J Clin Epidemiol Vol. 49, No. 6, pp. 665–672, 1996

0895-4356/96/$15.00
PII S0895-4356(96)00031-5

Diet and Plasma Lipids in Women. II. Macronutrients and Plasma Triglycerides, High-Density Lipoprotein, and the Ratio of Total to High-Density Lipoprotein Cholesterol in Women: The Framingham Nutrition Studies

Lillian M. Sonnenberg,[1] *Paula A. Quatromoni,*[2] *David R. Gagnon,*[3] *L. Adrienne Cupples,*[3] *Mary M. Franz,*[2] *Jose M. Ordovas,*[4] *Peter W. F. Wilson,*[5] *Ernst J. Schaefer,*[4] *and Barbara E. Millen*[2,6,*]

[1]AMBULATORY NUTRITION SERVICE, DEPARTMENT OF DIETETICS, MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASSACHUSETTS 02114, [2]DEPARTMENT OF SOCIAL AND BEHAVIORAL SCIENCES, BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH, BOSTON, MASSACHUSETTS 02118, [3]DEPARTMENT OF EPIDEMIOLOGY AND BIOSTATISTICS, BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH, BOSTON, MASSACHUSETTS 02118, [4]LIPID METABOLISM LABORATORY, USDA HUMAN NUTRITION RESEARCH CENTER ON AGING, TUFTS UNIVERSITY SCHOOL OF MEDICINE, BOSTON, MASSACHUSETTS 02111, [5]FRAMINGHAM STUDY, FRAMINGHAM, MASSACHUSETTS 01701, AND [6]OFFICE OF THE DIRECTOR, BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH, BOSTON, MASSACHUSETTS 02118

ABSTRACT. This study examined relationships between macronutrients and plasma triglycerides, HDL, and the total-to-HDL cholesterol ratio (T/H ratio) in a population-based sample of 695 premenopausal and 727 postmenopausal women participating in the Framingham Offspring/Spouse Study. Multivariate regression analyses revealed that plasma triglycerides were inversely related to protein, fiber, and polyunsaturated fat and directly related to saturated fat and oleic acid. Alcohol intake was directly related to HDL cholesterol and inversely related to the T/H ratio in all subgroups of women, except for postmenopausal women with the 3/2 or 2/2 apolipoprotein E phenotype. Similarly, a direct relationship between dietary fat and HDL cholesterol was limited to this single subgroup of postmenopausal women. Since dietary fat and alcohol do not appear to have consistent effects on plasma lipids in all groups of women, it is important to consider the genetic contribution to diet/lipid relationships in epidemiological studies and when evaluating lipid-lowering interventions. J CLIN EPIDEMIOL 49;6:665–672, 1996.

KEY WORDS. Diet, HDL, T/H ratio, triglycerides, apo E phenotype, menopausal status

INTRODUCTION

More attention is currently being focused on the role of plasma high-density lipoprotein (HDL) cholesterol, the total-to-HDL cholesterol ratio (T/H ratio), and plasma triglyceride levels as risk factors for coronary heart disease (CHD). A 10-mg/dl increase in HDL cholesterol has been associated with a 50% decrease in risk of CHD in both men and women [1]. The National Cholesterol Education Program Adult Treatment Panel II added the measurement of HDL cholesterol as part of the initial screening for hypercholesterolemia, recognizing that low HDL is an independent risk factor for CHD [2]. Studies have shown that the level of HDL cholesterol is a significant predictor of CHD in women and may have a greater predictive value than the level of total cholesterol or LDL cholesterol in determining CHD risk [3].

The T/H ratio has also been identified as an important predictor of CHD risk. Average risk of CHD is associated with a T/H ratio of 5, whereas an optimal ratio is thought to be about 3.5 [1].

*Address for correspondence: Barbara E. Millen, Boston University School of Public Health, 80 East Concord Street, Boston, Massachusetts 02118.
Accepted for publication on 16 August, 1995.

The association between plasma triglycerides and CHD is unclear at this time but appears to be stronger in women than in men. While other risk factors tend to be better predictors of CHD in men, studies have shown that plasma triglycerides are an independent risk factor for CHD in women [4].

