 61 items to 126 items (NHS, n.d.). Validity and reliability was examined using these HFFQs among nurses using two or four 1-week food records; most of the adjusted correlations for macro- and selected micronutrients were between 0.5 and 0.7 (Willett & Lenart, 1998). These are considered relatively good for epidemiologic measures of risk (Willett & Lenart, 1998).

Toenail (1982 and 1984) and blood samples (1989–1990 and 2000–2001) were also obtained on a subset of the original cohort; the former is useful for mineral analyses, and the latter can be used to identify potential biomarkers, such as hormone levels and genetic markers, although blood samples can also be used to assess the status of some vitamins and minerals (Gibson, 1990).

The NHS II was established in 1989 by Dr. Walter Willett to study oral contraceptives and to investigate effects of diet and life-style risk factors in a population younger than the original NHS cohort (NHS II, n.d.). The target age group was between 25 and 42 in 1989 with a sample size goal of 125,000 female registered nurses. In NHS II the sampling consciously aimed to enroll only those most enthusiastic about participating in this study to maximize future long-term participation. A single mailing was done to 517,000 women in 14 states, and those who responded to that first questionnaire were enrolled. Twenty-four percent of those sampled responded to that first questionnaire, with 22.6% in the final sample due to exclusions for incomplete forms or not meeting inclusion criteria, yielding a sample size of 116,686 women. Response rates to subsequent questionnaires were 90% for each 2-year cycle. Similar to the original NHS, the HFFQ was administered every 4 years beginning in 1991. Blood and urine samples were also collected on a subset of the sample (about 30,000 nurses) (NHS II, n.d.). Similar to the NHS I, this sample was predominately white (95.8%) (G. Chase, Data Manager, NHS, personal communication, August 16, 2006).

An example of the influence the NHS I and II had on the 2005 Dietary Guidelines for Americans is in the limiting of trans fatty acids in the diet, specifically the guideline "Limit intake of fats and oils high in saturated and/or trans fatty acids, and choose products low in such fats and oils" (U.S. Department of Health and Human Services and the U.S. Department of Agriculture [DHHS and USDA], 2005). The NHS was one of the early studies providing evidence that a high intake of trans fatty acids was associated with a significantly higher risk of myocardial infarction (Willett et al., 1993). Moreover, the NHS I and II were specifically cited in the 2005 Dietary Guidelines Advisory Committee report (DHHS and USDA, n.d.) as showing that trans fat intake was positively associated with the systemic inflammatory markers (i.e., soluble tumor necrosis factor receptors and C-reactive protein) for cardiovascular disease (Mozaffarian et al., 2004).

The strengths of both of these studies lie in their large sample sizes, their long follow-up period, their meticulous collection of dietary data using an instrument that produces a good relative measure of long-term (versus short-term) diet for the purposes of predicting disease outcomes (Caan et al., 1998; Wirfalt et al., 1998), and the high sample retention over the course of the studies. As previously mentioned, the prospective cohort design is one of the stronger epidemiologic designs (Rothman & Greenland, 1998); however, the potential that residual confounding may account for reported results is a real threat to internal validity in this design because the subjects self-select their behaviors and diets. Another potential limitation of both studies is their predominantly white cohort of women. This affects external validity, that is, to whom the results may be applied. Results may not be applicable to other diverse populations if the biological mechanisms underlying the

cause and effect relationships are different for different race and ethnic groups. For example, in the case of diet and breast cancer, the association between dietary factors and breast cancer has been shown to vary as a function of whether the cancer occurs pre- or postmenopausally and whether the cancer is estrogen positive or negative and other factors; ethnic or racially specific factors (biological or cultural practices) may also interact with dietary factors to affect breast cancer rates; however, there is no way to elucidate these if the sample is not racially or ethnically diverse.

