

11

Macronutrients and Healthful Diets

SUMMARY

Acceptable Macronutrient Distribution Ranges (AMDRs) for individuals have been set for carbohydrate, fat, *n*-6 and *n*-3 polyunsaturated fatty acids, and protein based on evidence from interventional trials, with support of epidemiological evidence that suggests a role in the prevention or increased risk of chronic diseases, and based on ensuring sufficient intakes of essential nutrients.

The AMDR for fat and carbohydrate is estimated to be 20 to 35 and 45 to 65 percent of energy for adults, respectively. These AMDRs are estimated based on evidence indicating a risk for coronary heart disease (CHD) at low intakes of fat and high intakes of carbohydrate and on evidence for increased risk for obesity and its complications (including CHD) at high intakes of fat. Because the evidence is less clear on whether low or high fat intakes during childhood can lead to increased risk of chronic diseases later in life, the estimated AMDRs for fat for children are primarily based on a transition from the high fat intakes that occur during infancy to the lower adult AMDR. The AMDR for fat is 30 to 40 percent of energy for children 1 to 3 years of age and 25 to 35 percent of energy for children 4 to 18 years of age. The AMDR for carbohydrate for children is the same as that for adults—45 to 65 percent of energy. The AMDR for protein is 10 to 35 percent of energy for adults and 5 to 20 percent and 10 to 30 percent for children 1 to 3 years of age and 4 to 18 years of age, respectively.

Based on usual median intakes of energy, it is estimated that a lower boundary level of 5 percent of energy will meet the Adequate Intake (AI) for linoleic acid (Chapter 8). An upper boundary for linoleic acid is set at 10 percent of energy for three reasons: (1) individual dietary intakes in the North American population rarely exceed 10 percent of energy, (2) epidemiological evidence for the safety of intakes greater than 10 percent of energy are generally lacking, and (3) high intakes of linoleic acid create a pro-oxidant state that may predispose to several chronic diseases, such as CHD and cancer. Therefore, an AMDR of 5 to 10 percent of energy is estimated for *n*-6 polyunsaturated fatty acids (linoleic acid).

An AMDR for α -linolenic acid is estimated to be 0.6 to 1.2 percent of energy. The lower boundary of the range meets the AI for α -linolenic acid (Chapter 8). The upper boundary corresponds to the highest α -linolenic acid intakes from foods consumed by individuals in the United States and Canada. A growing body of literature suggests that higher intakes of α -linolenic acid, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) may afford some degree of protection against CHD. Because the physiological potency of EPA and DHA is much greater than that for α -linolenic acid, it is not possible to estimate one AMDR for all *n*-3 fatty acids. Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA.

No more than 25 percent of energy should be consumed as added sugars. This maximal intake level is based on ensuring sufficient intakes of certain essential micronutrients that are not present in foods and beverages that contain added sugars. A daily intake of added sugars that individuals should aim for to achieve a healthy diet was not set.

A Tolerable Upper Intake Level (UL) was not set for saturated fatty acids, *trans* fatty acids, or cholesterol (see Chapters 8 and 9). This chapter provides some guidance in ways of minimizing the intakes of these three nutrients while consuming a nutritionally adequate diet.

INTRODUCTION

Unlike micronutrients, macronutrients (fat, carbohydrate, and protein) are sources of body fuel that can be used somewhat interchangeably. Thus, for a certain level of energy intake, increasing the proportion of one macronutrient necessitates decreasing the proportion of one or both of the other macronutrients. The majority of energy is consumed as carbo-

hydrate (approximately 35 to 70 percent, primarily as starch and sugars), and fat (approximately 20 to 45 percent), while the contribution of protein to energy intake is smaller and less varied (10 to 23 percent) (Appendix Tables E-3, E-6, and E-17). Therefore, a high fat diet (high percent of energy from fat) is usually low in carbohydrate and vice versa. In addition to these macronutrients, alcohol can provide on average up to 3 percent of energy of the adult diet (Appendix Table E-18).

A small amount of carbohydrate and as *n*-6 (linoleic acid) and *n*-3 (α -linolenic acid) polyunsaturated fatty acids and a number of amino acids that are essential for metabolic and physiological processes, are needed by the brain. The amounts needed, however, each constitute only a small percentage of total energy requirements. Food sources vary in their content of particular macro- and micronutrients. While some nutrients are present in both animal- and plant-derived foods, others are only present or are more abundant in either animal or plant foods. For example, animal-derived foods contain significant amounts of protein, saturated fatty acids, long-chain *n*-3 polyunsaturated fatty acids, and the micronutrients iron, zinc, and vitamin B₁₂, while plant-derived foods provide greater amounts of carbohydrate, *Dietary Fiber*, linoleic and α -linolenic acids, and micronutrients such as vitamin C and the B vitamins. It may be difficult to achieve sufficient intakes of certain micronutrients when consuming foods that contain very low amounts of a particular macronutrient. Alternatively, if intake of certain macronutrients from nutrient-poor sources is too high, it may also be difficult to consume sufficient micronutrients and still remain in energy balance. Therefore, a diet containing a variety of foods is considered the best approach to ensure sufficient intakes of all nutrients. This concept is not new and has been part of nutrition education programs since the early 1900s. For example, the first U.S. food guide was developed by the U.S. Department of Agriculture in 1916 and suggested consumption of a combination of five different food groups (Guthrie and Derby, 1998). This food guide has evolved to become known as the Food Guide Pyramid (USDA, 1996). Similarly, Canada has developed Canada's Food Guide to Healthy Eating (Health Canada, 1997).

A growing body of evidence indicates that an imbalance in macronutrients (e.g., low or high percent of energy), particularly with certain fatty acids and relative amounts of fat and carbohydrate, can increase risk of several chronic diseases. Much of this evidence is based on epidemiological studies of clinical endpoints such as coronary heart disease (CHD), diabetes, cancer, and obesity. However, these studies demonstrate associations; they do not necessarily infer causality, such as would be derived from controlled clinical trials. Robust clinical trials with specified clinical endpoints are generally lacking for macronutrients. Of importance, factors other than diet contribute to chronic disease, and multifactorial cau-

sality of chronic disease can confound the long-term adverse effects of a given macronutrient distribution. It is not possible to determine a defined level of intake at which chronic disease may be prevented or may develop. For example, high fat diets may predispose to obesity, but at what percent of energy intake does this occur? The answer depends on whether energy intake exceeds energy expenditure or is balanced with physical activity.

This chapter reviews the scientific evidence on the role of macronutrients in the development of chronic disease. In addition, the nutrient limitations that can occur with the consumption of too little or too much of a particular macronutrient are discussed. In consideration of the inter-relatedness of macronutrients, their role in chronic disease, and their association with other essential nutrients in the diet, Acceptable Macronutrient Distribution Ranges (AMDRs) are estimated and represented as percent of energy intake. These ranges represent (1) intakes that are associated with reduced risk of chronic disease, (2) intakes at which essential dietary nutrients can be consumed at sufficient levels, and (3) intakes based on adequate energy intake and physical activity to maintain energy balance. When intakes of macronutrients fall above or below the AMDR, the risk for development of chronic disease (e.g., diabetes, CHD, cancer) appears to increase.

DIETARY FAT AND CARBOHYDRATE

There are a number of adverse health effects that may result from consuming a diet that is too low or high in fat or carbohydrate (starch and sugars). Furthermore, chronic consumption of a low fat, high carbohydrate or high fat, low carbohydrate diet may result in the inadequate intake of certain essential nutrients.

Low Fat, High Carbohydrate Diets of Adults

The chronic diseases of greatest concern with respect to relative intakes of macronutrients are CHD, diabetes, and cancer. In this section, the relationship between total fat and total carbohydrate intakes are considered. Comparisons are made in terms of *percentage* of total energy intake. For example, a low fat diet signifies a lower percentage of fat relative to total energy. It does not imply that total energy intake is reduced because of consumption of a low amount of fat. The distinction between *hypocaloric* diets and *isocaloric* diets is important, particularly with respect to impact on body weight. Low and high fat diets can still be isocaloric. The failure to identify this distinction has led to considerable confusion in terms of the role of dietary fat in chronic disease.

In the past few decades, the prevalence of overweight and obesity has increased at an alarming rate in many populations, particularly in the United States. Overweight and obesity contribute significantly to various chronic diseases. Consequently, there are two issues to consider for the distribution of fat and carbohydrate intakes in high-risk populations: the distributions that predispose to the development of overweight and obesity, and the distributions that worsen the metabolic consequences in populations that are already overweight or obese. These issues will be considered in the following sections.

Maintenance of Body Weight

A first issue is whether a certain macronutrient distribution interferes with sufficient intake of total energy, that is, sufficient energy to maintain a healthy weight. Sonko and coworkers (1994) concluded that an intake of 15 percent fat was too low to maintain body weight in women, whereas an intake of 18 percent fat was shown to be adequate even with a high level of physical activity (Jéquier, 1999). Moreover, some populations, such as those in Asia, have habitual very low fat intakes (about 10 percent of total energy) and apparently maintain adequate health (Weisburger, 1988). Whether these low fat intakes and consequent low energy consumptions have contributed to a historically small stature in these populations is uncertain.

An issue of more importance for well-nourished but sedentary populations, such as that of the United States, is whether the distribution between intakes of total fat and total carbohydrate influences the risk for weight gain (i.e., for development of overweight or obesity). It has been shown that when men and women were fed isocaloric diets containing 20, 40, or 60 percent fat, there was no difference in total daily energy expenditure (Hill et al., 1991). Similar observations were reported for individuals who consumed diets containing 10, 40, or 70 percent fat, where no change in body weight was observed (Leibel et al., 1992), and for men fed diets containing 9 to 79 percent fat (Shetty et al., 1994). Horvath and colleagues (2000) reported no change in body weight after runners consumed a diet containing 16 percent fat for 4 weeks. These studies contain two important findings: fat and carbohydrate provide similar amounts of metabolic energy predicted from their true energy content, and isocaloric diets provide similar metabolic energy expenditure, regardless of their fat-carbohydrate distribution. In other words, at isocaloric intakes, low fat diets do not produce weight loss.

A number of short- and long-term intervention studies have been conducted on normal-weight or moderately obese individuals to ascertain the effects of altering the fat and energy density content of the diet on body weight (Table 11-1). In general, significant reductions in the percent of

TABLE 11-1 Decreased Fat Intake and Body Weight Change in Normal-Weight or Moderately Obese Individuals

Reference	Study Design	Dietary Fat (% of energy)	Weight Change (kg)	Comments
<i>Short-term studies (< 1 year)</i>				
Boyar et al., 1988	19 women 6-mo intervention Ad libitum diet	34 → 21%	-5.1	Decreased fat intake associated with decreased energy intake
Buzzard et al., 1990	29 postmenopausal women 3-mo parallel Ad libitum diet	38 → 23% 39 → 35%	-2.8 -1.3	Decreased fat intake associated with decreased energy intake
Bloemberg et al., 1991	80 men 26-wk parallel Ad libitum diet	39 → 34% 38 → 37%	-0.94 +0.06	
Kendall et al., 1991	13 women 11-wk crossover Controlled diet	20-25% 35-40%	-2.54 -1.26	Decreased fat intake associated with decreased energy intake Low fat diet, hypocaloric
Leibel et al., 1992	13 men and women 15- to 56-d intervention Controlled diet	0, 40, or 70%	No significant changes in body weight	Isocaloric diets
Westertep et al., 1996	217 men and women 6-mo parallel Ad libitum diet	35 → 33% 36 → 41%	+0.3 +1.1	

Raben et al., 1997	11 women 14-d crossover Ad libitum	46 → 28%	-0.7	Decreased fat intake associated with decreased energy intake
Gerhard et al., 2000	22 women 4-wk crossover Controlled diet	20% 40%	-1.1 -0.3	Low fat diet, hypocaloric
Saris et al., 2000	398 men and women 6-mo parallel Ad libitum diet	36 → 26% 36 → 28% 36 → 37%	-0.9 -1.8 +0.8	Decreased fat intake associated with decreased energy intake
Long-term studies (≥ 1 year)				
Lee-Han et al., 1988	57 women 1-y parallel Ad libitum diet	36 → 23 → 26% 36 → 34 → 36%	6 mo -1.16 +0.07	Decreased fat intake associated with decreased energy intake
Boyd et al., 1990	206 women 1-y parallel Ad libitum diet	37 → 21% 37 → 35%	-1.0 0	
Sheppard et al., 1991	276 women 1- and 2-y parallel Ad libitum diet	0 to 1 y 39 → 22% 39 → 37%	-3.0 -0.4	Decreased fat intake associated with decreased energy intake
		1 y to 2 y 22 → 23%	+1.1	

continued

TABLE 11-1 Continued

Reference	Study Design	Dietary Fat (% of energy)	Weight Change (kg)	Comments
Baer, 1993	70 men 1-y parallel Ad libitum diet	38 → 31% 37 → 36%	-5.0 +1.0	Decreased fat intake associated with decreased energy intake
Kasim et al., 1993	72 women 1-y parallel Ad libitum diet	36 → 18% 36 → 34%	-3.4 -0.8	Decreased fat intake associated with decreased energy intake
Black et al., 1994	76 men and women 2-y parallel Ad libitum diet	40 → 21% 39 → 39%	-2.0 -1.0	
Knopp et al., 1997	137 men 1-y parallel Ad libitum diet	36 → 27% 35 → 22%	-2.9 -2.9	
Stefanick et al., 1998	177 postmenopausal women and 190 men 1-y parallel Ad libitum diet	<u>Women</u> 23% 28% <u>Men</u> 22% 30%	<u>Women</u> -2.7 +0.8 <u>Men</u> -2.8 +0.5	Decreased fat intake associated with decreased energy intake
Kasim-Karakas et al., 2000	54 postmenopausal women 1-y intervention Controlled diet 4 mo Ad libitum diet 8 mo	34 → 14 → 12%	4 mo -1.3 12 mo -5.9	

energy consumed as fat (greater than 4 percent) resulted in small losses in body weight. The only study that provided isocaloric diets showed no differences in weight gain or loss, despite a wide range in the percent of energy from fat (Leibel et al., 1992). Four meta-analyses of long-term intervention studies associating a low fat diet with body weight concluded that lower fat diets lead to modest weight loss or prevention of weight gain (Astrup et al., 2000; Bray and Popkin, 1998; Hill et al., 2000; Yu-Poth et al., 1999). These studies thus suggest that low fat diets (low percentage of fat) tend to be slightly hypocaloric compared to higher fat diets when compared in outpatient intervention trials.

The finding that higher fat diets are moderately hypercaloric when compared with reduced fat intakes under ad libitum conditions provides a rationale for setting an upper boundary for percentage of fat intake in a population that already has a high prevalence of overweight and obesity. However, a second issue must also be addressed: whether the distribution of fat and carbohydrate modifies the metabolic consequences of overweight and obesity. Two of the more important consequences of obesity are dyslipidemic changes in serum lipoproteins (which predispose to CHD) and changes in glucose and insulin metabolism that accentuate an underlying insulin resistance (which may predispose to both CHD and diabetes). These consequences are discussed in the following sections.

Risk of CHD

Low fat, high carbohydrate diets, compared to higher fat intakes, can induce a lipoprotein pattern called the atherogenic lipoprotein phenotype (Krauss, 2001) or atherogenic dyslipidemia (National Cholesterol Education Program, 2001). In populations where people are routinely physically active and lean, the atherogenic lipoprotein phenotype is minimally expressed. In sedentary populations that tend to be overweight or obese, very low fat, high carbohydrate diets clearly promote the development of this phenotype. Whether this phenotype promotes development of coronary atherosclerosis when it is specifically induced by low fat diets is uncertain, but it is a pattern that is associated with increased risk for CHD when expressed in the general American population. The atherogenic lipoprotein phenotype is characterized by higher triacylglycerol and decreased high density lipoprotein (HDL) cholesterol concentrations and small low density lipoprotein (LDL) particles. A predominance of small LDL particles is associated with a greater risk of CHD (Austin et al., 1990), but it is not known if this association is independent of increased triacylglycerol and decreased HDL cholesterol concentrations.

Table 11-2 and Figures 11-1 and 11-2 show that with decreasing fat and increasing carbohydrate intake, plasma triacylglycerol concentrations

TABLE 11-2 Fat and Carbohydrate Intake and Blood Lipid Concentrations in Healthy Individuals

Reference	Study Design ^a	Total Fat/ Carbohydrate Intake (% of energy)
Coulston et al., 1983	11 men and women 10-d crossover P/S = 1.2–1.3	21 41
Bowman et al., 1988	19 men 10-wk parallel P/S = 0.4	29/60 33/58 45/42 46/42
Borkman et al., 1991	8 men and women 3-wk crossover	20/55 P/S = 0.46 50/31 P/S = 0.22
Kasim et al., 1993	72 women 1-y parallel P/S = 0.68–0.75	18 34
Leclerc et al., 1993	7 men and women 7-d crossover	11/64 30/45 40/45
Krauss and Dreon, 1995	105 men 6-wk crossover P/S = 0.69–0.74	24/60 46/39
O'Hanesian et al., 1996	10 men and women 10-d crossover	17/63 P/S = 0.25 28/57 P/S = 2.2 42/39 P/S = 1.7
Jeppesen et al., 1997	10 postmenopausal women 3-wk crossover P/S = 1.0	25/60 45/40
Kasim-Karakas et al., 1997	14 postmenopausal women 4-mo intervention	14 P/S = 1.2 23 P/S = 1.0 31 P/S = 0.9
Yost et al., 1998	25 men and women 15-d crossover P/S = 0.3	25/55 50/30
Straznicky et al., 1999	14 men 2-wk crossover	25/54 P/S = 1.3 47/36 P/S = 0.1
Kasim-Karakas et al., 2000	54 postmenopausal women 4- to 12-mo crossover P/S = 0.64	12/71 14/69 34/50

 Postintervention Blood Lipid Concentration
 (mmol/L)^b

Triacylglycerol	HDL-C	LDL-C
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1.51 ^c	0.98 ^c	
1.02 ^d	1.16 ^d	
0.91 ^c	1.42 ^c	2.35 ^c
1.11 ^c	1.22 ^c	2.17 ^c
0.84 ^c	1.53 ^c	2.59 ^c
1.01 ^c	1.50 ^c	2.40 ^c
0.82 ^c (+49%)	0.84 ^c (-24%)	2.88 ^c (-20%)
0.55 ^c	1.10 ^d	3.60 ^d
1.35 ^c	1.44 ^c (-8%)	2.79 ^c (-10%)
1.25 ^d	1.56 ^d	3.09 ^d
1.11 ^c	1.03 ^c	2.29 ^c
1.29 ^c	1.15 ^d	2.47 ^c
0.87 ^d	1.32 ^e	3.05 ^d
1.59 ^c	1.09 ^c	3.26 ^c
1.13 ^d	1.27 ^d	3.69 ^d
0.8	1.1	2.4
0.8	1.2	2.5
0.8	1.3	3.0
1.97 ^c	1.38 ^c	2.74 ^c
1.29 ^d	1.49 ^d	2.81 ^c
2.47 ^c	1.24 ^c	2.61 ^c
2.10 ^d	1.32 ^d	2.93 ^d
1.85 ^e	1.34 ^d	2.89 ^d
1.14 ^c	1.22 ^c	
0.88 ^d	1.30 ^d	
0.8 ^c	1.05 ^c	2.6 ^c
0.8 ^c	1.28 ^d	3.5 ^d
1.49 ^c	1.40 ^c	3.49 ^c
2.00 ^c	1.29 ^c	3.18 ^c
1.57 ^c	1.53 ^d	3.57 ^c

continued

TABLE 11-2 Continued

Reference	Study Design ^a	Total Fat/ Carbohydrate Intake (% of energy)
Marckmann et al., 2000	20 women 2-wk crossover	28/59 P/S = 0.7 46/41 P/S = 0.4
Obarzanek et al., 2001b	459 men and women, 8-wk parallel	27/58 P/S = 1.1 37/52 P/S = 0.5

^a P/S = polyunsaturated/saturated fatty acid ratio.