Dietary therapy is recommended as the first level of intervention to modify blood lipid levels in persons with moderate to high CHD risk; it is also recommended as a means of primary prevention for the general population [2]. Nonetheless, controversy exists on the optimal levels of dietary constituents to reduce total and LDL cholesterol levels while maintaining favorable levels of HDL cholesterol.

This article examines the relationships between dietary macronutrients, cholesterol and fiber, and plasma triglycerides, HDL cholesterol, and the T/H ratio in a large, population-based sample of pre- and postmenopausal women who participate in the Framingham Offspring/Spouse Study.

SUBJECTS AND METHODS

The Framingham Study was initiated in 1948 with the examination of 5209 individuals (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 (FOS). This second cohort consisted of 2650 offspring of the original spouse-pairs, 898 offspring of those original cohort members who had exhibited cardiovascular disease or abnormal lipid profiles, and an additional 1576 spouses of these offspring [5].

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 provided complete information on age, total kilocalories consumed, plasma lipids, body mass index (BMI), cigarette consumption, estrogen usage (birth control pills or supplements), glucose intolerance, and physical activity.

Lipoprotein 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. Plasma triglycerides and HDL cholesterol were measured by automated enzymatic methods [6,7]. 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.* [8] was used for apolipoprotein E (apo E) isoform phenotyping.

Several additional CVD risk factors were assessed according to previously published Framingham methods [9]. Body weight was evaluated using a calibrated spring balance scale; subjects wore only lightweight hospital gowns. Height was measured using a sationary anthropometer; subjects stood erect with their head in the Frankfurt plane. Single measurements of height and weight were taken. BMI was calculated as weight in kilograms divided by height in meters squared. Physical activity was self-reported at Exam II (1980–1984) and total kilocalories expended in leisure time activities in the past year were calculated according to a previously published method [10]. Quantitative measurements of activity levels were derived from activity-specific intensity codes, based on the ratio of the metabolic rate during the activity divided by the basal metabolic rate [11]. Total kilocalories expended were computed by summing across all categories of leisure time activities. Data on physical activity were not available at Exam III. 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 FOS cohort [12] revealed that the 24-hr recalls provided highly comparable estimates of population mean nutrient intake 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 previous 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.* [13], to aid respondents in accurately describing portions of food 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 [14]. The nutrient composition of foods was calculated using the computerized Michigan State nutrient database (copyright, 1984) [15].

Statistical Analyses

Women included in the analyses were those on whom complete data were available for age, plasma lipids, 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 not included in the analyses due 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. 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.

To examine the association between the dietary measures and plasma triglycerides, HDL cholesterol, and T/H ratio, multiple linear regression techniques were used [16] for each dietary measure within each group of women (pre- and postmenopausal). We examined three models for each dietary variable: (1) those that included age and the dietary component, (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, and the dietary component. In addition, we applied these same models for the combined sample of all women. Effect modification of the relationship between the dietary variable and the plasma lipid level by apolipoprotein E isoform phenotype, and by menopausal status, was checked by adding interaction terms to the models. We report stratified results in which significant interactions occurred with the apo E phenotype. Only women with complete information on apo E isoform status were included in the analyses for effect modification. In general, the relationships between nutrients and blood lipids were the same for those women with and without available apo E data. Finally, the independent effects of macronutrients were examined by the stepwise addition of carbohydrate (percent of kilocalories), oleic acid (percent),

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 (%)	42.0 ± 12.0	43.6 ± 11.7**
Protein (%)	17.2 ± 6.6	17.6 ± 6.1
Total fat (%)	39.1 ± 11.0	37.6 ± 10.2**
Saturated fat (%)	13.4 ± 5.6	12.8 ± 5.2*
Oleic acid (%)	11.4 ± 4.7	11.3 ± 4.7
Linoleic acid (%)	5.5 ± 3.7	5.3 ± 3.6
Alcohol (%)	2.7 ± 5.5	2.5 ± 5.8
Cholesterol (mg)	263.3 ± 208.6	252.0 ± 204.6
Dietary fiber (g)	9.5 ± 6.8	10.0 ± 7.2

*$p < 0.05$.
**$p < 0.01$.

linoleic acid (percent), saturated fat (percent), protein (percent), and alcohol (percent) to model 3 listed above.

