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Diet and Plasma Lipids in Women. I. Macronutrients and Plasma Total and Low-Density Lipoprotein Cholesterol in Women: The Framingham Nutrition Studies

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ABSTRACT. This study examined relationships between diet and plasma total and LDL cholesterol levels in a population-based sample of 695 premenopausal and 727 postmenopausal women participating in the Framingham Offspring/Spouse Study. Regression analyses controlled for age, caloric intake, apolipoprotein E isoform type, estrogen use, and important CVD risk factors indicated that plasma total and LDL-cholesterol levels were directly associated with consumption of saturated fat and inversely associated with total calorie intake. In contrast, dietary cholesterol was not a predictor of plasma total or LDL cholesterol levels. Total cholesterol levels were also directly associated with total fat, oleic acid, and animal fat, and inversely associated with carbohydrate intake.

Stepwise regressions with key nutrients indicated that saturated fat was consistently associated with total and LDL cholesterol levels in Framingham women. These analyses suggest that diet explains 2% of the variability in these lipid levels in a cross-sectional sample of women; the full model explains 22–27%. J CLIN EPIDEMIOL 49;6:657–663, 1996.

KEY WORDS. Diet, plasma lipids, lipoproteins, apo E phenotype, estrogen, menopausal status

INTRODUCTION

Cardiovascular disease is the leading cause of death among women, accounting for half of the deaths in any medical practice and exceeding mortality from all forms of cancer combined [1,2]. Premenopausal women experience lower rates of heart disease than comparably aged men and develop the disease about 6–10 years later [1]. Postmenopausally, heart disease rates in women become similar to those observed in men [1].

The delayed onset of cardiovascular disease in women is not fully understood but appears to stem in part from the favorable effect of circulating endogenous estrogen on one or more risk factors, in particular serum lipids. Lower levels of serum total and low-density lipoprotein (LDL) cholesterol are seen in premenopausal women [3], in comparison with postmenopausal women and comparably aged men. Estrogen replacement therapy (ERT) has been demonstrated to increase high-density lipoprotein (HDL) cholesterol levels and lower LDL levels in postmenopausal women [4,5].

While younger women appear to be protected from heart disease, the major risk factors for cardiovascular disease appear to be similar in men and women, including dyslipidemia, smoking, obesity, diabetes mellitus, and hypertension [6,7]. An elevated serum total cholesterol level has been identified as one of the most powerful predictors of cardiovascular disease in both males and females [6]. In addition, high levels of LDL cholesterol and low levels of HDL cholesterol have been identified as independent risk factors [6,8]. In women, low concentrations of HDL cholesterol and elevations in serum triglycerides are particularly associated with increased cardiovascular disease risk [1]. These factors take on increasing importance in light of recent trends that suggest that prevalence rates of smoking and obesity are increasing in certain segments of the population, particularly in young and minority women [9–11].

Clinical trials have demonstrated a favorable influence of dietary fat modification and weight reduction on serum lipids in men. Although evidence is emerging [12], considerably less is known about the relationships between dietary components and serum lipid levels in pre- and postmenopausal women [13]. This article examines associations between macronutrients, dietary cholesterol and fiber, and plasma total and LDL cholesterol levels in pre- and postmenopausal women in the Framingham Study. Relationships between diet and HDL cholesterol, the total-to-HDL cholesterol ratio, and triglyceride levels were investigated but will be published separately because

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of key differences observed within subgroups of women grouped by apolipoprotein E (apo E) phenotype.

SUBJECTS AND METHODS

The Framingham Study was initiated in 1948 with the examination of 5209 persons (2873 females and 2336 males) aged 28–62 years, including 1644 married couples (spouse-pairs). The survivors of this cohort have been examined biennially over 40 years of follow-up. In 1971, an offspring population of 5124 members was recruited into the Framingham Offspring/Spouse Study. This second cohort consisted of 2650 offspring of the original spouse pairs, 898 offspring of those original cohort members who had exibited cardiovascular disease or abnormal lipid profiles, and an additional 1576 spouses of these offspring [14].