Health Professionals Follow-Up Study

The Health Professionals Follow-Up Study is an all male prospective cohort study begun in 1986 that intended to complement the all female NHS (Health Professionals Follow-Up Study, n.d.). The hypotheses under investigation centered on the relationship between nutritional factors and the development of chronic diseases such as cardiovascular disease, cancer, and other vascular diseases. The study sample of 51,529 male health professionals (excluding medical doctors) was aged between 40 and 75 years who in 1986 were free of these diseases (Health Professionals Follow-Up Study, n.d.). The justification for examining this group was that, like the nurses, these health professionals would presumably be motivated to participate in a long-term study and would be committed to accurately responding to the questions asked of them. A small percentage of the sample was African-American (1.0%) or Asian-American (1.7%). Study participants received questionnaires about their health-related behaviors and diseases. Dietary data were collected every 4 years using the HFFQ previously described (Health Professionals Follow up Study, n.d.); both validity and reliability of this instrument were assessed using the Health Professionals Follow-Up Study sample (Jensen et al., 2004). Supplemental information on micronutrient supplements and cooking methods were also collected more frequently, some every 2 years (Health Professionals Follow-Up Study, n.d.).

One example of the study's use in the development of the 2005 Dietary Guidelines (DHHS and USDA, 2005) was in the area of the relationship between whole grain intake and risk of coronary heart disease. One of the major studies (DHHS and USDA, n.d.) cited the Health Professionals Follow-Up Study, in which it was found that for every 20-g increase in whole grain consumption there was a 6% risk reduction in coronary heart disease (Jensen et al., 2004).

The strengths and limitations of this prospective cohort study mirror those of the NHS because the design, instruments used, and implementation are so similar. Moreover, both used predominately white participants with very little diversity.

Physicians' Health Studies

The Physicians' Health Studies (PHS) are two studies, one completed and one ongoing, designed as randomized placebo-controlled trials and whose study samples are solely male medical doctors (Physicians' Health Studies II [PHS], 2006). Pertinent nutrition research that emerged from this study is primarily related to the further analyses of the data collected prospectively on these cohorts. PHS I was funded in 1980, and its original intent was to assess the effects of aspirin on cardiovascular outcomes and of beta-carotene on cancer (PHS I, 2002; PHS II, 2006). The original intent of PHS II was to investigate the effects of vitamin E, ascorbic acid, beta-carotene, and/or multivitamins on prevention of prostate cancer, other cancers, and cardiovascular disease in healthy older male doctors; however, beta-carotene was no longer given as of March 8, 2003 (PHS II, 2006). Because this study is a randomized controlled trial, it is discussed further under Randomized Controlled Trials, below. However, it should be noted that because of the long-term follow-up of these physicians (i.e., 8 years for the clinical trail [PHS II, 2002]), it is likely that this study's data will also be analyzed further as a prospective cohort study and therefore results will likely be published using this design.

Physicians were selected as the population from which to draw the samples because of their ability to accurately report data on their health status, medical conditions, and side effects of the intervention. In addition, given their strong interest in health, their compliance, an essential factor in the success of any randomized trial, was anticipated to be high (PHS I, 2002).

In PHS I physicians between the ages of 40 and 84 living in the United States and registered with the American Medical Association were contacted and screened. Of the 33,223 physicians who were willing and eligible to participate, 22,071 (66.4%) were enrolled in the randomized trial after participation in an 18-week run-in phase. Physicians were randomized to one of four interventions: 325 mg aspirin and beta-carotene placebo (n = 5,517), 325 mg aspirin and 50 mg beta-carotene (n = 5,520), aspirin placebo and 50 mg beta-carotene (n = 5,519), and aspirin placebo and beta-carotene placebo (n = 5,515) (PHS I, 2002).

The PHS sample was primarily non-Hispanic white with 7.5% of the sample composed of ethnic or racial minorities (Howard et al., 2006). Data related to nutritional status were collected via administration of an abbreviated version of the HFFQ, which included questions on breakfast cereals and alcohol (Liu, Sesso, Manson, Willett, & Buring, 2003). Multivitamin use was also assessed as well as self-reported weight and height. Questionnaires were administered annually. In addition, on a subset (n = 14,916) baseline blood specimens were collected and archived (PHS I, 2002). The selection of physicians as study participants in PHS I did indeed yield both a high level of compliance (greater than 80%) and minimal loss to morbidity and mortality follow-up (less than 1%) (PHS I, 2002).

