Influence of a 6-week cholesterol education program on blood lipids and LDL oxidation
by Kimberly Rae Monahan

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Abstract:
To evaluate the effectiveness of two different approaches of dietary education to reduce blood lipids and oxidative stress. METHODS: Volunteers with moderately elevated low-density lipoprotein cholesterol (LDL-C) levels (100mg/dL-159mg/dL) were randomized into either intensive or conventional education groups. The intensive education group (n=12) attended 6 classes and received a nutrition education manual. The conventional group (n=l1) received a nutrition education manual. Three-day weighed diet records, 3-day physical activity records, anthropometric measurements, blood pressure, plasma total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and LDL-C were collected at baseline, 6-weeks and 12 weeks. Oxidized LDL-C was measured via copper-mediated oxidation. RESULTS: At 6-weeks, there was a significant (P=0.05) decrease in TC (-4.96%) and a trend (P=0.05) to decrease LDL-C (-10.37%) for the intensive group. At 12-weeks, there was a significant (P=0.05) decrease in LDL-C for the conventional (-9.55%) and intensive (-10.54%) groups. The intensive group had greater increases in polyunsaturated fat (4.58%E at baseline; 6.67%E at midstudy; 7.08%E at study-end, P<0.05) and greater reductions in saturated fat (9.08%E at baseline; 6.83%E at mid-study, P<0.01); however these reductions returned to baseline values at Study-end (9-.42±2.02 %E, P<0.05). Neither educational method resulted in significant oxidative modifications of LDL-C. CONCLUSIONS: The reduction in LDL cholesterol level achieved after counseling through intensive education is not superior to that achieved by conventional education. The oxidative modification of LDL-C is not directly effected by nutrition education. Intensive nutrition education can result in alterations of dietary fat intake. Dietary education can result in significant reductions in LDL-C, regardless of the method used.

INFLUENCE OF A 6-WEEK CHOLESTEROL EDUCATION PROGRAM ON

BLOOD LIPIDS AND LDL OXIDATION

by

Kimberly Rae Monahan

A thesis submitted in partial fulfillment
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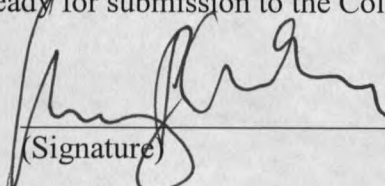MONTANA STATE UNIVERSITY-BOZEMAN
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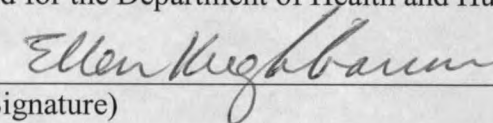
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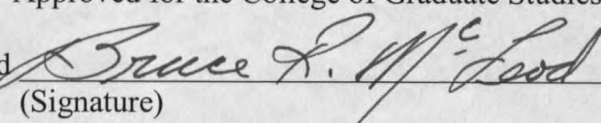Approved for the Department of Health and Human Development

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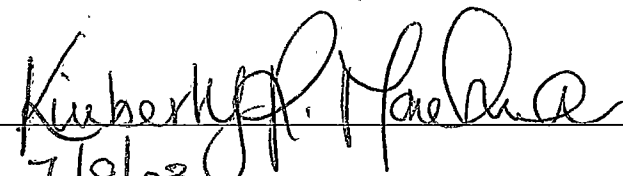(Signature)   Date

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GLOSSARY

Copper Mediated Oxidation	Isolated LDL oxidized in the presence of copper.
Hypercholesterolemia	High blood cholesterol
Hyperlipidemia	High lipid (fat) levels in the blood.
Initial Absorbance	The initial level of conjugated dienes or oxidation as assessed by the baseline copper absorbance of a sample subtracted from the uncatalyzed control sample
Lag Time	A phase of the LDL-oxidation process, where the oxidative modification is suppressed by endogenous antioxidants.
LDL oxidation	The oxidative modification of low-density lipoproteins.
Propagation Phase	The propagation phase of LDL oxidation begins after the endogenous antioxidants have been consumed.

