

Further analysis of the Mini-Sentinel and other claims databases is ongoing, as is routine postmarketing surveillance through FAERS.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD.

This article was published on March 13, 2013, at NEJM.org.

1. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51. [Erratum, *N Engl J Med* 2010;363:1877.]

2. Weber JCP. Epidemiology of adverse reactions to nonsteroidal anti-inflammatory drugs. *Adv Inflamm Res* 1984;6:1-7.

3. FDA drug safety communication: safety review of post-market reports of serious bleeding events with the anticoagulant Pradaxa (dabigatran etexilate mesylate) (<http://www.fda.gov/drugs/drugsafety/ucm282724.htm>).

4. FDA Sentinel Initiative. Mini-Sentinel home page (<http://mini-sentinel.org>).

DOI: 10.1056/NEJMp1302834

Copyright © 2013 Massachusetts Medical Society.

HISTORY OF MEDICINE

Something New under the Sun? The Mediterranean Diet and Cardiovascular Health

Sarah W. Tracy, Ph.D.

Related article, p. 1279

Increasingly, the Mediterranean diet has become the standard for healthy eating. Adherence to it appears to reduce the risk of cardiovascular disease, cancer, Alzheimer's disease, and Parkinson's disease, as well as the risk of death due to cardiovascular disease or cancer and even premature death overall.¹ Largely plant-centered, with high intakes of olive oil, fruit, nuts, and whole-grain cereals, moderate consumption of fish and poultry, low intakes of dairy, red meat, and sweets, and often moderate drinking of red wine, the "classic" Mediterranean diet is younger than the region's history suggests. In fact, this dietary pattern was first observed in Greece, Italy, and Spain in the decade after World War II — an artifact of postwar impoverishment that proved beneficial to health. Unfortunately, it is currently under siege in southern Europe from the globalization of fast foods rich in refined carbohydrates, sweets, and red meat.

In this issue of the *Journal*, Estruch et al. (pages 1279–1290) report the positive results of PREDIMED (Prevención con Dieta Mediterránea), a randomized trial of the Mediterranean diet (supplemented with either extra-virgin

olive oil or nuts) for the primary prevention of cardiovascular events. The data are impressive and seem to support the high ranking of the Mediterranean diet and its constituent foods among various cardioprotective vegetable- and fruit-rich regimens, such as DASH (Dietary Approaches to Stop Hypertension) and Japanese and traditional vegetarian diets. Yet in many ways, that is old news. The history of dietary guidelines for heart health — a project begun in the 1950s when the United States felt threatened by a perceived "epidemic" of heart attacks — reveals that the Mediterranean diet's cardiovascular benefits have been recognized for decades. As early as 1948, the Rockefeller Foundation assessed the health, economic, and social status of Cretan Greeks and noted that their "impoverished" diet was rich in cereal grains, legumes, wild greens and herbs, and fruits, paired with limited meat, milk, and fish. Meals were said to be "swimming" in olive oil and prepared simply in ways that "preserved the nutritive value of the food rather well."²

The first epidemiologic data supporting the Mediterranean diet came from the Seven Countries Study (SCS), a prospective investi-

gation of diet and other cardiovascular-disease risk factors in 16 cohorts totaling nearly 13,000 men in the United States, Italy, Greece, Yugoslavia, Finland, the Netherlands, and Japan, which began in 1958. The PREDIMED results would come as little surprise to the man behind the SCS, American physiologist and epidemiologist Ancel Keys, who advanced the low-fat diet and the low-saturated-fat Mediterranean diet for the primary and secondary prevention of heart disease. Keys "discovered" the Mediterranean diet's health benefits in the early 1950s, when visiting the region as a medical scientist concerned about the widely reported increase in heart attacks in the United States. After spending several years exploring the dietary patterns and cardiovascular status of men in Italy, Spain, and Crete, Keys launched the SCS. Study data (which are still being collected from elderly "survivors") offered strong population-level support for the effects of dietary fat and fatty acids on serum cholesterol levels and cardiovascular disease risk.