^b HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol.

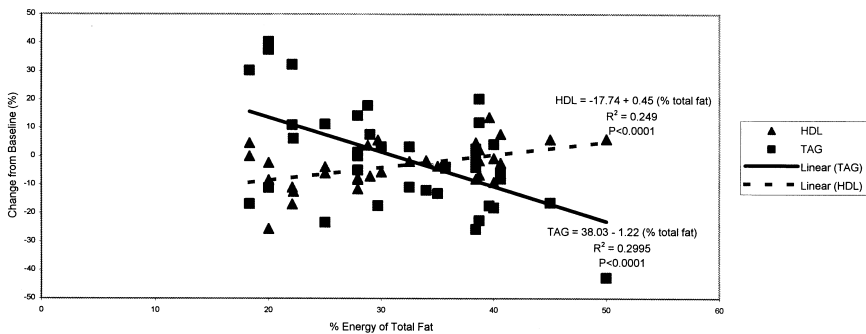


FIGURE 11-1 Relationship between percent of total fat intake and change in triacylglycerol (TAG) (—) and high density lipoprotein (HDL) cholesterol (---) concentrations. Regression equations for percent change in serum TAG and HDL cholesterol predicted by percent total fat in the experimental diets of controlled-feeding studies comparing low fat, high carbohydrate diets to high fat diets. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations (SAS Statistical package, version 8.00, SAS Institute, Inc., 1999). Percent of energy from total fat varied from 18.3% to 50%. All diets were low in saturated fat (less than 10% energy). Using these equations, for every 5% decrease in total fat, HDL cholesterol would decrease by 2.2% and triacylglycerol would increase by 6%.

DATA SOURCES: Berry et al. (1992); Curb et al. (2000); Garg et al. (1988, 1992a, 1994); Ginsberg et al. (1990); Grundy (1986); Grundy et al. (1988); Jansen et al. (1998); Kris-Etherton et al. (1999); Lefevre et al., unpublished; Lopez-Segura et al. (1996); Mensink and Katan (1987); Nelson et al. (1995); Parillo et al. (1992); Pelkman et al. (2001); Perez-Jimenez et al. (1995, 1999, 2001).

Postintervention Blood Lipid Concentration (mmol/L)^b

Triacylglycerol	HDL-C	LDL-C
0.81 ^c	1.34 ^c	2.43 ^c
0.70 ^d	1.56 ^d	2.71 ^d
+0.4	-0.09	-0.29
-0.09	-0.005	-0.05

^{c,d,e} Within each study, LDL-C, HDL-C, or Lp(a) concentrations that are significantly different between treatment groups have a different superscript.

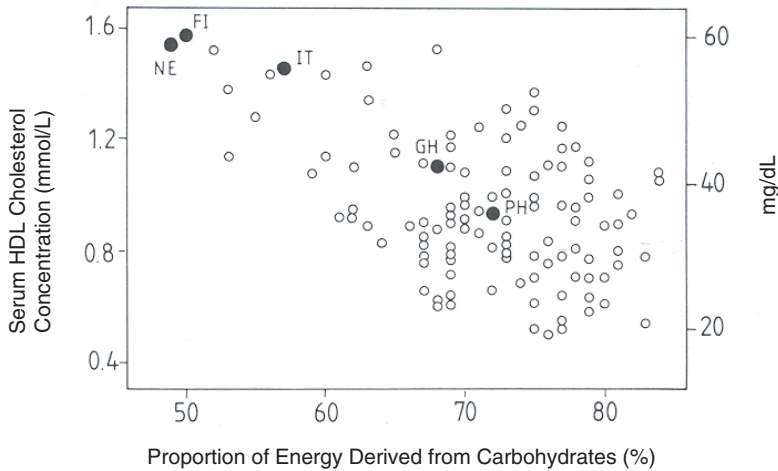


FIGURE 11-2 Relationship between proportion of energy from carbohydrates and serum high density lipoprotein (HDL) cholesterol concentration. ● = Mean values for approximately 120 boys from five countries, ○ = individuals values for boys from the Philippines, FI= Finland, NE = Netherlands, GH = Ghana, IT = Italy, PH = Philippines.

SOURCE: Knuiman et al. (1987).

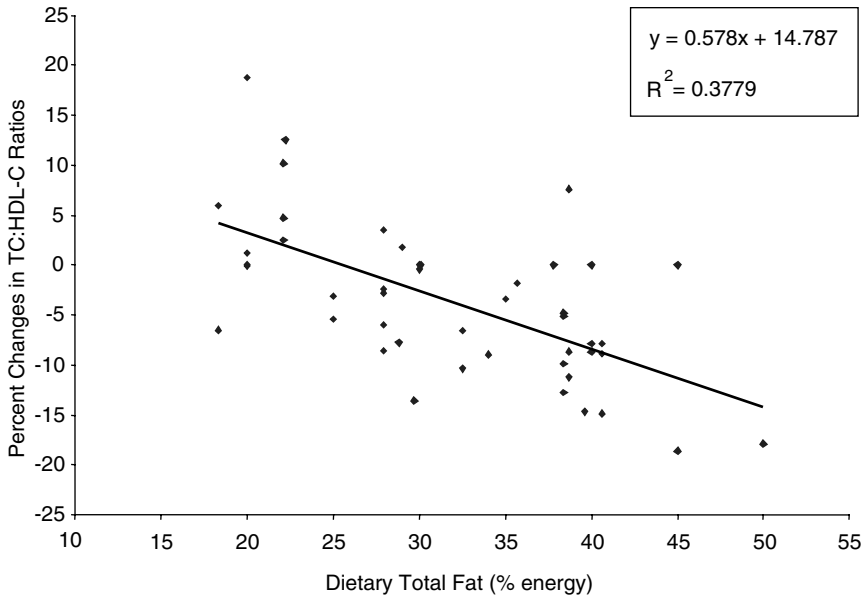


FIGURE 11-3 Relationship between total fat intake and change in total cholesterol (TC):high density lipoprotein (HDL) cholesterol ratio. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations (SAS Statistical package, version 8.00, SAS Institute, Inc., 1999).

DATA SOURCES: Berry et al. (1992); Curb et al. (2000); Garg et al. (1988, 1992a, 1994); Ginsberg et al. (1990); Grundy (1986); Grundy et al. (1988); Jansen et al. (1998); Kris-Etherton et al. (1999); Lefevre et al., unpublished; Lopez-Segura et al. (1996); Mensink and Katan (1987); Nelson et al. (1995); Parillo et al. (1992); Pelkman et al. (2001); Perez-Jimenez et al. (1995, 1999, 2001).

increase and plasma HDL cholesterol concentrations decrease. The reduction in HDL cholesterol concentration with low fat intake results in a rise in the total:HDL cholesterol concentration ratio (Figure 11-3). The total:HDL cholesterol ratio has been shown to be an important risk factor for CHD (Castelli et al., 1992; Kannel, 2000). Whether diet-induced changes in the total:HDL cholesterol ratio predispose to CHD remains unclear (Brussard et al., 1982; Jeppesen et al., 1997; Krauss and Dreon, 1995; West et al., 1990; Yost et al., 1998).

In support of the interventional studies, carbohydrate intake is negatively associated with HDL cholesterol concentrations (Table 11-3). Nonetheless, the association between atherogenic lipoprotein phenotype (higher

TABLE 11-3 Epidemiological Studies on Carbohydrate Intake and Blood Lipid Concentrations

Reference	Study Design	Low Density Lipoprotein (LDL) Cholesterol Concentration	High Density Lipoprotein (HDL) Cholesterol Concentration	Triacylglycerol Concentration
Ernst et al., 1980	4,855 men and women Cross-sectional		Inversely related to carbohydrate intake	
Knuiman et al., 1987	Multicountry regression analysis		Inversely related to carbohydrate intake	
Fehily et al., 1988	653 men Cross-sectional regression analysis	No association	Negative association between carbohydrate intake and HDL concentration	No association
West et al., 1990	719 boys Multicountry regression analysis	Decreased with increased carbohydrate intake	Decreased with increased carbohydrate intake	Increased with increased carbohydrate intake
Tillotson et al., 1997	Prospective cohort, 6-y follow-up			
	< 29% carbohydrate	4.18	1.13	2.11
	29–36% carbohydrate	4.13	1.11	2.26
	36–41% carbohydrate	4.13	1.09	2.23
	41–48% carbohydrate	4.11	1.07	2.25
	> 48% carbohydrate	4.14	1.05	2.13

total:HDL cholesterol ratios) and CHD risk provides one rationale for establishing a lower boundary for the Acceptable Macronutrient Distribution Range (AMDR) for high-risk populations.

Risk of Hyperinsulinemia, Glucose Intolerance, and Type 2 Diabetes

Other potential abnormalities accompanying changes in distribution of fat and carbohydrate intakes include increased postprandial responses in plasma glucose and insulin concentrations. These abnormalities are more likely to occur with low fat, high carbohydrate diets. They potentially could be related to the development of both type 2 diabetes and CHD. In particular, repeated daily elevations in postprandial glucose and insulin concentrations could “exhaust” pancreatic β -cells of insulin supply, which could hasten the onset of type 2 diabetes. Some investigators have further suggested these repeated elevations could worsen baseline insulin sensitivity, which could cause susceptible persons to be at increased risk for type 2 diabetes. This form of diabetes, defined by an elevation of fasting serum glucose concentration, is characterized by two defects in glucose metabolism: insulin resistance, a defect in insulin-mediated uptake of glucose by cells, particularly skeletal muscle cells, and a decline in insulin secretory capacity by pancreatic β -cells (Turner and Clapham, 1998). Insulin resistance typically precedes the development of type 2 diabetes by many years. It is known to be the result of obesity, physical inactivity, and genetic factors (Turner and Clapham, 1998). Before the onset of diabetic hyperglycemia, the pancreatic β -cells are able to respond to insulin resistance with an increased insulin secretion, enough to maintain normoglycemia. However, in some persons who are insulin resistant, insulin secretory capacity declines and hyperglycemia ensues (Reaven, 1988, 1995).

The mechanisms for the decline in insulin secretion are not well understood, but one theory is that continuous overstimulation of insulin secretion by the presence of insulin resistance leads to “insulin exhaustion” and hence to decreased insulin secretory capacity (Turner and Clapham, 1998). Whether insulin exhaustion is secondary to a metabolic dysfunction of cellular production of insulin or to a loss of β -cells is uncertain. The accumulation of pancreatic islet-cell amyloidosis may be one mechanism for loss of insulin-secretory capacity (Höppener et al., 2000).

High carbohydrate diets frequently causes greater insulin and plasma glucose responses than do low carbohydrate diets (Chen et al., 1988; Coulston et al., 1987). These excessive responses theoretically could predispose individuals to the development of type 2 diabetes because of prolonged overstimulation of insulin secretion (Grill and Björklund, 2001). The reasoning is similar to that for insulin resistance, namely, excessive stimulation of insulin secretion over a period of many years could result in

insulin exhaustion, and hence to hyperglycemia (Turner and Clapham, 1998). This mechanism, although plausible, remains hypothetical. Nonetheless, in the mind of some investigators, it deserves serious consideration.

Other consequences of hyperglycemic responses to high carbohydrate diets might be considered. For example, higher postprandial glucose responses might lead to other changes such as “desensitization” of β -cells for insulin secretion and production of glycated products or advanced glycation end-products, which could either promote atherogenesis or the “aging” process (Lopes-Virella and Virella, 1996). Again, these are hypothetical consequences that need further examination.

Epidemiological Evidence. A number of noninterventional, epidemiological studies have shown no relationship between carbohydrate intake and risk of diabetes (Colditz et al., 1992; Lundgren et al., 1989; Marshall et al., 1991; Meyer et al., 2000; Salmerón et al., 1997), whereas other studies have shown a positive association (Bennett et al., 1984; Feskens et al., 1991a).

Interventional Evidence. Interventional studies in healthy individuals on the influence of high carbohydrate diets on biomarker precursors for type 2 diabetes are lacking and the available data are mixed (Table 11-4) (Beck-Nielsen et al., 1980; Chen et al., 1988; Dunnigan et al., 1970; Fukagawa et al., 1990; Rath et al., 1974; Reiser et al., 1979). Factors such as carbohydrate quality, body weight, exercise, and genetics make the interpretation of such findings difficult. Nonetheless, in overweight and sedentary groups (which carry a heavy burden of insulin resistance and are common in North America), the accentuation of postprandial glucose and insulin concentrations that accompany high carbohydrate diets are factors to consider when setting an upper boundary for AMDRs for dietary carbohydrate (and a lower boundary for dietary fat).

Risk of Nutrient Inadequacy or Excess

Diets Low in Fats. For usual diets that are low in total fat, the intake of essential fatty acids, such as *n*-6 polyunsaturated fatty acids, will be low (Appendix K). In general, with increasing intakes of carbohydrate and decreasing intakes of fat, the intake of *n*-6 polyunsaturated fatty acids decreases. Furthermore, low intakes of fat are associated with low intakes of zinc and certain B vitamins.

The digestion and absorption of fat-soluble vitamins and provitamin A carotenoids are associated with fat absorption. Jayarajan and coworkers (1980) reported that the addition of 5 or 10 g of fat to a low fat (5 g) diet

TABLE 11-4 Intervention Studies on Carbohydrate Intake and Biochemical Indicators of Diabetes

Reference	Study Design
Dunnigan et al., 1970	9 men and women 4-wk crossover 31% sucrose Sucrose-free
Rath et al., 1974	6 men 2- to 5-wk crossover 17% sucrose 52% sucrose
Reiser et al., 1979	19 men and women 6-wk crossover 30% starch 30% sucrose
Beck-Nielsen et al., 1980	7-d intervention Normal diet + 250 g glucose Normal diet + 250 g fructose
Chen et al., 1988	8 men 3- to 5-d crossover 85% carbohydrate 41% carbohydrate 30% carbohydrate
Lundgren et al., 1989	1,462 women, Prospective cohort, 12-y follow-up
Fukagawa et al., 1990	6 men 21- to 28-d intervention 40% carbohydrate 69% carbohydrate

a,b,c Within each study, the indicators of diabetes that are significantly different between treatment groups have a different superscript.

 Results

No diet effect on glucose tolerance and plasma insulin

<u>Serum insulin ($\mu\text{g}/\text{mL}$)</u>	<u>Serum glucose (mg/dL)</u>
5.4 ^a	87.0 ^a
11.8 ^b	81.1 ^b

<u>Serum insulin ($\mu\text{units}/\text{mL}$)</u>	<u>Serum glucose (mg/dL)</u>
9.8 ^a	92.5 ^a
11.9 ^b	94.5 ^a

No significant difference in insulin concentrations
 The high fructose diet was accompanied by a
 significant reduction in insulin binding and insulin
 sensitivity

<u>Insulin sensitivity index</u>	<u>Glucose disappearance (%/min)</u>
5.6 ^a	2.2 ^a
6.1 ^b	2.3 ^b
3.9 ^{a,c}	1.6 ^{a,c}
5.6 ^a	2.2 ^a
6.1 ^b	2.3 ^b
3.9 ^{a,c}	1.6 ^{a,c}

Carbohydrate intake of women who developed
 diabetes (212 g/d) was not significantly different
 than women who did not develop diabetes (228 g/d)

<u>Serum insulin (pmol/L)</u>	<u>Glucose disposal ($\mu\text{mol}/\text{kg}/\text{min}$)</u>
67.4 ^a	21.2 ^a
50.2 ^b	27.8 ^b

significantly improved serum vitamin A concentrations. However, the addition of 10 g compared to 5 g did not provide any further benefit. The level of dietary fat has also been shown to improve vitamin K₂ bioavailability (Uematsu et al., 1996). Dose–response data are limited on the amount of dietary fat needed to achieve the optimal absorption of fat-soluble vitamins, but it appears that the level is quite low.

Diets High in Fiber. Most diets that are high in fiber are also high in carbohydrate. High fiber diets have the potential for reduced energy density, reduced energy intake, and poor growth. However, poor growth is unlikely in the United States where most children consume adequate energy and fiber intake is relatively low (Williams and Bollella, 1995). Miles (1992) tested the effects of daily ingestion of 64 g or 34 g of *Dietary Fiber* for 10 weeks in healthy adult males. The ingestion of 64 g/d of *Dietary Fiber* resulted in a reduction in protein utilization from 89.4 to 83.7 percent and in fat utilization from 95.5 to 92.5 percent. Total energy utilization decreased from 94.3 to 91.4 percent. Because most individuals consuming high amounts of fiber would also be consuming high amounts of energy, the slight depression in energy utilization is not significant (Miles, 1992). In other studies, ingestion of high amounts of fruit, vegetable, and cereal fiber (48.3 to 85.6 g/d) also resulted in decreases in apparent digestibilities of energy, crude protein, and fat (Göranzon et al., 1983; Wisker et al., 1988). Again, however, the *Dietary Fiber* intakes were very high, and because the recommendation for *Total Fiber* intake is related to energy intake, the high fiber consumers would also be high energy consumers.

Diets High in Added Sugars. Increased consumption of added sugars can result in decreased intakes of certain micronutrients (Table 11-5). This can occur because of the abundance of added sugars in energy-dense, nutrient-poor foods, whereas naturally occurring sugars are primarily found in fruits, milk, and dairy products that also contain essential micronutrients. Because some micronutrients (e.g., vitamin B₆, vitamin C, and folate), dietary fiber, and phytochemicals were not examined, the association between these nutrients and added sugars intakes is not known. Bowman (1999) used data from Continuing Survey of Food Intakes of Individuals (CSFII) (1994–1996) to assess the relationship between added sugars and intakes of essential nutrients in Americans' diets. The sample ($n = 14,704$) was divided into three groups based on the percentage of energy consumed from added sugars: (1) less than 10 percent of total energy ($n = 5,058$), (2) 10 to 18 percent of total energy ($n = 4,488$), and (3) greater than 18 percent of total energy ($n = 5,158$). Group 3, with a mean of 26.7 percent of energy from added sugars, had the lowest absolute mean intakes of all

the micronutrients, especially vitamin A, vitamin C, vitamin B₁₂, folate, calcium, phosphorus, magnesium, and iron. Compared with Groups 1 and 2, a decreased percentage of people in Group 3 met their Recommended Dietary Allowance (RDA) for many micronutrients. The individuals in Group 3 did not meet the 1989 RDA for vitamin E, vitamin B₆, calcium, magnesium, and zinc. In addition, the high sugar consumers (Group 3) had lower intakes of grains, fruits, vegetables, meat, poultry, and fish compared with Groups 1 and 2. At the same time, Group 3 consumed more soft drinks, fruit drinks, punches, ades, cakes, cookies, grain-based pastries, milk desserts, and candies. Similar trends were also reported by Bolton-Smith and Woodward (1995) and Forshee and Storey (2001), but were not observed by Lewis and coworkers (1992). Emmett and Heaton (1995) reported an overall deterioration in the quality of the diet in heavy users of added sugars.

