

What is the optimal macronutrient consumption for cardiovascular disease prevention?

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Dietary advice for preventing coronary heart disease (CHD) and type 2 diabetes has fluctuated considerably. Inability to substantiate evidence derived through epidemiology, use of surrogate biomarkers, and metabolic studies through randomized controlled trials is a major hindrance. Surveys of large populations have established eating patterns relating to the fewest and greatest rates of developing CHD. Clinical outcomes from consuming whole-grain cereals, cereal fiber, vegetables, fruits, fish, and unsaturated fats were in marked contrast to those of processed meats, high-fat dairy products, refined carbohydrates, fried foods, and sweets. This defined quantitative and qualitative criteria for macronutrients to combat CHD. Newer concepts of glycemic load and the increasing prevalence of the metabolic syndrome have led to reducing refined carbohydrates, emphasizing unsaturated and marine fatty acids, and substituting more protein to replace total fat.

Keywords: macronutrient; fat; carbohydrate; protein; fiber; coronary heart disease; glycemic load; obesity; metabolic syndrome

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The epidemic of coronary heart disease (CHD) that has been for decades the major cause of morbidity and mortality among the affluent populations of the world might well have been avoided had appropriate dietary and other lifestyle behavior been understood and implemented. The rapid and extensive spread of CHD, initially in “Western” countries during the 1960s, then through postwar eastern Europe, and more recently among Asians, testifies to the maladaptation of most populations to excess energy intake, especially from fat, together with smoking and lack of adequate energy expenditure. Equally impressive has been the decline in CHD incidence and mortality achieved through public health measures and medical management.

This review will evaluate the mix of macronutrients (fats, carbohydrates and protein) that might provide patterns of eating that have been associated in prospective and cross-sectional population studies with the least and the greatest rates of prevalence of CHD in Western populations. Whereas favorable and unfavorable patterns of consumption of foods have been shown with sufficient consistency to underpin valid public health messages, the amounts and types of required macronutrients remain in a perpetual state of flux. Since randomized controlled dietary intervention trials of the required scale are not feasible, the ev-

idence will not reach the consensus that is possible with trials of drugs. Nutritional science is therefore confounded by apparent changes in evidence so that the link between saturated fat consumption and CHD is being challenged, carbohydrates have shifted from being the foundation of an optimal diet to possibly contributing to disease, and higher consumption of protein is being strongly promoted.

Unlike essential micronutrients for which adequate intakes can be derived, thus quantifying their nutritional requirements, recommended macronutrient intakes are described as ranges. The AMDR (acceptable macronutrient distribution ranges) have been recently recommended by the Institute of Medicine (IOM) in the USA.¹ These are partly based on amounts considered optimal for

SELECTED ABBREVIATIONS AND ACRONYMS

AMDR	acceptable macronutrient distribution ranges
BMI	body mass index
DHA	docosahexaenoic acid
EPI	eicosapentaenoic acid
GI	glycemic index
IOM	Institute of Medicine
NHANES III	Third National and Nutrition Examination Survey
NHS	Nurses' Health Study

What is the optimal macronutrient consumption for CVD prevention? - Nestel

preventing chronic diseases while ensuring adequate intakes of essential nutrients (Table I). However, acceptance has not been unanimous, and of possibly greater importance are the qualitative differences within each major class of macronutrients. Finally, recommendations about the optimal mix or percentage contributions of the macronutrients must take into account the translation into attractive and nutritious foods.

Much of nutritional science including the determination of AMDRs is focused on the effects on cardiovascular risk factors of individual nutrients and of nonnutrients widely distributed in the food supply. The evidence derives mainly from surrogates or biomarkers for the probability of future clinical CHD. While having differing degrees of robustness, biomarkers represent a logical and feasible advance in our understanding of the role of foods, nutrients, and supplements in diminishing the risk of CHD. Whereas AMDRs represent a basis for public health advice advances in the understanding of genetic factors and the interactions between nutrients and foods on the one hand, the increasing range of single nucleotide polymorphisms of regulating genes has raised prospects for “personalized or individualized health.”