In addition to finding that aspirin significantly reduced the risk of first myocardial infarction by 44% ($p<0.0001$) and that there was no benefit or harm from 13 years of beta-carotene supplementation, this study was used to address a multitude of other research questions related to other risk factors for a variety of chronic diseases, including cardiovascular disease, stroke, diabetes, macular degeneration, and cataract (PHS I, 2002). Over 250 articles have been published using this study, many of which used the study as a prospective cohort to examine effects of other risk factors independent of the intervention (PHS I, 2002). These included other nutritional related factors such as weight status (Ajani et al., 2004), homocysteine (Bowman, Gaziano, Stampfer, & Sesso, 2006), breakfast cereal intake (Liu et al., 2003), multivitamin intake (Muntwyler, Hennekens, Manson, Buring, & Gaziano, 2002), and alcohol intake (Gaziano et al., 2000).

An example of how the results of the prospective data analyses were used in the development of dietary recommendations is in the area of alcohol consumption and mortality, in which the advisory committee concluded that research supported the contention that among middle-aged adults one or two drinks per day was associated with the lowest overall mortality (DHHS and USDA, n.d.). Although the PHS I study results in conjunction with other studies were used to support this reduction in mortality in males (Gaziano et al., 2000), research from other studies was used to support this finding in females.

Although the original design of the PHS I was a randomized controlled trial, most of the nutrition-related findings stemmed from the prospective cohort design. Strengths and limitations of this type of design were previously mentioned. Similar to both the NHS and the Health Professionals Follow-Up Study, the PHS I was a well-carried-out prospective cohort study that had a high response rate and low loss to follow-up. In addition, PHS I collected a broad range of nutrition-related data that are important for elucidating the relationship between diet and disease development.

Iowa Women's Health Study

In 1986, the Iowa Women's Health Study began following more than 41,000 postmenopausal women (Bisgard, Folsom, Hong, & Sellers, 1994). The study's initial aim was to explore life-style and exposure risk factors related to cancer in a prospective population-based cohort of older women. Over time, the study has broadened its scope to include other chronic diseases (A. Folsom, University of Minnesota, School of Public Health, personal communication, 2006), among them type 2 diabetes (Pereira, Parker, & Folsom, 2006), heart disease (Ellsworth, Kushi, & Folsom, 2001), and rheumatoid arthritis (Merlino et al., 2004).

Researchers randomly selected study participants from a list of women with Iowa driver's licenses who were between the ages of 55 and 69 years (Folsom et al., 1993). The baseline and five follow-up surveys gathered self-reported information on life-style, medical history, and other factors, including waist-to-hip ratio (the study subjects were mailed a paper tape measure and written instructions on how to have a friend take body circumference measurements) (University of Minnesota Cancer Center, 2006). The most recent questionnaire was completed in 2004, with a response rate of roughly 70% (A. Folsom, University of Minnesota, School of Public Health, personal communication, 2006). Diet was only assessed twice: at baseline (using a modified version of the Willett semiquantitative FFQ) (Hunger, Folsom, Kushi, Kaye, & Sellers, 1992) and in 2004.

A linkage to the Iowa Cancer Registry provides annual data on cancer incidence in the cohort; a linkage to the National Death Index provides information on mortality. At this writing, study investigators are working to link to the Center for Medicare and Medicaid Services Database, which will enable them to collect information on additional chronic diseases and exposures (University of Minnesota Cancer Center, 2006).