RESULTS

Mean nutrient intake and risk factor levels for Framingham women appear in Tables 1 and 2, respectively. Mean intakes of total fat (38–39% of calories) and saturated fat (13% of calories) appeared to be high, and intake of dietary fiber (10 g/day) was low in comparison with population-based recommendations [2] among both pre- and postmenopausal women. However, mean dietary cholesterol intakes (252–263 mg/day) did not exceed published standards. Premenopausal women consumed significantly more calories, total fat, and saturated fat than did their postmenopausal counterparts, who consumed significantly more carbohydrate. Framingham women consumed low levels of alcohol. On average, both groups of women were consuming the equivalent of less than one-half of an alcoholic drink per day.

Postmenopausal women had a significantly higher mean T/H ratio, plasma triglyceride level, rate of glucose intolerance, and BMI 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, the distribution of apo E phenotype, or HDL cholesterol level.

A summary of the associations between nutrient consumption and plasma triglycerides, HDL cholesterol, and the T/H ratio is presented for pre- and postmenopausal women and for all women combined in Tables 3–5. 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 in a multivariate model and found similar effects in pre- and postmenopausal women on all associations except the following three: fiber was directly related to HDL cholesterol in postmenopausal women and unrelated to HDL cholesterol levels in premenopausal women; protein intake was indirectly associated with the T/H ratio in premenopausal women but was unrelated to the ratio in postmenopausal women; total fat intake was marginally directly related to plasma triglycerides in premenopausal women ($p = 0.086$) and unrelated to triglyceride levels in postmenopausal women. We also examined whether the relationships between plasma lipids and nutrients were modified by apo E phenotype in all groups of women. Effect modification by apo E phenotype was found only in postmenopausal women for the relationships between a few select nutrients and plasma HDL cholesterol and the T/H ratio. These results are presented in Tables 6 and 7.

The relationships between macronutrients and plasma triglyceride (Table 3) did not appear to differ by menopausal or apo E status in Framingham women, except for total fat as noted above. Dietary protein, fiber, and polyunsaturated fat (linoleic acid) appeared to have an inverse association with plasma triglyceride levels, whereas

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%
HDL cholesterol (mg/dl)	57.3 ± 13.9	57.9 ± 15.4
T/H ratio[d]	3.6 ± 1.3	4.2 ± 1.4**
Plasma triglycerides (mg/dl)	85.6 ± 152.3	120.4 ± 87.4**

[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.
[d]Ratio of total to HDL cholesterol.
*$p < 0.01$.
**$p < 0.001$.

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

	β Coefficient					
	Premenopausal (n = 695)		Postmenopausal (n = 727)		All women (n = 1422)	
Nutrient	Age and calorie adjusted	Multivariate[a] model	Age and calorie adjusted	Multivariate[a] model	Age and calorie adjusted	Multivariate[a] model
Calories (100 kcal)	−0.171[b]	0.267	−0.013[b]	0.021	−0.108[b]	0.235
Carbohydrate (%)	−0.612	−0.068	0.026	0.270	−0.290	0.000
Protein (%)	−0.650	−1.968**	−0.038	−0.576	−0.363	−1.053**
Total fat (%)[c]	1.166**	0.882*	−0.041	−0.151	0.584*	0.475
Saturated fat (%)	1.471	1.328	1.126*	1.028*	1.289**	1.243**
Oleic acid (%)	3.342**	2.226*	1.258	0.816	2.305***	1.827**
Linoleic acid (%)	−0.548	−0.934	−2.561***	−2.691***	−1.582*	−1.681*
Alcohol (%)	−0.843	−0.409	−0.343	−0.282	−0.565	−0.464
Cholesterol (100 mg)	0.473	−1.377	0.296	−1.277	0.363	−1.071
Fiber (g)	−1.430	−1.200	−0.710	−0.620	−1.040**	−0.940**

[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.
[b]Age-adjusted β coefficient for total calories.
[c]Significant interaction by menopausal status exists in the relationship between total fat and plasma triglycerides. See results that are stratified by menopausal status.
*$0.05 \leq p \leq 0.10$.
**$p < 0.05$.
***$p < 0.01$.

saturated fat and oleic acid had a direct association with plasma triglyceride. Women who consumed 5% more polyunsaturated fat (10 versus 5% of calories) and 5 g more fiber daily (15 versus 10 g) had a plasma triglyceride level that was 8.4 and 4.7 mg/dl lower than in other women, respectively. In contrast, women who consumed 5% more saturated fat (15 versus 10% of calories) had a plasma triglyceride level that was 6.2 mg/dl higher.

