

## Effects of exercise and diet on chronic disease

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**Roberts, Christian K., and R. James Barnard.** Effects of exercise and diet on chronic disease. *J Appl Physiol* 98: 3–30, 2005; doi:10.1152/jappphysiol.00852.2004.—Currently, modern chronic diseases, including cardiovascular diseases, Type 2 diabetes, metabolic syndrome, and cancer, are the leading killers in Westernized society and are increasing rampantly in developing nations. In fact, obesity, diabetes, and hypertension are now even commonplace in children. Clearly, however, there is a solution to this epidemic of metabolic disease that is inundating today's societies worldwide: exercise and diet. Overwhelming evidence from a variety of sources, including epidemiological, prospective cohort, and intervention studies, links most chronic diseases seen in the world today to physical inactivity and inappropriate diet consumption. The purpose of this review is to 1) discuss the effects of exercise and diet in the prevention of chronic disease, 2) highlight the effects of lifestyle modification for both mitigating disease progression and reversing existing disease, and 3) suggest potential mechanisms for beneficial effects.

cancer; diabetes; coronary artery disease; hypertension; metabolic syndrome

### CHRONIC DISEASES ARE EPIDEMIC IN MODERN WESTERN SOCIETY

Chronic diseases develop over one's lifetime, with clinical sequelae occurring many years after the underlying pathogenesis of the disease has occurred. As we move ahead in the 21st century, cardiovascular diseases [i.e., coronary artery disease (CAD), hypertension, stroke, and heart failure], Type 2 diabetes (diabetes), metabolic syndrome, and cancer are the leading killers in Westernized society and are increasing dramatically in developing nations (83). Recent data from the Centers for Disease Control document that cardiovascular diseases, various forms of cancer, and diabetes combine to make up ~70% of all deaths in the United States (15). Additionally, overweight and obesity [as defined by a body mass index (BMI) of >25] has been estimated to be present in ~60% of the adult US population (107, 261, 262), and obesity, diabetes, and metabolic syndrome are now common in children (381).

Chronic diseases present an enormous burden to society by increasing medical costs and human suffering (153). Recent data estimate that physical inactivity and poor diet caused 400,000 deaths in 2000, ranking second only to tobacco, and that it is likely that inactivity and diet will soon rank as the leading cause of death in the United States (263). This number may be an underestimate given that it reflects deaths attributable only to those with obesity, and physical inactivity and inappropriate diet impact mortality at any BMI (45). Although these health problems (CAD, diabetes, etc.) have been virtually nonexistent in underdeveloped countries, they are on the rise as these people change their diets and become more sedentary (83). Physical activity and diet are effective interventions, for what Booth and coworkers (51, 53) have coined "the war on chronic disease." Clearly, there is overwhelming evidence

linking most chronic diseases seen in the world today to physical inactivity and inappropriate diet consumption.

### GENE-ENVIRONMENT INTERACTION

Humans living today inherited a genome that was programmed for daily physical activity and a high-fiber diet (88). The onset and progression of chronic diseases are mediated in the vast majority of cases by an interaction between genetic factors, namely gene polymorphisms, and their interaction with environmental factors. These environmental factors are largely lifestyle factors, namely physical activity and dietary patterns, but also include other factors, such as smoking, alcohol consumption, stress, and hazardous environmental compounds. These factors are modifiable, and, as such, disease manifestations from these factors are largely preventable. In fact, it has been estimated that ~50% of all deaths in the United States are due to preventable causes (248). Nevertheless, most have the perception that genes cause chronic disease. A more appropriate interpretation is that genetic factors (i.e., "thrifty genotype," genetic polymorphisms, etc.) predispose the individual, but the environmental factors determine whether phenotypic expression of the disease manifests. As previously pointed out by Booth et al. (53), "100% of the increase in the prevalence of Type 2 diabetes and obesity in the United States during the latter half of the 20th century must be attributed to a changing environment interacting with genes, because 0% of the human genome has changed during this time period." Evidence for this phenomenon includes data from secular and migration studies (184) and studies on the Tarahumara Indians (249) and the Pima Indians (40, 391). For instance, Mormon cohort studies indicate that this group exhibits a low standardized mortality ratio, relative to that of whites in the general population in the United States, attributed to their lifestyles (92). Seventh-Day Adventists have higher life expectancies than other whites, attributed in part to behavioral choices regarding diet, exercise, and cigarette smoking. The Pima Indians living on the Indian reservation in Arizona have one of the highest