ACRONYMS

AHA	American Heart Association
ATP III	Adult Treatment Panel III
CAD	Coronary Artery Disease
CVD	Cardiovascular Disease
HDL	High-density Lipoprotein
LDL	Low-density Lipoprotein
MUFA	Monounsaturated Fatty Acid
NCEP	National Cholesterol Education Program
NHLBI	National Heart Lung and Blood Institute
OxLDL	Oxidized Low-density Lipoprotein
PUFA	Polyunsaturated Fatty Acid
SF	Saturated Fat
TC	Total Cholesterol
TF	Total Fat
TG	Triglycerides
TLC	Therapeutic Lifestyle Changes
USPSTF	US Preventive Services Task Force

ABSTRACT

PURPOSE: To evaluate the effectiveness of two different approaches of dietary
education to reduce blood lipids and oxidative stress. METHODS: Volunteers with
moderately elevated low-density lipoprotein cholesterol (LDL-C) levels (100mg/dL-
159mg/dL) were randomized into either intensive or conventional education groups. The
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The oxidative modification of LDL-C is not directly effected by nutrition education.
Intensive nutrition education can result in alterations of dietary fat intake. Dietary
education can result in significant reductions in LDL-C, regardless of the method used.

CHAPTER 1

INTRODUCTION

The National Heart Lung and Blood Institute (NHLBI), American Heart Association (AHA), and other organizations have mounted a major effort to reduce risk factors for cardiovascular disease (CVD) in the United States. These risk reduction programs emphasize the importance of healthy eating habits, coupled with other healthful lifestyle behaviors, to reduce the risk of CVD. With an average of one death every 33 seconds from CVD in the United States, the increased need for continuing research on improved methods for risk reduction and active promotion of theses programs in community settings is exceedingly apparent (1).

The most important risk factors for atherosclerosis include smoking, hypertension, dyslipidemia (increased concentrations of low-density lipoproteins (LDL) and decreased concentrations of high-density lipoproteins [HDL]), diabetes, aging, and a family history of premature atherosclerosis (2). The U.S. Preventive Services Task Force (USPSTF) recommends intensive behavioral dietary counseling for adult patients with hyperlipidemia and other known risk factors for cardiovascular and diet-related chronic disease (3). The USPSTF recommends that intensive counseling be delivered by primary care clinicians or other specialists, such as nutritionists or dietitians (3).

Intensive nutrition education programs, defined as two or more contacts between advisor and patient per month (4), counseling, and behavioral interventions that reduce dietary fat and cholesterol intake can result in significant improvements in blood lipid levels, therefore reducing the development and progression of coronary artery disease

(CAD) (5). What is less clear is the effect of conventional dietary education, defined as less than one contact between patient and advisor per month (4), on blood lipids and hypercholesterolemia management. The National Cholesterol Education Program's (NCEP) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults Adult Treatment Panel III (ATP III) (6) recommends dietary therapy as the first line of treatment for individuals with elevated LDL-C (7). ATP III recommends a LDL-C <160 mg/dL as the goal for persons with 0 or 1 CVD risk factor; the primary aim of therapy in this category is to reduce long-term risk. In individuals with a LDL-C between 100mg/dL and 160mg/dL, baseline blood lipids are assessed and persons are started on dietary therapy. The LDL-C response to a cholesterol-lowering diet has been well documented in inpatient and outpatient diet studies (8).