In 1984–1988, the third examination (Exam III) of the offspring cohort was carried out among 3873 individuals, including 1953 women. This article examines dietary and risk factor data collected from 695 premenopausal and 727 postmenopausal women who had information on age, total kilocalories consumed, plasma cholesterol, body mass index, cigarette consumption, hormone usage, glucose intolerance, and physical activity at that time.

Lipopotein and Cardiovascular Risk Assessment Analyses

Venous plasma was drawn from all subjects after a 12- to 24-hr fast, and was mixed with EDTA to give a final concentration of 0.1%. Aliquots were obtained by centrifugation at 2500 rpm for 20 min at 4°C. Total cholesterol and HDL cholesterol were measured by automated enzymatic methods [15,16]. The cholesterol content of VLDL and LDL were estimated by the method of Freidewald *et al.* [17]. All lipid analyses were performed at the Framingham Heart Study laboratory (Framingham, MA), which participates in the Standardization Program of the Centers for Disease Control (CDC, Atlanta, GA) and the National Heart, Lung, and Blood Institute (Bethesda, MD) Lipid Research Clinics. The method of Ordovas *et al.* [18] was used for apolipoprotein E (apo E) isoform phenotyping.

Several additional CVD risk factors were assessed according to previously published Framingham methods [19]. Body weight was evaluated using a calibrated spring balance scale; subjects wore only lightweight hospital gowns. Height was measured using a stationary anthropometer; subjects stood erect with heads in the Frankfurt plane. Single measurements of height and weight were taken. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Physical activity was self-reported and total kilocalories expended in leisure time activities in the past year were calculated according to the method of Dannenberg *et al.* [20]. Glucose intolerance was defined as a fasting blood sugar >110 mg/dl, the presence of glycosuria, or a diagnosis of diabetes. Cigarette smoking was self-reported as the average number of cigarettes smoked per day in the past year. Women were classified as estrogen users if they used oral contraceptives or received estrogen replacement therapy.

Framingham Offspring/Spouse Nutrition Studies

Exam III dietary assessment protocols were designed to explore associations between eating behaviors and cardiovascular disease risk. The estimates of nutrient intake reported here were derived from a single 24-hr dietary recall; the response rate for this protocol was 99%. A comparison of Framingham dietary assessment methods among a subsample of the offspring-spouses [21] revealed that the 24-hr recalls provided highly comparable estimates of population mean nutrient intakes when compared with 3-day food records. This was true even for nutrients with reportedly high day-to-day variability, such as cholesterol and fiber.

The 24-hr recalls were administered by a trained nutritionist who elicited subject intake on the prior day, from midnight to midnight. The days of the week that were surveyed included Sundays through Fridays. Food portion sizes were quantified using a two-dimensional (2D) food portion visual, previously validated by Millen Posner *et al.* [22], to aid respondents in accurately describing portions of foods consumed.

The recalls were reviewed and coded by trained personnel using an interactive, computerized Nutrition Data Management System (copyright Boston University, 1984). Formal coding protocols were followed. When subjects were unable to describe food items completely, coders referred to predetermined standards; when portion sizes were unknown, U.S. Department of Agriculture (USDA) protocols were used to default to commonly consumed portion sizes [23]. The nutrient composition of foods was calculated using the computerized Michigan State nutrient database (copyright, 1984) [24].

Statistical Analyses

Women included in the analyses were those on whom complete data were available for age, plasma total cholesterol, caloric intake, BMI, cigarette consumption, estrogen use, physical activity, and glucose intolerance. The primary reason for exclusion of women was lack of data on physical activity. Women who were excluded from the analyses owing to missing/incomplete data were significantly younger (by 1.2 years on average), had higher BMIs (by 1.1 kg/m^2 on average), and lower levels of HDL cholesterol (by 3.2 mg/dl on average) than women who were included. There were also differences in apo E phenotype among those who were included versus those who were excluded. We found no differences in dietary intake between those who were included or excluded. As well, we carried out analyses for the complete cohort of women, dropping the physical activity variable. The results were completely consistent with those we report here.

Means and standard deviations for continuous measures and percentages for categorical measures were computed for both pre- and postmenopausal women. Comparison of the two groups of women on these measures was performed by applying Student's t test for continuous measures and the chi-square test for categorical measures. In addition, correlation coefficients were computed for the macronutrient dietary measures.