OPTIMAL PATTERNS OF EATING FOR DIMINISHING CHD RISK

The consistency of findings in major prospective population studies defines a pattern of eating characterized by higher consumption of whole grains, fish, legumes, vegetables and fruit, low-fat dairy products, nuts, and unsaturated fats, which associates with least risk of CHD.² By contrast, in the same populations, consumption of red and processed meats, fats rich in either saturated

Fats	20%-35%
Carbohydrates	45%-65%
Protein	10%-35%

Table I. Acceptable macronutrient distribution range.¹

fat or *trans* fatty acids, fried foods, refined grains, and desserts and sweets was linked to the highest CHD risk (Table II). Hu et al³ have provided semiquantitative data on the likely reduction in CHD risk with various substitutions of dietary fats as well as of carbohydrate (Table III). The benefits of the prudent diet were independent of other lifestyle measures, although clearly augmented in the absence of smoking and increased physical activity. In the Nurses’ Health Study (NHS), the combination of a prudent diet, non-smoking, and regular exercise resulted in an 83% lesser risk of CHD compared with women in whom the corresponding risk factors were present.² In the same cohort of women, in whom there was a 31% decline in CHD incidence during 14 years of observation, improved pattern of eating contributed substantially. Among the macronutrients that showed significant change over this period, *trans* fat declined, while the consumption of cereal fiber, and marine n-3 fatty acids increased, as did the ratio of polyunsaturated to

saturated fat.⁴ In the United States Health Professionals’ Study of 44 875 men, followed for 8 years, a prudent pattern of eating comprising higher intakes of vegetables, fruit, whole grains, legumes, fish, and poultry was associated with substantially lower risk of future CHD compared with men eating the Western type American diet of French fries, high-fat dairy products, red and processed meats, refined grains, and sweets and desserts.²

Apart from these long-term prospective studies, analysis of the dietary patterns among 13 130 healthy adults in the Third National Health and Nutrition Examination Survey (NHANES III) showed that the Western pattern characterized by high intakes of red and processed meats, eggs and high-fat dairy products was associated with biomarkers of increased CHD risk.⁵ These included surrogate markers of insulin resistance (C-peptide, serum insulin, and glycated hemoglobin) that identify subjects with the metabolic syndrome. This survey also appears to have identified high carbohydrate consumption as a risk factor for the metabolic syndrome, at least in men. A higher risk of developing type 2 diabetes has also been attributed to the Western diet of red and processed meats, high-fat dairy products, French fries, and refined

Reduced risk	Increased risk
<ul style="list-style-type: none"> • Whole-grain cereals • Poultry • Low-fat dairy products • Fish • Unsaturated fats • Vegetables and fruits • Legumes • Nuts • Cereal fiber 	<ul style="list-style-type: none"> • Refined carbohydrate • Red and processed meats • Full-cream dairy products • Fried foods & French fries • <i>Trans</i> and saturated fats • Sweets • Desserts

Table II. Eating patterns that influenced CHD risk in prospective cohort studies.²⁻⁴



carbohydrates and sweets.⁶ Diabetes is of course a major risk factor for CHD.

MACRONUTRIENT CONSUMPTION AND CHD RISK

The healthy pattern of eating is a simple public health message. However, nutritionists and health authorities have focused on recommending diets on the basis of proportions

but not total fat, were components of the high-risk diet in the large prospective studies. A Cochrane report that systematically examined high-level evidence-based publications concluded cautiously that dietary saturated fat did raise the risk of CHD.⁷ By contrast, the progression of atherosclerosis measured by quantitative coronary angiography in a large group of postmenopausal women was recently reported to be less in those who ate relatively less