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incidences of diabetes known, at ~50%, whereas a group of Pima Indians with the same genetic background as those from Arizona living in Mexico, where they are physically active and consume the traditional Indian diet of natural foods, the incidence of diabetes is low (~10%). Additionally, when the Tarahumara Indians of Mexico consume a Western diet, rapid hyperlipidemia ensues (249). For exercise, the Machiguenga Indians expend greater than one-third more calories daily than average Americans (264), as a result of energy-requiring work. Furthermore, chronic diseases are nearly nonexistent in modern-day hunter-gatherer societies. These examples underscore the importance of lifestyle. Additionally, these responses are most likely integrative, and changes cannot generally be attributed to a single cause but rather are additive with respect to physical activity, diet, smoking, and other contributing factors.

#### LIFESTYLE MODIFICATION CAN MITIGATE DISEASE PROGRESSION AND REVERSE EXISTING DISEASE

The question of what are the causes of chronic diseases such as CAD is not novel, and research has investigated these issues for over 100 years (71). Consequently the search for therapies that can prevent and reverse existing disease has been investigated over this same time period. Early studies focused on cholesterol and saturated fat and their relation to CAD, whereas more recent studies have progressed to investigate diabetes, hypertension, cancer, and metabolic syndrome. This has been emphasized in the recent report from the World Health Organization (WHO; Ref. 83):

Diet has been known for years to play a key role as a risk factor for chronic diseases. — Traditional, largely plant-based diets have been replaced by high-fat, energy-dense diets with a substantial content of animal foods. But diet, although critical to prevention, is just one risk factor. Physical inactivity, now recognized as an increasingly important determinant of health, is the result of a progressive shift of lifestyle toward more sedentary pattern, in developing countries as much as in industrialized ones.

There is overwhelming evidence that diet, smoking, alcohol, and physical inactivity are important determinants of CAD and other chronic disorders and that modifying these environmental influences can significantly impact the incidence of chronic disease. Evidence over the past 20 years from a variety of sources, including epidemiological, prospective cohort, and intervention studies, has documented that physical activity, diet, and combined activity and diet interventions can mitigate progression of chronic disease and in fact reverse existing disease.

Although many diets have been studied, for example the National Cholesterol Education Program (NCEP) Step I diet (414, 420) and high-fat, low-carbohydrate diets (110, 341), they have documented that benefits are modest. These diets have not been demonstrated to thwart the progression of CAD, and their efficacy on other chronic diseases has not been documented (48, 57, 59, 283, 420). For example, in a study of 67,272 nurses followed for 12 yr, adherence to the dietary guidelines did not reduce the risk for heart disease or cancer (246). Other studies highlight the value of diets consisting primarily of whole grains (rich in fiber, antioxidants, minerals, and phytochemicals), fruits, vegetables, and omega-3-containing fish, with limited intake of saturated fats, trans-fatty acids, cholesterol, and refined carbohydrates (13, 21, 141, 177),

which falls in line with the American Heart Association's newer dietary guidelines (203–205). Recently, other organizations, namely the Institute of Medicine (84) and the WHO (83), have made recommendations for diet.

With respect to physical activity, recent studies have highlighted the importance of regular physical activity in decreasing the risk of chronic disease (46, 52). Booth et al. (51) have emphasized that humans evolved to be active, and, in 2002, the Institute of Medicine recommended 1 h of moderate physical activity daily “to accrue additional, weight-independent health benefits” (84), a recommendation in agreement with the WHO report (83), which is to include both aerobic (303) and resistance exercise (309).