ATP III promotes diet and lifestyle changes as essential strategies for reducing risk for cardiovascular diseases (9). Dietitians are encouraged to adopt these recommendations in treating all patients with elevated blood cholesterol levels and apply their professional experience to the task of blending and tailoring the best dietary approaches for each patient (9). Evidence suggests that intervention programs, taught by dietitians and other health care professionals, which utilize strategies such as two-way-communication as the primary means of managing risk factors, provide a greater benefit to individuals when compared to one-way-communication strategies, such as printed educational materials (10). Two-way communication implies that the two parties in communication have a two-way flow of ideas and information. When communication

exists without the opportunity for the second party to respond or initiate, it is one-way communication (4). Additionally, patients who have received intensive nutrition education, with the objective of lowering serum blood lipids, have been documented as having gained significantly more nutrition knowledge, having greater perceptions of the efficacy of following a cholesterol-lowering diet, consuming a significantly lower percentage of fat, a higher percentage of carbohydrates, and less dietary cholesterol (11). These outcomes are particularly of interest because the objective of nutrition education is not simply to impart knowledge, but also to provide individuals with the knowledge to make wise food choices to aid in reducing serum blood lipids.

The conventional risk factors, such as dyslipidemia, hypertension, diabetes, and smoking, cannot account for all the cases of coronary artery disease. Thus, there are other novel risk factors that appear to be related to premature atherosclerosis. One plausible phenomenon may be the oxidative modification of LDL, rendering the molecule more atherogenic (12). As levels of LDL-C molecules become elevated in the circulation, the opportunity for oxidative modification increases. These modified molecules are then taken up by macrophages inside the arterial wall. It is these cholesterol-laden macrophages that form the start of atherosclerotic plaques (13). In addition, increased oxidation, specifically of the LDL-C molecules, may cause premature atherosclerosis in spite of a lipoprotein profile within reference values (2).

Diet may also play a prominent role in the oxidative modification of LDL-C. Dietary factors such as dietary fat and cholesterol can influence the fatty acid and antioxidant composition of LDL-C, which regulates LDLs susceptibility to oxidation

(14). A significant increase in the capacity of LDL-C to resist oxidation has been associated with behavioral interventions that reduce dietary fat and cholesterol intake and may be associated with a decrease in CAD risk (15).

Statement of Problem

Research comparing the effectiveness and practicality of intensive and conventional approaches to dietary counseling in the area of hyperlipidemia has been mixed (16). We performed a randomized controlled study employing the NCEP ATP III dietary guidelines in subjects with elevated LDL-C. The objective of the present study was to compare the effect, on serum blood lipids and the oxidative modification of LDL, of additional dietary counseling provided through six, one-hour nutrition education classes with conventional nutrition education provided through printed educational materials.

Hypothesis

We hypothesized that when compared to education provided through printed materials, intensive nutrition education, provided through nutrition education classes, would result in greater reductions in serum lipids, greater appropriate changes in macronutrient intake consistent with the NCEP ATP III recommendations, greater use of cardioprotective foods, more favorable awareness regarding appropriate nutrition and high blood cholesterol knowledge, and greater appropriate changes in LDLs susceptibility to *ex-vivo* oxidation:

$$H_O: \mu_{\text{post Intensive}} = \mu_{\text{post conventional}}$$

$$H_A: \mu_{\text{post Intensive}} > \mu_{\text{post Conventional}}$$

where H_A is equal to greater appropriate changes in blood lipids, markers of oxidative stress, use of cardioprotective foods, and nutrition and high blood cholesterol knowledge at study-end.

Delimitations

The inclusion of subjects for this investigation integrated specific fixed limits and boundaries. The first and most significant delimitation is the narrow scope of the inclusion criteria limiting the magnitude of the study population. Subjects were included based on the criteria that their pre-screening calculated LDL-C values were within the range of 100-159 mg/dL. Since any LDL-C above 100 mg/dL has been shown to be atherogenic and high LDL-C ($\geq$160 mg/dL) is considered a potential target for LDL-C–lowering drug therapy, particularly in persons with multiple CHD risk factors we excluded individuals with a LDL-C < 100mg/dL and > 160mg/dL. This inclusion criterion excluded approximately 47% of the screened individuals. In addition, the scope of individuals that our subject recruitment was able to reach was limited to the Montana State University campus and the reading population of the local newspaper. The combined effects of these factors limited the sampling of subjects and ultimately limits the generalizablity of our findings