advice to reduce total fat consumption has been related to the potential disadvantages of increasing carbohydrate intake. The suggested IOM range of 20% to 35% energy from fat is linked to 45% to 65% energy from carbohydrate. Diets deriving <20% energy from fat and >65% from carbohydrate are likely to reduce the LDL cholesterol concentration, but raise plasma triglyceride and lower high-density lipoprotein (HDL) cholesterol.¹⁰ The latter combination of high triglyceride and low HDL cholesterol is the phenotype commonly occurring in the metabolic syndrome and insulin resistance that raises CHD risk. It is, however, also seen in populations eating little fat and much carbohydrate, as in Asian countries, where this lipoprotein phenotype does not appear to cause risk. However, provided the fat is predominantly monounsaturated and polyunsaturated and the carbohydrate unrefined, diets that are within the above ranges are unlikely to distort significantly the HDL cholesterol and triglyceride levels nor increase the risk of obesity and diabetes. The relationship of total fat consumption to developing obesity remains controversial, but given its energy value and metabolic propensity for storage, the suggested ceiling for fat intake of 35% seems reasonable.

The effects of individual fatty acids have been extensively researched, so that several meta-analyses have been reported with general consistency.¹¹ Equations have been computed for the estimation of the LDL cholesterol raising or lowering effects of individual fatty acids. In a meta-analysis of 60 controlled trials that examined the effects of individual fats and fatty acids on lipoprotein lipids, the total cholesterol-HDL cholesterol ratio as an index of risk was found to have changed little when carbohydrates replaced satu-

Substitution	Changed risk
Polyunsaturated for saturated fat (5% energy)	↓ 40%
Monounsaturated for saturated fat (5% energy)	↓ 40%
Unsaturated for <i>trans</i> fats (2% energy)	↓ 50%
Carbohydrates for saturated fat (5% energy)	↓ 15%
Carbohydrates for polyunsaturated fat (5% energy)	↑ 60%

Table III. Calculated approximate effect on CHD risk of substituting fats and carbohydrate (based on reference 3).

of the major macronutrients (fat, carbohydrate, and protein) expressed as percentages of total energy intake. Individual fatty acids and fiber can also be regarded as falling into the definition of AMDRs.

Dietary fat

The amounts and types of fats that constitute the least risk for CHD have been the foundation of recommended diets. The initial evidence came from comparisons of populations with very different patterns of fat consumption and from the large changes in dietary fat among migrating populations. In both circumstances, strong associations between fat consumption and CHD prevalence have been documented.² However, it has been more difficult to demonstrate such a linkage within Western populations in whom fat is a major component of the diet. Nevertheless, *trans* and saturated fats,

saturated fat and more carbohydrate, a finding that might be explained by an adverse response to dietary carbohydrate in subjects with the metabolic syndrome.⁸ However, the carbohydrate was mostly refined and there was no evidence that progression was related to total fat consumption. A conclusion might be that reducing fat should not be replaced with refined carbohydrate in the common disorder of the metabolic syndrome. The nutritional issues and the dietary management of the metabolic syndrome have been reviewed recently.⁹

The strongest evidence derives from the effects of fat and specific fatty acids on the major surrogate of future CHD, serum cholesterol, or low-density lipoprotein (LDL) cholesterol. However, changes in one macronutrient influence the proportions of the other macronutrients, and recent concern about the key

What is the optimal macronutrient consumption for CVD prevention? - Nestel

rated fat, whereas substitution with *cis*-unsaturated fatty acids lowered the ratio significantly.¹⁰ *Trans* fats resulted in the highest ratio. Of individual saturated fatty acids, the increase in HDL cholesterol together with LDL cholesterol led to an actual decrease in the total cholesterol-HDL cholesterol ratio with lauric acid, no change with myristic and palmitic acids, and a slight decrease with stearic acid. Replacing fats with carbohydrate raised plasma triglyceride and led to the highest total cholesterol-HDL cholesterol ratio because of the reduction in HDL cholesterol despite a smaller reduction in LDL cholesterol. Replacing carbohydrate with polyunsaturated oils resulted in the lowest lipoprotein risk profile, resembling the marked difference in CHD risk in population studies (*Table III*).

Two comments are needed. First, the question of which lipoprotein phenotype influences CHD risk more: LDL cholesterol, which is generally lower when dietary fats are reduced, or HDL cholesterol, which is also reduced when carbohydrate replaces fat substantially. Both phenotypes are associated with increased CHD risk, although, given the large influence of genetic factors that determine individuals' responses to dietary change,¹² it is not certain, in the absence of randomized controlled intervention trials, that small changes in lipoprotein phenotypes increase risk. The second point is that high-fat diets have other deleterious effects on cardiovascular risk.¹¹ Thrombogenicity and endothelial dysfunction worsen after a high-fat meal, and insulin sensitivity probably deteriorates.