The study has yielded more than 200 publications addressing risk factors for cancer and chronic disease, such as body fat distribution, diet, smoking, and other life-style factors. The 2005 Dietary

Guidelines for Americans recommendation to increase whole grain consumption (DHHS and USDA, 2005) was based, in part, on findings from the Iowa Women's Health Study. These findings confirmed the findings of the NHS (Liu et al., 1999, 2000), the Health Professionals Follow-Up Study (Fung et al., 2002), and the Framingham Offspring Study (McKeown, Meigs, Liu, Wilson, & Jacques, 2002; McKeown et al., 2004) that suggested whole grain consumption protects against type 2 diabetes and heart disease (Jacobs, Meyer, Kushi, & Folsom, 1998; Meyer et al., 2000).

The strengths of the Iowa Women's Health Study include the size of the cohort and the two decades of follow-up, which provided data on more than 7,800 incident cancer cases and more than 10,000 deaths (University of Minnesota Cancer Center, 2006). Limitations include the population's lack of ethnic diversity (99% of participants are white) and that the published dietary analyses to date have been based on one FFQ (at this writing no analyses have been published based on the 2004 dietary data). In addition, early diet exposures have not been assessed, and these exposures may play an important role in cancer etiologies.

Randomized Controlled Trials

Randomized controlled trials are studies in which subjects are randomly assigned either to a treatment/intervention or a placebo/no intervention. Ideally, the group not assigned to the intervention is assigned to a placebo or sham intervention that is unrecognizable from the actual intervention; however, this kind of blinding of the participants (and researchers) is not always possible. The **randomized design**, particularly if placebo controlled and blinded, is the gold standard for providing evidence for a cause and effect relationship. Possible limitations of this study design are the timing of the intervention in relation to the development of the disease (if the intervention does not take place during the time in which the exposure occurs), then null findings may occur because there is no intervention effect. Another possible limitation is the question of whether results seen in a controlled research setting will occur in free-living populations.

Randomized design: When individuals are randomly assigned to a treatment or control group.

Dietary Approaches to Stop Hypertension

The original Dietary Approaches to Stop Hypertension (DASH) study was a multicenter randomized feeding study to examine the effects of dietary patterns on blood pressure (Appel, Moore, Obarzanek, & Vollmer, 1997). The sample consisted of 459 adults 22 years of age or older not taking any antihypertensive medications and with systolic blood pressure less than 160 mm Hg and diastolic blood pressure between 80 and 95 mm Hg. About two-thirds of the sample was a racial or ethnic minority, with African-American the most common race reported (about 60% of the sample). There were three phases to the trial: screening, run-in (3 weeks), and intervention (8 weeks). At the beginning of the intervention phase subjects were randomly assigned to one of three diets all of which contained 3,000 mg of sodium:

1. Control diet: typical of the American diet, with potassium, magnesium, and calcium levels approximately at the 25th percentile of the U.S. consumption and macronutrient levels and fiber content at the average U.S. consumption
2. Fruit and vegetable diet: provided more fruits and vegetables and fewer snacks and sweets, with a commensurate level of potassium and magnesium that were at the 75th percentile of U.S. consumption
3. Combination diet: rich in fruits and vegetables, low-fat dairy, and lower in saturated fat, total fat, and cholesterol, with potassium, magnesium, and calcium levels approximately at the 75th percentile of U.S. consumption.

All food was provided by the researchers with research kitchens doing all preparation, including all meals and snacks on weekdays and weekend days, although lunch was eaten at the research centers on weekdays. The combination diet was associated with significantly greater declines in both systolic (5.5 mm Hg, $p<0.001$) and diastolic (3.0 mm Hg, $p<0.001$) blood pressure than the control diet. Those with hypertension benefited the most from this diet, with average declines exceeding 11 mm Hg for systolic and 5 mm Hg for diastolic blood pressure after 8 weeks. Although significant effects of lowering both systolic and diastolic blood pressure was also seen among those on the fruit and vegetable diet, these effects were not as dramatic as on the combination diet and not as significant in men or nonminority groups (Appel et al., 1997). The aforementioned combination diet henceforth became known as the DASH diet. However, it was unknown what effects sodium restriction would have while subjects were following the DASH diet, and it was not known what the DASH diet's effects on blood pressure would

be when sodium intake was restricted (Svetkey et al., 1999). Thus the DASH-sodium study was developed.

