# The Portfolio Diet for Cardiovascular Risk Reduction

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Prompted by current dietary recommendations for the control of serum cholesterol to new targets to reduce the risk of coronary heart disease (CHD), and by the CHD risk reduction claims made for certain foods or food components, studies are now being undertaken using combinations of cholesterol-lowering foods in one diet (eg, a dietary portfolio) rather than single foods to achieve more effective dietary control of serum cholesterol. This approach has increased the potential relevance of dietary therapy and may yield nutrition strategies that bridge the gap between what is regarded as a good diet and drug therapy.

## Introduction

Studies are now emerging in which more than one cholesterol-lowering element or food is included in the same diet in order to maximize the cholesterol-lowering effect of the diet. Major influences promoting this approach during the past 10 years have been the dietary recommendations given by the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP) III [1] to increase plant sterol and viscous fiber intakes, general advice coming from the American Heart Association [2], and the establishment of a framework by the US Food and Drug Administration (FDA) [3] allowing the use of coronary heart disease (CHD) risk reduction health claims based on low-density lipoprotein cholesterol (LDL-C) reduction by specific foods [3–6]. The effect of these combination diets is reviewed here.

## Treating to New Targets

Acceptable levels for serum lipids are falling, as are desirable levels of risk factors in other chronic diseases, including diabetes and hypertension [7]. A number of dietary options are available to reduce blood lipids individually, but their effects are not large. Simple restriction of saturated fat and dietary cholesterol has the potential to achieve significant lipid reductions under metabolically controlled conditions, but adequate restrictions are difficult to apply to the larger general population [8]. At the same time, success of statins in reducing LDL-C and coronary events, as shown in the early trials [9–12], has prompted the reformulation of the guidelines for high-risk individuals, which were revised downward so that the new target is now 70 mg/dL (1.89 mmol/L) as opposed to 100 mg/dL (2.00 mmol/L) [13,14]. The emphasis has therefore been on the more effective drug therapy, although the combination, or portfolio, approach to diet was also mentioned [7].

## The Evolutionary Origins of the Combination Approach to Diet Therapy

Interest in the origins of the human diet has focused on the Paleolithic period and the high consumption of meat, first as carrion and then as fresh meat as a result of advances in hunting technology [15]. Nevertheless, the genetic change between Neolithic and modern humans is likely to have been small. We must therefore look to much earlier times to determine what diets were likely to have shaped our gastrointestinal physiology and intermediary metabolism. Our interest therefore focused on the Miocene epoch, at the end of which human ancestors adapted to a life on the African savannah, developing an upright gait as they transitioned from a diet of leafy vegetables, fruit, and nuts to one containing a significant amount of animal products [16]. The question, therefore, arises as to whether there is a serious mismatch between ancient human genes and our contemporary Western diet and life-

style. In order to test this concept, studies were performed to determine the effect of reconstructed diets representing different stages in human evolution on the blood lipid response of modern humans. An isocaloric diet of fruit, vegetables, and nuts reduced LDL-C by 35% in 2 weeks in a group of 10 normocholesterolemic or moderately hyperlipidemic men and women [17]. The aim of the diet was to reproduce the pattern of food eaten by human ancestors at the end of the Miocene epoch, just over 5 million years ago, when the many evolutionary pressures at the time would have shaped the human genome. The actual volume of food was large and required subjects to consume 5.5 kg of food daily per 70 kg of body weight. Such a diet would provide a natural barrier to overconsumption due to its large volume and contrast markedly with contemporary energy-dense diets that, together with low physical activity, are associated with the current high rates of obesity. The ancestral diet was high in vegetable protein (93 g/d), dietary fiber (143 g/d), plant sterols (1 g/d), and nuts (64 g/d of almonds and hazelnuts), based on a 2000-kcal diet. It is probably more than coincidence that the four classes of foods or food components that formed the basis of the evolutionary diet are the same four categories for which the FDA now permits claims of heart disease–risk reduction based on their cholesterol-lowering potential [3–6,18]. NCEP-ATP III recommendations also seek to enhance the cholesterol-lowering potential of the diet with added viscous fiber and plant sterols [1]. These two sets of recommendations have increased awareness of functional foods. The demonstration of the magnitude of the lipid-lowering effect of the ancestral diet, which is high in cholesterol-reducing elements, has further supported "combination" or "dietary portfolio" approaches to controlling elevated serum cholesterol.