Using 1990–1991 cross-sectional data, Guthrie (1996) found that women whose diets met their RDA for calcium consumed significantly more milk products, fruit, and grains, and less regular soft drinks than women who did not meet their calcium recommendations. Others have shown that intakes of soft drinks are negatively related to intakes of milk (Guenther, 1986; Harnack et al., 1999; Skinner et al., 1999).

To further look at the association between added sugars and certain micronutrient intakes, the median intakes of various micronutrients at every 5th percentile of added sugars intake was determined using data from the Third National Health and Nutrition Examination Survey (NHANES III) (Appendix J). In addition, the prevalence of subpopulations not meeting the Estimated Average Requirement (EAR) or exceeding the Adequate Intake (AI) for these micronutrients was determined. Because not all micronutrients and other nutrients, such as fiber, were evaluated, it is not known what the association is between added sugars and these nutrients. While the trends are not consistent for all age groups, reduced intakes of calcium, vitamin A, iron, and zinc were observed with increasing intakes of added sugars, particularly at intake levels exceeding 25 percent of energy. Although this approach has limitations, it gives guidance for the planning of healthy diets.

Diets High in Total Sugars. In one large dietary survey, linear reductions were observed for certain micronutrients when total sugars intakes increased (Bolton-Smith and Woodward, 1995), whereas no consistent reductions were observed in another survey (Gibney et al., 1995) (Table 11-6). Bolton-Smith (1996) reviewed the literature on the relation of sugars intake to micronutrient adequacy and concluded that, provided consumption of sugars is not excessive (defined as less than 20 percent of total energy intake), no health risks are likely to ensue due to micronutrient inadequacies.

TABLE 11-5 Survey Data on Added Sugars and Micronutrient Intake

Reference	Study Population/Survey	Diet Information
Nelson, 1991	143 children, 11–12 y	7-d weighed diet record
Rugg-Gunn et al., 1991	405 children, 11–14 y	3-d diet record
Lewis et al., 1992	Nationwide Food Consumption Survey (1977–1978)	
Bolton-Smith and Woodward, 1995	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Food frequency questionnaire
Gibson, 1997	1,675 boys and girls, 1.5–4.5 y U.K. National Diet and Nutrition Survey of Children	4-d weighed diet record
Bowman, 1999	Continuing Survey of Food Intakes by Individuals (1994–1996)	Two 24-h recalls
Forshee and Storey, 2001	Continuing Survey of Food Intakes by Individuals (1994–1996)	

Added Sugars Intake (% of energy)	Change in Micronutrient Intake
16 21 27	Decrease in nicotinic acid for girls
10 20	Decrease in vitamin D, protein
Percentile of intake 26th–75th > 75th	Decrease in calcium
Men: 1.0–6.2, 6.3–8.9, 9.0–13.0, 13.1–15.7, 15.8–47.9 Women: 0.8–4.8, 4.9–6.3, 6.4–8.1, 8.2–11.6, 11.7–50.2	Linear reduction in vitamin E, vitamin C, and vitamin A for both men and women
< 12 12–16 16–20 20–25 > 25	Decrease in zinc, calcium, riboflavin
< 10 10–18 > 18	Decrease in calcium Decrease in vitamin A, vitamin E, vitamin C, niacin, vitamin B ₆ , folate, vitamin B ₁₂ , phosphorus, magnesium, iron, zinc, copper; large decrease in calcium
	Negative correlation between added sugar intake and intake of vitamin A, calcium, and folate

TABLE 11-6 Survey Data on Total Sugar and Micronutrient Intake

Reference	Study Population/Survey	Diet Information
Gibson, 1993	2,705 children Department of Health Survey of British School Children	7-d weighed food record
Bolton-Smith and Woodward, 1995	11,626 men and women, 25–64 y Scottish Heart Health and MONICA studies	Food frequency questionnaire
Gibney et al., 1995	8,296 men and women Nationwide Food Consumption Survey (1987–1988)	3-d food record
Nicklas et al., 1996	568 children, 10 y Bogalusa Heart Study	24-h dietary recall
Farris et al., 1998	568 children, 10 y Bogalusa Heart Study	24-h dietary recall

The impact of total sugar intake on the intake of micronutrients does not appear to be as great as for added sugars. Furthermore, a preliminary analysis of data from NHANES III on the intake of various micronutrients at every 5th percentile of total sugar intake did not reveal any significant associations as was observed for added sugars (Appendix J).

High Fat, Low Carbohydrate Diets of Adults

Risk of Obesity

Epidemiological Evidence. Cross-country epidemiological data of dietary fat intake and obesity have yielded mixed results (Bray and Popkin, 1998;

Total Sugar Intake (% of energy)	Change in Micronutrient Intake
< 20.7	Decrease in iron, nicotinic acid
20.7–25.2	Large decrease in iron, nicotinic acid
> 25.2	No marked changes in micronutrient intake
Men: 2.5–12.0, 12.1–14.7, 14.8–17.2, 17.3–20.7, 20.8–51.4	Linear reduction in vitamin E, retinol, and vitamin A intake
Women: 1.5–11.7, 11.8–14.1, 14.2–16.3, 16.4–19.6, 19.7–52.8	Linear reduction in vitamin E, retinol, carotene, and vitamin A intake
< 10	
10–24	Decrease in riboflavin, thiamin, calcium, iron, zinc, vitamin A
> 24	Decrease in vitamin B ₆ , vitamin E
18.0	
22.1	
26.4	
31.2	Decrease in percent meeting the Recommended Dietary Allowance for niacin and zinc
16.1	
23.5	Linear reduction in vitamin B ₆ , vitamin E, thiamin, iron, zinc, and niacin intake with increasing total sugar intake
28.2	
35.6	

Willett, 1998). In some countries, low fat, high carbohydrate diets are associated with a low prevalence of obesity, whereas in others they are not.

Within-country surveys of dietary intake and body mass index (BMI) have also yielded mixed results. Many case-control and prospective studies failed to find a strong correlation between percent of energy intake from fat and body weight (Heitmann et al., 1995; Lissner et al., 2000; Ludwig et al., 1999b; Rissanen et al., 1991; Samaras et al., 1998; Willett, 1998), whereas some did find significant associations (Bray and Popkin, 1998; Dreon et al., 1988; George et al., 1990; Klesges et al., 1992; Miller et al., 1990; Romieu et al., 1988; Tucker and Kano, 1992). Colditz and coworkers (1990) observed no association between fat intake and weight gain prospectively, but did find a positive association between previous weight

gain and high fat intake. One statistically well-designed study that included direct measurements of body fat and considered potentially confounding factors such as exercise concluded that total dietary fat was positively correlated with fat mass (adjusted for fat-free mass, $r = 0.22$, $p < 0.0001$) in adults (Larson et al., 1996). Most multiple regression studies found that about 3 percent of the total variance in body fatness was explained by diet, though some studies placed the estimate at 7 to 8 percent (Westerterp et al., 1996). Longitudinal studies generally supported dietary fat as a predictive factor in the development of obesity (Lissner and Heitmann, 1995). However, bias in subject participation, retention, and underreporting of intake may limit the power of these epidemiological studies to assess the relationship between dietary fat and obesity or weight gain (Lissner et al., 2000).

Another line of evidence often cited to indicate that dietary fat is not an important contributor to obesity is that although there has been a reduction in the percent of energy from fat consumed in the United States, there has been an increase in energy intake and a marked gain in average weight (Willett, 1998). Survey data showed an increase in total energy intake over this period (McDowell et al., 1994), so that despite the decline in percent of energy from fat, the total intake of fat (g/d) remained stable. Another study that used food supply data showed that fat intake may indeed be rising in the United States (Harnack et al., 2000).

Mechanisms for Obesity and Interventional Evidence. Several mechanisms have been proposed whereby high fat intakes could lead to excess body accumulation of fat. Foods containing high amounts of fat tend to be energy dense, and the fat is a major contributor to the excess energy consumed by persons who are overweight or obese (Prentice, 2001). The energy density of a food can be defined as the amount of metabolizable energy per unit weight or volume (Yao and Roberts, 2001); water and fat are the main determinants of dietary energy density. Energy density is an issue of interest to the extent that it influences energy intake and thus plays a role in energy regulation, weight maintenance, and the subsequent development of obesity.

Three theoretical mechanisms have been identified by which dietary energy density may affect total energy intake and hence energy regulation (Yao and Roberts, 2001). Some studies suggest that, at least in the short-term, individuals tend to eat in order to maintain a constant volume of food intake because stomach distension triggers vagal signals of fullness (Duncan et al., 1983; Lissner et al., 1987; Seagle et al., 1997; Stubbs et al., 1995a). Thus, consumption of high energy-dense foods could lead to excess energy intake due to the high energy density to small food volume ratio.

A second proposed mechanism is that high energy-dense foods are often more palatable than low energy-dense foods (Drewnowski, 1999; Drewnowski and Greenwood, 1983). A survey of American adults reported that taste is the primary influence for food choice (Glanz et al., 1998). In single-meal studies, high palatability was also associated with increased food consumption (Bobroff and Kissileff, 1986; Price and Grinker, 1973; Yeomans et al., 1997). These results suggest that high energy-dense foods may be overeaten because of effects related to their high palatability.

The third mechanism is that energy-dense foods reduce the rate of gastric emptying (Calbet and MacLean, 1997; Wisen et al., 1993). This reduction, however, does not occur proportionally to the increase in energy density. Although energy-dense foods reduce the rate at which food leaves the stomach, they actually increase the rate at which energy leaves the stomach. Thus, because energy-containing nutrients are digested more quickly, nutrient levels in the blood fall quicker and hunger returns (Friedman, 1995). While a subjective measure, highly palatable meals have also been shown to produce an increased glycemic response compared with less palatable meals that contain the same food items that are combined in different ways (Sawaya et al., 2001). This suggests a generalized link among palatability, gastric emptying, and glycemic response in the underlying mechanisms determining the effects of energy density on energy regulation. Further research on this potential link is needed.

Researchers have used instruments such as visual analogue scales to measure differences in appetite sensations (e.g., hunger and satiety) between treatments in order to examine the effects of altering nutrients that play a major role in energy density, such as dietary fat, on energy regulation (Flint et al., 2000). A number of studies have been conducted in which preloads of differing energy density were given and hunger and satiety were measured either at the subsequent meal or for the remainder of the day. In the studies that administered preloads that had constant volume but different energy content (energy density was altered by changing dietary fat content), there was no consistent difference in subsequent satiety or hunger between the various test meals (Durrant and Royston, 1979; Green et al., 1994; Hill et al., 1987; Himaya et al., 1997; Hulshof et al., 1993; Louis-Sylvestre et al., 1994; Porrini et al., 1995; Rolls et al., 1994). However, in those studies using isoenergetic preloads that differed in volume (energy density was altered by changing dietary fat content), there was consistently increased satiety and reduced hunger after consumption of the low energy-dense preload meals (i.e., those with higher volume) (Blundell et al., 1993; Holt et al., 1995; van Amelsvoort et al., 1989, 1990). It has been reported, however, that diets low in fat and high in carbohydrate may lead to more rapid return of hunger and increased snacking between meals (Ludwig et al., 1999a).

These data suggest that in the short-term, low energy-dense foods appear to increase satiety and decrease hunger compared to high energy-dense foods. Because individuals were blinded to the dietary content of the treatment diets, the results from these studies demonstrate the short-term effects of energy density after controlling for cognitive influences on food intake.

It is important that cognitive factors are taken into account during the interpretation of results of preload studies. When individuals were aware of dietary changes, they generally (Ogden and Wardle, 1990; Shide and Rolls, 1995; Wooley, 1972), but not always (Mattes, 1990; Rolls et al., 1989), compensated for changes in energy density and thus minimized changes in energy intake.

In well-controlled, short-term intervention studies lasting several days or more, high fat diets were consistently associated with higher spontaneous energy intake (Lawton et al., 1993; Proserpi et al., 1997; Thomas et al., 1992). From short- and longer-term studies, volunteers consistently consumed less dietary energy on low fat, low energy dense diets compared to high energy-dense diets (Glueck et al., 1982; Lissner et al., 1987; Poppitt and Swann, 1998; Poppitt et al., 1998; Stubbs et al., 1995b; Thomas et al., 1992; Tremblay et al., 1989, 1991). The extent to which energy intake was reduced on low energy-dense diets was similar for short- and long-term studies.

An alternative way to study the effects of energy density on energy intake in short-term studies has been to compare energy intake between diets of similar energy density that differ in dietary fat content. Using this approach, when fat content was covertly varied between 20 and 60 percent of energy, there was no significant difference in energy intake between groups (Saltzman et al., 1997; Stubbs et al., 1996; van Stratum et al., 1978). These results suggest that energy density plays a more significant role than fat per se in the short-term regulation of food intake.

During overfeeding, fat may be slightly more efficiently used than carbohydrate (Horton et al., 1995), but in one study, no difference was seen (McDevitt et al., 2000). Thus, high fat diets are not intrinsically fattening, calorie for calorie, and will not lead to obesity unless excess total energy is consumed. It is apparent, however, that with the consumption of high fat diets by the free-living population, energy intake does increase, therefore predisposing to increased weight gain and obesity if activity level is not adjusted accordingly (see Table 11-1). While many of the short-term studies showed a more dramatic effect on weight reduction with reduced fat intake, the long-term studies showed weight loss as well.

Conclusions. Epidemiological studies provide mixed results on the question of whether high fat (low carbohydrate) diets predispose to over-

weight and obesity and promote weight gain. However, a number of short-term studies suggest mechanisms whereby high fat intake could promote weight gain in the long-term. In addition, short- and long-term intervention studies provide evidence that reduced fat intake is accompanied by reduced energy intake and therefore moderate weight reduction or prevention of weight gain. For these reasons, it may be concluded that higher fat intakes are accompanied with increased energy intake and therefore increased risk for weight gain in populations that are already disposed to overweight and obesity, such as that of North America.

Risk of CHD

Epidemiological Evidence. In populations that consume very low fat diets, such as those of rural Asia and Africa, the prevalence of CHD is low (Campbell et al., 1998; Singh et al., 1995; Tao et al., 1989; Walker and Walker, 1978). This fact has led to the concept that low fat diets will protect against CHD. However, this conclusion must be drawn with caution when it is applied to societies in which dietary and exercise habits differ markedly from societies in rural Asia and Africa. In the latter societies, people are highly active and lean (Singh et al., 1995; Walker and Walker, 1978). Both of these factors independently reduce risk for CHD and could offset any potentially detrimental effects of very low fat diets. For this reason, the effects of low fat diets must be viewed in the context of current societal habits in the United States and Canada and of changing habits in developing countries. Furthermore, in more recent years it has become clear that the relationship between fat intake and CHD is related more to the quality of fat than to the quantity. The relationship is clearly shown by cross-population studies. For example, some Mediterranean populations consume diets that are high in total fat and unsaturated fatty acids but low in saturated fatty acids; in these populations, rates of CHD are relatively low (Keys et al., 1980, 1984). In contrast, in northern Europe, where intakes of saturated fatty acids are high, so are rates of CHD (Keys et al., 1980, 1984). Two epidemiological studies showed no relationship between carbohydrate intake and LDL cholesterol concentration (Fehily et al., 1988; Tillotson et al., 1997).

In several recent, long-term prospective studies of diet and chronic disease, rates of CHD did not substantially differ across populations that consumed approximately 25 to 45 percent of energy from fat (Ascherio et al., 1996; Hu et al., 1997). Men who developed CHD were shown to consume a slightly higher percentage of energy from fat (34.7 percent) compared with those who did not develop CHD (33.3 percent); however, this small difference in fat intake may not be significant since intake was based on a

24-hour recall, and the data were not adjusted for energy intake (McGee et al., 1984). Furthermore, Hawaiians, who have a higher incidence of CHD than Japanese living in Hawaii, consumed more energy from fat (35 percent) than the Japanese (31 percent) (Bassett et al., 1969). It has been reported that those who developed CHD consumed slightly less energy from carbohydrate compared to those who did not develop CHD (Kushi et al., 1985; McGee et al., 1984) (Table 11-7). Other studies showed no significant association between risk of CHD and total carbohydrate or sugar intake (Bolton-Smith and Woodward, 1994; Liu et al., 1982, 2000).

Interventional Evidence. Increasing fat intake, as a result of increased saturated fat intake, has been shown to increase LDL cholesterol concentrations (Table 11-2), and therefore risk of CHD. Intervention studies that have investigated the effect of carbohydrate intake on LDL cholesterol concentration have shown mixed results (Table 11-3). Two intervention studies agree with the findings of West and colleagues (1990) in that LDL cholesterol concentration increased when the percent of energy from carbohydrate was decreased from 55 to 31 percent (Borkman et al., 1991) and 59 to 41 percent (Marckmann et al., 2000). However, in other studies in which saturated fatty acids have remained constant, varying the percentage of total fat was found to not alter the LDL cholesterol concentration (Garg et al., 1994; Grundy et al., 1988).

Yu-Poth and colleagues (1999) conducted a meta-analysis on 37 intervention studies that evaluated the effects of the National Cholesterol Education Program's Step I and Step II dietary interventions on various cardiovascular disease risk factors. Reductions in plasma total cholesterol and LDL cholesterol concentrations were significantly correlated with reductions in percentages of total dietary fat, but these also included a decrease in saturated fatty acids. Similarly, individuals who consumed the Dietary Approaches to Stop Hypertension diet, which contains 27 percent of energy from fat and only 7 percent of energy from saturated fat, had reduced total and LDL cholesterol concentrations (Obarzanek et al., 2001b). Singh and colleagues (1992) reported that mortality from CHD and other causes was significantly lower when patients with acute myocardial infarction were fed a reduced fat diet.

The increase in LDL cholesterol concentration observed with increased fat intake is due to the strong positive association between total fat and saturated fat intake and the weak association between total fat and polyunsaturated fat intake (Masironi, 1970; Stamler, 1979). This association is also observed in Appendix Tables K-4, K-5, K-7, and K-8. As shown in many studies, saturated fatty acids raise LDL cholesterol concentrations (see Chapter 8), whereas unsaturated fatty acids do not. In fact, *n*-6 polyunsaturated fatty acids reduce serum LDL cholesterol concentrations some-

what compared with carbohydrate (Hegsted et al., 1993; Mensink and Katan, 1992). The adverse effects of saturated fats are discussed in Chapter 8.

It has been postulated that a high fat intake predisposes to a prothrombotic state, which contributes to venous thrombosis, coronary thrombosis, or thrombotic strokes (Barinagarrementeria et al., 1998; Kahn et al., 1997; Salomon et al., 1999). Consumption of diets high in fat (42 or 50 percent) have been shown to increase blood concentrations of the prothrombotic markers, blood coagulation factor VII (VIIc), and activated factor VII (VIIa) (Bladbjerg et al., 1994; Larsen et al., 1997). The concentration of factor VII is associated with increased risk of CHD (Kelleher, 1992). Furthermore, a significant and positive association was found between the level of dietary fat and factor VIIc concentration (Miller et al., 1989).

Relation of Intakes of Saturated Fatty Acids and Total Fat. When fat is consumed in typical foods it contains a mixture of saturated, polyunsaturated, and monounsaturated fatty acids. Even when the content of saturated fatty acids in consumed fats is relatively low, the intakes of these fatty acids can be high with high fat intakes. For example, if all of the dietary fats consumed were low in saturated fatty acids (e.g., 20 percent of fat energy), a total fat intake of 35 percent of total energy would yield a saturated fatty acid intake of 7 percent of total energy. Consumption of a variety of dietary fats would likely result in an even higher percentage of saturated fatty acids. Thus, in practical terms, it would be difficult to avoid high intakes of saturated fatty acids for most persons if total fat intakes exceeded 35 percent of total energy. This fact is revealed by attempts to create a variety of heart-healthy menus (National Cholesterol Education Program, 2001). Moreover, data from CSFII show that with increased fat intake, there tends to be a greater increase in saturated fatty acid intake relative to polyunsaturated fatty acid intake (Appendix Tables K-4, K-5, K-7, K-8; Masironi, 1970; Stamler, 1979). It should be pointed out, however, that when replacing saturated fatty acid intake with carbohydrate, there is no effect on the total cholesterol:HDL cholesterol ratio (Mensink and Katan, 1992).