DASH-sodium was also a randomized controlled intervention study in which subjects were assigned to either a control diet (previously described) or the DASH diet. Then, using a crossover design, subjects were fed three different levels of sodium daily: low (1,150 mg/2,100 kcal), intermediate (2,300 mg/2,100 kcal), and high (3,450 mg/2,100 kcal) each for a 30-day period (Svetkey et al., 1999). The sodium-varied diets were fed in random order separated by a 3- to 5-day break (Svetkey et al., 1999). The sample of 412 subjects was again about 60% African-American (Sacks et al., 2001).

Implementation of this study was similar to that of the original DASH study in terms of providing all food, requiring that subjects ate lunch at the research center on the weekdays, and using standardized methods of collecting blood pressure data. In addition, weight was kept constant. The results showed that the subjects on the DASH diet had significantly lower mean systolic blood pressure at every level of sodium compared with that of the control subjects and lower diastolic blood pressure at the high and intermediate sodium levels than the control group. As compared with the high sodium control diet, the DASH diet combined with a low sodium level resulted in systolic blood pressure that was 7.1 mm Hg lower in those without hypertension and 11.5 mm Hg lower in those with hypertension. Conversely, diastolic blood pressure was not different for DASH versus control diet when subjects' sodium consumption was at the lowest sodium level. The implications of this study according to the authors (Sacks et al., 2001) was that the DASH diet effectively lowers blood pressure at different levels of sodium and that reducing sodium intake does result in declines in blood pressure, not only among those with hypertension but also among those without it even when using the typical diet consumed in the United States.

One aspect, however, not mentioned is that the 11.5 mm Hg difference between the low sodium DASH diet and the high sodium control diet among those with hypertension is similar to that found in the original DASH study in which the DASH diet at a 3,000-mg level of daily sodium was associated with a 11.4mm Hg greater decline in blood pressure than the 3,000-mg control diet. The fact that both DASH and DASH-sodium were well-implemented randomized controlled trials with high adherence (over 93% to 95% completed the studies and biochemical markers corroborated dietary adherence) and that blinded measurements of blood pressure used a standardized methodology are all strengths of these intervention studies. Moreover, the ethnic diversity of the samples implies that extrapolation of these results to the very groups with high risk (i.e., ethnic minorities) of developing hypertension is appropriate. The limitation of both studies, however, is that it is unknown whether the effects seen under these highly controlled research conditions with all food provided can be replicated in a free-living U.S. population.

Both DASH and DASH-sodium have had tremendous influence on the 2005 Dietary Guidelines. This is illustrated in the declaration in the Dietary Guidelines for Americans that the DASH eating plan is an example of a healthy eating plan promoted by the dietary guidelines. In fact, several of the key recommendations in the 2005 Dietary Guidelines for Americans name the DASH diet specifically (DHHS and USDA, 2005). For example, one of the key recommendations in the section on adequate nutrients within energy needs is "Meet recommended intakes within energy needs by adopting a balanced eating pattern, such as the USDA Food Guide or the DASH Eating Plan" (DHHS and USDA, 2005). Moreover, the results of the DASH-sodium study guided the recommendation of the lower sodium levels (<1,500 mg) among those with hypertension (DHHS and USDA, n.d.). Given the pervasiveness of the DASH studies' influence on the 2005 Dietary Guidelines and the fact that through our national nutrition surveillance systems the dietary intake of the U.S. population is tracked, the effectiveness of the DASH diet in a free-living population may be ascertained through this natural experiment.