To examine the association between the dietary measures and plasma total or LDL cholesterol, multiple linear regression techniques were used [25] for each dietary measure within each group of women (pre- and postmenopausal). We examined three types of models for each dietary variable: (1) those that included age and the dietary measure, (2) those that included age, total kilocalorie consumption, and the dietary measure, and (3) those that included age, total kilocalorie consumption, BMI, number of cigarettes per day, estrogen use, physical activity (total kilocalories expended per year), glucose intolerance, apolipoprotein E phenotype, and the dietary measure. In addition, we applied these same models for the combined sample of all women. Effect modification of the relationship between the dietary measure and the plasma lipid level by menopausal status was checked by adding interaction terms to the combined sample models. Finally, the independent effects of macro-

nutrients were examined by the stepwise addition of saturated fat (percent of kilocalories), oleic acid (percent), linoleic acid (percent), carbohydrate (percent), and dietary cholesterol (mg/1000 kcal) to model 3 listed above.

RESULTS

Mean nutrient intake and risk factor levels for Framingham women appear in Tables 1 and 2, respectively. Intakes of total and saturated fat appear to be high in comparison with population-based recommendations [26] among both pre- and postmenopausal women, while mean dietary cholesterol intakes did not exceed published standards. Premenopausal women consumed significantly more calories, animal fat, fatty acids, and alcohol than did their postmenopausal counterparts, who consumed significantly more carbohydrate. The higher consumption of calories in premenopausal women explains most of these differences. Absolute levels and the proportions of calories consumed as total and saturated fat were also significantly higher among premenopausal women. However, postmenopausal women had less favorable blood lipid levels, higher rates of glucose intolerance, higher body mass indices, and were less physically active than premenopausal women, probably reflecting their older ages. More postmenopausal women were taking estrogens. No differences were observed between pre- and postmenopausal women in terms of cigarette consumption or apo E phenotype.

A summary of the associations between dietary consumption and plasma total and LDL cholesterol levels are presented for pre- and postmenopausal women in Tables 3 and 4. Data for macronutrients are expressed as a percentage of total calorie intake to adjust for variability in energy intake. We examined the issue of effect modification by menopausal status and found similar effects in pre- and postmenopausal women on all associations except that of alcohol, which was directly related to total cholesterol in postmenopausal women and unrelated to lipid levels in premenopausal women ($p < 0.034$).

The multivariate regression models indicate a direct association between saturated fat intake and plasma total cholesterol levels in both groups of Framingham women (Table 3). These results indicate that premenopausal women who consume 5% more saturated fat (i.e., 15% of calories versus 10% of calories) have a plasma total cholesterol that is about 2.7 mg/dl higher, while postmenopausal women have levels that are 3.6 mg/dl higher. A direct association with animal fat was observed for premenopausal women, although of borderline significance ($p = 0.08$). Also in premenopausal women, plasma total cholesterol levels were directly related to total fat consumption and inversely associated with total calories and dietary fiber. These data indicate that premenopausal women who consume 10% more total fat (i.e., 40% of calories versus 30% of calories) have a plasma total cholesterol that is approximately 2.8 mg/dl higher. In postmenopausal women, there was a direct association between plasma total cholesterol and alcohol consumption and an inverse association with carbohydrate and linoleic acid.

LDL cholesterol levels were inversely associated with total calorie intake in both pre- and postmenopausal Framingham women (Table 4). Saturated fat intake was directly associated with LDL levels in

TABLE 1. Mean nutrient intake levels, Framingham women ages 22–79 years in 1984–1988, by menopausal status