Conclusions. A few case-control studies have shown an association between total fat intake and risk for CHD. However, a detailed evaluation of these studies shows that it is not possible to separate total fat intake from saturated fatty acid intake, which is known to raise LDL cholesterol concentrations. Unsaturated fatty acids, which do not raise LDL cholesterol concentrations compared with carbohydrate, have not been implicated in risk for CHD through adverse effects on lipids or other risk factors. Nonetheless, practical efforts to create "heart-healthy" menus reveal that intakes of total fat exceeding 35 percent of total energy result in unacceptably high intakes

TABLE 11-7 Epidemiological Studies on Total Carbohydrate and Sugar Intake and Risk of Coronary Heart Disease (CHD)

Reference	Study Design	Results	Comments
Liu et al., 1982	Multi-country bivariate analysis		No significant association between sugar intake and CHD
McGee et al., 1984	7,088 men Prospective cohort, 10-y follow-up	<u>Mean carbohydrate intake (% of energy)</u> Non-CHD 46.5 ^a CHD 45.0 ^b	Those who developed CHD consumed less energy as carbohydrates No association between sugar intake and risk of CHD
		<u>Mean sugar intake (% of energy)</u> Non-CHD 8.0 ^a CHD 8.1 ^a	
Kushi et al., 1985	1,001 men Prospective cohort, 20-y follow-up	<u>Mean carbohydrate intake (% of energy)</u> No CHD death 42.7 ^a CHD death 41.2 ^b <u>Mean sugar intake (% of energy)</u> No CHD death 17.3 ^a CHD death 16.9 ^a	Those who died from CHD consumed significantly less total carbohydrate No association between sugar intake and risk of CHD death

Bolton-Smith and Woodward, 1994	11,626 men and women	Mean sugar intake (% of energy)			No association between risk of CHD and either intrinsic or extrinsic sugar intake	
	Cross-sectional survey	<u>Intrinsic sugar</u>	<u>Men</u>	<u>Women</u>		
		Control	2.06	3.31		
		CHD	1.89-2.19	3.15-3.31		
		Added sugar				
	Control	11.2	8.55			
	CHD	10.5-11.4	8.63-9.10			
Liu et al., 2000	75,521 women	<u>Relative risk of CHD</u>			No significant association between risk of CHD and total carbohydrate, sucrose, or fructose intake	
	Prospective cohort, 10-y follow-up	<u>Quintile of intake</u>	<u>Carbo-hydrate</u>	<u>Sucrose</u>		<u>Fructose</u>
		1	1.00	1.00		1.00
		2	1.02	1.03		0.91
		3	1.09	1.16		0.96
		4	1.03	1.02		1.11
	5	1.23	1.22	1.07		

a, b Within each study, the mean sugar or carbohydrate intakes that are significantly different between treatment groups have a different superscript.

of saturated fatty acids. Moreover, there is the possibility that high fat intakes may enhance a prothrombotic state, although the evidence to support this mechanism for enhancing CHD risk is not strong enough alone to make solid recommendations.

Risk of Hyperinsulinemia, Glucose Intolerance, the Metabolic Syndrome, and Type 2 Diabetes

The metabolic syndrome (insulin-resistance syndrome) describes a clustering of metabolic abnormalities including insulin resistance (with or without glucose intolerance), an atherogenic lipid profile (high triacylglycerol concentration, low HDL cholesterol concentration, and high small, dense LDL), raised blood pressure, a prothrombotic state, and a proinflammatory state (Reaven, 2001). A prothrombotic state is characterized by elevations of plasminogen activator inhibitor and high fibrinogen concentrations, whereas a proinflammatory state is indicated by high c-reactive protein concentrations and other inflammatory markers. Abdominal obesity (waist circumference > 102 cm in men and 88 cm in women) is highly correlated with the presence of insulin resistance (NHLBI/NIDDK, 1998) and is considered to be one of the clinical components of the metabolic syndrome (National Cholesterol Education Program, 2001). An excess of intra-abdominal fat has been identified as being highly associated with the lipid risk factors of the metabolic syndrome (Després, 1993), although total abdominal fat appears to be even more highly predictive of the insulin resistance component of the syndrome (Abate et al., 1996; Peiris et al., 1988). Many persons with the metabolic syndrome eventually develop type 2 diabetes. Thus, both obesity and weight gain are undisputed as major risk factors for the development of type 2 diabetes (defined as fasting plasma glucose ≥ 7 mmol/L) (American Diabetes Association, 2001).

The contribution of diet per se to the development of type 2 diabetes is less clear. In some laboratory animals (e.g., some species of rodents), a high percentage of fat in the diet will induce insulin resistance (Budohoski et al., 1993; Chisholm and O'Dea, 1987). An important question is whether humans are similarly susceptible to this phenomenon independent of the effects of total fat intake on body fat content. Human studies do not provide a clear answer to this question. Thus, if higher intakes of total fat lead to obesity, this in and of itself will reduce insulin sensitivity and predispose to the metabolic syndrome and type 2 diabetes. Recent studies have demonstrated that reduced fat intake and weight loss result in improved glucose tolerance and reduced risk of type 2 diabetes (Swinburn et al., 2001; Tuomilehto et al., 2001).

Epidemiological Evidence. In several population studies, investigators have attempted to determine the contribution of total fat intake to either insulin sensitivity or diabetes. These analyses are difficult to interpret because of the multiplicity of potential confounding variables. Nevertheless, several studies have reported an association between higher fat intakes and insulin resistance as indicated by high fasting insulin concentration, impaired glucose tolerance, or impaired insulin sensitivity (Lovejoy and DiGirolamo, 1992; Marshall et al., 1991; Mayer et al., 1993), as well as to the development of type 2 diabetes (West and Kalbfleisch, 1971). A number of studies, however, have not shown this association (Coulston et al., 1983; Liu et al., 1983; Salmerón et al., 2001). In the Insulin Resistance Atherosclerosis Study, total fat intake univariately correlated with less insulin sensitivity (Mayer-Davis et al., 1997); however, in multiple regression analyses, the presence of obesity appeared to be a confounding variable. Lovejoy and DiGirolamo (1992) likewise found intercorrelations among insulin resistance, total fat intake, and obesity. In contrast, Larsson and coworkers (1999) found no evidence of independent effects of diet on insulin secretory or sensitivity among 74 postmenopausal women. Although several studies suggest an association between total fat intake and the presence of insulin resistance (Lovejoy, 1999; Vessby, 2000), the degree to which the relationship is mediated by obesity remains uncertain. Decreased physical activity is also a significant predictor of higher postprandial insulin concentrations and may confound some studies (Feskens et al., 1994; Parker et al., 1993).

Interventional Evidence. A number of metabolic and intervention studies have examined the relationships among fat intake, fasting glucose and insulin concentrations, areas under curves for plasma glucose and insulin concentrations, insulin sensitivity, glucose effectiveness, and glucose disposal rates (Table 11-8). Several studies reported that diets containing 35 percent fat were accompanied by more impaired glucose tolerance than diets containing 25 percent fat or less (Fukagawa et al., 1990; Jeppesen et al., 1997; Straznicky et al., 1999; Swinburn et al., 1991). Coulston and coworkers (1983) found that a diet containing 41 percent fat led to significantly higher concentrations of insulin in response to meals compared with a diet containing 21 percent fat, but there were no alterations in fasting concentrations. In other studies, no effect on measures of glucose tolerance were reported when diets varied in fat content from 11 to 30 (Leclerc et al., 1993) or 20 to 50 percent fat (Abbott et al., 1989; Borkman et al., 1991; Howard et al., 1991; Thomsen et al., 1999). When the diet was high in fat (50 percent of energy), the area under the curve for plasma glucose and insulin concentration was lower than when the diet had a low fat content (25 percent of energy) (Yost et al., 1998). In this study, the decreased

TABLE 11-8 Interventional Studies on the Effect of Dietary Fat on the Metabolic Parameters for Glucose and Insulin in Healthy Individuals

Reference	Study Design	Percent of Fat	Fasting Glucose	Fasting Insulin
Coulston et al., 1983	11 men and women 10-d crossover	41-21	NSC ^a	NSC
Chen et al., 1988	8 young men 3- to 5-d crossover	0		
		42	ND	ND
		55	ND	ND
	10 elderly men 3- to 5-d crossover	0-37	ND	ND
Abbott et al., 1989	9 men and women 5-wk crossover	42-21	NSC	NSC
Fukagawa et al., 1990	6 young men 21- to 28-d intervention	42-14	Decreased ^b	Decreased ^b
	6 elderly men and women 21- to 28-d intervention	38-15	Decreased ^b	Decreased ^b
Borkman et al., 1991	8 men and women 3-wk crossover	20-50	NSC	NSC
Howard et al., 1991	7 men and women 5- to 7-wk crossover	42-21	NSC	NSC
	9 men and women 3- to 5-wk longitudinal	42-21	NSC	NSC
	12 Caucasians and 12 Pima Indians 2-wk crossover	15-50	Increased ^d	NSC

Area Under the Curve for Glucose	Area Under the Curve for Insulin	Insulin Sensitivity	Glucose Effectiveness	Glucose Disposal/Disappearance Rate
NSC	Decreased ^b	ND ^c	ND	ND
ND	ND	Decreased ^b	NSC	ND
ND	ND	Increased ^b	NSC	ND
ND	ND	Decreased ^b	NSC	ND
ND	ND	ND	ND	ND
ND	ND	ND	ND	Increased ^b
ND	ND	ND	ND	NSC
ND	ND	ND	ND	NSC
NSC	ND	ND	ND	ND
ND	ND	ND	ND	ND
Increased ^e	Increased ^e	NSC	Decreased ^d	ND

continued

TABLE 11-8 Continued

Reference	Study Design	Percent of Fat	Fasting Glucose	Fasting Insulin
Swinburn et al., 1991	24 Caucasians and Pima Indians 2-wk crossover	15–50	Increased ^d	NSC
Leclerc et al., 1993	7 men and women 7-d crossover	11–30	NSC	NSC
Jeppesen et al., 1997	10 women 3-wk crossover	25–45	ND	ND
Yost et al., 1998	25 men and women 15-d crossover	25–50	NSC	NSC
Straznicky et al., 1999	14 men 2-wk crossover	25–47	Increased ^b	NSC
Thomsen et al., 1999	16 men and women 4-wk crossover	28–42	NSC	NSC
Kasim-Karakas et al., 2000	54 postmenopausal women 4- to 12-mo crossover	15, 25, and 34	NSC	NSC

^a NSC = no significant change.

^b $p < 0.05$.

^c ND = no data available.

^d $p < 0.001$.

^e $p < 0.01$.

fat intake was accompanied by an increased percentage of energy from carbohydrate. Garg and coworkers (1992b) reported that insulin sensitivity, indicated by insulin-mediated glucose disposal, was similar after almost a month of ingestion of either a reduced fat (25 percent of energy) or an increased fat diet (50 percent of energy). However, favorable effects of substituting a monounsaturated fat diet for a saturated fat diet on insulin sensitivity were seen at a total fat intake of up to 37 percent of energy (Vessby et al., 2001). A large, long-term intervention trial in adults showed that reducing total fat intake, in part, reduced the risk of the onset of type 2 diabetes by 58 percent (Tuomilehto et al., 2001). Similarly, the Diabetes Prevention Program Research Group reported that diet modification,

Area Under the Curve for Glucose	Area Under the Curve for Insulin	Insulin Sensitivity	Glucose Effectiveness	Glucose Disposal/Disappearance Rate
Increased ^e	Increased ^e	NSC	Decreased ^d	ND
NSC	NSC	ND	ND	ND
NSC	Increased ^d	ND	ND	ND
Decreased ^e	Decreased ^c	ND	ND	ND
Increased ^e	NSC	Decreased ^b	ND	ND
ND	NSC	NSC	NSC	ND
ND	ND	ND	ND	ND

including a reduction of total fat intake from 34 to 27 percent of energy reduced the incidence of type 2 diabetes by 58 percent. Thus, there is no definitive evidence from metabolic and interventional studies that higher fat intakes impair insulin sensitivity in humans as they do in various laboratory animals. Any suggestive links between fat intake and either insulin secretion or sensitivity may be mediated through confounding factors, such as body-fat content, making it difficult to detect any independent contribution of total fat intake to insulin sensitivity.

Conclusions. Although high fat diets can induce insulin resistance in rodents, investigations in humans fail to confirm this effect. Moreover, an

association between dietary fat intake and risk for diabetes has been reported in some epidemiological studies, but this association is most likely confounded by various factors, such as obesity and glycemic index.

Risk of Cancer

High intakes of dietary fat have been implicated in the development of cancer, especially cancer of the lung, breast, colon, and prostate gland. Early support for this theory comes from laboratory animal and cross-cultural studies. The latter were based largely on international food disappearance data and migrant and time trend studies. In recent years, the theory that a diet high in fat predisposes to certain cancers has been weakened by additional epidemiological studies. Early cross-cultural and case-control studies reported strong associations between total fat intake and breast cancer (Howe et al., 1991; Miller et al., 1978; van't Veer et al., 1990), yet a number of epidemiological studies, most in the last 15 years, have found little or no association between fat intake and breast cancer (Hunter et al., 1996; Jones et al., 1987; Kushi et al., 1992; van den Brandt et al., 1993; Velie et al., 2000; Willett et al., 1987, 1992). A meta-analysis of 23 studies yielded a relative risk of 1.01 and 1.21 from cohort and case-control studies, respectively (Boyd et al., 1993).

Total fat intake in relation to colon cancer has strong support from animal studies (Reddy, 1992). However, evidence from epidemiological studies has been mixed (De Stefani et al., 1997b; Giovannucci et al., 1994; Willett et al., 1990). Howe and colleagues (1997) reported no association between fat intake and risk of colorectal cancer from the combined analysis of 13 case-control studies.

Epidemiological studies tend to suggest that dietary fat intake is not associated with prostate cancer (Ramon et al., 2000; Veierød et al., 1997b). Giovannucci and coworkers (1993), however, reported a positive association between total fat consumption, primarily animal fat, and risk of advanced prostate cancer. Findings on the association between fat intake and lung cancer have been mixed (De Stefani et al., 1997a; Goodman et al., 1988; Veierød et al., 1997a; Wu et al., 1994).

Risk of Nutrient Inadequacy or Excess

Diets High in Fat. With increasing intakes of carbohydrate, and therefore decreasing fat intakes, there is a trend towards reduced consumption of dietary fiber, folate, and vitamin C (Appendix K). With higher fat intakes, it is difficult to create practical high fat menus that do not contain unacceptably high amounts of saturated fatty acids (National Cholesterol Education Program, 2001).

Diets Low in Total Sugars. Micronutrient inadequacy can occur when sugars intake is very low (less than 4 percent of total energy) (Bolton-Smith and Woodward, 1995) because many foods that are abundant in micronutrients, such as fruits and dairy products, also contain naturally occurring sugars. A wide variety of foods from different food groups are needed to meet nutrient requirements. Because sugars are important for the palatability of foods, the complete omission of sugars from the diet could endanger overall nutrient adequacy by leading to low total energy intake, as well as low micronutrient intakes (Bolton-Smith, 1996). Although reduced nutrient intakes have been reported, adverse affects on health have not. Individuals with fructose intolerance, a condition caused by fructose-1-phosphate aldolase deficiency, strictly avoid foods containing fructose and sucrose and yet remain in good health (Burmeister et al., 1991).

AMDRs for Adults

When fat intakes are low and carbohydrate intakes are high, intervention studies, with the support of epidemiological studies, demonstrate a reduction in plasma HDL cholesterol concentration, an increase in the plasma total cholesterol:HDL cholesterol ratio, and an increase in plasma triacylglycerol concentration, which are all consistent with an increased risk of CHD. Conversely, many interventional studies show that when fat intake is high, many individuals consume additional energy, and therefore gain additional weight. Weight gain on high fat diets can be detrimental to individuals already susceptible to obesity and can worsen the metabolic consequences of obesity, particularly the risk of CHD. Moreover, high fat diets are usually accompanied by increased intakes of saturated fatty acids, which can raise plasma LDL cholesterol concentrations and further increase risk for CHD. Based on the apparent risk for CHD that may occur on low fat diets, and the risk for increased energy intake and therefore obesity with the consumption of high fat diets, the AMDR for fat and carbohydrate is estimated to be 20 to 35 and 45 to 65 percent of energy, respectively, for all adults. By consuming fat and carbohydrate within these ranges, the risk for obesity, as well as for CHD and diabetes, can be kept at a minimum. Furthermore, these ranges allow for sufficient intakes of essential nutrients while keeping the intake of saturated fatty acids at moderate levels.

There is no lower limit of intake and no known adverse effects with the chronic consumption of *Dietary Fiber* or *Functional Fiber* (Chapter 7). Therefore, an AMDR is not set for *Dietary*, *Functional*, or *Total Fiber*.

Maximal Intake Level for Added Sugars

Data from various national surveys show that increasing intakes of added sugars is associated with a decline in the consumption of certain micronutrients, thus increasing the prevalence of those consuming below the EAR or the AI. While such trends exist, it is not possible to determine a defined intake level at which inadequate micronutrient intakes occur. Furthermore, at very low or very high intakes, unusual eating habits most likely exist that allow for other factors to contribute to low micronutrient intakes. Based on the available data, no more than 25 energy from added sugars should be consumed by adults. A daily intake of added sugars that individuals should aim for to achieve a healthy diet was not set. Total sugars intake can be lowered by consuming primarily sugars that are naturally occurring and present in micronutrient-rich foods, such as milk, dairy products, and fruits, while at the same time limiting consumption of added sugars from foods and beverages that contain minimal amounts of micronutrients, such as soft drinks, fruitades, and candies.

Low Fat, High Carbohydrate Diets of Children

Fat Oxidation

Jones and colleagues (1998) reported a significantly greater fat oxidation in children (aged 5 to 10 years, $n = 12$) than in adults (aged 20 to 30 years, $n = 6$). Breath $^{13}\text{CO}_2$ was measured in 12 children and 6 men following an oral bolus dose of $[1-^{13}\text{C}]$ palmitic acid (10 mg/kg of body weight) consumed with a test meal. Breath $^{13}\text{CO}_2$ excretion was less in the men (35.1 percent of absorbed dose, $P = 0.005$) than in the children (57.0 percent of absorbed dose). The children exhibited greater fat oxidation in the postabsorptive state (2.43 g/h) and postprandial (11.89 g/6 h) states than the men (0.93 g/h postabsorptive, 9.86 g/6 h postprandial). The children also had greater fat oxidation compared with women studied previously by these investigators (0.53 g/h postabsorptive, 0.03 g/6 h postprandial) (Murphy et al., 1995).