## The "Combination" or "Dietary Portfolio" Approach to Cholesterol Reduction

All diets by definition are combinations of foods. Recently, use of combination diets of functional foods or foods containing specific therapeutic components to facilitate cholesterol reduction has been seen as important to make diet relevant in the modern world. Also, consistent advice given from the mid 1990s through the turn of the century has advocated multiple dietary changes that significantly and favorably affect lipid risk factors [2,19]. A further impetus to combine foods was the lack of effect of existing dietary strategies when applied singly by comparison with the comparatively large and consistent effect in lowering serum cholesterol seen with statins.

Starting just before the year 2000 and continuing through to the present, at least 14 studies have explored the effect of combining two to four of the FDA-approved cholesterol-lowering components in the same diets and assessing the effect on LDL-C and other lipid and nonlipid risk factors for CHD (Table 1) [20,21,22••,23,24,25•–28•,29–31,32•,33•]. The combinations included soy and viscous fiber [20,21,22••], soy and plant sterols [23,24,25•], and viscous fiber and plant sterols or stanols [26•–28•]. Studies have also explored the effects of all four FDA-approved cholesterol-lowering foods or food components combined [29–31,32•,33•]. Studies tended to be 1 month in duration [20,21,22••,26•,28•,29–31,32•], of crossover or parallel design, and involve hyperlipidemic subjects, although one study assessed "healthy individuals" [26•] and one studied subjects with type 2 diabetes [27•]. Reductions in LDL-C ranged from 4% to 35%. The greatest reductions in LDL-C were seen in studies of two active components that used higher doses of viscous fiber or plant sterols in combination (14.8%–15.4%) [25•,27•] and in metabolically controlled studies where all four FDA health claim–approved components were used in combination (28.6%–35.%) [30,31]. Doses used for plant sterols and stanols ranged from approximately 1.5 to 4.0 g/d. The corresponding figures for viscous fiber were approximately 10 to 20 g/d from a variety of sources, including β-glucan, psyllium, and glucomannan, 8 to 45 g/d of soy protein, and approximately 16.6 to 46.0 g/d of almonds (Table 1). No clear dose response was apparent. Part of the reason for the lack of a dose response may be the difficulty of seeing a dose response when different doses (high and low) are used at the same time for different components in combination.

## Benefits in Addition to LDL-C Reduction

### Combinations of two major components

Vegetable protein and viscous soluble fiber combinations, largely from soy and oats, have been shown to increase bile acid losses and the synthesis rates of cholate and chenodeoxycholate [20], although the effects on oxidized LDL-C have been inconsistent [20,21]. Soy and phytosterol combinations in one recent study tended to raise high-density lipoprotein cholesterol (HDL-C) and apolipoprotein A-1 [23]. In another study, this combination tended to reduce body weight, C-reactive protein, homocysteine, and glyocsylated hemoglobin [25•], although no effect was seen in lipoprotein(a) or oxidized LDL-C antibodies in a third study, suggesting a lack of significant antioxidant activity [24]. When viscous fibers such as psyllium [26•], glucomannan [27•], or oat β-glucan [28•] were taken with plant sterols, the combination was shown to decrease lathosterol concentrations as an index of cholesterol biosynthesis in comparison with plant sterols given alone [27•]. The authors hypothesized that reduced serum insulin, which might have been seen with viscous fiber, reduced the insulin stimulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase, and hence cholesterol biosynthesis [27•]. However, in a second study, cholesterol synthesis was increased [28•]. This combination was also reported to be associated with increased HDL-C and a decreased LDL-C pattern B (from 27% to 18%), which

is another risk factor for CHD [26•]. At the same time, cholesteryl ester transfer protein was reduced by 11% and LDL receptor activity or circulating mononuclear cells was increased by 26%, suggesting increased LDL receptor–mediated cholesterol uptake [26•].

**Dietary portfolio combinations**

Plant sterols have been implicated in increased risk of stroke due to increased membrane fragility [34]. Studies with the dietary portfolio combination of plant sterols, soy protein, viscous fibers, and almonds indicated no physiologically significant increase in erythrocyte fragility, despite increases in campesterol by 50% and sitosterol by 27% [35]. Furthermore, LDL particle size was reduced across the spectrum of particle size, including both large and small [36•]. In general, reductions of 23.8% to 32.9% have been seen in C-reactive protein [31,37], with no effect on lipoprotein(a) or homocysteine [30]. There was also evidence for a reduced level of circulating oxidized LDL, although the ratio of oxidized to unoxidized LDL was unaltered [32•], as was the ratio of apolipoprotein B to apolipoprotein A-1 [32•]. In the longer term, in addition to 20% or greater reductions in LDL-C in one third of the participants at 1 year [33•], blood pressure was also reduced by 4.2 mm Hg systolic and 2.3 mm Hg diastolic despite a very small mean weight loss of only 0.7 kg [38]. Neutrophils and the neutrophil:lymphocyte ratio, which are other risk factors for cardiovascular disease, were also reduced [39].