Women's Health Initiative

The Women's Health Initiative (WHI) study was launched in 1991 to investigate major diseases affecting postmenopausal women, including heart disease, breast and colorectal cancers, and osteoporosis. The 15-year study includes 161,000 women aged 50 to 79 years at baseline in a total of three clinical trials and one observational trial conducted across 40 clinical centers in the United States. One of its most striking findings was that postmenopausal hormone replacement therapy with estrogen–progestin increases the risk of breast cancer (Writing Group, 2002).

Two of the WHI's clinical trials tested two of the most widely recommended nutrition therapies aimed at preventing chronic disease: low-fat diets and calcium–vitamin D supplements. The dietary

modification trial examined the effect of a low-fat high-carbohydrate diet on breast cancer, colorectal cancer, heart disease, and stroke. The calcium plus vitamin D trial looked at the effect of taking daily supplements of 1,000 mg calcium and 400 IU vitamin D on osteoporosis-related fractures and colorectal cancer. Overall, both trials failed to demonstrate that these preventive regimens had a protective effect, prompting controversy about the studies' merits and flaws as well as their implications for future nutrition recommendations.

In the dietary modification trial, 48,835 women were randomly assigned to the intervention group or the control group (Prentice et al., 2006). Women in the intervention group were instructed to adopt a low-fat diet (20% of total calories from fat) that was high in grains (at least six servings a day) and fruits and vegetables (at least five servings a day). The intervention subjects also received extensive dietary counseling, including personalized fat intake goals and nutritionist-led group counseling sessions (18 during the first year and quarterly follow-up meetings during subsequent years). Women in the control group were given general information on healthy diets but were instructed not to make any changes in their diets.

Dietary intake was assessed via FFQ (administered to everyone at baseline and then to a third of subjects each year thereafter), 4-day food records (collected from everyone at baseline and from ~5% of subjects after year 1), and single 24-hour recalls (collected from ~5% of subjects in year 3 and 6 and from an additional 1% of subjects every year). Serum samples were also analyzed for biomarkers of dietary intake, such as carotenoids, lipids, and glucose. During yearly clinic follow-up visits investigators measured subjects' height, weight, waist circumference, and blood pressure. Outcomes were assessed by self-report and medical record examination.

Overall, after roughly 8 years of follow-up the study found that the low-fat dietary pattern did not significantly decrease risk of invasive breast cancer, colorectal cancer, heart disease, or stroke (Beresford et al., 2006; Howard et al., 2006; Prentice et al., 2006). Although breast cancer incidence was 9% lower in the intervention group compared with the control group, this difference was not statistically significant (Hazard Ratio (HR) = 0.91; 95% confidence interval, 0.83–1.01; $p = 0.07$). Secondary analyses, however, suggested that the low-fat dietary pattern had a protective effect in women who had the highest baseline fat intake.

The study authors suggested that the lack of statistically significant overall findings could be due to several factors. Only a small percentage of women in the intervention group achieved the 20% of calories from fat dietary goal; furthermore, the differences in fat intake and fruit and vegetable intake between the intervention and control groups were lower than anticipated by the original study design (Prentice et al., 2006). The authors pointed to the secondary findings as evidence that the intervention did have a protective effect against breast cancer. Other observers, however, suggested that the slight decrease in breast cancer incidence could be due to modest weight loss among intervention group subjects (Lagiou, Trichopoulos, & Adami, 2006). Although the intervention phase of the study has ended, study participants will be followed for another 5 years, so it is possible that further differences between the intervention and control groups will emerge over time.

The calcium plus vitamin D trial, which followed 36,282 postmenopausal women for an average of 7 years, had similarly mixed results. The study found that daily supplementation with 1,000 mg of calcium and 400 IU vitamin D slightly increased hip bone density but did not lead to a decrease in hip fractures and that supplementation was linked with a higher risk of kidney stones. Secondary subgroup analyses did show a protective effect in the most adherent women (Jackson et al., 2006). The supplementation regimen also had no effect on the women's risk of colorectal cancer (Wactawski-Wende et al., 2006). The authors and other observers suggested several explanations for the bone findings, among them that the dose of vitamin D may not have been sufficient (600 IU or higher of supplementation may be required to reduce fracture risk), that many women in the control group had a high daily intake of calcium from diet and supplements (800 mg calcium and 400 IU vitamin D a day), and that more than half of the women in the intervention and control groups were receiving hormone replacement therapy (some as part of the WHI trial) (Finkelstein, 2006). The lack of a protective effect on colorectal cancer could be because such cancers are slow growing and a 7-year follow-up may not be enough time to show evidence of benefit. It remains to be seen whether any effects emerge during the planned postintervention 5-year follow-up (Wactawski-Wende et al., 2006).