Nutrient	Premenopausal (n = 695) (mean ± SD)	Postmenopausal (n = 727) (mean ± SD)
Calories (kcal)	1621 ± 672	1505 ± 673***
Carbohydrate		
Grams	167.0 ± 77.0	161.0 ± 79.3
Percent	42.0 ± 12.0	43.6 ± 11.7***
Protein		
Grams	67.1 ± 31.5	64.2 ± 33.2*
Percent	17.2 ± 6.6	17.6 ± 6.1
Total fat		
Grams	72.7 ± 41.5	65.1 ± 39.9****
Percent	39.1 ± 11.0	37.6 ± 10.2***
Saturated fat		
Grams	25.1 ± 16.7	22.3 ± 16.2***
Percent	13.4 ± 5.6	12.8 ± 5.2**
Oleic acid		
Grams	21.6 ± 14.7	19.7 ± 14.6**
Percent	11.4 ± 4.7	11.3 ± 4.7
Linoleic acid		
Grams	10.0 ± 8.9	9.1 ± 7.9**
Percent	5.5 ± 3.7	5.3 ± 3.6
Animal fat (g)	41.1 ± 32.0	36.7 ± 30.3***
Plant fat (g)	24.1 ± 22.2	22.0 ± 19.5*
Cholesterol (mg)	263.3 ± 208.6	252.0 ± 204.6
Alcohol		
Grams	6.6 ± 13.9	5.2 ± 11.9**
Percent	2.7 ± 5.5	2.5 ± 5.8
Dietary fiber (g)	9.5 ± 6.8	10.0 ± 7.2

*$0.05 \le p \le 0.10$.
**$p < 0.05$.
***$p < 0.01$.
****$p < 0.001$.

TABLE 2. Mean risk factor levels, Framingham women ages 22–79 years in 1984–1988, by menopausal status

Risk factor	Premenopausal (n = 695) (mean ± SD)	Postmenopausal (n = 727) (mean ± SD)
Age (years)	40.9 ± 6.1	55.8 ± 6.9**
Body mass index (weight [kg]/height [m^2])	24.4 ± 4.7	25.8 ± 5.0**
Cigarette smoking (number/day)	6.1 ± 11.7	5.6 ± 11.0
Glucose intolerance[a] (%)	1.9%	9.3%**
Physical activity[b]	48.2 ± 56.5	39.1 ± 51.9*
Estrogen use[c] (%)	6.3%	10.4%*
apo E phenotype		
2/4	0.7%	0.5%
Unknown or rare	36.7%	32.6%
3/2 or 2/2	8.5%	10.0%
3/3	38.3%	43.0%
3/4 or 4/4	15.8%	13.9%
Plasma total cholesterol (mg/dl)	194.5 ± 36.1	229.2 ± 40.2**
LDL cholesterol (mg/dl)	118.6 ± 31.8	144.7 ± 36.7**

[a]Glucose intolerance defined as fasting blood sugar > 110 mg/dl, presence of glycosuria, or diagnosis of diabetes.
[b]Physical activity reported as total kilocalories expended per year (× 1000).
[c]Estrogen use defined as use of oral contraceptives or estrogen replacement therapy.
*$p < 0.01$.
**$p < 0.001$.

TABLE 3. Dietary determinants of plasma total cholesterol in Framingham women, ages 22–79 years in 1984–1988, by menopausal status

	β Coefficient					
	Premenopausal (n = 695)			Postmenopausal (n = 727)		
Nutrient	Age adjusted	Age and calorie adjusted	Multivariate[a]	Age adjusted	Age and calorie adjusted	Multivariate[a]
Calories	−0.005***	—	−0.004**	−0.004*	—	−0.003
Carbohydrate (%)	−0.167	−0.212*	−0.123	−0.312**	−0.362***	−0.315**
Protein (%)	−0.072	−0.211	−0.348	0.320	0.246	0.126
Total fat (%)	0.220*	0.325***	0.275**	0.048	0.137	0.130
Saturated fat (%)	0.351	0.536**	0.549**	0.575**	0.748***	0.722**
Oleic acid (%)	0.353	0.617**	0.465	0.450	0.623*	0.564*
Linoleic acid (%)	−0.159	−0.108	−0.159	−0.874**	−0.825**	−0.781**
Alcohol (%)	−0.090	−0.051	−0.090	0.631**	0.615**	0.589**
Cholesterol (mg)	−0.004	0.006	0.005	−0.006	−0.000	−0.004
Animal fat (g)	−0.007	0.125**	0.098*	0.007	0.099	0.088
Fiber (g)	−0.580***	−0.470**	−0.420**	−0.140	−0.030	−0.050