Finally, another study that combined multiple interventions, including soy at 16.2 g/d, other legumes, and nuts and seeds, in a low–saturated fat diet with increased soluble fiber, more vegetables, and less beef, poultry, fish, and eggs demonstrated a 9.3% reduction of LDL-C. No difference from the control group was reported in the ratio of total to HDL-C cholesterol, and no other effects were reported, such as reduced oxidized LDL-C or changes in apolipoproteins [22••].

All the diets were low in saturated fat and restricted in total fat (≤ 30% energy). The successful use of low-carbohydrate diets (26% of energy) in reducing triglyceride and apolipoprotein B and increasing LDL particle diameter raises the question of whether combination diets may benefit by being lower in carbohydrate [40••].

## The Dietary Portfolio: A Concept Under Development

The idea of combining foods or food components to achieve more effective cholesterol reductions was first suggested in 1999 [20]. The idea followed from what had been practiced in drug therapy for many years, which was combining a number of drugs to achieve therapeutic goals. The concept of a portfolio followed the financial strategy of spreading risks and benefits over a range of options to achieve stability, and in the case of a dietary portfolio, to avoid unreasonably large doses of any single component.

In the most controlled form, as a metabolic diet, reductions in LDL-C of approximately 30% can be achieved, which are similar to those achieved with a first-generation statin [31]. A typical template of the dietary portfolio is provided in Table 2 to illustrate this approach.

The dietary portfolio currently contains four main elements with proven cholesterol-lowering efficacy. These elements are soy, viscous fibers, plant sterols, and nuts, but the concept is open to expansion by addition of other potentially useful agents, such as Quorn (Quorn Food, Westport, CT) [41,42] or red yeast rice [43,44], or more potent members of an existing class, such as more effective viscous fiber sources [45]. To these cholesterol-lowering foods, new foods and other lifestyle strategies that reduce nonlipid risk factors for CHD can be added. Indeed, such an approach could give rise to tailored diet and lifestyle treatments as preventive and therapeutic strategies for a range of chronic diseases, including portfolios for diabetes, renal disease, and possibly cancer.

## Conclusions

The use of combination diets is in its infancy, encouraged by the need to achieve more effective lipid control [7], supportive advice by official agencies [1,2], and a changing regulatory environment that has permitted industry to make relevant health claims for CHD risk reduction [3–6].

The data suggest that combinations are indeed more useful than single dietary additions, even if the effects are only additive rather than being multiplicative. Even if some quenching of the cholesterol-lowering effect occurs, it still appears to be proportionately less than that seen with increasing doses of statin, where at high doses there are diminished returns on lipid reduction even if improvement in CHD outcomes remain [46•].

The concept of a portfolio of lipid and nonlipid risk reduction components for the prevention of CHD is open to further expansion and is very relevant to dietary strategies because diet is, by definition, a combination of foods. The extension of this approach to other chronic diseases may increase the relevance of diet as a treatment modality at a time when only drug therapy appears to be making advances, even in primary prevention.