The still-unfolding story of dietary fat has proven more complicated than Keys envisioned, but his observations about dietary pat-

terns in various cultures — Mediterranean, northern European, and Asian — appear prescient today. The nutritional properties of whole foods and food patterns — rather than macronutrients (such as protein, carbohydrate, and fat) and micronutrients (such as vitamins and minerals) — are an important focus of recent research. Many who study diet's effects on disease note that we do not eat isolated nutrients. Instead, we form food patterns, consuming diets rich in fruits, nuts, vegetables, and oils or, alternatively, in highly processed foods, and these constituent foods interact synergistically.³ Sometimes these synergies confer long-term benefits.

This holistic turn in nutrition science represents something of a paradigm shift. Early in the 20th century, research focused on the roles of micronutrients, often specific vitamins, and the prevention of deficiency diseases such as beriberi, pellagra, and scurvy. By mid-century, chronic diseases such as atherosclerosis, hypertension, and cancer were recognized as the dominant health threats in the developed world. Yet the reductionism that guided the early studies continued to influence explorations of diet and heart disease. In the 1950s and 1960s, biochemists, clinical scientists, and epidemiologists focused on macronutrients as potential contributors to cardiovascular disease and debated what constituted proof of a causal link between dietary fat and heart disease. Individual macronutrients and bioactive compounds in food, such as cholesterol, were the focus of research exploring diet's relation to the health status of populations.

In this context, the American Heart Association (AHA) Ad Hoc Committee on Dietary Fat and Atherosclerosis issued the first dietary guidelines for the prevention

of cardiovascular disease in 1957. The guidelines were brief and tentatively worded, reflecting controversy over the hypothesized link between dietary fat and heart disease. Obese people or those with a personal or family history of heart disease were urged to control their weight, reduce dietary fat to 25 to 35% of total energy intake, and substitute polyunsaturated fats for animal fats. The guidelines thus focused on macronutrients, specifically fats. Committed to reducing heart disease, the AHA revised its guidelines throughout the 1960s. By 1968, people of all ages were urged to limit dietary cholesterol as well and to adhere to principles of good nutrition.

When the AHA issued its first “heart healthy” cookbook, in 1973, it was a latecomer. Cookbooks catering to heart health first appeared in the 1950s, offering recipes for limiting caloric intake and reducing dietary fat and cholesterol. The first cookbook to promote the hypothesized relationship between diet and heart health was probably that of physician Helen Gofman, *The Low Fat Low Cholesterol Diet* (1951). Gofman's husband, the medical physicist and lipidologist John Gofman, also wrote a cookbook, *Dietary Prevention and Treatment of Heart Disease* (1958), examining the relationship of dietary carbohydrates to dietary fat in atherogenesis. There were many others, but the most popular were two cookbooks by Keys and his biochemist wife, Margaret, *Eat Well and Stay Well* (1959) and *How to Eat Well and Stay Well the Mediterranean Way* (1975). These interpreted “diet” in the classic Greek sense, as a “way of life,” and advocated moderate exercise in addition to “heart-healthy eating” that was grounded largely in Italian and Greek cuisine. Cookbooks, with their focus on dietary pattern, al-

lowed Keys to explore the irreducible elements of a healthy diet, something he and others struggled to do in the laboratory. As food-policy expert Marion Nestle has observed, there is striking similarity between Keys's 1959 recommendations and those in recent editions of the *Dietary Guidelines for Americans* from the U.S. Department of Agriculture (USDA) and the Department of Health and Human Services.⁴

Since 1980, these guidelines, revised every 5 years, have set dietary standards for an increasingly obese and diabetic American public. In part, they reflect an ongoing dance between evidence-based dietary advice and the food-industry lobby. In part, they reflect a stable dietary foundation for avoiding degenerative diseases: eat more fruits, vegetables, and nuts; limit red meat and dairy; consume more fish and poultry; curtail salt and sugar; use olive and other vegetable oils; and substitute whole grains for refined ones. This advice should sound familiar, yet because the 2010 guidelines often use difficult-to-translate macronutrient language and fill more than 95 pages, they have become less accessible to the public. And the USDA nutritional icon “MyPyramid” (2005) and its replacement, “MyPlate” (2011), intended to distill cumbersome dietary advice, have been criticized for being too simple, misleading, or excessively influenced by the food industry.⁵

In 2010, the United Nations Educational, Scientific, and Cultural Organization (UNESCO) placed the Mediterranean diet on its Intangible Cultural Heritage list, a sort of endangered-species list of treasured elements of cultures, valuable both in their native lands and globally. The PREDIMED results reinforce the Mediterranean diet's value for

health internationally, suggesting a dietary template that may be of particular value as chronic disease becomes a global issue.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From McClendon Honors College, University of Oklahoma, Norman.