[a]Multivariate model includes age, calories, body mass index, number of cigarettes smoked per day, estrogen use, physical activity, glucose intolerance, and apolipoprotein E phenotype.
*$0.05 \leq p \leq 0.10$.
**$p < 0.05$.
***$p < 0.01$.

both groups of women, although the relationship in premenopausal women was of marginal significance ($p = 0.07$). Premenopausal women who consume 5% more saturated fat (i.e., 15% of calories versus 10% of calories) have a plasma LDL level that is approximately 2.0 mg/dl higher, while postmenopausal women have LDL levels that are about 3.6 mg/dl higher. Dietary cholesterol was not related to plasma total or LDL cholesterol levels in either pre- or postmenopausal women.

Similar relationships between macronutrient consumption and plasma lipid levels were observed for all Framingham women combined (Table 5). Plasma total cholesterol levels were directly related to consumption of total fat, saturated fat, oleic acid, and animal fat; and inversly related to total calories and carbohydrate. LDL cholesterol levels were directly related to saturated fat and inversely related to total calories. The relationship between animal fat and LDL cholesterol was of marginal significance in the combined sample of Framingham women ($p = 0.06$).

The results of these analyses suggest that differences in dietary intake, particularly saturated fat intake, exert a modest but significant effect on plasma lipid levels in pre- and postmenopausal

TABLE 4. Dietary determinants of LDL cholesterol in Framingham women, ages 22–79 years in 1984–1988, by menopausal status

	β Coefficient					
	Premenopausal (n = 616)			Postmenopausal (n = 655)		
Nutrient	Age adjusted	Age and calorie adjusted	Multivariate[a]	Age adjusted	Age and calorie adjusted	Multivariate[a]
Calories	−0.004**	—	−0.004**	−0.006***	—	−0.005**
Carbohydrate (%)	0.007	−0.026	0.024	−0.189	−0.258**	−0.206*
Protein (%)	0.009	−0.100	−0.234	0.377	0.266	0.177
Total fat (%)	0.025	0.101	0.093	0.088	0.223	0.186
Saturated fat (%)	0.175	0.324	0.414*	0.564**	0.800***	0.727***
Oleic acid (%)	−0.073	0.121	0.081	0.374	0.605	0.501
Linoleic acid (%)	−0.291	−0.249	−0.292	−0.559	−0.474	−0.398
Alcohol (%)	−0.247	−0.213	−0.237	0.018	−0.005	0.009
Cholesterol (mg)	−0.005	0.003	0.002	−0.005	0.005	0.000
Animal fat (g)	−0.015	0.080	0.072	−0.028	0.109*	0.079
Fiber (g)	−0.260	−0.150	−0.140	−0.280	−0.130	−0.130

[a]Multivariate model includes age, calories, body mass index, number of cigarettes smoked per day, estrogen use, physical activity, glucose intolerance, and apolipoprotein E phenotype.
*$0.05 \leq p \leq 0.10$.
**$p < 0.05$.
***$p < 0.01$.

TABLE 5. Dietary determinants of plasma lipids in Framingham women, ages 22–79 years in 1984–1988: All women combined

	β Coefficient[a]	
Nutrient	Total cholesterol ($n = 1422$)	LDL cholesterol ($n = 1271$)
Calories	−0.004**	−0.004***
Carbohydrates (%)	−0.235***	−0.101
Protein (%)	−0.069	−0.003
Total fat (%)	0.218**	0.140
Saturated fat (%)	0.625****	0.545***
Oleic acid (%)	0.538**	0.287
Linoleic acid (%)	−0.424	−0.316
Alcohol (%)	0.244	−0.108
Cholesterol (mg)	0.001	0.002
Animal fat (g)	0.100**	0.077*
Dietary fiber (g)	−0.220	−0.130

[a]Age, calorie, and risk factor-adjusted model.
*$0.05 \leq p \leq 0.010$.
**$p < 0.05$.
***$p < 0.01$.
****$p < 0.001$.

women. A difference in saturated fat intake of the magnitude of 5% of total caloric intake (i.e., 15% of calories versus 10% of calories) would be associated with a difference in plasma total cholesterol concentrations of approximately 3.1 mg/dl among Framingham women. Similarly, differences in carbohydrate, fiber, and linoleic acid intakes were associated with slight differences in plasma total cholesterol levels within groups of women.