**Table 1. Studies assessing a combination of cholesterol-lowering foods and food components**

| Study | Subjects, *n* | Subject characteristics | Intervention | Study design | Duration | Change in LDL-C, % |
|---|---|---|---|---|---|---|
| Jenkins et al. [20] | 31* | Hypercholesterolemic | 33 g soy protein<br>9 g soluble fiber | Metabolic, crossover | 1 mo | +6.7% |
| Jenkins et al. [21] | 20* | Hypercholesterolemic | 12 g soy protein<br>5 g soluble fiber | Ad libitim, crossover | 1 mo | -4%† |
| Cicero et al. [23] | 20 | Moderate hyperlipidemic | 8 g soy protein<br>2 g plant sterols | Single phase | 40 d | -9% |
| Jenkins et al. [29] | 13 | Hyperlipidemic | Per 1000 kcal diet:<br>1 g plant sterols<br>23 g soy protein<br>9 g viscous fiber<br>14 g almonds | Metabolic, single phase | 1 mo | -29% |
| Jenkins et al. [30] | 13 | Hyperlipidemic | Per 1000 kcal diet:<br>1.2 g plant sterols<br>16.2 g soy protein<br>8.3 g viscous fiber<br>16.6 g almonds | Metabolic, parallel | 1 mo | -35% |
| Jenkins et al. [31] | 46 | Hyperlipidemic | Per 1000 kcal diet:<br>1 g plant sterols<br>21.4 g soy protein<br>10 g viscous fiber<br>14 g almonds | Metabolic, parallel | 1 mo | -28.6% |
| Cicero et al. [24] | 36 | Moderate hypercholesterolemic | 8 g soy protein<br>2 g plant sterols | Single phase | 40 d | -11.6% |
| Gardner et al. [22••] | 120 | Normal to mild hyperlipidemic | 16 g soy protein<br>1.4 cloves of garlic<br>5 g soluble fiber | Metabolic, parallel | 4 wk | -9.3% |

*Study included postmenopausal women.
†No baseline data were available, therefore treatment difference is given.
‡Body weight decreased 8% on intervention.

**Table 1. Studies assessing a combination of cholesterol-lowering foods and food components *(Continued)***

| Study | Subjects, *n* | Subject characteristics | Intervention | Study design | Duration | Change in LDL-C, % |
|---|---|---|---|---|---|---|
| Jenkins et al. [32•] | 34 | Hyperlipidemic | Per 1000 kcal diet:<br>1 g plant sterols<br>21.4 g soy protein<br>10 g viscous fiber<br>14 g almonds | Metabolic, crossover | 1 mo per phase | -29.6% |
| Shrestha et al. [26•] | 33 | Healthy individuals | 7.8 g psyllium<br>2.6 g plant sterols | Crossover | 4 wk per phase | -9.8% |
| Yoshida et al. [27•] | 18 | Nondiabetic | 10 g β-glucomannan | Crossover | 21 d per phase | -17.5% |
| | 16 | Type 2 diabetes | 1.8 g plant sterols | | | |
| Lukaczer et al. [25•] | 59 postmenopausal women | Mild hypercholesterolemic | 30 g soy protein<br>4 g plant sterols | Parallel | 12 wk | -14.8%‡ |
| Jenkins et al. [33•] | 66 | Hyperlipidemic | Per 1000 kcal diet:<br>1 g plant sterols<br>22.5 g soy protein<br>10 g viscous fiber<br>23 g almonds | Open label, single phase | 1 y | -12.8% |
| Theuwissen et al. [28•] | 40 | Mild hypercholesterolemic | 5 g oat β-glucan<br>1.5 g plant stanols | Crossover | 4 wk per phase | -9.6% |

*Study included postmenopausal women.
†No baseline data were available, therefore treatment difference is given.
‡Body weight decreased 8% on intervention.

**Table 2. A representative metabolic diet menu plan of a typical day on the dietary portfolio**

| Breakfast | Lunch | Dinner |
|---|---|---|
| Hot oat-bran cereal | Soup: lentil with curry‡ | Entrée: tofu bake with ratatouille** |
| Soy beverage | Sandwich: | Firm tofu†† |
| Blueberries* | Soy deli slices§ | Eggplant |
| Sugar and psyllium | Oat-bran bread | Onions |
| Oat-bran bread | Test margarine† | Sweet peppers |
| Test margarine† | Lettuce | Side dish: |
| Double fruit jam | Tomato | Pearled barley‡‡ |
| **Snack** | Cucumber | Vegetables (cauliflower)§§ |
| Almonds | **Snack** | **Snack** |
| Soy beverage | Almonds | Apple* |
| Fresh fruit* | Soy beverage | Soy beverage |
| | Psyllium¶ | Psyllium¶ |

*Fruit alternatives: apple, pear, blueberries, strawberries.
†Plant sterol margarine.
‡Lunch, soup alternatives: vegetable barley, black bean, minestrone and pasta, vegetarian curry.
§Lunch, soy alternatives: soy hot dogs.
¶Taken each time with 250 mL of water.
**Dinner, frozen meal (4 times a week) alternative: three-bean chili, vegetable curry.
††Dinner, soy alternatives: soy burger, ground soy.
‡‡Four times a week.
§§Vegetable alternatives: broccoli, carrots.

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