The associations between macronutrients and plasma HDL cholesterol and the T/H ratio were similar between pre- and postmenopausal women (or among subgroups of postmenopausal women based on apo E phenotype), with a few exceptions. Carbohydrates were inversely associated with HDL (Table 4) and directly associated with the T/H ratio (Table 5) in both pre- and postmenopausal women.

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

	β Coefficient					
	Premenopausal (n = 691)		Postmenopausal (n = 726)		All women (n = 1417)	
Nutrient	Age and calorie adjusted	Multivariate[a] model	Age and calorie adjusted	Multivariate[a] model	Age and calorie adjusted	Multivariate[a] model
Calories (100 kcal)	0.052[b]	0.027	0.154*[,b]	0.095	0.102*[,b]	0.058
Carbohydrate (%)	−0.169****	−0.203****	−0.087*	−0.138***	−0.129****	−0.168****
Protein (%)	0.052	0.195**	−0.047	0.031	0.006	0.106*
Total fat (%)[c]	0.099*	0.087*	−0.060	−0.023	0.023	0.036
Saturated fat (%)[c]	0.146	0.098	−0.150	−0.120	0.003	−0.000
Oleic acid (%)[c]	0.067	0.079	−0.187	−0.095	−0.059	−0.002
Linoleic acid (%)	0.039	0.065	−0.015	0.023	0.012	0.042
Alcohol (%)[c]	0.466****	0.437****	0.602****	0.583****	0.538****	0.514****
Cholesterol (100 mg)	0.470	0.509*	−0.381	−0.121	0.219	0.175
Fiber (g)[d]	−0.070	−0.070	0.248***	0.214***	0.102*	0.080

[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.
[b]Age-adjusted β coefficient for total calories.
[c]Significant interaction by apo E phenotype exists in the relationship between this nutrient and plasma HDL among postmenopausal women. See results in Tables 6 and 7 that are stratified by apo E grouping.
[d]Significant interaction by menopausal status exists in the relationship between dietary fiber and plasma HDL. See results that are stratified by menopausal status.
*$0.05 \leq p \leq 0.10$.
**$p < 0.05$.
***$p < 0.01$.
****$p < 0.001$.

TABLE 5. Dietary determinants of plasma T/H ratio in Framingham women, ages 22–79 years in 1984–1988, by menopausal status

	β Coefficient					
	Premenopausal (n = 691)		Postmenopausal (n = 726)		All women (n = 1417)	
Nutrient	Age and calorie adjusted	Multivariate[a] model	Age and calorie adjusted	Multivariate[a] model	Age and calorie adjusted	Multivariate[a] model
Calories (100 kcal)	−0.013*[,b]	−0.009	−0.020**[,b]	−0.014*	−0.016***[,b]	−0.011**
Carbohydrate (%)	0.006	0.011***	−0.001	0.004	0.002	0.007**
Protein (%)[c]	−0.012	−0.026****	0.009	−0.000	−0.002	−0.012**
Total fat (%)[d]	0.002	0.001	0.006	0.002	0.004	0.002
Saturated fat (%)	0.001	0.004	0.025**	0.022**	0.012*	0.012*
Oleic acid (%)[d]	0.014	0.008	0.024*	0.015	0.019**	0.012
Linoleic acid (%)	−0.005	−0.008	−0.025*	−0.028**	−0.015	−0.018*
Alcohol (%)[d]	−0.031****	−0.029****	−0.029***	−0.028****	−0.029****	−0.029****
Cholesterol (100 mg)	−0.019	−0.030	0.023	−0.006	0.003	−0.015
Fiber (g)	−0.010	−0.009	−0.018**	−0.016**	−0.015***	−0.013**

[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.
[b]Age-adjusted β coefficient for total calories.
[c]Significant interaction by menopausal status exists in the relationship between protein and total/HDL ratio. See results that are stratified by menopausal status.
[d]Significant interaction by apo E phenotype exists in the relationship between this nutrient and total/HDL ratio among postmenopausal women. See results in Tables 6 and 7 that are stratified by apo E grouping.
*$0.05 \leq p \leq 0.10$.
**$p < 0.05$.
***$p < 0.01$.
****$p < 0.001$.

