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NUTRITIONAL RESEARCH WITHIN THE FRAMINGHAM HEART STUDY

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Abstract: Fifty years of research at the Framingham Heart Study have made important contributions to the diagnosis and treatment of cardiovascular disease (CVD). Within the scope of this prospective population-based cohort study, research investigations from the Framingham Nutrition Studies have developed and advanced nutritional epidemiologic methods, many of which are highlighted here. Ongoing nutrition research explores relationship between diet, nutritional status, and the development of chronic diseases, including CVD. This paper summarizes key findings from decades of nutrition research within the Framingham Heart Study. Cross-sectional and longitudinal investigations are described, including recent research on dietary patterns and coronary heart disease risk among women. Implications for the development of national nutrition policy, population-based dietary guidance for chronic disease prevention, and nutrition-related health promotion campaigns for CVD risk reduction are discussed.

Key words: Diet, cardiovascular diseases, Framingham study, epidemiology.

Introduction

The Framingham Heart Study recently celebrated its 50th anniversary, marking achievements as one of the longest standing prospective investigations of cardiovascular diseases (CVD) globally. The study emphasizes continuing examinations of two major study populations - the original Framingham cohort (2,336 men and 2,873 women of whom 779 are currently alive and are at their 26th biennial examination) and the Framingham Offspring-Spouses, children of the original cohort and their spouses (5135 persons including 4347 survivors who are at their 7th exam). In addition, the Framingham Children's studies and the Omni cohort have been initiated to add investigations on the third generation of Framingham family members and a representative local minority cohort, respectively. At the anniversary events, Dr. David Satcher, the US Surgeon General, noted the invaluable resources of the Framingham studies including their scientific rigor, longitudinal nature, community and family focus, gender representativeness, and the foundation of mutual trust between the investigators and research participants.

The Framingham Nutrition Studies were formally initiated in 1984; however, the historical involvement of the Heart Study in the nutritional epidemiology of CVD dates back to the 1950s. Framingham Study investigators developed landmark methods for use in nutritional epidemiology and, more recently, have explored innovations in the applications of both new and existing dietary assessment methodologies. Currently, there are many ongoing Framingham collaborations which enrich the understanding of diet, nutritional status, and the development of CVD as well as other chronic diseases. The studies have provided information on secular trends in nutrient intake and estimates of the population's progress toward, but continued deviation from, the Healthy People 2010 Nutrition Objectives for the Nation and other expert recommendations. The ongoing Framingham nutrition investigations have made significant contributions to the understanding of the relationships between CVD risk and various clinical and biochemical indicators of nutritional status, particularly obesity and selected biomarkers. Framingham researchers have examined the relationships between food and nutrient intake, patterns of dietary behavior, CVD risk factors (including lipid profiles, blood pressure, and body weight), CVD endpoints (including CHD and stroke), and pre-clinical markers for heart disease (including carotid artery atherosclerosis). Framingham nutrition research has important implications for the development of national nutrition policy, particularly concerning guidelines for population-based chronic disease prevention and health promotion, and the formulation of effective nutrition and health promotion campaigns for CVD risk reduction. Each of these areas of investigation will be discussed in greater detail.

Framingham Methods in Nutrition Epidemiology

The Framingham Study initiated its work on the relationships between dietary behavior and CVD risk during the early 1950s. Dietary assessments were carried out in the original Framingham cohort during their fourth through sixth

examinations (1954-56) and again during their ninth to eleventh exams (1966-69). Samples of male and female participants were included in the first dietary investigations; however, in the 1960s only the dietary behaviors of male participants were evaluated. During these first Framingham nutrition studies, researchers utilized and expanded the diet history method—a technique that involves an hour-long (or longer), in-depth interview aimed at a profiling the subject's usual dietary intake. The interview resembled a combination of a 24-hour dietary recall methodology and a semi-quantitative food frequency questionnaire. Utilizing a structured interview format, foods consumed throughout a typical day were queried; portions quantified; and week-day versus weekend variations in food intake patterns were explored. A major contribution of these earlier Framingham nutrition investigations was the introduction of the Composite Food Table, a resource that allowed investigators to summarize data derived from the diet history and estimate an individual's usual daily nutrient intake profile. These data sets enabled the earliest exploration of relationships between diet and cardiovascular disease risk in Framingham (1).