Although the reduction in LDL cholesterol is modest when monounsaturates, generally from olive oil, have been substituted for saturates, adverse metabolic changes such as

may occur with carbohydrates are avoided. Some Mediterranean populations consume up to 40% energy from fat mainly as olive oil and such diets have been reported to be associated with a lower prevalence of CHD.¹³

The suggested adequate intake for linoleic acid (18:2, n-6) is 5% to 10% energy, although considerably less is required for its essential fatty acid requirement. Dietary linoleic acid is part of the prudent, low-CHD risk pattern of eating that in prospective studies has diminished the incidence of CHD events; it is also the most potent LDL cholesterol-lowering fatty acid. Several controlled dietary intervention trials with large amounts of linoleic acid reduced the incidence of CHD events.^{2,14} Concerns about undesirable effects at 10% energy appear unfounded. At such an intake, there is little in vivo evidence for increased oxidant burden or significant in vivo interference with the conversion of α -linolenic acid (18:3, n-3) to eicosapentaenoic acid (EPA; 20:5, n-3).

The benefits of EPA and of DHA (docosahexaenoic acid [20:6, n-3]) on cardiovascular risk, predominantly on the prevention of sudden cardiac death, appear highly consistent.¹⁵ Initial evidence arose from fish-eating populations, although not all studies have confirmed the reduction in CHD risk among fish eaters. A meta-analysis has usefully demonstrated that eating more fish benefits people who had eaten little fish, but not habitual consumers of fish.¹⁶ In one of the few randomized clinical trials with a nutrient in which patients with CHD were given moderate amounts of EPA and DHA,¹⁷ sudden cardiac deaths were significantly lowered. The biological plausibility is strong: EPA and DHA reduce myocardial arrhythmogenic-

ity, correct endothelial dysfunction and arterial stiffness, improve the lipoprotein profile, and inhibit several key atherogenic processes.¹⁵

The major plant n-3 fatty acid, α -linolenic acid, may also reduce CHD risk independently of other fatty acids.² The suggested adequate intake for α -linolenic acid is between 1.1 and 1.6 g/d remembering that it is probably also an essential fatty acid, but the recommendation that EPA and DHA should comprise only 10% of total n-3 fatty acids is an underestimate for CHD prevention. Intakes of the marine n-3 fatty acids (EPA plus DHA) should be nearer 400 mg daily for healthy individuals, and on the basis of the secondary prevention trial, 1 g daily for patients with clinical CHD.¹⁷

Dietary carbohydrates

This macronutrient is undergoing a major revision in terms of the balance between its favorable and unfavorable effects on cardiovascular risk. Since dietary fat was regarded as the major contributor to CHD risk, less attention was paid to the amount and type of carbohydrate that might replace fat, and, as shown in *Table III*, substituting carbohydrate for saturated fat appears less effective than unsaturated fat substitutions. The concept of unrefined being preferable to refined carbohydrate, partly because of its greater fiber content, was considered adequate for public health advice. Indeed, starch-rich foods such as whole-grain cereal, vegetables, legumes, and fruits were prominent within the low-CHD-risk group of foods.²⁻⁴ Consumption of whole-grain cereals and of cereal fiber¹⁸ has been confirmed in numerous population studies to independently predict reduced CHD risk. By contrast, the increased consumption of refined carbohydrates in the United



States during the 20th century is positively correlated with the prevalence of type 2 diabetes.¹⁹

Metabolic explanations for the beneficial effects of eating whole-grain cereals include improved insulin sensitivity, especially in overweight subjects, diminished prevalence of overweight itself, and the rich micronutrient content of the bran that includes antioxidants and folate.