Stepwise addition of calorie-adjusted macronutrients to the multivariate regression models indicated that saturated fat, carbohydrate, and linoleic acid were significantly associated with plasma total cholesterol levels in the combined sample of Framingham women. In premenopausal women, saturated fat was the only nutrient that was significantly associated with total cholesterol levels, whereas carbohydrate and linoleic acid were the significant nutrients in postmenopausal women. Since saturated fat and carbohydrate are highly correlated ($r = -0.53$), collinearity may partially explain the observed difference in nutrients associated with total cholesterol in pre- versus postmenopausal women. In contrast to the findings for total cholesterol, only saturated fat was associated with LDL cholesterol levels in pre- and postmenopausal women and in the combined sample.

The final regression models including age, total calories, important cardiovascular disease (CVD) risk factors, estrogen use, apo E phenotype, and key nutrients (percent carbohydrate, percent protein, percent saturated fat, percent oleic acid, percent linoleic acid, percent cholesterol, and dietary fiber) explained 27% of the variability in total cholesterol levels and 22% of the variability in LDL cholesterol levels in Framingham women. The addition of the macronutrients explained 2% of the variability in total cholesterol and LDL cholesterol levels. Similarly, apo E phenotype explained 3% of the variability in these lipid levels.

DISCUSSION

There is considerable clinical evidence, particularly in men, that serum total and LDL cholesterol levels are influenced by changes in dietary saturated fat and to a lesser extent cholesterol. Few population-based studies, however, have assessed the relationship between dietary macronutrient intake and plasma lipoprotein levels in women or determined whether diet explains a similar proportion of the population variability in plasma lipid levels as compared with certain genetic factors. The Framingham data reported here may, therefore, be among the first evaluations of diet, apo E phenotype, and lipoprotein levels in a large population-based sample of pre- and postmenopausal women.

The results reveal that plasma total cholesterol levels were consistently related to saturated fat intake in pre- and postmenopausal Framingham women. The direct association between saturated fat intake and hypercholesterolemia in women has been established [8] in a limited number of cross-sectional [27] and intervention studies [28].

To a lesser degree, plasma total cholesterol levels were directly related to total fat intake in premenopausal women and in the combined sample of all Framingham women. Several clinical trials have supported this relationship. Consistent reductions in serum total cholesterol levels have been achieved in both pre- and postmenopausal women consuming fat-modified diets [29–31].

In this article, plasma total cholesterol levels were directly related to oleic acid intake in the combined sample of women. Our results appear to be inconsistent with the few intervention studies that have appeared to date examining this relationship [32,33]. It should be noted, however, that within the Framingham population, dietary oleic acid was derived predominantly from animal sources. This may explain the apparent discrepancy between our findings and those previously published using vegetable oil sources of oleic acid. In our study, consumption of animal fat was also shown to be directly associated with total cholesterol levels in the combined sample of Framingham women. Further investigation is needed to determine the role that monounsaturated fat, derived from various food sources, may play in lipid metabolism in women.

Inverse associations were observed between plasma total cholesterol levels and total calories, linoleic acid, fiber, and carbohydrate intake in either pre- or postmenopausal Framingham women. A number of researchers have documented an inverse association between caloric intake and CHD incidence [34–37], which has been attributed to differences in physical activity. Physical activity may be the intervening variable accounting for the inverse association between total calories and plasma cholesterol observed here. The confirmed hypocholesterolemic effect of linoleic acid demonstrated in clinical trials [38] is consistent with our cross-sectional finding of an inverse relationship with plasma total cholesterol levels. Reductions in total cholesterol levels have been demonstrated in women eating diets that are lower in total fat, have favorable polyunsaturated to saturated fatty acid (P:S) ratios, and are higher in complex carbohydrate and fiber [12,28,39]. Other studies [40–42], including a meta-analysis of clinical trials [43], have demonstrated reductions in both total and LDL cholesterol levels associated with increased intakes of soluble fiber.