Alcohol intake was directly associated with HDL and inversely associated with the T/H ratio in premenopausal women and in all postmenopausal women except those with 3/2 or 2/2 apo E status. In this subgroup of postmenopausal women, there was a direct association between alcohol and the T/H ratio and no association with plasma HDL. While postmenopausal women with the 3/4 or 4/4 apo E grouping exhibited an inverse association between alcohol and the T/H ratio, the relationship was not significant, probably due to a similar sample size and limited power.

The predicted influences of alcohol intake on plasma HDL levels and the T/H ratio are as follows: premenopausal women who consume one drink per day would have a plasma HDL level that is 2.74 mg/dl higher than those who abstain. Among postmenopausal women, those in the 3/4 or 4/4 apo E group who consume one drink per day would have an HDL level that is 5.22 mg/dl higher than nondrinkers, and those in the 3/3 apo E group who consume one drink per day would have an HDL level that is 2.80 mg/dl higher than nondrinkers. Similarly, premenopausal women who drink one alcoholic beverage per day would have a T/H ratio that is lower than nondrinkers by 0.18. Among postmenopausal women, those in the 3/2 or 2/2 apo E group who consume one drink per day would have a T/H ratio that is higher than nondrinkers by 0.33, whereas those in the 3/3 apo E group who consume one drink per day would have a T/H ratio that is lower than those who abstain by 0.19. Alcohol consumption was inversely associated with HDL levels in postmenopausal women with the 3/2 or 2/2 apo E phenotype, and with the T/H ratio in postmenopausal women with the 3/4 or 4/4 phenotype, but these relationships were not significant.

Dietary fats did not appear to be related to HDL or the T/H ratio in premenopausal women. Total and saturated fat and oleic acid

TABLE 6. Dietary determinants of plasma HDL cholesterol in postmenopausal women, by apo E grouping

	β Coefficient[a]		
Nutrient	Apo E 3/2 or 2/2 (n = 73)	Apo E 3/3 (n = 313)	Apo E 3/4 or 4/4 (n = 101)
Total fat (%)	0.475***	0.023	−0.222*
Saturated fat (%)	0.682**	−0.113	−0.261
Oleic acid (%)	0.968***	0.128	−0.603**
Alcohol (%)	−0.269	0.446***	0.832****

[a]Age, calorie, and risk factor-adjusted model run separately for each apo E grouping.
*$0.05 \leq p \leq 0.010$,
**$p < 0.05$.
***$p < 0.01$.
****$p < 0.001$.

TABLE 7. Dietary determinants of plasma T/H ratio in postmenopausal women, by apo E grouping

	β Coefficient[a]		
Nutrient	Apo E 3/2 or 2/2 (n = 73)	Apo E 3/3 (n = 313)	Apo E 3/4 or 4/4 (n = 101)
Total fat (%)	−0.032**	0.003	0.015
Saturated fat (%)	−0.025	0.024	0.024
Oleic acid (%)	−0.059*	0.006	0.045
Alcohol (%)	0.053**	−0.030**	−0.030

[a]Age, calorie, and risk factor-adjusted model run separately for each apo E grouping.
*$0.05 \leq p \leq 0.010$.
**$p < 0.05$.

were directly related to HDL in postmenopausal women with the 3/2 or 2/2 apo E phenotype. However, in the 3/4 or 4/4 apo E group, oleic acid was inversely associated with HDL. The T/H ratio in the 3/2 or 2/2 group was inversely related to total fat intake.

Stepwise addition of calorie-adjusted macronutrients to the multivariate regression models indicated that plasma triglycerides were directly related to oleic acid and inversely related to linoleic acid and protein. Plasma HDL levels were directly related to alcohol and inversely related to carbohydrate. Finally, the T/H ratio was inversely related to alcohol, protein, and linoleic acid. These findings apply to the combined sample of Framingham women. Although we saw effect modification by menopausal status for the relationship between dietary protein and the T/H ratio, the sign for the coefficient was in the same direction (inverse) for both groups of women, thus data for the combined sample are reported.