Limitations

There are limitations which create a potential weakness for this examination. First, although these analyses provide data on intake from foods, they cannot provide information on the specific behavioral changes associated with these reductions in intake. A three day weighed diet record can not accurately predict the specific changes in

behavioral data, (i.e. increased or reduced frequency of consumption and portion size, or substitution with a lower fat alternative) (8). Second, this was an intent-to-treat analysis. Intent to treat analysis is a broad strategy to assess randomized data; it requires that individuals remain in the group to which they were randomized regardless of compliance, crossover to other treatments or withdrawal. In addition this study did not adjust or control for compliance, weight loss, or life style changes beyond recorded dietary, blood lipid results and energy expenditure alterations. Subjects were free living and self selected their foods and represent a cross section of the general population that would be likely to select general clinical care for hyperlipidemia. These subjects received more dietary instructions and support than usually provided in a routine clinical care setting. Additionally, subjects included in the investigation were volunteers and may have had a greater vested interest in reducing blood lipids through behavior modification. Consequently, the amount of LDL-C lowering achieved may represent about the best that can be expected through community-based or intensive clinical programs. Finally, the intervention utilized in this study was relatively short term (6-weeks) and the subsequent follow-up may have not been long enough to detect changes in serum blood lipids in response to dietary modifications.

CHAPTER 2

REVIEW OF LITERATURE

New food-based dietary recommendations issued by the American Heart

Association, to reduce risk for CVD, promote a multifaceted approach (17). The 2000

AHA dietary guidelines recommend a variety of foods to target four major goals: achieve

a healthy overall diet, achieve a healthy weight, promote desirable lipid levels, and

promote desirable blood pressure (18). Specific foods recommended include fruits and

vegetables, grain products, fish, lean meat and poultry, fat-free or low-fat dairy products,

and legumes. In addition, NCEPs ATP III therapeutic lifestyle changes (TLC) (Table 1)

recommend restrictions of SF and dietary cholesterol and therapeutic dietary options to

lower LDL-C: the inclusion of plant stanols/sterols (2-3 g/day), soy protein (25-40g/d)

and increased viscous (soluble) fiber (5-10 g/day) (6). Additional cardioprotective foods

include nuts and legumes. This chapter will review the scientific basis of cholesterol-

lowering diets and strategies for their implementation.

The Cholesterol-Lowering Diet

Diet is associated with several common adult diseases in Western countries,

including CVD, diabetes, and several cancers (19). The ATP III guidelines focus

extensively on the nonpharmacologic therapy used to specifically prevent CVD for those

individuals with abnormal blood lipids. ATP III redirects the public focus from the high-

SF atherogenic diet, obesity, and a sedentary lifestyle to a program of therapeutic lifestyle

changes. The TLC diet de-emphasizes total fat and focuses on the types of fat ingested.

Initiating TLC begins with reducing intakes of SF and cholesterol to begin

Table 1. Dietary recommendations based on the ATP III TLC diet.

Nutrient	Recommended Intake
Saturated fat[1,2]	<7%
Polyunsaturated fat[2]	Up to 10%
Monounsaturated fat[2]	Up to 20%
Total fat[2]	25%–35%
Carbohydrate[2]	50%–60%
Fiber	20–30 g/d
Viscous (soluble) fiber	5-10g/d
Protein[2]	15%
Cholesterol	<200 mg/d
Plant stanols/sterols	2-3g/d
Soy protein	25–40 g/day when replacing animal food products

[1]Trans fatty acids also raise LDL-C and should be kept at a low intake.
[2]As percent of total calories
Note: Regarding total calories, balance energy intake and expenditure to maintain desirable body weight.

lowering LDL C. Subsequently, and additionally, is the emphasis of the health-promoting aspects of the diet that include, among other things, fish, omega-3 fatty acids, and the addition of viscous fiber and plant stanol/sterol esters to reduce LDL-C beyond that previously seen with the NCEPs previous recommendations, the Step I and II diets. At all stages of TLC, ATP III encourages the referral to registered dietitians or other qualified nutritionists for medical nutrition therapy. The ATP III guidelines can provide guidance to practitioners who wish to prevent and treat atherogenic progression, by lowering LDL-C levels, and improve the overall health of the patient.