The strengths of the WHI nutrition investigations include the enrollment of a large number of

women drawn from diverse ethnic and socioeconomic groups across the country as well as the careful long-term follow-up of outcomes. Potential limitations include the postmenopausal study population itself and the timing of the interventions; breast and colorectal cancer, heart disease, and osteoporosis outcomes may be determined by exposures or preventive measures taken earlier in life.

The ultimate effect of the WHI findings on nutrition recommendations remains to be seen. Government dietary recommendations have already moved away from advocating a uniformly low-fat diet, focusing instead on reducing saturated and trans fat to prevent chronic disease. The Institute of Medicine's latest recommendations, echoed by the 2005 Dietary Guidelines for Americans, suggest a daily fat intake for adults between 20% and 35% of total calories. There is also increasing evidence that the current daily recommended intake for vitamin D is too low and that at least 1,000 IU/day of vitamin D may be needed to promote optimum blood levels for prevention of hip fractures (Bischoff-Ferrari, Giovannucci, Willett, Dietrich, & Dawson-Hughes, 2006).

Optimal Macro-Nutrient Intake Trial to Prevent Heart Disease (OmniHeart)

The Optimal Macro-Nutrient Intake Trial to Prevent Heart Disease (OmniHeart) study was designed to determine whether altering the DASH diet's macronutrient composition could further lower heart disease risk (Appel et al., 2005; Carey et al., 2005). The feeding study used a randomized, three-period, crossover design to examine the effect of three healthy diets—high carbohydrate, high protein, and high unsaturated fat—on blood pressure, LDL, HDL, triglycerides, and overall cardiovascular disease risk in men and women. The subjects (n = 164) were healthy adults with prehypertension or stage 1 hypertension; in light of the higher prevalence of cardiovascular disease among African-Americans, the study investigators sought to recruit a cohort that was 50% African-American (the final cohort was 55% African-American and 40% non-Hispanic white).

Like DASH, all three study diets were low in saturated fat (6% of total energy), sodium (2,300 mg/day), and cholesterol (<150 mg/day). Furthermore, the diets emphasized vegetables, fruit, grains, and low-fat dairy products; had similar levels of potassium (4,700 mg/day), magnesium (500 mg/day), and calcium (1,200 mg/day); and used commonly available foods. The carbohydrate diet was most similar to the DASH diet, with 58% of total energy from carbohydrate, 15% from protein, and 27% from fat (6% saturated fatty acid, 13% monounsaturated fatty acid, 8% polyunsaturated fatty acid). The protein diet substituted 10% of carbohydrate with primarily nonmeat sources of protein, for a final dietary composition of 48% carbohydrate, 25% protein, and 27% fat. The unsaturated fat diet substituted 10% of carbohydrate with primarily monounsaturated fat, for a final dietary composition of 48% carbohydrate, 15% protein, and 37% fat (21% monounsaturated fatty acid, 10% polyunsaturated fatty acid, 6% saturated fatty acid).

Each subject was randomly assigned to follow one of six feeding period sequences (e.g., carbohydrate, unsaturated fat, protein; unsaturated fat, protein, carbohydrate; and so on). Each feeding period lasted 6 weeks, with a short washout period in between; 97% of subjects completed all three feeding periods.