During the 1960s, the Framingham investigators utilized a 24-hour dietary recall to estimate food and nutrient intake among all original cohort male subjects who were 44-65 years of age. These data were used subsequently to examine relationships between dietary lipids and selected foods, such as margarine, and the prospective development of CHD among Framingham men (2), as well as the association between fruit and vegetable intake and the onset of stroke (3).

During the 1980s, Framingham substantially increased its investigation of dietary behavior and cardiovascular disease risk. As the Framingham Nutrition Studies were introduced into the Framingham Offspring Studies, investigators sought to validate a set of research methods and establish a framework for subsequent cross-sectional and longitudinal investigations. The array of dietary assessment methods included the Framingham Food Frequency and Food Behavior questionnaires, the 24-hour dietary recall and three day food records, and the two-dimensional food portion estimation tool for use in telephone-administered or self-appraisals of dietary intake. Complete details on the research methods and validation studies have been previously published (4-6). Since the 1980s, Framingham has carried out one or more assessments of food and nutrient intake utilizing a variety of dietary assessment methods at numerous follow-up investigations of the original cohort and the Offspring cohort.

Among the areas of most recent methodological interest is the advancement of our understanding of the complexities of dietary behavior in the Framingham Offspring male and female populations and of the relationship between overall dietary patterns and CVD risk. Utilizing the validated Framingham Food Frequency Questionnaire, the investigators have characterized five distinct dietary patterns in women and five more in men (7). Table 1 identifies the key discriminating components of the dietary patterns observed in the Framingham Offspring population. Dietary patterns among women, for example, differ markedly in consumption levels of both energy-dense and nutrient-dense foods. Consequently they differ in content of *protective* nutrients (antioxidant vitamins, calcium, magnesium, fiber, and selected B vitamins) and *risk* nutrients (saturated fat, cholesterol, sodium, and alcohol). These eating patterns have the potential to form the basis for more insightful dietary counseling and the development of population-based nutrition recommendations (8). Mathematical algorithms have been developed and are currently being tested for application of the Framingham dietary pattern methodology to other prospective cohort and population studies.

Table 1

Key components of dietary clusters of Framingham women and men.

WOMEN'S DIETARY PATTERNS	
Heart Healthy	Higher in fruits, vegetables, low-fat dairy, and other lower-fat foods including whole grains, skinless poultry, and fish; lowest in total and saturated fat content.
Light Eating	Lower in sweets, animal and vegetable fats, and refined grains; lowest in caloric content.
Wine and Moderate Eating	Lower intake of desserts; higher intake of snack foods, eggs, and wine; highest alcohol content.
High Fat	Higher in sweets, animal and vegetable fats, refined grains and margarine; fewer lower-fat foods; highest in total and saturated fat content.
Empty Calorie	Higher in sweetened beverages, red meats, and desserts; lower in fruits and vegetables; high in sugar, total fat, and saturated fat.
MEN'S DIETARY PATTERNS	
Transitional Diet	Higher in fruits, whole grains, low-fat dairy, skinless poultry, and other lower fat foods; higher carbohydrate content; low alcohol with total and saturated fat intakes still above recommended levels.
Wine and Moderate Eating	Higher in fish, shellfish, legumes and wine; lower in refined grains, sweets, and vegetable fats; lowest in total and saturated fat content but high in alcohol.
Western Diet with Beer	Highest beer intake within the context of an otherwise more traditional western dietary pattern; high in total and saturated fat with moderate alcohol content.
Western Diet with Liquor	Highest liquor intake within the context of an otherwise more traditional western dietary pattern; high in total and saturated fat with high alcohol content.
Empty Calorie	Higher in refined grains, sweets, animal protein, animal and vegetable fats; lower in vegetables, fish, and low-fat foods; highest in total calories, total and saturated fat, and cholesterol.