The combined effects of the components in the cholesterol-lowering diet can result in substantial TC and LDL-C reductions. Jenkins et al (20) examined the

combined effects of the cholesterol-lowering dietary components on blood lipids in hypercholesterolemic subjects, consuming low-fat diets. Thirteen subjects (7 men 6 post menopausal women) with a baseline LDL-C of 174 ± 7.7mg/dL participated in a 6-week feeding trial which included the combined use of 1g of plant stanols/1,000kcal via enriched margarine, 8.2g of viscous soluble fiber/1,000kcal via oats, barley, and psyllium, and 22.7g of soy protein/1,000kcal via soymilk, soy sausage, soy cold cuts, and soy burgers. Data collection occurred at baseline while subjects were consuming a Step II diet, at weeks 2 and 4, during the 4-week combination diet, and after week-6, during which subjects resumed the Step II diet. The combination diet was compared to the AHA Step II diet. During the combination diet, no significant weight loss was observed. However, when the subjects resumed the Step II diet, there was a significant ($P<0.01$) – 0.20 ± 0.05kg/week weight loss. This may be explained by the significant ($P<0.05$) decrease in energy intake when compared to the combination diet (1,999 $\pm$ 118 kcal/d; 1,703 $\pm$ 104 kcal/d, for the combination and Step II diets, respectively). Significant reductions were observed in blood lipids during the combination diet. At baseline TC levels were 249.8 ± 8.1mg/dL. After consuming the combination diet, TC was significantly reduced ($P<0.01$) by 22.3% $\pm$ 2.0% (193.7 ± 7.7mg/dL). At baseline LDL-C levels were 163.2 ± 4.3mg/dL. With the combination diet, LDL-C levels were significantly reduced ($P<0.01$) by 29.0% $\pm$ 2.7% (116.4 ± 6.6mg/dL). After the combination diet therapy phase, TC levels returned to 228 ± 8.5mg/dL while LDL-C levels increased to 146.9 ± 7.7mg/dL. The combined effects of the cholesterol-lowering dietary components, plant sterols, viscous fibers, and vegetable proteins, caused a

subsequent reduction in dietary cholesterol and SF and ultimately reduced TC and LDL-C levels.

Components of a Cholesterol-Lowering Diet

Dietary Fat The type of dietary fat can influence the development and progression of chronic diseases. Additionally, a significant relationship has been demonstrated between the predominant type of fat in the diet and the lipid-laden cellular membrane composition. The best understood risk factor for atherogenesis is serum cholesterol, which can be easily modified by alterations of dietary fatty acids (21).

Fats, such as SF, have been shown to be particularly harmful due to their role in the development of diseases, such as CVD (22, 23). Reductions of dietary fat are associated with changes in plasma TC and LDL-C (22, 23). The Delta-1 Study, (24) demonstrated that reductions in total fat and SF acids in the diet are accompanied with clinically important reductions in TC and LDL-C concentrations. The three diets were examined in this investigation; the AHA Step I diet (55% energy [E%]) from carbohydrate, 15E% protein, 30E% fat, with 9E%, 14E%, 7E% and <1.5E% from SF, MUFA, PUFA, and *trans* fatty acids, respectively), an Average American diet (AAD) (48E% carbohydrate, 15E% protein, 37E% fat, and 16E%, 14E%, 7E% and <1.5E% from SF, MUFA, PUFA, and *trans* fatty acids, respectively) and a low SF (Low-Sat) diet (59E% carbohydrate, 15E% protein, 26E% fat, with 5E%, 14E%, 7E% and <1.5E% from SF, MUFA, PUFA, and *trans* fatty acids, respectively). The Delta-1 Study utilized a randomized crossover design which included three feeding periods. Each subject was randomized to one of six diet sequences (ABC, ACB, BAC, BCA, CAB, or CBA) with