Growth

Most studies have reported no effect of the level of dietary fat on growth when energy intake is adequate (Boulton and Magarey, 1995; Fomon et al., 1976; Lagström et al., 1999; Lapinleimu et al., 1995; Niinikoski et al., 1997a, 1997b; Obarzanek et al., 1997; Shea et al., 1993). Two well-controlled trials demonstrated that a diet providing less than 30 percent energy from fat does not result in adverse effects on growth in

children up to 8 years of age (Lapinleimu et al., 1995; Niinikoski et al., 1997a, 1997b). A cohort study with a 25-month follow-up showed that there was no difference in stature or growth of children aged 3 to 4 years at baseline across quintiles (27 to 38 percent) of total fat intake (Shea et al., 1993). The Special Turku Coronary Risk Factor Intervention Project showed no difference in growth of children 7 months to 5 years of age when they consumed 21 to 38 percent fat (Lagström et al., 1999). Niinikoski and coworkers (1997a) reported that 1-year-old children who consistently consumed low fat diets (less than 28 percent) grew as well as children with higher fat intakes. A cohort study showed that children aged 2 years in the lower tertile of fat intake (less than 30 percent) had a height and weight similar to that of the higher fat intake groups (Boulton and Magarey, 1995).

A few studies have observed impaired growth among hypercholesterolemic children who were advised to consume 30 percent or less of energy from fat. However, the energy intake was also reduced (Lifshitz and Moses, 1989) or not reported (Hansen et al., 1992). In a group of Canadian children 3 to 6 years of age, a fat intake of less than 30 percent of energy was associated with an odds ratio of 2.3 for weight-for-age below the 50th percentile at 6 years of age (Vobecky et al., 1995). A comprehensive evaluation of the effect of diet-related variables on the growth of children under 6 years of age from 18 Latin American countries (FAO/WHO, 1996) demonstrated that diets providing less than 22 percent energy from fat and with less than 45 percent of total fat from animal fat were related to low birth weight, underweight, and stunting (height-for-age ≤ 2 standard deviations) (Uauy et al., 2000). The dietary determinants that best explained low birth weight were energy, protein, and animal fat, suggesting that high-quality animal protein and associated nutrients are important for growth and development.

Risk of Nutrient Inadequacy or Excess

Diets High in Carbohydrate and Low in Fats. Because the diets of young children are less diversified than that of adults, the risk of inadequate micronutrient intake is increased in these children. A cohort of 500 children aged 3 to 6 years showed that those who consumed less than 30 percent of energy from fat consumed less vitamin A, vitamin D, and vitamin E compared with those who consumed higher intakes of fat (30 to 40 percent) (Vobecky et al., 1995). Calcium intakes decreased by more than 100 mg/d for 4- and 6-year-old children who consumed less than 30 percent of energy from fat (Boulton and Magarey, 1995). Lagström and coworkers (1997, 1999), however, did not observe reduced intakes of micronutrients in children with low fat intakes (26 percent).

The Dietary Intervention Study in Children (DISC), a multi-center, randomized trial of children 8 to 10 years of age, demonstrated that reducing the intake of fat to 28 percent of energy over a 3-year period increased the percentage of children not meeting the RDA for vitamin E and zinc; however, no biochemical evidence of deficiency of these nutrients was found (Obarzanek et al., 1997). Tonstad and Sivertsen (1997) observed no reduced intake of micronutrients with diets providing 25 percent of energy as fat. Nicklas and coworkers (1992) reported reduced intakes of certain micronutrients by 10-year-old children who consumed less than 30 percent of energy as fat; however, this level of fat intake was associated with marked increased intakes of candy. It has been suggested that children who consume a low fat diet can meet their micronutrient recommendation by appropriate selection of certain low fat foods (Peterson and Sigman-Grant, 1997). This is especially true for older children whose diets are typically more diverse.

The tables in Appendix K show the intakes of nutrients at various intake levels of carbohydrate. With increasing intakes of carbohydrate, and therefore decreasing intakes of fat, the intake levels of calcium and zinc markedly decreased in children 1 to 18 years of age (Appendix Tables K-1 through K-3).

Diets High in Added Sugars. Several surveys have evaluated the impact of added sugars intake on micronutrient intakes in children (Table 11-5). Gibson (1997) examined data from the U.K. National Diet and Nutrition Survey of Children Aged 1.5 to 4.5 Years (boys, $n = 848$; girls, $n = 827$) and found evidence of a nutrient dilution effect by nonmilk extrinsic sugars (NMES). Children consuming the highest concentrations of NMES (greater than 24 percent of energy) had intakes of most micronutrients that were between 6 and 20 percent below average. Gibson (1997) concluded that the inverse association of NMES with micronutrient intakes was of most significance for the 20 percent of children with the diets highest in NMES (24.9 percent of energy for boys and 24.5 percent of energy for girls).

In a study of British adolescents, reduced intakes of calcium, phosphorus, iron, vitamin A, vitamin D, and folic acid were associated with increased sugars intakes (mean added sugars intake for the high sugars consumers was 122 g/d for boys and 119 g/d for girls) (Rugg-Gunn et al., 1991). In a smaller survey ($n = 143$), added sugars intakes at levels as high as 27 percent of energy did not have a significant impact on micronutrient intakes (Nelson, 1991).

Similar to that observed for adults using data from NHANES III, increasing the added sugars intake by every 5th percentile tended to be associated with reduced intakes of certain micronutrients, including

calcium, vitamin A, iron, and zinc (Appendix Tables J-1 through J-3, J-6, and J-7). This reduction in micronutrient intake was most significant when added sugars intake levels exceeded 25 percent of energy.

From 1989 to 1995, energy intakes increased for U.S. children aged 2 to 17 years primarily due to increased carbohydrate consumption. Beverages, particularly soft drinks, were important contributors to the increased carbohydrate consumption. During this period, micronutrient intakes (except for iron) did not increase and calcium intakes decreased. This was attributed to the fact that increased energy was largely obtained from soft drinks, which do not add nutrients and displace milk in children's diets, with negative consequences for total diet quality (Morton and Guthrie, 1998).

Children who were high consumers of nondiet soft drinks had lower intakes of riboflavin, folate, vitamin A, vitamin C, calcium, and phosphorus in comparison with children who were nonconsumers of soft drinks (Harnack et al., 1999). Several of these nutrients (folate, vitamin A, and calcium) have been identified in national surveys as "shortfall" or "problem" nutrients among various age and gender groups (ARS, 1998). Ballew and colleagues (2000) demonstrated that in U.S. children, milk consumption was positively associated with the likelihood of achieving recommended vitamin A, vitamin B₁₂, folate, calcium, and magnesium intakes in all age groups. Juice (100 percent fruit or vegetable juice) consumption was positively associated with achieving vitamin C and folate recommended intakes in all age groups, as well as magnesium intake among children aged 6 years and older. Soft drink intake was negatively associated with achieving recommended vitamin A intake in all age groups, calcium in children younger than 12 years of age, and magnesium in children 6 years of age and older.

Others have shown that children who consumed milk at the noon meal had the highest daily intakes of vitamin A, vitamin E, calcium, and zinc, whereas the opposite was true for children who consumed soft drinks and tea (Johnson et al., 1998). Hence, beverages that are major contributors of the naturally occurring sugars, such as lactose and fructose, in the diet (e.g., milk and fruit juice) have been positively associated with nutrient adequacy, while beverages that are the principal source of added sugars in the diet (e.g., soft drinks) have been negatively associated with nutrient adequacy in the diets of U.S. children and adolescents (Ballew et al., 2000; Johnson et al., 1998).

Diets High in Total Sugars. The findings from three surveys on the relationship between total sugars intake and micronutrient intake in children are mixed (Table 11-6). Gibson (1993) did not observe reduced micronutrient intakes when total sugars intake exceeded 25 percent of energy. Nicklas and coworkers (1996) reported that the percent of children meeting the RDA for only niacin and zinc was significantly reduced

when the intake of total sugars exceeded 31 percent of energy. A linear reduction in several micronutrients was observed with increasing total sugars intake (Farris et al., 1998).

High Fat, Low Carbohydrate Diets of Children

Risk of Obesity

In the United States and Canada, there is evidence that children are becoming progressively overweight (Flegal, 1999; Gortmaker et al., 1987; Tremblay and Willms, 2000; Troiano et al., 1995). Furthermore, Serdula and coworkers (1993) reviewed a number of longitudinal studies with varying cut-off levels for obesity and concluded that 26 to 41 percent of obese preschool children and 42 to 63 percent of obese school-age children became obese adults. Clinical evidence of disease associated with excess body weight, reduced physical activity, or high dietary fat intakes, however, are generally absent. The evidence for a role of dietary fat intakes in promoting higher energy intakes and thus promoting obesity in young children is conflicting.

A positive trend in energy intake was associated with an increased percent of energy from fat for children up to 8 years of age (Boulton and Magarey, 1995). A positive correlation between fat intake and fat mass has been reported for boys 4 to 7 years of age (Nguyen et al., 1996). A lack of effect of dietary fat on BMI and adiposity, however, has been reported for children 1.5 to 4.5 years of age (Atkin and Davies, 2000; Davies, 1997).

The DISC trial found no difference in BMI for children 8 to 10 years of age who consumed diets containing 29 or 33 percent fat over a 3-year period (Lauer et al., 2000). However, several studies showed a positive correlation between dietary fat intake and body fatness in children 8 to 12 years of age (Maffeis et al., 1996; Obarzanek et al., 1994; Ricketts, 1997). The average fat intake of nonobese children was measured to be 31 to 34 percent for children 9 to 11 years old, whereas the average fat intake of obese children was 39 percent of energy (Gazzaniga and Burns, 1993). A positive association between fat intake and several adiposity indices were observed, but only for up to 35 percent of energy (Maillard et al., 2000). Other factors that have been associated with increased BMI include physical activity.

Risk of CHD

Clinical studies have provided some evidence that serum cholesterol concentration is modified in children the same way as in adults, with serum total, LDL, and non-HDL cholesterol concentrations being increased by

consuming diets higher in total fat (Lauer et al., 2000; Niinikoski et al., 1996; Obarzanek et al., 2001a; Shannon et al., 1994; Simell et al., 2000; Vartiainen et al., 1986). However, no significant association between dietary fat and LDL cholesterol concentration was observed for boys and girls (aged 8 to 10 years) consuming fat ranging from 10 to 50 percent of energy ($R = -0.04$ to 0.14) (Kwiterovich et al., 1997). Furthermore, a significant positive association between fat intake and total cholesterol concentration was observed in only two of five countries (Knuiman et al., 1983).

Another potential indicator for children's future risk of CHD is the presence of fatty streaks, which are found in the aortas of almost all children over 3 years of age in North America (Holman et al., 1958), and begin to appear in the coronary arteries about 5 to 10 years later than in the aorta (Berenson et al., 1992; McGill, 1968; Stary, 1989; Strong et al., 1992). The prevalence of aortic fatty streaks differs only slightly among children and adolescents of all populations studied, regardless of the frequency of atherosclerosis and coronary artery disease in adults of the respective population (Holman et al., 1958; McGill, 1968). The absence of a relation between aortic fatty streaks and the clinically relevant lesions of atherosclerosis in epidemiological and histological studies has thus raised questions on the clinical significance of fatty streaks in the aorta of young children (Newman et al., 1995; Olson, 2000). The Pathobiological Determinants of Atherosclerosis in Youth Study, however, has provided evidence that an unfavorable lipoprotein pattern (i.e., elevated non-HDL cholesterol and low HDL cholesterol concentrations), obesity, and hyperglycemia are associated with raised fatty streaks in the coronary artery and abdominal aorta in late teenage years (McGill et al., 2000a, 2000b). Similarly, the Bogalusa Heart Study observed a positive association between LDL cholesterol concentration and the percentage of surface with fatty streaks in the aorta (Berenson et al., 1992). These findings are consistent with the hypothesis of the progression of fatty streaks to fibrous plaques under the influence of the prevailing risk factors for coronary artery disease (McGill et al., 2000a, 2000b).

It is still unclear, however, how reduction in serum cholesterol concentration in childhood, if maintained, is associated with risk of CHD in adulthood. In addition, there are still pivotal issues that must be examined further, including the relationship between fatty streaks found in the arteries of young children and the later appearance of raised lesions associated with coronary vascular disease, the effects of dietary total fat modification on predictive risk factors in children, the safety of the diet with respect to total energy and micronutrients for the general population, and the long-term health benefit of establishing healthy dietary patterns early in childhood.

Risk of Nutrient Inadequacy or Excess

Appendix Tables K-1 through K-3 and K-6 provide data from CFSII on the intake of various nutrients based on the level of carbohydrate intake. It can be seen from these tables that as the level of carbohydrate intake decreases, and therefore the level of fat increases, certain nutrients such as folate and vitamin C markedly decrease. Furthermore, with increasing levels of fat intake, the intake of saturated fat relative to linoleic acid intake markedly increases.

AMDRs for Children

The evidence suggests that children have a higher fat oxidation rate compared to adults, and that reduced intake of certain micronutrients can occur with the consumption of low fat diets, whereas there is potential risk of obesity with high fat intakes. High intakes of fat may promote increased risk for CHD and obesity. Dietary fat provides energy, which may be important for younger children with reduced food intakes, particularly during the transition from a diet high in milk to a mixed diet. Thus, there should be a transition from the high fat intake during infancy (55 and 40 percent of energy for the 0- to 6- and 7- to 12-months age groups, respectively) (Chapter 8) to an AMDR for adults (20 to 35 percent of energy). Therefore, it is estimated that the AMDR for fat intake is approximately 30 to 40 percent of energy for children 1 to 3 years of age and 25 to 35 percent of energy for children 4 to 18 years of age. The AMDR for carbohydrate is the same as for adults (45 to 65 percent of energy). The ranges of fat intake include intakes of saturated fat that should be consumed at levels as low as possible while consuming a nutritionally adequate diet.

Maximal Intake Level for Added Sugars

As for adults, no more than 25 percent of energy from added sugars should be consumed by children to ensure adequate micronutrient intakes. For those children whose intake is above this level, added sugars intake can be reduced by consuming sugars that are primarily naturally occurring and present in foods such as milk, dairy products, and fruits, which also contain essential micronutrients.

***n*-9 MONOUNSATURATED FATTY ACIDS**

Approximately 20 to 40 percent of fat is consumed as *n*-9 mono-unsaturated fatty acids, almost all of which is oleic acid (Appendix Tables E-1 and E-8). Monounsaturated fatty acids are not essential fatty acids, but they may have some benefit in the prevention of chronic disease. Although

early research pointed to this potential benefit, most attention has been given to it in the past decade.

Low n-9 Monounsaturated Fatty Acid Diets

Risk of CHD

Epidemiological Evidence. Population data on monounsaturated fatty acid intake and risk of coronary heart disease (CHD) are limited. However, in long-term follow-up studies of the Seven Countries Study, higher intakes of monounsaturated fatty acids were associated with decreased rates of CHD mortality (Keys et al., 1986). Other reports indicate that monounsaturated fatty acids have a neutral or beneficial effect on risk (Hu et al., 1997; Kromhout and de Lezenne Coulander, 1984; Pietinen et al., 1997).

Interventional Evidence. Much work has been conducted and is ongoing to identify the ideal substitute for saturated fat in a blood cholesterol-lowering diet. The effects of a high monounsaturated fatty acid versus a low fat, high carbohydrate diet on serum lipid and lipoprotein concentrations have been a focus of considerable scientific inquiry. Eighteen well-controlled clinical studies that compared the effects of substituting monounsaturated fatty acids versus carbohydrate for saturated fat in a blood cholesterol-lowering diet have recently been reviewed (Kris-Etherton et al., 2000). In these studies, when on both high monounsaturated fat and low fat, high carbohydrate diets, saturated fatty acids contributed to 4 to 12 percent of energy and dietary cholesterol varied from less than 100 up to 410 mg/d. Diets high in monounsaturated fatty acids provided 17 to 33 percent of energy from monounsaturated fatty acids and contained more total fat (33 to 50 percent energy) than the low fat, high carbohydrate diets (18 to 30 percent energy). The low fat, high carbohydrate diets provided 55 to 67 percent of energy from carbohydrate. Compared to baseline values, serum total cholesterol concentrations changed from -17 to +3 percent on the low fat, high carbohydrate diet, whereas it changed from -20 to -3 percent on the high monounsaturated fatty acid diet. The range of decrease in plasma low density lipoprotein (LDL) cholesterol concentration was similar (-22 to +1 percent) among individuals on the two diets. The change in serum triacylglycerol concentrations ranged from -23 to +37 percent for individuals consuming the low fat, high carbohydrate diets and from -43 to +12 percent for diets high in monounsaturated fatty acids. Changes in high density lipoprotein (HDL) cholesterol concentrations ranged from -25 to +2 percent for individuals on the low fat, high carbohydrate diets compared to a -9 to +6 percent change for individuals on diets high in monounsaturated fatty acids.

These data indicate that in weight-stable individuals, a high monounsaturated fatty acid, low saturated fatty acid diet results in a more favorable metabolic profile with respect to total cholesterol, HDL cholesterol, and triacylglycerol concentrations. Figure 11-4 shows that with increased monounsaturated fatty acid intake, there is a favorable reduction in the total cholesterol:HDL cholesterol ratio. Furthermore, a meta-analysis of feeding studies estimated that the regression coefficients for the effects of monounsaturated fatty acids on LDL and HDL cholesterol concentrations were -0.008 and $+0.006$, respectively, suggesting a slight positive benefit (Clarke et al., 1997).

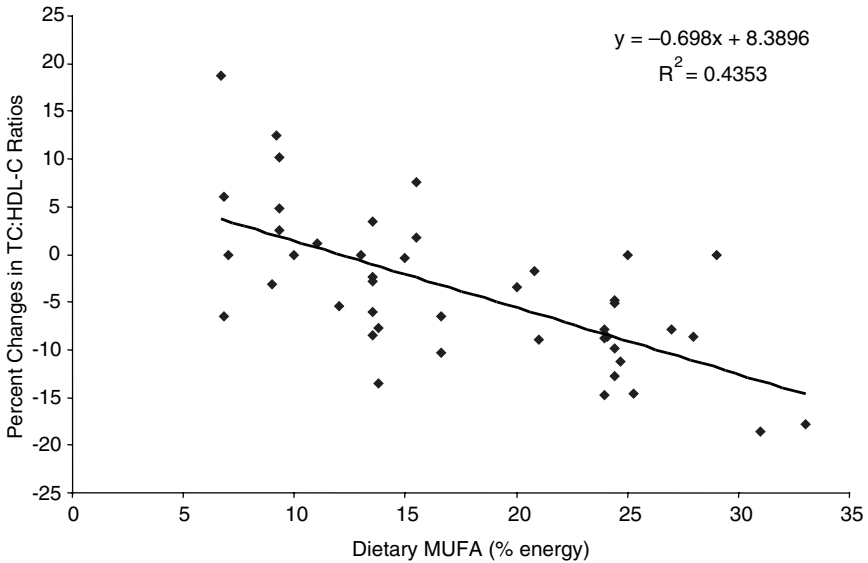


FIGURE 11-4 Relationship between monounsaturated fatty acid (MUFA) intake and total cholesterol (TC):high density lipoprotein cholesterol (HDL-C) concentration ratio. Weighted least-squares regression analyses were performed using the mixed procedure to test for differences in lipid concentrations (SAS Statistical package, version 8.00, SAS Institute, Inc., 1999).

DATA SOURCES: Berry et al. (1992); Curb et al. (2000); Garg et al. (1988, 1992a, 1994); Ginsberg et al. (1990); Grundy (1986); Grundy et al. (1988); Jansen et al. (1998); Kris-Etherton et al. (1999); Lefevre et al., unpublished; Lopez-Segura et al. (1996); Mensink and Katan (1987); Nelson et al. (1995); Parillo et al. (1992); Pelkman et al. (2001); Perez-Jimenez et al. (1995, 1999, 2001).