Secular Trends in Nutrition Intake and Compliance with Expert Recommendations

Nutritional studies over the past four decades in Framingham provide an opportunity to evaluate secular trends in diet and risk factors profiles of study participants. Despite well-defined reductions in dietary cholesterol and saturated fat, total fat intakes remained relatively stable until the late 1980s but have declined since then (9). These dietary patterns are consistent with improvements in certain CVD risk factors, such as plasma lipids and blood pressure. Nonetheless, there continues to be marked deviation from NCEP dietary lipid guidelines (10, 11) and distinct patterns of dietary behavior among various subgroups of men and women that contribute to lower than recommended intake levels of key foods (such as fruits, vegetables, and whole grains) and protective essential nutrients (7). Framingham Study participants who report conscious efforts to improve dietary behaviors are more likely to meet NCEP recommendations and nutrient intake levels defined by other expert groups. They also have more favorable CVD risk factor profiles. Projections of longer-term disease risk based upon the Framingham CHD algorithm (12) suggest that dietary profiles which more closely approximate current dietary guidelines are associated with lower future risk for the development of CHD (13).

Dietary Behavior, Nutrient Intake, and CVD Risk

The relationship between nutrient intake, assessed by dietary recall, and the 16-year incidence of CHD morbidity and mortality was examined among original Framingham cohort men (14). In the younger subset of men (those 44-55 years of age), the development of CHD was directly related to total and saturated fat intake. Those whose average daily dietary fat intake met NCEP guidelines (≤30% of total calories) had a 29% lower risk for CHD [RR 0.71, 95% CI (0.56, 0.90)] compared to those who consumed the sample's average level of fat intake (39.7% of calories). A direct association was also observed for monounsaturated fats, derived largely from animal products in the Framingham population. These dietary effects persisted even after controlling for traditional CVD risk factors, suggesting the independent and important role of dietary behavior in the etiology of CHD in men. In subsequent analyses, fruit and vegetable intake was found to have a protective effect on the development of ischemic stroke [RR 0.76, 95% CI (0.57, 1.02)] and for hemorrhagic stroke [RR 0.49, 95% CI (0.25, 0.95)] over 20 years of follow-up in Framingham original cohort men (3).

The nutrient intake and dietary profiles of Framingham Offspring men and women have been explored more comprehensively in relation to CVD risk factor profiles and the development of CHD. In cross-sectional analyses, dietary lipids were found to be independently associated with serum cholesterol levels in men (15) and with total-, LDL-, and HDL-cholesterol levels in women (16, 17), controlling for traditional CHD risk factors including age, BMI, and genetic markers. Among women, saturated fat was consistently and directly related to total and LDL-cholesterol levels. In addition, the various dietary patterns of women were found to be associated with distinctly different levels of nutritional risk and levels of CVD risk factors (6, 13, 18). For example, women whose dietary patterns were most lipid dense and resulted in the consumption of comparatively lower levels of many essential nutrients had higher total:HDL cholesterol levels, blood pressure, and rates of obesity than women whose diets were more "heart healthy."

Using Framingham data and a statistical model for predicting CHD risk, it was estimated that a 10% reduction in serum cholesterol level without other risk factor changes would be expected to result in a 12% and 14% reduction in CHD risk among men and women, respectively, given an initial serum cholesterol level of 6.21 mmol/L (240 mg/dL) (Figures 1 and 2) (10). The reduction in CHD risk increases as the percent reduction in serum cholesterol rises. It was soon realized that individuals embarking on cholesterol lowering regimens emerged from different segments of the population that had varying risk profiles and displayed unique patterns of dietary behavior. Dietary patterns among subgroups of women, for example, differed notably in terms of consumption of nutrient-dense versus other foods (Figure 3). Recognition of these baseline differences in dietary behavior will facilitate the appropriate targeting of behavioral modification strategies to promote cholesterol lowering and risk reduction at the population level.