It is critical to public health policy to recognize that these key observations have not been negated by the controversy over carbohydrates. What has changed is the recognition that, as in the case of fats, carbohydrates need to be redefined in qualitative terms. The concept of rapidly and slowly digestible and absorbable carbohydrates is not new, and the term resistant starch has been applied to the latter form of starch reflecting structure and chemical composition, such as higher amylose content, which contributes to slower digestion. Slowly digestible starch results in diminished rate of glycemia, requiring a smaller insulin response. In an environment of obesity and the metabolic syndrome characterized by insulin resistance, carbohydrates that elicit lower insulin secretion are likely to preserve pancreatic islet cell function and delay conversion to diabetes.

That concept has led to classification of carbohydrates, comprising both starch and simple sugars as having a high or low glycemic index (GI) based on the rise of blood glucose following a meal.²⁰ The index alone does not take into account the amount of high GI foods that may confer increased risk for CHD and type 2 diabetes. That has led to the term of glycemic load, which is the product of the GI times the amount of carbohydrate load, and has been

shown to be predictive for future diabetes,²⁰ although possibly only in people with a family history of diabetes or low-energy expenditure.²¹ In the Framingham Offspring Study the prevalence of the metabolic syndrome was greater in those eating high GI foods even after accounting for body mass index (BMI).²² In this context, the GI concept is useful. However, other studies have not confirmed the link between GI or glycemic load and future diabetes or CHD, and this area remains controversial.

Unease about the GI concept includes concern that some foods that contain sugar and fats have a relatively low GI value, yet might seem intuitively undesirable. Furthermore, not all nutritionists are convinced that potatoes, rice, and white bread should be avoided by people at risk for insulin resistance because of their relatively high GI. That they should contribute less to the total glycemic load than lower GI foods such as whole-grain cereals, fibrous vegetables, and legumes in diets for insulin-resistant subjects differs little from past advice. For subjects with the metabolic syndrome, an overall reduction in carbohydrate intake and substitution with higher protein foods and monounsaturated fats seems appropriate.

The obsession with unusual weight-loss diets has added to the unfortunate concept of "bad carbohydrates" and recommendations for substantial reduction in the AMDR for carbohydrates that currently stands at 45% to 65% energy.¹ The marked reduction in carbohydrates has led to proportionately more protein and fat, up to 40% as protein. These diets undoubtedly result in short-term weight loss that exceeds conventional balanced overall reduction in energy.²³ However, studies over 1 year cannot distinguish between the

eventual weight loss from most energy reduced diets. A major public health concern about the very-low-carbohydrate diets is less about safety (which is marginal) than that the hard facts about the protective benefits of whole-grain and other slowly digestible carbohydrates will be lost.

Dietary fiber or nonstarch polysaccharide also clearly reduces CHD risk, especially as part of a prudent diet as discussed above, and has been documented in a recent meta-analysis.²⁴ Both "insoluble" fiber such as that in cereals and "soluble" fiber (beta-glucans, psyllium, pectin, etc) reduce risk factors such as postprandial glycemia and LDL cholesterol. The Food and Drug Administration (FDA) has given qualified support for the inclusion of soluble nonstarch polysaccharides within diets that may reduce the risk of CHD.

Dietary protein

It is self-evident that the AMDR for protein will depend on the proportions of energy allocated to fat and carbohydrate. A range of 10% to 25% appears rational, although there has been a trend to higher values. In severely energy-reduced weight-loss diets, the protein content may reach 40%, reflecting limitations in carbohydrates and fat. Modeling of such diets suggests that 40% may be required for adequate micronutrients such as iron and zinc. During weight loss, lean body mass, bone mineralization, and insulin sensitivity are better maintained when protein intake is high.²³ The success of such diets may reflect the satiating effects of protein.

Earlier concerns that high protein intake may lead to bone demineralization and even to renal impairment have not been confirmed.

Qualitative differences in protein reflecting amino acid content are well known. Recent interest in soy protein as potentially superior to animal protein within diets to reduce the risk of CHD has recently received FDA support. The claim is based on the perceived effect of soy protein on LDL cholesterol. However, several editorials have expressed uncertainty about the importance of the minor reductions in LDL cholesterol, which have not been consistently observed.²⁵

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