Given the ineffectiveness of popular weight-loss diets (258), adoption of a healthy lifestyle is more appropriate for winning the war against chronic disease. The scientific evidence supporting the value of daily exercise and a diet focusing on the consumption of whole grains, fruits, and vegetables for the prevention and treatment of the major diseases seen in the industrialized countries today is overwhelming. This review will provide evidence that when daily physical activity of 1 h is performed in combination with a natural food diet, high in fiber-containing fruits, vegetables, and whole grains, and naturally low in fat, containing abundant amounts of vitamins, minerals, and phytochemicals, the vast majority of chronic disease may be prevented. It will discuss the effects of physical activity and diet on CAD, hypertension, diabetes, metabolic syndrome, and cancer; discuss the value of lifestyle modification for mitigating progression to clinical manifestations from chronic disease and reversal of existing disease as documented from the Pritikin lifestyle intervention and numerous other interventions; suggest potential mechanisms for beneficial effects; and give directions for future research.

#### CORONARY ARTERY DISEASE

Atherosclerotic disease is the leading cause of mortality in developed countries, with CAD being the number one killer of both men and women. In fact, every year since 1919, cardiovascular diseases have ranked as the no. 1 killer in the United States. In 2001, cardiovascular diseases accounted for ~39% of all deaths (931,108 deaths) (9, 15). Despite estimates that death rates from cardiovascular diseases declined 17% from 1990 to 2000, secondary to improvements in disease diagnostics, surgical procedures, and drug therapy, the actual number of deaths increased 2.5% during this period (390).

The association between lifestyle, diet, and CAD has been investigated since the early 1900s. In the latter half of the 20th century, with feeding studies demonstrating that saturated fat and dietary cholesterol increased serum cholesterol (247), dietary fat emerged as a determinant of serum cholesterol (251). Epidemiological and clinical studies established a link between dietary saturated fat, dietary cholesterol, serum cholesterol, and CAD mortality (192, 193). Keys' Seven Countries Study examined risk factors for CAD in over 12,000 men and both the average population intake of saturated fat (192), and changes in average serum cholesterol levels (252) were strongly related to CAD mortality rates. Interestingly, intakes of flavonols (antioxidant polyphenols) were also independent contributors in explaining population differences in CAD mortality rates (147), suggesting that low-density lipoprotein

(LDL) modification may also be critical to the progression of atherosclerosis. The Framingham Heart Study and MRFIT Study emphasized the relationship between serum cholesterol, especially LDL-cholesterol (LDL-C), and CAD (68, 311, 358). Cross-culturally, in rural China for example, fat intake was less than half that in the United States, and fiber intake was three times higher. Animal protein intake was low, at ~10% of the US intake. Mean serum total cholesterol (Total-C) was 127 mg/dl in rural China vs. 203 mg/dl for adults aged 20–74 yr in the United States, and CAD mortality was 16.7-fold greater for US men and 5.6-fold greater for US women than for their Chinese counterparts. Importantly, there was no evidence of a threshold beyond which further benefits did not accrue with increasing proportions of plant-based foods in the diet (63). Migration studies have also provided compelling evidence for the relation between saturated fat intake and CAD (184). These early data have been confirmed by the more recent cohort studies. The Nurses' Health Study reported that saturated and trans-fatty acids are associated with increased risk for CAD (162). It is now well established that LDL-C levels are increased by saturated fatty acids, especially those with 12–16 carbon atoms, and by trans-fatty acids (193).

In addition, carbohydrate type affects CAD risk. Refined carbohydrates are highly processed, resulting in removal of fiber, vitamins, minerals, phytonutrients, and essential fatty acids. Consumption of refined carbohydrates compared with whole grains increases the risk of CAD (173, 232), resulting, in part, from the increased glycemic load of these types of carbohydrates (233). Furthermore, increased fiber consumption is inversely related to both CAD (228, 413) and all-cause mortality (174). High-fiber foods lower LDL-C levels and improve insulin sensitivity (58). The large Women's Health Study showed an inverse relation between dietary fiber intake and the risk of CAD events (228). This may be attributed in part to increased consumption of fruits and vegetables, which have been documented in numerous studies to decrease CAD risk (38, 179, 230). Additionally, moderate consumption of protein is associated with a reduced risk of CAD (163), whereas substitution of red meat with poultry and fish also decreases risk (161). As a consequence of this research, diet has gone to the forefront as a regulator of CAD progression.