Risk of Diabetes

Epidemiological studies tend to suggest no association between monounsaturated fatty acid intake and risk of indicators for diabetes (Feskens et al., 1995; Marshall et al., 1997). Similarly, some intervention studies showed no effect of monounsaturated fatty acid intake on indicators for risk of diabetes (Fasching et al., 1996; Roche et al., 1998; Thomsen et al., 1999; Vessby et al., 2001). Uusitupa and coworkers (1994), however, reported a significantly lower area under the curve for plasma glucose concentration and a greater glucose disappearance rate when healthy women consumed a diet rich in monounsaturated fatty acids (19 to 20 percent) compared with a diet rich in saturated fatty acids.

Risk of Cancer

Bartsch and colleagues (1999) reported a protective effect of oleic acid on cancer of the breast, colon, and possibly the prostate. A few epidemiological studies have reported an inverse relationship between monounsaturated fatty acid intake and risk of breast cancer (Willett et al., 1992; Wolk et al., 1998), while a number of studies reported no association (Holmes et al., 1999; Hunter et al., 1996; Jones et al., 1987; Kushi et al., 1992; van den Brandt et al., 1993; van't Veer et al., 1990). Increased consumption of olive oil was associated with significantly reduced breast cancer risk (La Vecchia et al., 1995; Martin-Moreno et al., 1994; Trichopoulou et al., 1995).

A diet high in monounsaturated fatty acid-rich vegetable oils, including olive, canola, or peanut oils, has been associated with a protective effect or no risk of prostate cancer (Norrish et al., 2000; Ramon et al., 2000; Schuurman et al., 1999; Veierød et al., 1997b). Some speculate that the apparent protective effects of olive oil (and other vegetable oils) reflect constituents other than monounsaturated fatty acids including squalene (Newmark, 1999), phenolic compounds, antioxidants, and other compounds (Owen et al., 2000).

No significant association has been reported for monounsaturated fatty acid intake and risk of colorectal cancer (Giovannucci et al., 1994; Howe et al., 1997).

Risk of Nutrient Inadequacy

In the United States, monounsaturated fatty acids provide 12 to 13 percent of energy intake. About 50 percent of these fatty acids are consumed via animal products, primarily meat fat (Jonnalagadda et al., 1995). Vegetable oils that are good sources of monounsaturated fatty acids include canola

oil and olive oil. Although the major sources of monounsaturated fatty acids (animal fat and vegetable oils) are not required to supply essential nutrients, very low intakes of monounsaturated fatty acids would require increased intakes of other types of fatty acids to achieve recommended fat intakes. Consequently, intakes of saturated and *n*-6 polyunsaturated fatty acids would probably exceed a desirable level of intake (see “*n*-6 Polyunsaturated Fatty Acids” and Chapter 8).

High n-9 Monounsaturated Fatty Acid Diets

There are limited data on the adverse health effects from consuming high levels of *n*-9 monounsaturated fatty acids (see Chapter 8, “Tolerable Upper Intake Levels”).

Acceptable Macronutrient Distribution Range

n-9 Monounsaturated fatty acids are not essential in the diet, and the evidence relating low and high intakes of monounsaturated fatty acids and chronic disease is limited. Therefore, an Acceptable Macronutrient Distribution Range (AMDR) for *n*-9 monounsaturated fatty acids is not provided. Nonetheless, practical limits on intakes of monounsaturated fatty acids will be imposed by AMDRs for total fat and other types of fatty acids.

n-6 POLYUNSATURATED FATTY ACIDS

Low n-6 Polyunsaturated Fatty Acid Diets

Risk of CHD

Epidemiological Evidence. Many populations of the world, such as in Crete and Japan, have low total intakes of *n*-6 polyunsaturated fatty acids (e.g., < 4 percent of total energy) without obvious health consequences (Okita et al., 1995; Renaud et al., 1995). However, high intakes of *n*-6 polyunsaturated fats have been associated with blood lipid profiles (e.g., reduced total and low density lipoprotein [LDL] cholesterol, reduced triacylglycerol, and increased high density lipoprotein [HDL] cholesterol concentrations) that are associated with low risk of coronary heart disease (CHD) (Arntzenius et al., 1985; Becker et al., 1983; Sonnenberg et al., 1996). Prospective epidemiological evidence suggests that after controlling for other components of the diet, replacing saturated fats with unsaturated fats decreases risk of CHD (Hu et al., 1997); however, the dose–response

relationship between *n*-6 fatty acids and risk of CHD was not adequately established with certainty. An inverse association between linoleic acid intake and risk of coronary death was observed in several prospective studies (Arntzenius et al., 1985; Gartside and Glueck, 1993), while Pietinen and coworkers (1997) did not observe a relationship between linoleic acid intake and risk of CHD. A cross-sectional study showed that linoleic acid was inversely related to the prevalence of CHD, and this effect was stronger with higher intakes of linolenic acid (Djousse et al., 2001). It is difficult to provide a direct assessment of *n*-6 fatty acids on risk of CHD without taking into consideration the impact of several dietary and nondietary factors, in addition to serum cholesterol concentrations, that lead to CHD and may be modified by the intake of saturated fat and *n*-6 fatty acids.

Interventional Evidence. From the standpoint of blood lipid concentration and CHD, higher *n*-6 polyunsaturated fatty acid intake generally alters blood lipid concentration to result in a decreased risk profile (Katan et al., 1994) (Table 11-9). Controlled trials have examined the effects of substituting *n*-6 fatty acids in the diet to replace carbohydrate or saturated fatty acids (Mensink et al., 1992). In general, any fat that replaces carbohydrate in the diet raises HDL cholesterol and decreases triacylglycerol concentrations, with only small differences between individual fatty acids. *n*-6 Fatty acids decrease LDL cholesterol concentrations to a much greater degree than do saturated fatty acids (Mensink et al., 1992).

Risk of Diabetes

A number of epidemiological studies have been conducted to ascertain whether the quality of fat can affect the risk for diabetes. An inverse relationship was reported for vegetable fats and polyunsaturated fats and risk of diabetes (Colditz et al., 1992; Salmerón et al., 2001; Trevisan et al., 1990). One study reported a positive association between 2-hour glucose concentrations and polyunsaturated fatty acid intake (Mooy et al., 1995). A review of epidemiological studies on this relationship concluded that higher intakes of polyunsaturated fats could be beneficial in reducing the risk for diabetes (Hu et al., 2001).

Risk of Nutrient Inadequacy

Dietary *n*-6 polyunsaturated fatty acids have been reported to contribute approximately 5 to 7 percent of total energy intake of adults (Allison et al., 1999; Fischer et al., 1985), and range up to no more than 10 percent of energy intake (Willett et al., 1987; Appendix Tables E-1 and E-9). The

TABLE 11-9 Interventional Studies on *n*-6 Fatty Acid Intake and Blood Lipid Concentrations

Reference	Study Design	Percent of Energy from Fatty Acid ^a
Becker et al., 1983	12 men	4.3 18:2
	4-wk crossover	6.8 18:2
		18 18:2
Mattson and Grundy, 1985	20 adults	3.9 18:2
	4-wk crossover	29 18:2
McDonald et al., 1989	18 men	7.9 18:2 and 18.8 18:1
	18-d parallel	21.3 18:2 and 7.0 18:1
Zock and Katan, 1992	56 men and women 3-wk crossover	3.8 18:2 (<i>trans</i> diet)
		3.9 18:2 (18:0 diet)
		12 18:2 (18:2 diet)
Kris-Etherton et al., 1993	30 and 33 men 26-d crossover	7.2 → 1.7 18:2
		7.2 → 2.1 18:2
		7.2 → 17.8 18:2
		5.7 → 1.6 18:2
		5.7 → 1.8 18:2
		5.7 → 2.1 18:2
Howard et al., 1995	63 men and women 6-wk crossover	3.0 18:2
		4.2 18:2
		7.0 18:2
		12.8 18:2

^a 18:2 = linoleic acid, 18:1 = oleic acid.

^b LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol.

main sources of *n*-6 polyunsaturated fatty acids are vegetable oils (e.g., soybean oil, safflower oil, and corn oil). Linoleic acid, the predominant *n*-6 polyunsaturated fatty acid, is essential in the diet, and therefore an Adequate Intake (AI) is set (see Chapter 8). Based on the estimated energy requirement for each age group, a minimum intake of 5 percent of energy from linoleic acid would be needed to meet the AI.

Postintervention Blood Lipid Concentration (mmol/L)^b

LDL-C	HDL-C	Total Cholesterol	Triacylglycerol
2.11	1.03	3.44	0.81
1.83	1.12	3.28	0.84
1.68	1.17	3.17	0.79
3.70 ^c	1.01 ^c	5.80 ^c	2.93 ^c
3.10 ^d	0.91 ^c	4.94 ^d	2.61 ^c
2.52 ^c	1.35 ^c	3.97 ^c	0.82 ^c
2.03 ^d	1.19 ^d	3.39 ^d	0.82 ^c
3.07 ^c	1.37 ^c	4.90 ^c	1.00 ^c
3.00 ^c	1.41 ^c	4.89 ^c	1.04 ^d
2.83 ^d	1.47 ^d	4.74 ^d	0.95 ^c
2.92 ^c	1.16 ^c	4.55 ^c	0.99 ^c
2.66 ^c	1.14 ^c	4.27 ^d	0.98 ^c
2.15 ^d	1.16 ^c	3.59 ^e	0.82 ^d
3.23 ^c	1.34 ^c	4.89 ^c	0.90 ^c
2.79 ^d	1.40 ^c	4.45 ^c	0.79 ^c
2.82 ^d	1.34 ^c	4.40 ^c	0.76 ^c
4.14	1.16	5.92	1.43
4.14	1.16	5.89	1.41
4.11	1.14	5.87	1.37
4.03	1.16	5.79	1.34

^{c,d,e} Within each study, the blood lipid concentrations that are significantly different between treatment groups have a different superscript.

High n-6 Polyunsaturated Fatty Acid Diets

Risk of LDL Oxidation

When exposed to oxidant stress, *n-6* fatty acids are vulnerable to attack by free radicals and oxidation into lipid peroxides (Halliwell and Chirico, 1993). An example of lipid peroxidation is LDL oxidation, which plays an important role in the development of atherosclerosis (Steinberg et al.,

1989). Oxidation products of lipids and proteins are found in atherosclerotic plaque and in macrophage foam cells. Compared with mono-unsaturated fatty acids, *in vitro* susceptibility of LDLs to undergo oxidative modification has been shown to increase with increased linoleic acid content in LDLs as a result of increased intakes of linoleic acid (Abbey et al., 1993; Berry et al., 1991; Bonanome et al., 1992; Louheranta et al., 1996; Reaven et al., 1991, 1993, 1994).

The mechanism whereby incorporation of polyunsaturated fatty acids into LDLs enhances susceptibility of LDL oxidation has been studied extensively (Chisolm and Steinberg, 2000; Jessup and Kritharides, 2000). Nonetheless, the hypothesis suggesting that a diet rich in polyunsaturated fat increases the polyunsaturated fatty acid content of LDL particles and increases their susceptibility to oxidation, which in turn leads to atherosclerosis and CHD, still needs to be substantiated in human studies before measures of oxidation can be used as adequate indicators of chronic disease.

Risk of Inflammatory Disorders

There has been significant interest in the use of dietary *n*-6 fatty acids to modulate inflammatory response. γ -Linolenic acid (GLA, 18:3*n*-6) is the Δ 6 desaturase product of linoleic acid and is elongated to dihomo- γ -linolenic acid (DGLA, 20:3*n*-6). The Δ 6 desaturase enzyme is the initial step in desaturation of linoleic acid to arachidonic acid (see Figure 8-1). When given as a dietary supplement, GLA has been found to reduce symptoms of several chronic inflammatory diseases such as rheumatoid arthritis and atopic dermatitis (Andreassi et al., 1997; Leventhal et al., 1993, 1994; Lovell et al., 1981; Tate et al., 1989; Zurier et al., 1996). Even though GLA is the precursor to arachidonic acid, human neutrophils contain an elongase enzyme that converts GLA to DGLA, but they lack the Δ 5 desaturase needed to form arachidonic acid. As a result, GLA supplementation results in accumulation of DGLA, but not arachidonic acid, and a reduction in leukotriene B₄ production in neutrophils (Chilton-Lopez et al., 1996; Johnson et al., 1997; Ziboh and Fletcher, 1992). However, plasma arachidonic acid concentrations increase after GLA supplementation (Johnson et al., 1997), and this could have adverse implications for other problems such as platelet aggregation (Rodier et al., 1993).

Risk of Cancer

An 8-year controlled clinical trial of 846 men demonstrated a significant increase in fatal carcinomas when the amount of *n*-6 polyunsaturated fatty acids fed was 15 percent of energy compared to 4 percent of energy

(Pearce and Dayton, 1971). Epidemiological studies, however, suggest that *n*-6 polyunsaturated fatty acids are not associated (or have an inverse relationship) with cancer. Howe and coworkers (1990) analyzed 12 case-control studies conducted prior to 1990 and determined that the relative risk of breast cancer for an increment of 45 g of polyunsaturated fat per day was only 1.25. More recent case-control and prospective studies further support the minimal effect of *n*-6 polyunsaturated fatty acids on breast cancer risk (Männistö et al., 1999; Toniolo et al., 1994). A similar relationship has been reported for linoleic acid intake and prostate cancer (Giovannucci et al., 1993; Schuurman et al., 1999). A meta-analysis of 7 cohort studies (Hunter et al., 1996) and a combined analysis of 12 case-control studies (Howe et al., 1990) consistently found no relationship between polyunsaturated fats or vegetable fats and risk of breast cancer. The range of intake of polyunsaturated fat was sufficiently large in these combined studies to comfortably conclude that the epidemiological evidence largely contradicts the animal studies; at least to date, no association between polyunsaturated fat, mainly *n*-6 fatty acids, and risk of breast cancer has been detected. Furthermore, in a review of the literature and meta-analyses of case-controlled and prospective epidemiological studies, Zock and Katan (1998) concluded that it was unlikely that high intakes of linoleic acid substantially raise the risk of breast, colorectal, or prostate cancer.

Risk of Nutrient Excess

High intakes of linoleic acid can inhibit the formation of long-chain *n*-3 polyunsaturated fatty acids from α -linolenic acid, which are precursors to the important eicosanoids (see Chapter 8).

Acceptable Macronutrient Distribution Range

Based on the median energy intakes for each age group (Appendix Table E-1), a minimum intake of 5 percent of energy from linoleic acid would be needed to meet the AI (see Chapter 8). An upper boundary of 10 percent of energy is estimated based on the following information: (1) the highest intake of *n*-6 polyunsaturated fatty acids for individuals in North America is approximately 10 percent of energy, (2) there is not a large body of epidemiological evidence that demonstrates the long-term safety of *n*-6 polyunsaturated fatty acid intakes exceeding 10 percent of energy from typical mixed diets, and (3) evidence from human studies demonstrates that enrichment of lipoproteins and cell membranes with *n*-6 polyunsaturated fatty acids contributes to a pro-oxidant state, thus

suggesting caution for recommending intakes that exceed 10 percent of energy. For these reasons, an Acceptable Macronutrient Distribution Range (AMDR) is estimated to be 5 to 10 percent of energy for children and adults.

n-3 POLYUNSATURATED FATTY ACIDS

Low n-3 Polyunsaturated Fatty Acid Diets

Risk of CHD and Stroke

Growing evidence suggests that dietary *n*-3 polyunsaturated fatty acids (eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) reduce the risk of coronary heart disease (CHD) and stroke. *n*-3 Polyunsaturated fatty acids may reduce CHD risk through a multitude of mechanisms by (1) preventing arrhythmias (Billman et al., 1999; Kang and Leaf, 1996; McLennan, 1993), (2) reducing atherosclerosis (von Schacky et al., 1999), (3) decreasing platelet aggregation by inhibiting the production of thromboxane A₂ (Harker et al., 1993), (4) decreasing plasma triacylglycerol concentration (Harris, 1989), (5) slightly increasing high density lipoprotein (HDL) cholesterol concentration and decreasing triacylglycerol concentration (Harris, 1989, 1997), (6) modulating endothelial function (De Caterina et al., 2000), (7) decreasing proinflammatory eicosanoids (James et al., 2000), and (8) moderately decreasing blood pressure (Morris, 1994).

Epidemiological Evidence. Many of the epidemiological studies used fish or fish oil intake as a surrogate for *n*-3 polyunsaturated fatty acid intake. The amounts of *n*-3 fatty acids vary greatly in fish, however, and unless the amounts of *n*-3 fatty acids are known, any conclusions are open to question. Furthermore, other components in fish may have effects that are similar to *n*-3 fatty acids and therefore may confound the results. Early epidemiological studies of Greenland Eskimos suggested that diets high in *n*-3 fatty acids, predominantly EPA and DHA, might protect against CHD (Bang et al., 1976; Dyerberg and Bang, 1979). Subsequent observational epidemiological studies have shown mixed results. In the Zutphen study, eating fish one or two times per week was associated with a significant reduction in CHD mortality (Kromhout et al., 1985). A similar result was found in Rotterdam that compared older people who ate fish with those who did not (Kromhout et al., 1995). In three cohorts from the Seven Countries Study, the consumption of fatty fish, but not total fish or lean fish, was associated with a 34 percent decrease in CHD mortality (Oomen et al., 2000). In the Chicago Western Electric Study, eating more than 35 g/d of fish resulted in decreased CHD mortality, mainly of the nonsudden death type (Daviglus

et al., 1997). Utilizing data from 36 countries, an inverse correlation was found between fish consumption and CHD and all-cause mortality (Zhang et al., 1999). In the Multiple Risk Factor Intervention Trial, CHD mortality and intake of *n*-3 fatty acids from fish were significantly and inversely correlated (Dolecek, 1992). In the Physicians' Health Study, eating fish once per week decreased the relative risk of sudden cardiac death by 52 percent compared with eating fish less than once per month (Albert et al., 1998). In this study, although dietary total *n*-3 fatty acid intake correlated inversely with total mortality, no effect on total myocardial infarction, nonsudden cardiac death, or total cardiovascular mortality was observed. The relative risk of sudden death was only 0.58 when 0.3 to 2.6 g/mo of total *n*-3 fatty acids were consumed. Siscovick and colleagues (1995) reported that a mean intake of 2.9 and 5.5 g/mo of long-chain *n*-3 fatty acids reduced the risk of primary cardiac arrest by 30 and 50 percent, respectively. A cross-sectional study showed that α -linolenic acid was inversely related to the prevalence of CHD; this effect was stronger with increasing intakes of linoleic acid (Djoussé et al., 2001).

In contrast to the above studies, the Health Professionals' Follow-up Study showed no significant association between fish intake and risk of CHD (Ascherio et al., 1995). In 16 cohorts from the Seven Countries Study, an inverse association between fish consumption and CHD mortality was found, but after correcting for saturated fat and flavonoid intakes and smoking, this association was not significant (Kromhout et al., 1996). Finally, in the EURAMIC study, adipose tissue biopsy from cases with first myocardial infarction and controls indicated lower α -linolenic acid intake in cases and a relative risk reduction of 58 percent comparing the highest versus lowest quintile of α -linolenic acid intake (Guallar et al., 1999). After adjustment for classical risk factors, the reduction was only 32 percent and no longer significant. In a meta-analysis of 11 prospective cohort studies of fish intake and CHD mortality, the two largest studies found no protective effect and the two smallest found an inverse relationship, with intermediate size studies showing intermediate benefits (Marckmann and Grønbaek, 1999). This analysis suggested that 40 to 60 g/d of fish provided a reduction in CHD mortality in high-risk, but not low-risk, individuals.