DISCUSSION

The Framingham data presented here represent the cross-sectional relationships between diet and plasma triglycerides, HDL cholesterol, and the T/H ratio in both pre- and postmenopausal women and in all women combined. The observed relationships between dietary variables and plasma lipid levels were independent of other known potentially confounding factors. We considered in these models other cardiovascular disease risk factors, including body mass index, physical activity, glucose intolerance, cigarette smoking, and estrogen use. This research makes a unique contribution to the literature given its cross-sectional design in a large, population-based sample of pre- and postmenopausal women. Most research that examines the relationships between diet and plasma lipids has been done in high-risk patient populations and in clinical trial settings with relatively small samples of individuals.

Plasma triglyceride levels of Framingham women were directly associated with dietary intake of saturated fat and oleioc acid. The type of fat appears to have a specific effect on triglyceride levels since linoleic acid had an inverse marginal association. Consistent with our data, saturated fatty acids have been shown to raise triglyceride levels in other settings [17]. In contrast to our findings, diets high in oleic acid have been shown to lower triglyceride levels [18]. In our cross-sectional study, oleic acid was associated with higher triglyceride levels. However, most of the oleic acid in the Framingham diet was derived from animal products, which are also high in saturated fat, rather than from vegetable sources of monounsaturated fats as have been used in most clinical trials.

Plasma triglyceride levels were inversely associated with protein intake and dietary fiber in Framingham women. Diets high in carbohydrate and low in fiber have been shown to raise triglyceride levels in intervention studies, whereas high-carbohydrate, fiber-rich diets lower triglycerides [19]. In postmenopausal women, there was an inverse association between triglycerides and linoleic acid. Intakes of linoleic acid have been associated with lowering of triglyceride levels in clinical trials [20].

Plasma HDL cholesterol was consistently directly related to alcohol intake in pre- and most postmenopausal women, and in all women combined. This association has been established in other cross-sectional studies of women [21] and in clinical trials [22–25]. In postmenopausal women, however, the direct association between alcohol intake and plasma HDL was evident in the 3/3 and 3/4 or 4/4 apo E groupings, but not in the 3/2 or 2/2 apo E grouping. This suggests that the benefit of alcohol consumption on HDL cholesterol, at the relatively low levels consumed by Framingham women (on average less than one-half an alcohol-containing drink per day), may be limited to some subgroups of the population. Alcohol consumption may, in fact, be detrimental to HDL levels in certain groups of women categorized by apo E phenotype.

Carbohydrate intake was consistently inversely related to plasma HDL cholesterol. This observation is consistent with results from intervention studies that demonstrated that low-fat, high-carbohydrate diets tended to lower plasma HDL cholesterol levels [26,27]. Similarly, a cross-sectional study in premenopausal women found an inverse association between refined carbohydrates and plasma HDL cholesterol [28].

Protein intake was directly associated with plasma HDL in premenopausal Framingham women. This finding requires confirmation with further study. One intervention study showed that protein, in particular vegetable protein, raised HDL cholesterol levels in children with familial hypercholesterolemia [29].

Because low-fat diets have been shown to reduce HDL cholesterol levels, it is thought that high-fat diets may be beneficial in maintaining higher levels of plasma HDL [30]. In this article, total fat, saturated fat, and oleic acid were directly related to plasma HDL cholesterol levels in only one group of postmenopausal women categorized by apo E phenotype (3/2 or 2/2 grouping). Thus, the association of increased fat intake with increased HDL does not appear to be consistent across the entire population.

In this article, fiber intake was directly associated with plasma HDL cholesterol in postmenopausal women. While dietary fiber, specifically soluble fiber, has been shown to lower total plasma cholesterol levels [31], its association with HDL cholesterol remains controversial [32–34] and the potential mechanism of its effect unclear. Dietary fiber may alter HDL metabolism or possibly estrogen metabolism. However, we were unable to explore such mechanisms in this cross-sectional study.

Dietary determinants of the T/H ratio in Framingham women included carbohydrate, protein, alcohol, and fiber. The inverse influence of alcohol on the T/H ratio would appear to be related to the strong positive and consistent influence of alcohol intake on HDL cholesterol. Of interest in this article was the direct association between the T/H ratio and alcohol intake in postmenopausal women in the 3/2 or 2/2 apo E group. Thus, alcohol does not appear to have a beneficial influence on plasma lipids in all groups of women.