1. Sofi F, Abbate R, Gensini GF, Casini A. Accruing evidence on benefits of adherence to the Mediterranean diet on health: an updated systematic review and meta-analysis. *Am J Clin Nutr* 2010;92:1189-96.
2. Allbaugh LG. Crete — a case study of an underdeveloped area. Princeton, NJ: Princeton University Press, 1953.
3. Jacobs DR Jr, Tapsell LC. Food, not nutrients, is the fundamental unit in nutrition. *Nutr Rev* 2007;65:439-50.

4. Nestle M. Mediterranean diets — historical and research overview. *Am J Clin Nutr* 1995;61:Suppl:1313S-1320S.

5. Datz T. Harvard serves up its own 'plate': Healthy Eating Plate shows shortcomings in government's MyPlate. *Harvard Gazette*. September 24, 2011 (<http://news.harvard.edu/gazette/story/2011/09/harvard-serves-up-its-own-plate/>).

DOI: 10.1056/NEJMp1302616

Copyright © 2013 Massachusetts Medical Society.

Lessons from Vermont's Health Care Reform

Laura K. Grubb, M.D.

In May 2011, Vermont Governor Peter Shumlin signed legislation to implement Green Mountain Care (GMC), a single-payer, publicly financed, universal health care system. Vermont's reform law passed 15 months after the historic federal Affordable Care Act (ACA) became law. In passing reforms, Vermont took matters into its own hands and is well ahead of most other states in its efforts to implement federal and state health care reforms by 2014. The Supreme Court decision last June to uphold most of the ACA left many states scrambling, since they had postponed reforms pending the judgment. Although Vermont is a small state, its reform efforts provide valuable lessons for other states in implementing ACA reforms.

First, Vermont instigated change from within the state and engaged local stakeholders in the process. Vermont's administration provided information to residents, promoted transparency, and actively engaged citizens on all levels. The administration established a health care reform website, hcr.vermont.gov, which provides regular reform updates, educational presentations, timelines, and links to legislation and other reform resources. Administrators host frequent public listening sessions throughout the state. In addition, Shumlin engaged health

care providers in the reform process, in part through the GMC Health Care Professional Technical Advisory Group, which consists of 68 physicians, dentists, physical and occupational therapists, pharmacists, and naturopathic doctors, and the Mental Health and Substance Abuse Technical Advisory Group, consisting of 24 mental health professionals. The engagement of such stakeholders has helped to smooth the transition to large-scale reform.

Second, Vermont created the Green Mountain Care Board (GMCB), an independent board with responsibility for all the major factors influencing the cost of health care in the state. Whereas other states split responsibility for the oversight of different parts of the health system among different agencies, Vermont's legislature created one board to consider all the variables. The GMCB has jurisdiction over payment reform, insurance exchanges, rate setting, hospital-budget authorization, resource and workforce allocation, state formulary establishment, regulation of insurance carriers, and maintenance of a statewide quality-assurance program. The board will establish and maintain a publicly financed health insurance program and a unified health budget. In addition, it is overseeing the development of two ac-

countable care organizations: the Accountable Care Coalition of the Green Mountains, which includes 100 independent physicians statewide, and OneCare Vermont, whose network of 13 community hospitals, 2 federally qualified health clinics, 5 rural health centers, and 58 independent physician practices is responsible for the care of 42,000 Medicare recipients. The fact that many types of health care-related transactions must pass through the GMCB supports synchronization of reform efforts.

Third, Vermont is advanced in its development of a state insurance exchange that will offer essential benefits through at least three tiers of insurance packages while providing transparency and comparability.¹ The ACA mandates that states establish their own exchanges or default to the federal exchange, and to date 24 states and the District of Columbia have declared their intent to establish their own exchange or a joint state-federal exchange (see table).² Although the development of a state exchange is a massive task, Vermont administrators believe that their exchange will serve as a foundation for a streamlined system for single-payer reform. "The infrastructure is useful because it would build the portal we would use for single payer, including eligibility screening, enrollment pro-