The study found that compared with the carbohydrate diet, the protein and unsaturated fat diets further decreased mean systolic blood pressure; the protein diet also lowered LDL, slightly lowered HDL (an unexpected finding), and lowered triglycerides, whereas the unsaturated fat diet had no effect on LDL, increased HDL, and lowered triglycerides. When compared with baseline, the carbohydrate, protein, and unsaturated fat diets all lowered estimated 10-year coronary heart disease risk (by 16.1%, 21.0%, and 19.6%, respectively); when compared with the carbohydrate diet, the protein diet and unsaturated fat diets further decreased coronary heart disease risk (by 5.8% and 4.2%, respectively).

The strengths of the study include subjects' high adherence to the study diets and the fact that study participants maintained their body weight over the course of the study (so that weight loss or gain was not a confounding factor). Limitations include the fact that subjects were on each study diet for only 6 weeks and that the measured outcomes were risk factors for cardiovascular disease rather than cardiovascular disease events.

PHS II

The PHS II, previously noted, is an ongoing **double-blind placebo-controlled** primary prevention trial of vitamin E, ascorbic acid, beta-carotene, and/or multivitamins on prevention of prostate cancer, other cancers, or cardiovascular disease in healthy older male doctors. It is actually the only such prevention

Double-blind placebo-controlled design: When neither the individuals nor the investigator know whether participants are assigned to a treatment or a placebo group. This study design is usually considered to provide the most compelling evidence of a cause and effect relationship.

trial of its kind on apparently healthy men (Christen, Gaziano, & Hennekens, 2000). Since August 1997, 14,642 men have been randomized into 1 of 16 possible combinations of vitamin C (500 mg synthetic ascorbic acid), vitamin E (400 IU of synthetic alpha-tocopherol), beta-carotene (50 mg Lurotin), a multivitamin (Centrum Silver), or their placebos. Vitamin C and the multivitamin or their placebos are taken daily, whereas vitamin E and beta-carotene or their placebos are taken every other day (PHS II, 2002). Ethnic minorities comprise 9.4% of the sample, with the primary minority group being Asian (5.1%) (Howard et al., 2006); thus this sample, like PHS I, is primarily non-Hispanic white.

The trial is scheduled to end in December 2007 (PHS II, 2002); however, the beta-carotene portion was discontinued in 2003 (PHS II, 2006). Baseline blood samples were obtained on 76% of the sample (PHS II, 2002), and questionnaires are administered annually with questions about compliance with the study treatments, use of nonstudy medications, occurrence of major illnesses or adverse effects, and other risk factor information (PHS II, 2002). Although not stated in the description of the study design, some of these risk factors may include dietary information (Christen et al., 2000). The strengths of this study lie in its strong design, enabling researchers to attribute cause and effect to the treatment(s) and apply such results to an older healthy male population. However, like many of the other studies previously described, the external validity of applying these results to racial ethnic minority populations is limited because of the sample's homogeneity.

Conclusion

This section reviewed several epidemiologic studies, some that have been important contributors to dietary recommendations that have been promulgated and some that have potential for informing future recommendations. Although all have limitations, as the perfect study has yet to be conducted, these designs have strong internal validity. Nevertheless, many do not include samples that represent ethnic minorities, and this appears to be the "Achilles' heel" of chronic disease prevention research. Looking to the future, therefore, this gap needs to be filled with more studies that include a larger proportion of ethnic minorities (like DASH and OmniHeart) so that national nutrition policy, which currently is considered to apply to all, can be grounded in research that was not conducted on a primarily white non-Hispanic samples.

As the evolution of national dietary guidelines on fat has illustrated, it takes many years for research findings to be applied to the transformation of nutrition policy. Early studies on trans fat were published in 1993, but the U.S. Food and Drug Administration regulations on labeling to include trans fat did not begin until January 2006. Nevertheless, the studies described herein, although not exhaustive, exemplify that well-conducted epidemiologic research has made important contributions to national dietary guidelines. Broadening such research to diverse populations and other innovative nutrition-related research questions will likely help shape future dietary recommendations.

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