Interest has focused on the effect of diet on plasma lipids, particularly plasma total and LDL cholesterol, within categories of apo E isoform phenotype. It has been reported that levels of plasma total and LDL cholesterol are related to apo E phenotype and range from highest to lowest levels as follows: 4/4 > 4/3 > 3/3 > 3/2 > 2/2 [35]. Thus, the presence of apo E4 is associated with higher plasma levels of LDL cholesterol, whereas apo E2 is associated with lower levels. Within the Framingham Offspring cohort, Schaefer *et al.* [36] showed that LDL cholesterol and the apo E phenotype were most strongly related in postmenopausal women. The apo E locus explained 5% of the variance in LDL cholesterol levels in postmenopausal women, whereas only 0.5% of the variance was due to apo E polymorphism in premenopausal women [36]. These findings suggest that sex hormones can modulate the impact of the apo E phenotype on certain plasma lipids.

It is possible that the relationship between diet and plasma lipids may be dependent on the apo E phenotype of an individual, since the relationship between LDL cholesterol levels and apo E phenotype is not independent of environmental factors, including diet. For example, the association of apo E4 with elevated serum cholesterol levels is greater in populations consuming diets rich in saturated fat and cholesterol than in other populations [37]. Therefore,

the response to dietary manipulation may differ among individuals with different apo E phenotypes. An intervention study showed that the LDL cholesterol-lowering response to a National Cholesterol Education Program (NCEP) Step 1 diet was modified by apo E phenotype, such that presence of the apo E4 allele was associated with increased LDL lowering [37]. A meta-analysis showed that apo E4 carriers were more responsive to dietary interventions than those who did not have the apo E4 allele [37]. We did not find that relationships between dietary macronutrients and plasma total and LDL cholesterol were modified by apo E phenotype in a previous cross-sectional study [38]; however, we do report in this article effect modification by apo E phenotype on relationships between dietary fats and alcohol, and HDL cholesterol and the T/H ratio in postmenopausal women. Although previous reports have not shown a relationship between plasma HDL and apo E phenotype, our findings suggest that certain nutrient relationships with HDL and the T/H ratio do differ by apo E phenotype in postmenopausal women. Additional research is needed to explore these observations further.

Although this research was conducted in a large, population-based sample of pre- and postmenopausal women, we are somewhat limited in our ability to describe diet/lipid relationships owing to the cross-sectional study design. A second limitation of these data relates to the use of a single 24-hr recall to estimate macronutrient intake levels. Errors in nutrient estimates are likely to attenuate observed relationships between diet and blood lipid levels. Therefore, we may have underestimated the true associations between diet and lipid levels. However, we are confident in our nutrient estimates for the population as they have been shown to be highly comparable with estimates derived from 3-day food records [12]. We have also reported previously [39] that our estimates of nutrient intake are quite consistent with other data published on the U.S. population. Finally, we considered only linear models in these analyses.

CONCLUSIONS

Alcohol intake was the strongest predictor of HDL cholesterol and the T/H ratio in Framingham women. It is important to note, however, that the effect of alcohol on plasma lipids differed across genetic subgroups of women and was not always favorable. Dietary guidelines that emphasize reduction in total fats, particularly saturated fats, and increases in dietary fiber are consistent with lower population plasma triglyceride levels. At the same time, these guidelines may be associated with lower HDL levels among certain segments of the population. However, the favorable influence of lower total fat, particularly saturated fat, and higher fiber on the T/H ratio as well as plasma total and LDL cholesterol makes these population recommendations quite sound. Dietary fat and alcohol appear to have different effects on certain plasma lipids depending on the apo E phenotype of the individual. Thus, it appears important to consider the genetic contribution to diet/lipid relationships when conducting epidemiological investigations and evaluating lipid-lowering intervention strategies.

This research was supported in part by the National Heart, Lung and Blood Institute Contracts and Grants: N01-HV-38038, NHLBI N01-HC-38038, R01-HL-40423-02, R01-HL-39144-01, and R01-HL-46193-01,02.

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