The most recent longitudinal research on dietary patterns and CHD risk among Framingham Offspring women has demonstrated that women whose dietary patterns most closely resemble the NCEP guidelines have the lowest prevalence of carotid artery stenosis, a pre-clinical marker for CHD, compared with other subgroups of women after 12 years of follow-up (18). In contrast, those women whose diets were most concentrated in dietary lipids and foods with relatively lower nutrient density had almost a doubling in risk for carotid stenosis [multivariate adjusted RR 1.87, 95% CI (1.04, 3.36)]. These findings confirm the importance of the key dietary behaviors that Framingham investigators have identified in relation to CHD risk among women, and provide useful information for identifying candidates and population subgroups to target for early preventive nutrition intervention. Ongoing investigations are extending these analyses into the Framingham Offspring male cohort.

Figure 1
Relative risk of coronary heart disease (CHD) with serum cholesterol reduction in women

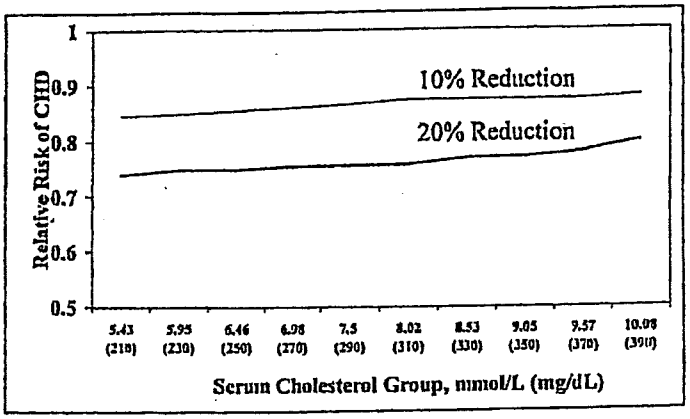


Figure 2
Relative risk of coronary heart disease (CHD) with serum cholesterol reduction in men

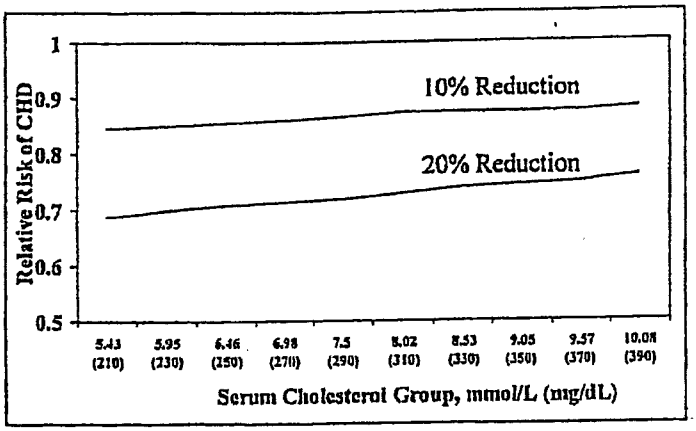
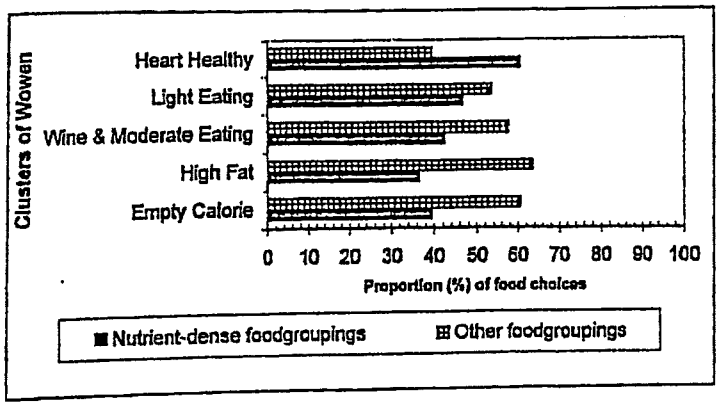


Figure 3
Selection of nutrient-dense vs other foods by subgroups of women



Nutritional Status Indicators, CVD Risk, and Other Chronic Diseases

During the 1960s and 1970s, there was controversy concerning the role of overweight in the development of CVD. It was commonly believed that obesity per se had little or nothing to do with the promotion of CVD. Framingham studies, however, confirmed that changes in relative weight were associated with CVD risk factors, including plasma lipids, blood pressure, and uric acids (19). It was estimated that a 10 percent reduction in relative weight was associated with a 20 percent reduction of CHD incidence in men. Continuing work in the 1980s established the independent effect of obesity on, the 26-year incidence of CVD and longevity in the Framingham cohort. These studies contributed to the end of the "obesity per se" hypothesis.