each diet period lasting 8 weeks, and included breaks of 4 to 6 weeks between diet periods. One hundred three healthy, normolipidemic volunteers (57 women, 46 men) were randomized to one of six diet sequences, separated by 4-6 weeks. All meals, except Saturday dinner, were prepared on site with two weekday meals consumed in a supervised cafeteria. The reduction in TC averaged a significant decrease ($P<0.01$) of 5% between the AAD and Step I diet (202.1 ± 2.8mg/dL to 191.0 ± 2.7mg/dL, respectively) and an additional 4% ($P<0.01$) during the Low-Sat diet (183.4 ± 2.7mg/dL). Similarly, LDL-C decreased significantly ($P<0.01$) by 7% between the AAD and the Step I diet (131.4 ± 2.7mg/dL to 122.2 ± 2.6mg/dL) with an additional stepwise reduction of 4% ($P <0.01$) with the Low-Sat diet (116.9 ± 2.6mg/dL). Between the AAD and the Step I diet, TG concentrations significantly increased ($P <0.01$) by 9% (85.1 ± 3.4 to 92.4 ± 3.7mg/dL), but did not change with the consumption of the Low-Sat diet. The reductions in total and LDL-C observed on the Low-Sat diet indicate that reducing total fat and SF, in a 6 week feeding period, can have a significant impact on lipoproteins in normolipidemic individuals. The TLC diet recommends 25-35%, or less, of the day's total calories come from fat; a range similar to the Step I and Low-Sat diets which produced a 7-11% reduction in LDL-C in the previous investigation. Given the beneficial effects of low total and low-SF diet on several biomarkers of CVD risk, it seems prudent to recommend inclusion of these new recommendations into healthy lifestyle and cholesterol-lowering diets, or as a start, in self-selected diets.

Saturated Fat The collective investigations of Ignatowski in 1908 and McGill in 1979 have led to the classic diet-heart hypothesis (25), which postulates the link between

the development of atherosclerosis and the dietary intake of SF and cholesterol (26, 27).

Further examinations, such as the Keys Seven Countries correlations between

international CHD mortality and SF intake (28) and the investigations of migrant workers

adopting the Westernized lifestyles (29), have led to the overwhelming support of the

diet-heart hypothesis.

There is a dose-response relationship between SFA and LDL-C, although the

mechanisms, whereby saturated fatty acids (SFAs) raise LDL-C levels are not completely

understood (30). The most logical evidence for this correlation (see Figure 1) is that

SFAs interfere with the LDL-C receptors ability to clear LDL-C particles. Investigations

tracking the clearance of the LDL apolipoprotein B-100 have determined that SFA impair

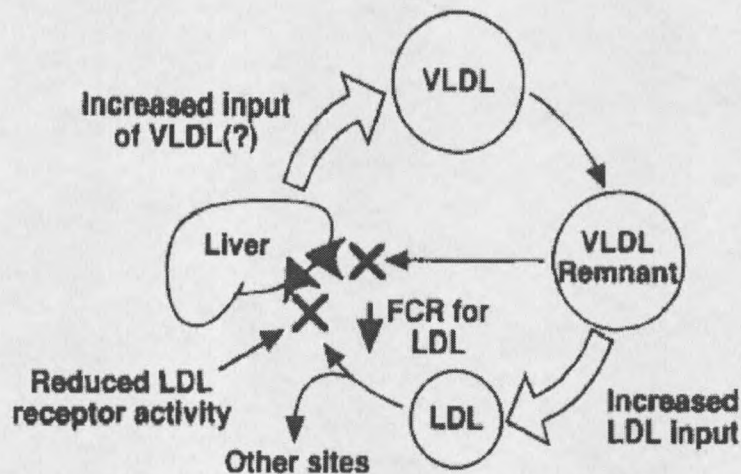the removal of LDL-C from circulation (31).