While there was no relationship between alcohol consumption and plasma total cholesterol levels in premenopausal women, a direct association was observed among postmenopausal women. A biological mechanism that would explain the observed effect modification by menopausal status is unclear and requires further investigation.

Levels of LDL cholesterol were directly associated with saturated fat intake in pre- and postmenopausal Framingham women, and with animal fat in the combined sample. Total calories were in-

versely related to LDL cholesterol levels in both groups of Framingham women. While the saturated fat relationship is quite consistent with other observations [27–30], the inverse relationship with total calories needs to be confirmed.

Dietary cholesterol was not found to be associated with plasma total or LDL cholesterol levels in Framingham women. In intervention studies, dietary cholesterol has been shown to raise plasma cholesterol levels in a predictable manner, but to a much lesser degree than saturated fat [8].

In an earlier study using the Burke diet history methodology to assess nutrient intake, we were not able to demonstrate associations between dietary fats and total cholesterol in Framingham women surveyed between 1957 and 1960 [44]. The reasons for these observed differences are unclear, but may be due to differences in dietary methodologies. The database used to code data from the diet history was extremely limited in scope. This may have narrowed the range of variability in nutrient estimates, as would be suggested by the standard deviations, which are one-half the size of those seen in this article, thereby limiting our ability to detect associations between nutrients and blood lipids. Nonetheless, the dietary recall method used in the present analysis does not account for day-to-day variability in subject nutrient intake. The resulting error in dietary measurement tends to attenuate diet and risk factor relationships. Therefore, the results reported here probably underestimate the true associations between macronutrients and plasma total and LDL levels in women.

The order of magnitude of differences in plasma total cholesterol levels associated with specific differences in nutrient intake in Framingham women is smaller than findings from clinical trials indicate. It is important to note that our results are derived from a cross-sectional investigation of diet and plasma lipid levels in the Framingham female population. Therefore, direct comparisons of these results with metabolic or intervention studies, particularly those carried out in dyslipidemic individuals, is not possible. A review that summarized the findings of numerous controlled clinical trials suggested that a 1% change in saturated fat intake was associated with a 2.10-mg/dl change in serum total cholesterol level; a 1% change in polyunsaturated fat intake was associated with a 1.16-mg/dl change in serum cholesterol [38]. While the majority of these trials were conducted in men, it is important to note that there is controversy about gender differences in lipid response to dietary intervention [12,13,45–47].

This research did not examine possible relationships between serum lipids and other dietary factors, such as trans fatty acids, B vitamins, or antioxidants. These dietary components are of considerable interest because of the emerging evidence that they are related to heart disease risk. However, data on their consumption were not available at the time we conducted this research.

Our finding that diet explained 2% of the variability in total and LDL cholesterol levels in women is important when considered in light of the fact that apo E phenotype accounted for 3% of the variability in these lipid levels. Consistent with our observation, Schaefer *et al.* [48] reported that the apo E locus explained 2.1% of the variance in LDL cholesterol levels in Framingham women and 1.0% in Framingham men. Thus, in our study, dietary variables explained a proportion of the variance in plasma lipid levels that was similar to a genetic factor.

CONCLUSIONS

This cross-sectional, population-based study indicates that saturated fat is most consistently associated with both plasma total and LDL cholesterol levels in Framingham pre- and postmenopausal women. Dietary cholesterol was not found to be associated with either blood lipid. This observation supports the need for modifications in public policies and food industry marketing strategies that have focused health messages and nutrient claims predominantly on dietary cholesterol. A shift toward improving public awareness of the total and saturated fat content of foods is clearly indicated by these data. A favorable lipid profile appears to be associated with a diet that is lower in total fat, saturated fat, and oleic acid from animal sources, proportionately higher in linoleic acid and carbohydrates, and higher in fiber. Furthermore, in postmenopausal women, an unfavorable direct association between alcohol and plasma total cholesterol levels warrants caution in alcohol-related population recommendations.

Well-designed clinical trials are needed to assess further the effects of changes in macro- and micronutrient intake on blood lipids in women, and to explore differences in serum lipid levels between men and women, and between pre- and postmenopausal women. Future investigations should attempt to identify dietary interventions that most effectively lower serum total and LDL cholesterol levels without detriment to HDL levels.

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