Consistent with the emerging epidemic of obesity nationally, overweight and obesity are prevalent conditions in the Framingham Study population. Ongoing investigations in the Offspring cohort are examining dietary influences on body weight (20, 21). Between the mid-1980s and early-1990s, both men and women tended to gain weight over time. Over seven years, men gained about 4 pounds on average and women gained 6 pounds, although weight change varied widely from a loss of 60 to a gain of nearly 100 pounds. The participant characteristic most closely related to weight gain in both genders was a chronic pattern of weight instability. Individuals who reportedly experienced frequent fluctuations in their weight actually tended to gain more weight in the long run. Individual macronutrients were found to be weakly related to weight change, and saturated fat appeared to have an effect on weight gain that was relatively larger than the effect observed for total fat.

These observations prompted investigators to look beyond the influence of individual nutrients to further consider the impact of overall dietary patterns on weight gain. Among women who were lean at baseline, those who consumed a dietary pattern that was rich in fats and sweets with lower than recommended daily servings of fruits, vegetables, whole grains, and low-fat dairy foods were at increased risk for becoming overweight over 12 years of follow-up compared to women who ate a more varied, lower-fat, nutrient dense "heart healthy" diet [multivariate adjusted RR 1.4, 95% CI (0.9, 2.2)]. Together, these findings support the independent role of dietary behavior in the development of obesity.

In the 1990s, Framingham investigators began exploring the role of other nutritional status indicators, notably B vitamin status and plasma homocysteine levels, in cardiovascular disease (22, 23). Mild to moderate homocysteinemia is an independent risk factor for vascular disease (24). Both dietary intake levels and plasma concentrations of nutritional cofactors for homocysteine metabolism appear to be related to elevated plasma levels of homocysteine (25). Among elderly members of the Framingham Offspring cohort, plasma homocysteine

levels were inversely related to dietary intake levels of folacin and vitamin B6 and to plasma concentrations of folate. Some 29% of the study sample had hyperhomocysteinemia and 67% of those cases were attributed to inadequate plasma concentrations of one or more B-vitamins. Subsequently, Framingham researchers demonstrated that inadequate folic acid intake was the main determinant of the homocysteine-related increase in risk of extracranial carotid artery atherosclerosis (23). Other researchers at Framingham are currently examining the role of diet in the etiology of other health-related outcomes, including arthritis, bone health, and their related comorbidities (26-29).

Implications for Nutrition and CVD Prevention

Nutrition investigations in the Framingham populations provide several levels of information that are key to the development of national population-based nutrition policy and guidelines for chronic disease prevention and health promotion. The continued deviation of the population from NCEP and other expert recommendations for chronic disease risk reduction and health promotion underscores the importance of continued public education and research to support the innovative creation of successful intervention programs. The identification of dietary nutrients that remain particularly problematic overall and notably among certain subgroups, including saturated fat, sodium, alcohol, calcium, and fiber, suggest targets for educational campaigns. In addition, the identification of unique eating patterns, dietary behaviors, and lifestyle characteristics of men and women, and their associations with CVD risk factor profiles, point to the importance of targeted nutrition messages and preventive nutrition interventions which consider the distinct food preferences and combined lifestyle behavioral profile (smoking habits, exercise, and alcohol consumption) that may influence long-term dietary behavior change and compliance. Furthermore, the emerging understanding of the influence of the complexity of dietary behavior on food consumption patterns, nutrient intake, and long-term disease risk, including early markers of disease, point to exciting opportunities for primary prevention of cardiovascular disease.

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