There are fewer data with regard to the effects of fish and *n*-3 polyunsaturated fatty acids on stroke. In the Zutphen Study, consumption of more than 20 g/d of fish was associated with a decrease in the risk of stroke (Keli et al., 1994). In the NHANES Epidemiological Follow-up Study, for white women and for black women and men, but not white men, consumption of fish more than once a week was associated with decreased age-adjusted stroke incidence (Gillum et al., 1996). In the Nurses' Health Study, higher consumption of fish and *n*-3 polyunsaturated fatty acids were associated with a reduced risk of total stroke and thrombotic infarction

but not hemorrhagic stroke (mainly among women who did not take aspirin regularly) (Iso et al., 2001). In contrast, in the Chicago Western Electric Study and the Physicians' Health Study, fish intake was not significantly associated with decreased stroke risk (Morris et al., 1995; Orenca et al., 1996).

Nonclinical Interventional Evidence. Supplementation with fish oil, which is high in EPA and DHA, reduces triacylglycerol concentrations; low density lipoprotein (LDL) and HDL cholesterol concentrations are either increased or unchanged (Ågren et al., 1996; Axelrod et al., 1994; Bhatena et al., 1991; Bønaa et al., 1992; DeLany et al., 1990; Eritsland et al., 1994a; Haglund et al., 1990; Lungershausen et al., 1994; Mori et al., 1991; Nelson et al., 1997a; Sanders and Hinds, 1992; Saynor and Gillott, 1992; Schmidt et al., 1992).

Data from studies on the effects of EPA and DHA as a percent of energy on blood lipid concentrations in healthy individuals are presented in Table 11-10. In general, EPA+DHA intake is associated with small increases in LDL and HDL cholesterol concentrations and a significant decrease in triacylglycerol concentrations (Harris, 1997).

The consumption of 3.65 to 6 g/d of *n*-3 polyunsaturated fatty acids inhibits platelet aggregation, which in turn prevents the risk of CHD (Mori et al., 1997; Tremoli et al., 1995). Some studies, however, did not show an effect on platelet aggregation after the consumption of 4.5 to 6 g/d of EPA+DHA (Nelson et al., 1997b; Turini et al., 1994).

Randomized, Controlled Clinical Trials Evidence. There are four randomized, controlled clinical trials that show a benefit of fish, fish oils, or α -linolenic acid on CHD prevention. In the Diet and Reinfarction Trial (DART), male myocardial infarction (MI) survivors were encouraged to increase their oily fish intake to 200 to 400 g/wk in order to increase EPA and DHA intake. Over a 2-year period, this resulted in a significant reduction in total mortality, with the greatest benefit in a lower rate of fatal MI (Burr et al., 1989a, 1989b). In the DART trial, of the group randomized to ingest dietary fish, a subgroup chose to ingest 1.5 g/d of fish oil capsules rather than to consume fish. The capsule group had a significant reduction in CHD death and a significant reduction in all-cause mortality, suggesting that the benefits of the fish consumption were in the fish oil fraction (Burr et al., 1994). In the Indian Experiment of Infarct Survival, MI survivors were treated with either fish oil capsules (1.08 g/d of EPA) or mustard oil (2.9 g/d of α -linolenic acid) or placebo for 1 year (Singh et al., 1997). The fish oil and mustard oil groups had decreased total cardiac events, non-fatal infarctions, arrhythmias, left ventricular enlargement, and angina

pectoris. The fish oil group, but not the mustard oil group, had decreased cardiac deaths. In the Lyon Diet Heart Study, post-MI patients were randomized into a control group or into an experimental group that received dietary counseling and a special margarine containing α -linolenic acid (de Lorgeril et al., 1994, 1999). The control and experimental groups consumed approximately 0.27 and 0.81 percent of energy as α -linolenic acid, respectively. There was a significant reduction in risk for cardiac death for the experimental group after 27 months, and a reduction after a 4-year follow-up. The extent to which these reductions in risk were due to *n*-3 fatty acids is uncertain.

In another trial, patients with recent MI were randomized to receive 300 mg of vitamin E, 850 mg of *n*-3 fatty acids (EPA+DHA), both, or neither (GISSI-Prevenzione Investigators, 1999). After 3.5 years, the *n*-3 fatty acid group experienced a 15 percent reduction in the primary endpoints of death, nonfatal myocardial infarction, and nonfatal stroke, and a 20 percent reduction in the other primary endpoints of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. This group also experienced a 20 percent reduction in all-cause mortality and a 45 percent reduction in sudden deaths compared with the control group. Vitamin E, in contrast to *n*-3 polyunsaturated fatty acids, had no beneficial effects on cardiovascular endpoints.

n-3 Polyunsaturated fatty acids have also been reported to reduce blood pressure in hypertensive individuals. A meta-analysis of 31 placebo-controlled trials estimated a mean reduction in systolic and diastolic blood pressure of 3.0 and 1.5 mm Hg, respectively (Morris et al., 1993). Furthermore, a statistically significant dose-response effect occurred with the smallest reduction observed with intakes of less than 3 g/d and the largest reduction observed with intakes at 15 g/d.

When 55 individuals were randomized to receive either 5.2 g/d of *n*-3 fatty acids or a placebo for 12 weeks, heart rate variability (naturally occurring irregular heart beats) significantly increased after supplementation with *n*-3 fatty acids (Christensen et al., 1997). Because impaired heart rate variability is associated with increased arrhythmic events (Farrell et al., 1991), this finding supports the hypothesis that *n*-3 polyunsaturated fatty acids have antiarrhythmic effects in humans (Christensen et al., 1997). A more recent study by Christensen and coworkers (1999) reported a dose-response effect on heart rate variability, suggesting antiarrhythmic effects in men but not women, given 3 g/d of EPA plus 2.9 g/d of DHA or 0.9 g/d of EPA plus 0.8 g/d of DHA for 12 weeks. However, the beneficial effect was found only in men with low initial heart rate variability.

TABLE 11-10 *n*-3 Fatty Acid (EPA and DHA)^a Intake and Blood Lipid Concentrations

Reference	Study Design	Percent of Energy from Fatty Acid	Postintervention Blood Lipid Concentration (mmol/L) ^b		
			LDL-C	HDL-C	Triacylglycerol
Flaten et al., 1990	64 men 6-wk parallel	Control diet (0 <i>n</i> -3)		1.28 ^c	1.71 ^c
		Control diet + 2.2 EPA/DHA		1.15 ^c	1.23 ^d
Kestin et al., 1990	33 men 6-wk parallel	0.6 18:3 <i>n</i> -3	4.44 ^c	1.26 ^c	1.62 ^c
		2.7 18:3 <i>n</i> -3	4.55 ^c	1.16 ^c	1.85 ^c
		1.1 EPA/DHA	4.62 ^d	1.28 ^c	1.24 ^d
Bhathena et al., 1991	40 men 10-wk crossover	0 EPA/DHA			1.62 ^c
		2.2 EPA/DHA			1.17 ^d
Bønaa et al., 1992	144 men and women Cross-sectional	0.28 EPA/DHA/22:5	4.65	1.32	1.95
		0.30 EPA/DHA/22:5	4.71	1.31	1.49
		0.52 EPA/DHA/22:5	4.43	1.36	1.32
		0.72 EPA/DHA/22:5	4.47	1.36	1.34
Eritsland et al., 1994a	511 men and women 9-mo parallel	Control diet	5.03 ^c	1.08 ^c	2.08 ^c
		Control diet + 1.46 EPA/DHA	5.11 ^c	1.16 ^c	1.57 ^d
Eritsland et al., 1994b	57 men and women 6-mo parallel	Control diet	4.84 ^c	1.01 ^c	1.80 ^c
		Control diet + 1.4 EPA/DHA	5.03 ^c	0.97 ^c	1.71 ^c

Ågren et al., 1996	55 men 15-wk parallel	0 <i>n</i> -3	2.60 ^c	1.42 ^c
		0.36 <i>n</i> -3 (fish)	2.56 ^c	1.16 ^d
		0.60 <i>n</i> -3 (DHA oil)	2.42 ^c	0.97 ^d
		0.76 <i>n</i> -3 (fish oil)	2.51 ^c	0.89 ^d
Grimsgaard et al., 1997	224 men 7-wk parallel	0.19 <i>n</i> -3 (corn oil)	4.10 ^c	1.40 ^c
		0.52 <i>n</i> -3 (DHA oil)	4.13 ^c	1.42 ^d
		0.55 <i>n</i> -3 (EPA oil)	3.98 ^c	1.34 ^c
Sanders et al., 1997	26 men 3-wk crossover	0 EPA/DHA (saturated fat diet)	2.60 ^c	1.18 ^c
		0 EPA/DHA (<i>n</i> -6 diet)	2.29 ^d	1.19 ^c
		1.5 EPA/DHA (<i>n</i> -3 diet)	2.30 ^d	1.22 ^c

^a EPA = eicosapentaenoic acid, DHA = docosahexaenoic acid.

^b LDL-C = low density lipoprotein cholesterol, HDL-C = high density lipoprotein cholesterol.

^{c,d} Within each study, the blood lipid concentrations that are significantly different between treatment groups have a different superscript.

Risk of Obesity

One study in laboratory mice suggested that diets containing *n*-3 polyunsaturated fatty acids lead to lower levels of fat accumulation compared with diets containing other fatty acids (Hun et al., 1999). Several studies have examined whether *n*-3 polyunsaturated fatty acids affect growth of adipose tissue. Parrish and colleagues (1990, 1991) found that rats given a high fat diet supplemented with fish oil had less fat in perirenal and epididymal fat pads and decreased adipocyte volumes compared with rats fed lard. Adipose tissue growth restriction appeared to be the result of limiting the amount of triacylglycerol in each adipose tissue cell rather than by limiting the number of cells. Rustan and colleagues (1993) found similar results using rats fed either lard or lard supplemented with EPA and DHA. Although body weight gain and mean energy expenditure were similar for both groups, the mean respiratory quotient was significantly higher during both fasting and fed periods in rats fed the EPA+DHA supplement. The researchers concluded that the rats supplemented with *n*-3 fatty acids demonstrated reduced oxidation of fat and increased carbohydrate utilization. Little data exist with respect to the specific effects of dietary *n*-3 polyunsaturated fatty acids on adiposity in humans; therefore, prevention of obesity cannot be considered an indicator at this time.

Risk of Diabetes

Epidemiological Evidence. While several studies have reported a negative relationship between polyunsaturated fatty acid intake and risk of diabetes (Colditz et al., 1992; Salmerón et al., 2001; Trevisan et al., 1990), fish intake has specifically been reported to have a negative association (Feskens et al., 1991b, 1995). A review of the epidemiological data on this association concluded that polyunsaturated fatty acids, and possibly long-chain *n*-3 fatty acids, could be beneficial in reducing the risk of diabetes (Hu et al., 2001).

Interventional Evidence. Studies conducted in rodents have shown that administration of fish oil results in increased insulin sensitivity (Chicco et al., 1996) and corrected hyperinsulinemia (Luo et al., 1996). Substituting a proportion of the fat in a high fat diet with fish oil prevented the development of insulin resistance in rats (Storlien et al., 1987) and normalized insulin action in rats experiencing severe insulin resistance (Storlien et al., 1991). Additionally, rats prone to spontaneous diabetes mellitus that were given EPA in doses of 0.1, 0.3, and 1.0 g/kg/d for 8 months had reduced incidences of diabetes (92, 50, and 17 percent, respectively) (Nobukata et

al., 2000). Thus, animal evidence suggests that the fatty acid composition of the diet may be an important factor in the effect of dietary fat on insulin action.

Whether a change of dietary fat composition will alter insulin sensitivity in humans remains an open question. Studies in humans have demonstrated a relationship between increased insulin sensitivity and the proportion of long-chain *n*-3 polyunsaturated fatty acids in skeletal muscle phospholipids (Borkman et al., 1993; Clore et al., 1998). Supplementation with EPA and DHA resulted in improved insulin sensitivity in diabetic individuals (Popp-Snijders et al., 1987) and increased the insulin-stimulated glucose disposal rate in patients with impaired glucose tolerance (Fasching et al., 1991). However, other studies in nondiabetic individuals (Toft et al., 1995) and individuals with type 2 diabetes (Annuzzi et al., 1991; Luo et al., 1998) reported no beneficial effect of *n*-3 fatty-acid supplementation on insulin action.

Risk of Cancer

Experimental evidence suggests several mechanisms in which *n*-3 polyunsaturated fatty acids may protect against cancer. *n*-3 Polyunsaturated fatty acids, particularly DHA and EPA, have been shown to suppress neoplastic transformation (Takahashi et al., 1992), inhibit cell growth and proliferation (Anti et al., 1992; Calviello et al., 1998; Grammatikos et al., 1994), induce apoptosis (Calviello et al., 1998; Lai et al., 1996), and inhibit angiogenesis (Rose and Connolly, 2000), which may occur by suppressing *n*-6 fatty acid eicosanoid production (see Chapter 8). Animal studies with *n*-3 fatty acid or fish-oil supplementation have shown inhibition of mammary carcinogenesis and tumor growth (Grammatikos et al., 1994; Karmali et al., 1984), colon carcinogenesis (Deschner et al., 1990; Reddy et al., 1991), and prostate tumorigenesis and tumor cell growth (Karmali et al., 1987).

Across-country epidemiological studies have shown an inverse relationship between dietary fish intake and breast cancer incidence and mortality (Kaizer et al., 1989; Sasaki et al., 1993), but the intakes of *n*-3 fatty acids in these studies are not well defined. Moreover, despite these results, most case-control and prospective studies have not reported a protective effect of fish consumption on breast cancer (Willett, 1997). Ecological studies have also shown inverse relationships between fish and fish oil intake and colorectal cancer (Caygill and Hill, 1995; Caygill et al., 1996), although some were nonsignificant (Hursting et al., 1990). Results from case-control and prospective studies have been somewhat equivocal (Boutron et al., 1991). However, Willett and colleagues (1990) found that higher fish consumption was associated with less colon cancer in women. No significant

associations were reported in the few studies that have examined fish consumption and risk of prostate cancer (Giovannucci et al., 1993; Severson et al., 1989; Talamini et al., 1992).

Risk of Nutrient Inadequacy

Vegetable oils, such as soybean oil, flaxseed oil, and canola oil, contain high amounts of α -linolenic acid. Fatty fishes and fish oils provide a mixture of biologically active EPA and DHA. *n*-3 Polyunsaturated fatty acids (α -linolenic acid) are essential in the diet and Adequate Intakes (AIs) have been set (see Chapter 8). Intakes of α -linolenic acid range from approximately 0.6 to 1.2 percent of energy (Appendix Tables E-1 and E-11). Low intakes of α -linolenic acid can result in inadequate biosynthesis of the longer-chain *n*-3 polyunsaturated fatty acids, resulting in an excessive ratio of *n*-6 polyunsaturated fatty acids (see Chapter 8).

High n-3 Polyunsaturated Fatty Acid Diets

There is evidence to suggest that high intakes of *n*-3 polyunsaturated fatty acids (EPA and DHA) may have adverse effects on immune function and may increase the risk of excessive bleeding and hemorrhagic stroke (see Chapter 8). High intakes of *n*-3 polyunsaturated fatty acids (α -linolenic acid) can also result in inadequate biosynthesis of long chain *n*-6 polyunsaturated fatty acids that are important for prostaglandin and eicosanoid synthesis (see Chapter 8).

Acceptable Macronutrient Distribution Range

α -Linolenic acid is essential in the diet and therefore AIs have been set (see Chapter 8). Up to 10 percent of the AI can be consumed as EPA and/or DHA. The above studies suggest that α -linolenic acid, EPA, and DHA may provide beneficial health effects when consumed at moderate levels. Based on the median energy intake by the various age groups (Appendix Table E-1), it is estimated that approximately 0.6 percent of energy from α -linolenic acid is needed to meet the AI. This level is used as the lower boundary for the Acceptable Macronutrient Distribution Range (AMDR) for α -linolenic acid. The upper boundary of the AMDR for α -linolenic acid is set at 1.2 percent of energy and represents the highest levels of α -linolenic acid consumed in the form of foods by individuals in North America. Data from interventional studies to support the benefit of even higher intakes of α -linolenic acid were not considered strong enough to justify establishing an upper boundary greater than 1.2 percent of

energy. Approximately 10 percent of the AMDR for *n*-3 fatty acids (α -linolenic acid) can be consumed as EPA and/or DHA (0.06 to 0.12 percent of energy).

SATURATED FATTY ACIDS, *TRANS* FATTY ACIDS, AND CHOLESTEROL

Low Saturated Fatty Acid, Trans Fatty Acid, and Cholesterol Diets

There are no known risks of chronic disease from consuming low intakes of saturated fatty acids, *trans* fatty acids, or cholesterol. In the United States, saturated fatty acids provided 11 to 12 percent of energy in adult diets and 12.2 to 13.9 percent of energy in the diets of children and adolescents (CDC, 1994). It is estimated that the intake of *trans* fatty acids is approximately 2.6 percent of energy (Allison et al., 1999). The intake of cholesterol by American adults ranges from less than 100 mg/d to just under 770 mg/d (Appendix Table E-15).

It is important to recognize that lower intakes of saturated fatty acids and cholesterol are observed for vegetarians, especially vegans (Janelle and Barr, 1995; Shultz and Leklem, 1983). Because certain micronutrients, saturated fats, and cholesterol are consumed mainly through animal foods, it is possible that diets low in saturated fat and cholesterol are associated with low intakes of these micronutrients. When the micronutrient intakes of Seventh-day Adventist vegetarians and nonvegetarians were measured, there were no significant reductions in micronutrient intakes with the lower saturated fat (7.3 versus 12.6 percent of energy) and cholesterol intakes (186 versus 404 mg/d) of vegetarian compared to nonvegetarian men (12.6 percent of energy and 404 mg/d) (Shultz and Leklem, 1983). Similarly, the intakes of most micronutrients were not significantly lower for vegans, except for vitamin B₁₂ (0.51 versus 3.79 mg/d), riboflavin (1.32 versus 1.72 mg/d), and calcium (578 versus 950 mg/d). Vegans had significantly lower intakes of saturated fat (6.9 versus 10.6 percent of energy) and cholesterol (94 versus 231 mg/d) than nonvegetarians (Janelle and Barr, 1995).

Analysis of nutritionally adequate menus indicates that there is a minimum amount of saturated fat that can be consumed so that sufficient levels of linoleic and α -linolenic acid are consumed (as an example see Appendix Tables G-1 and G-2). Other than soy products that are high in *n*-6 and *n*-3 fatty acids, many vegetable-based fat sources are also high in saturated fatty acids, and these differences should be considered in planning menus.

High Saturated Fatty Acid, Trans Fatty Acid, and Cholesterol Diets

There is a body of evidence suggesting that saturated and *trans* fatty acids and cholesterol increase blood total and low density lipoprotein cholesterol concentrations, and therefore the risk of coronary heart disease (CHD) (see Chapters 8 and 9). Because the intake of each of these three nutrients and risk of CHD is a positive linear trend, even very low intakes of each may increase risk.