Figure 1. The mechanisms of increased LDL-C levels due
to high intakes of SFAs. The major effect of SFAs appears
to be a reduced activity of LDL receptors (Reprinted with
permission(30)).

Interventions to avoid atherosclerosis might be more successful if launched early

in life when eating and life-style patterns are formed. In the STRIP baby trial,

investigators found that decreasing intakes of SF in infants markedly influenced serum lipid values as early as 13 months. The STRIP baby trial was a randomized, prospective trial of more than 1000 healthy children. These children were regularly monitored for nutrient intakes, serum lipid values, growth, and development (32). One thousand sixty-two infants were randomized to intervention and control groups at 7 months of age. The families of the 540 intervention children were counseled to reduce the child's intake of SF and cholesterol and to ensure adequate energy intake. Five hundred twenty-two control children consumed an unrestricted diet. Food records were kept and serum lipids were measured at 5- to 12-month intervals. Intakes of SF and cholesterol were lower in the intervention children than in control children at 13, 24, and 36 months of age. Between 7 and 13 months serum cholesterol and non-high-density-lipoprotein cholesterol concentrations did not change significantly in the intervention group but increased significantly ($P < 0.001$) in the control group. When compared to the control group, the intervention group had lower daily intakes of energy (967.8 ± 189.5 kcal/d; 1040.5 ± 178.1 kcal/d, for the intervention and control groups, respectively, $P < 0.05$) and SF intake (9.3 ± 3.5g/d; 14.5 ± 4.8 g/d, for the intervention and control groups, respectively $P < 0.001$), and intake of polyunsaturated fat (PUFA) was higher (5.8 ± 2.2; 4.4 ±1.4 g/d, for the intervention and control groups, respectively $P < 0.001$). Thus, increases in serum cholesterol and non-HDL-C concentration that occur in infants between the ages of 7 and 13 months can be avoided by individualized diets which reduce SFA intake.

As a class, saturated fatty acids (SFA) pose a potential risk for increasing LDL-C. However, SFA at varying chain lengths, may not affect serum levels of TC and LDL-C

equally. In the prospective cohort Nurses' Health Study, 80,082 women, aged 34–59, completed validated food-frequency questionnaires in 1980. Women were free from known CVD, cancer, hypercholesterolemia, and diabetes (33). During the 14 year of follow-up, 939 documented incident cases of CVD events were reported. In multivariate analyses in which age, smoking, and other covariates were controlled for, intakes of short- to medium-chain SFA (4:0–10:0) were not significantly associated with the risk of CVD. In contrast, intakes of longer-chain SFA (lauric [12:0]; myristic [14:0]; palmitic [16:0]) were each separately associated with a small increase in risk. The multivariate relative risk (RR) for a 1% energy increase from the neutral stearic acid was 1.19 (95% CI: 1.02, 1.37). The ratio of PUFA to SFA was strongly and inversely associated with CHD risk (multivariate RR for a comparison of the highest with the lowest deciles: RR 0.58; 95% CI: 0.41, 0.83; P <0.0001) (33). These data suggest that replacement of long-chain SFA with PUFA will likely reduce the risk of CHD. Intake of the longer chain SFA, lauric, myristic, and palmitic have all been linked to a subsequent rise in LDL-C and TC (34, 22). With the aim of reducing LDL-C, NCEPs TLC diet recommends that all SFAs be reduced to ≤ 7% of total energy (6).

Polyunsaturated Fat Two types of PUFAs occur in the diet, linoleic acid (n-6), mainly from plant oils and animal fats, and linolenic acid (n-3) primarily from certain vegetable and fish oils. Controlled clinical trials indicate that the substitution of PUFA for SFA reduces the risk of CVD (30) (see Figure 2). Additionally, prospective and clinical trial data suggest that higher intakes of n-3 fatty acids reduce the risk for coronary events and mortality. The major n-3 fatty acids include: eicosapentaenoic acid