To minimize saturated fatty acid intake requires decreased intake of animal fats (e.g., meat fat and butter fat) and certain oils, such as coconut and palm kernel oil. Saturated fatty acids can be reduced by choosing lean cuts of meat, trimming away visible fat on meats, and eating smaller portions. The amount of butter that is added to foods can be minimized or replaced with vegetable oils or nonhydrogenated vegetable oil spreads. Vegetable oils, such as canola and safflower oil, can be used to replace more saturated oils such as coconut and palm oil. Such changes can reduce saturated fat intake without altering the intake of essential nutrients.

A reduction in the frequency of intake or serving size of certain foods such as liver (375 mg/3 oz slice) and eggs (250 mg/egg) can help reduce the intake of cholesterol, as well as foods that contain eggs, such as cheese-cake (170 mg/slice) and custard pie (170 mg/slice). There are a number of meats and dairy products that contain low amounts of cholesterol (e.g., lean meats [30 mg/2 slices] and 2 percent milk [18 mg/cup]). Therefore, there are a variety of foods that are low in saturated fat and cholesterol and also abundant in essential nutrients such as iron, zinc, and calcium.

Trans fatty acids are high in stick margarine and those foods containing vegetable shortenings that have been subjected to hydrogenation. Examples of foods that contain relatively high levels of *trans* fatty acids include cakes, pastries, doughnuts, and french fries (Litin and Sacks, 1993). Therefore, the intake of *trans* fatty acids can be reduced without limiting the intake of most essential nutrients by decreasing the serving size and frequency of intake of these foods, or by using unhardened oil.

CONJUGATED LINOLEIC ACID

Conjugated linoleic acid (CLA) has been shown to play a role in the alteration of body composition in animals (Park et al., 1997), the inhibition of tumor cell growth (Whigham et al., 2000), and the inhibition of experimental atherosclerosis in animals (Lee et al., 1994). The *trans*-10,*cis*-12 CLA isomer appears to be the isomer primarily responsible for the induction of changes in body composition (de Deckere et al., 1999; Park et al., 1999). Several studies suggest that these changes are primarily due to a reduction in lipid uptake by adipocytes (Pariza et al., 2001), which results

from the action of CLA on the activities of stearoyl-coenzyme A desaturase (Choi et al., 2000; Lee et al., 1998) and lipoprotein lipase (Park et al., 1997, 1999). The *trans*-10,*cis*-12 CLA isomer has also been reported to inhibit proliferation and differentiation in cultured mouse adipocytes (Brodie et al., 1999) and to induce apoptosis in vivo in the adipose tissue of mice (Tsuboyama-Kasaoka et al., 2000). In addition to body fat reduction, dietary CLA may increase whole body protein accretion in animals, suggesting the enhancement of lean body mass (Ostrowska et al., 1999; Park et al., 1997; Stangl, 2000).

Research on the effects of CLA on body composition in humans has provided conflicting results. Blankson and coworkers (2000) conducted a study in overweight and obese men and women given either placebo or 1.7, 3.4, 5.1, or 6.8 g/d of a CLA preparation consisting of equal parts of the *cis*-9,*trans*-11 and *trans*-10,*cis*-12 isomers. After 12 weeks, none of the groups exhibited significant reductions in body weight or body mass index. However, the groups given 1.7, 3.4, and 6.8 g/d of CLA showed significant decreases in body fat mass compared to the placebo group. No differences in lean body mass were observed. Zambell and coworkers (2000) studied the effects of CLA supplementation in healthy adult women given either placebo or 3 g/d of CLA for 64 days. They found no significant changes in fat-free mass, fat mass, body weight, or percentage of body fat with CLA supplementation.

CLA has been studied for its potential anticancer benefits in numerous animal and in vitro models. CLA mixtures have been shown to exhibit anticarcinogenic properties in skin, lung, forestomach, colorectal, prostate, and mammary tissues (Cesano et al., 1998; Ha et al., 1990; Liew et al., 1995; Schønberg and Krokan, 1995; Shultz et al., 1992), although the majority of the research has been conducted with breast cancer. Ip and Scimeca (1997) conducted a study in female rats chemically induced for mammary tumors and fed a diet containing either 2 percent or 12 percent linoleic acid. The rats were also supplemented with 0, 0.5, 1, 1.5, or 2 percent CLA. The researchers found that increasing CLA from 0.5 to 1 percent resulted in a dose-dependent decrease in both tumor incidence and total number of tumors. No further protection was observed in the groups receiving 1.5 or 2 percent CLA. In addition to inhibiting tumor growth, CLA eliminated the spread of breast cancer cells to the lungs, peripheral bone, and bone marrow of mice supplemented with 1 percent CLA (Visonneau et al., 1997).

Although the exact mechanisms of the anticarcinogenic effects of CLA are not fully understood, several explanations have been offered. It has been suggested that growth inhibition of cancer cells may be due to the ability of CLA to inhibit protein and nucleotide biosynthesis (Ip et al., 1999; Shultz et al., 1992) and to induce cell apoptosis (Ip et al., 1999,

2000). Antioxidant activity of CLA has also been suggested (Ha et al., 1990; Ip et al., 1991); however, this theory has been contradicted by studies showing that CLA does not decrease lipid peroxide formation (Cunningham et al., 1997; van den Berg et al., 1995). Another possible mechanism of cancer cell growth inhibition by CLA includes alteration of eicosanoid metabolism. CLA may compete with linoleic acid in its conversion to arachidonic acid, thereby reducing the biosynthesis of eicosanoids (Banni et al., 1999), which have been associated with the proliferation of cultured breast cancer cells (Karmali, 1986; Noguchi et al., 1995). CLA has been shown to reduce leukotriene B₄ and prostaglandin E₂ levels in animals (Kavanaugh et al., 1999; Sugano et al., 1998). To date, there are insufficient data in humans to recommend a level of CLA at which beneficial health effects may occur.

DIETARY FIBER AND FUNCTIONAL FIBER

Low Fiber Diets

A low fiber diet is often attributed to the intake of a low carbohydrate diet. A number of adverse clinical effects, including impaired laxation and increased risk of cancer, obesity, heart disease, and type 2 diabetes, have been associated with the chronic consumption of low amounts of *Dietary Fiber* or *Functional Fiber*. The studies to support a beneficial role of these fibers are reviewed in Chapter 7.

Certain animal studies have shown that some fibers can actually enhance mineral absorption (Demigné et al., 1989; Levrat et al., 1991a, 1991b). There are several potential mechanisms by which ingestion of *Dietary Fiber* may actually enhance mineral status. For example, a more acidic pH in the colon is produced with fiber fermentation, and this results in more ionized calcium, which is better absorbed (Rémésy et al., 1992). *Dietary Fiber* in the colon can also stimulate bacterial fermentation, which has been associated with increases in calcium, magnesium, and potassium absorption (Demigné et al., 1989; Levrat et al., 1991a). Many fiber sources, such as karaya gum, sugar beet fiber, and coarse bran, are also excellent sources of minerals (Behall et al., 1987; Fairweather-Tait and Wright, 1990; Van Dokkum et al., 1982).

Several investigators have shown that inulin and fructooligosaccharides actually enhance calcium and magnesium absorption (Coudray et al., 1997; Delzenne et al., 1995; Levrat et al., 1991b; Ohta et al., 1995). There is also indirect evidence of this same enhancement with calcium in humans (Trinidad et al., 1993, 1996). A direct effect of fiber on mineral absorption has also been reported in humans where inulin increased the apparent absorption and balance of calcium (Coudray et al., 1997).

High Fiber Diets

There is limited data to suggest that chronic consumption of high fiber diets results in adverse health effects (see Chapter 7). Gastrointestinal distress can occur with the consumption of high fiber diets, but this often subsides with time.

DIETARY PROTEIN

Low Protein Diets

Although uncommon in North America, protein–energy malnutrition (PEM) is one of the most common nutritional diseases in developing countries (Torun and Chew, 1999). The etiology of PEM is complex as there are a number of factors that are attributed to its onset, including insufficient food intake or intake of low protein-containing foods, which in turn is attributed to poverty, unsanitary conditions, and food insecurity. Because PEM is attributed to insufficient food intake, not only are protein and energy limited, but the micronutrients that are often present in protein-containing foods are also limited. Epidemiological analysis from 53 developing countries indicated that 56 percent of deaths in young children were due to the potentiating effects of malnutrition in infectious diseases (Pelletier et al., 1995). The increased duration or susceptibility to infectious diseases such as respiratory infections and diarrhea are due, in part, to the involvement of protein in immune function.

Impaired Immune Function

Chandra (1972) showed that in individuals with PEM, a variety of immune responses were impaired. The major defects observed with severe PEM involve T lymphocytes and the complement system. With PEM, the number of lymphocytes is markedly reduced and delayed cutaneous hypersensitivity responses to both recall and new antigens are depressed (Chandra, 1991), as is the production of several components of the complement system (Keusch et al., 1984). Furthermore, antibody affinity (Chandra et al., 1984) and lysozyme concentrations (Chandra and Newberne, 1977) are decreased.

Impaired Growth

Low protein intake during pregnancy is correlated with a higher incidence of low birth weight (King, 2000). Furthermore, in children, diets low in protein and energy are most frequently associated with a deficit in

weight-for-height (wasting) and height-for-age (stunting) (Waterlow, 1976). These deficits can be corrected by the provision of a high protein diet (Badaloo et al., 1999) and with an adequate energy intake to permit catch-up growth. For these reasons, various anthropometric measures are used for diagnosis and monitoring the treatment of PEM.

Low Birth Weight

Rush and coworkers (1980) found decreases in both gestational length and birth weight and increases in very early premature births and mortality with high density protein supplementation (additional 40 g/d) in poor, black pregnant women at risk of having low birth weight infants. In contrast, Adams and coworkers (1978) reported no differences from the controls in mean birth weights of infants of mothers at risk of having a low birth weight infant when these women were supplemented with 40 g/d of protein. No reports were found of protein toxicity in healthy pregnant or lactating women that were not at risk of having a low birth weight infant. Thus, at the present time, low birth weight cannot be utilized to set a Tolerable Upper Intake Level (UL) for protein for women.

Risk of Nutritional Inadequacy

High quality protein is typically consumed via animal products, and therefore vegetarians may consume less high quality protein than omnivores. Because animal foods are the primary sources of certain nutrients, such as calcium, vitamin B₁₂, and bioavailable iron and zinc, low protein intakes may result in inadequate intakes of these micronutrients. As an example, Janelle and Barr (1995) reported significantly lower intakes of riboflavin, vitamin B₁₂, and calcium by vegans who also consumed lower amounts of protein (10 versus 15 percent of energy) compared with nonvegetarians.

Vegetable protein has been shown to decrease plasma cholesterol concentrations in experimental animals and humans (Nagata et al., 1998; Nicolosi and Wilson, 1997; Terpstra et al., 1991). When the ratio of casein:soybean protein in the diet was decreased, there was a reduction in total and non-high density lipoprotein cholesterol concentrations (Fernandez et al., 1999; Teixeira et al., 2000). In laboratory animals, it was shown that the onset of atherosclerosis was significantly reduced when animals were fed a textured vegetable protein diet compared to a beef protein diet (Kritchevsky et al., 1981).

High Protein Diets

Osteoporosis

There is a substantial amount of literature that documents the increase in urinary excretion of calcium with increasing protein intake (Allen et al., 1979; Heaney, 1993; Lemann, 1999). The magnitude of this effect for a doubling of the protein intake, in the absence of change in any other nutrient, is a 50 percent increase in urinary calcium (Heaney, 1993). This has two potential detrimental consequences: loss of bone calcium and increased risk of renal calcium stone formation. Loss of calcium from bone is thought to occur because of bone mineral resorption that provides the buffer for the acid produced by the oxidation of the sulfur amino acids of protein (Barzel and Massey, 1998). However, although increased resorption of bone with increased protein intake has been shown (Kerstetter et al., 1999; Whiting et al., 1997), whether this in practice leads to bone loss and osteoporosis is controversial (Barzel and Massey, 1998; Heaney, 1998). It has recently been concluded that there may be no need to restrain dietary protein intake. Poor protein status itself leads to bone loss, whereas increased protein intake may lead to increased calcium intake, and bone loss does not occur if calcium intake is adequate (Heaney, 1998). In a recent prospective study of men and women aged 55 to 92 years, consumption of animal protein was positively associated with bone mineral density in women, but not in men (Promislow et al., 2002). In contrast, Dawson-Hughes and Harris (2002) reported no association between protein intake and bone mineral density in 342 healthy men and women aged 65 years and older. However, when the individuals were given calcium citrate malate and vitamin D in addition to the high protein intake, there was a favorable change in bone mineral density.

Kidney Stones

It has been estimated that 12 percent of the population in the United States will suffer from a kidney stone at some time (Sierakowski et al., 1978). The most common form of kidney stone is composed of calcium oxalate, and its formation is promoted by high concentrations of calcium and oxalate in the urine. A high animal protein intake in healthy humans increases urinary calcium and oxalate and the overall probability of forming kidney stones by 250 percent (Robertson et al., 1979). Conversely, restricting protein intake improved the lithogenic profile in hypercalciuric patients (Giannini et al., 1999). Also, the incidence of calcium oxalate stones has been shown to be associated with consumption of animal protein (Curhan et al., 1996; Robertson and Peacock, 1982). In contrast, the

only long-term prospective trial (4.5 years) of the effect of animal protein restriction on stone formation in newly diagnosed patients with calcium stones gave a negative result (Hiatt et al., 1996). The relative risk factor for recurrent stone formation was 5.6 (confidence interval 1.2–26.1), suggesting that the dietary advice was detrimental. In this study, 50 patients were given low animal protein (56 to 64 g/d) and high fiber, plus adequate fluid and calcium, whereas 49 control patients were only instructed to take adequate water and calcium. However, as protein intake was not the only variable, and in view of the data described above suggesting benefits from lower protein intake, further investigation is necessary.

Renal Failure

Restriction of dietary protein intake is known to lessen the symptoms of chronic renal insufficiency (Walser, 1992). This raises two related, but distinct questions: Do high protein diets have some role in the development of chronic renal failure? Do high protein intakes accelerate the progression of chronic renal failure? The concept that protein restriction might delay the deterioration of the kidney with age was based on studies in rats in which low energy or low protein diets attenuated the development of chronic renal failure (Anderson and Brenner, 1986, 1987). Walser (1992) has argued that this mechanism is unlikely to operate in humans. In particular, the decline in kidney function in the rat is mostly due to glomerulosclerosis, whereas in humans it is due mostly to a decline in filtration by nonsclerotic nephrons. Also, when creatinine clearance was measured in men at 10- to 18-year intervals, the decline with age did not correlate with dietary protein intake (Tobin and Spector, 1986). Correlation of creatinine clearance with protein intake showed a linear relationship with a positive gradient (Lew and Bosch, 1991), suggesting that the low protein intake itself decreased renal function. These factors point to the conclusion that the protein content of the diet is not responsible for the progressive decline in kidney function with age.

Coronary Artery Disease

It is well documented that high dietary protein in rabbits induces hypercholesterolemia and arteriosclerosis (Czarnecki and Kritchevsky, 1993). However, this effect has not been consistently shown in either swine (Luhman and Beitz, 1993; Pfeuffer et al., 1988) or humans. In humans, analysis of data from the Nurses' Health Study showed an inverse relationship between protein intake and risk of cardiovascular disease (Hu et al., 1999). The association was weak but suggests that high protein intake does not increase the risk of cardiovascular disease. Similar conclusions have

been reached in observational studies showing an inverse relationship between protein intake and blood pressure (Obarzanek et al., 1996) and that replacement of carbohydrate with protein resulted in lower very low density cholesterol, low density cholesterol, and triglycerides (Wolfe and Piché, 1999).

Obesity

A number of short-term studies indicate that protein intake exerts a more powerful effect on satiety than either carbohydrate or fat (Hill and Blundell, 1990; Rolls et al., 1988; Stubbs et al., 1996). However, some epidemiological studies have shown a positive correlation between protein intake and body fatness, body mass index, and subscapular skinfold (Buemann et al., 1995; Rolland-Cachera et al., 1995). In contrast, a 6-month randomized trial demonstrated that the replacement of some dietary carbohydrate by protein improved weight loss as part of a reduced fat diet (Skov et al., 1999).

Cancer

The fact that the growth of tumor cells in culture is often increased by high amino acid concentrations (Breillout et al., 1990; Collins et al., 1998) raises concern that high dietary protein intake might enhance the incidence or the progression of cancer. Reviews of the literature on colon cancer have concluded that high meat intake may be associated with increased risk, but that high total protein intake is not (Clinton, 1993; Giovannucci and Willett, 1994; Parnaud and Corpet, 1997). A lack of correlation with total protein intake has been found in a case-control study (Slattery et al., 1997), but other studies have reported both increased (Slattery et al., 1994) and decreased (Kato et al., 1997) risk.

For breast cancer, the geographical distribution of incidence is correlated with the availability of dietary protein, especially animal protein (Clinton, 1993). Furthermore, migration to an area with typically higher protein intakes is associated with increased risk of breast cancer (Buell, 1973; Buell and Dunn, 1965). In accord with this, several studies have indicated an association among breast cancer and the intakes of animal protein and fat (Hislop et al., 1986; Lubin et al., 1981, 1986). However, others showed a relationship with fat, but not protein intake (Miller et al., 1978; Phillips, 1975). More recently, a case-control study on 2,569 patients and 2,588 controls showed a slightly negative relationship between total protein and breast cancer (Decarli et al., 1997). Another case-control study on 180 breast-cancer patients and 829 controls also showed no relation-

ship with total protein intake, but there was an increased risk ratio for meat consumption (Toniolo et al., 1994).

For other types of tumors, there also is no clear indication of greater risk with higher protein intakes. Total protein intake was not associated with increased risk of lung cancer (Lei et al., 1996), prostate cancer (Schuurman et al., 1999), endometrial cancer (Barbone et al., 1993; Shu et al., 1993), oral and pharynx cancer (Franceschi et al., 1999), esophageal cancer (Gao et al., 1994), and non-Hodgkin's lymphoma (Chiu et al., 1996; Ward et al., 1994), although some studies detected a positive relationship with animal protein (Chiu et al., 1996; Shu et al., 1993) or cured meat consumption (Schuurman et al., 1999). Moreover, in some of these studies, there was an inverse relationship with total protein intake (Barbone et al., 1993; Franceschi et al., 1999; Gao et al., 1994). On the other hand, higher protein intake was associated with an increased risk of cancer of the upper digestive tract (De Stefani et al., 1999) and kidney (Chow et al., 1994).

Overall, despite the demonstration of a positive influence of dietary fat and total energy, as well as meat (especially red meat), on some types of tumors, no clear role for total protein has yet emerged. The current state of the literature, therefore, does not permit any recommendation of an upper limit to be made on the basis of cancer risk.

Acceptable Macronutrient Distribution Range

There is no evidence to suggest that the Acceptable Macronutrient Distribution Range (AMDR) for protein should be at levels below the Recommended Dietary Allowance (RDA) for protein (about 10 percent of energy) for adults. There was insufficient evidence to suggest a UL for protein (see Chapter 10) and insufficient data to suggest an upper limit for an AMDR for protein. To complement the AMDRs for fat (20 to 35 percent energy) and carbohydrate (45 to 65 percent energy) for adults, protein intakes may range from 10 to 35 percent of energy intake to ensure a nutritionally adequate diet. For young and older children, the RDA is approximately 5 and 10 percent of energy, respectively. To complement the AMDR for fat (30 to 40 percent of energy) and carbohydrate (45 to 65 percent of energy) for young children and for older children (25 to 35 percent of energy from fat and 45 to 65 percent of energy from carbohydrate), protein intakes may range from 5 to 20 percent for young children and 10 to 30 percent for older children.

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