Physical activity also plays a critical role in the pathogenesis of CAD. The Adult Treatment Panel III summary concluded that physical inactivity is a major risk factor for CAD (98). Total physical activity and vigorous activities associate inversely and strongly with CAD risk (349), as Blair et al. (46) documented an inverse association between cardiorespiratory fitness and both all-cause and CAD mortality in over 13,000 individuals. The relative risk of CAD has been estimated to be about twofold higher for inactive subjects compared with physically active persons (314). In the Women's Health Initiative Observational Study (239) and the Nurses' Health Study (240), 30–40% of CAD was prevented by simply walking briskly >2.5 h/wk, compared with less than this amount of physical activity. Additionally, in the Harvard alumni study, mortality risk, primarily from cardiovascular diseases, varied inversely with calories expended (286). In a study of 4,276 men, the relative risk of death from CAD was about threefold higher for unfit individuals independent of conventional coronary risk factors (91), and several additional studies have documented that physical activity is comparable to conven-

tional risk factors in the ability to predict risk (44, 406). Laukkanen et al. (214) noted an inverse relation between maximal oxygen consumption ( $\dot{V}O_{2\max}$ ) and relative risk of cardiovascular death, as high fitness was associated with slower progression of carotid atherosclerosis as measured by B-mode ultrasonography (212). Additionally, in the Health Professionals Follow-up Study, men who trained with weights for at least 30 min/wk had a 25% reduction in CAD risk (370).

Several cohort studies have assessed the combined effects of a healthy lifestyle on CAD. In the Nurses' Health Study cohort, in which 84,129 women aged 30–55 yr were enrolled and followed up for 14 yr (359), a healthy lifestyle was defined as not smoking, consuming at least half a drink of alcoholic beverage per day, engaging in moderate to vigorous physical activity for >30 min/day, and a BMI <25 kg/m<sup>2</sup>. A healthy diet included components such as cereal fiber, marine n-3 fatty acids, folate, low trans-fatty acids, and glycemic load. Adherence to these factors correlated inversely with 14-year CAD incidence. Stampfer et al. (359) noted that 82% of CAD events could be prevented by a combination of physical activity and diet, providing additional evidence for a combined effect. When comparing dietary intake, consumption of vegetables, fruit, legumes, whole grains, fish, and poultry was associated with a decreased risk of CAD, whereas typical Westernized diet patterns high in red and processed meats, refined grains, sweets/desserts, and high-fat dairy products was associated with increased risk independent of other lifestyle factors (114, 159).

*Intervention studies and mechanisms.* Despite the abundance of evidence that lifestyle modification can mitigate the burden of cardiovascular diseases, they are still the major cause of death in developing nations. Several clinical trials and intervention studies have been conducted, unequivocally documenting the benefits of regular physical activity and diet for CAD risk reduction, mediated by changes in plasma lipids, blood pressure, inflammation, insulin sensitivity, coronary blood flow, endothelial function, and oxidative stress, among others. One of the earliest intervention trials was the Oslo-Diet Heart Study, in which 412 men were randomized to either a cholesterol-lowering diet or a control diet 1 to 2 yr after their first myocardial infarction (220). Men consuming a diet lower in saturated fat and cholesterol had a 17.6% reduction in Total-C compared with 3.7% in the control group over 5 yr and after 11 yr, significantly fewer CAD-related deaths. Schuler et al. (346) investigated progression of coronary atherosclerotic lesions in patients with stable angina pectoris. Intervention patients consumed <20% fat calories and exercised for >3 h/wk. Significant regression of coronary atherosclerotic lesions by angiography was noted in 7 of the 18 patients; no change or progression was present in 11 patients, whereas in patients receiving usual care, regression was detected in only 1, with no change or progression in 11 patients. In addition, there was a significant reduction in stress-induced myocardial ischemia, indicative of improvement of myocardial perfusion, which was not limited to patients with regression of coronary atherosclerotic lesions, suggesting that not only does lifestyle modification retard progression of CAD, but improvement of myocardial perfusion may be achieved independently from lesion regression. In a larger group of patients, this group noted that CAD progressed more slowly with daily activity and diet modification (347).

In the Stanford Coronary Risk Intervention Project, 300 patients with angiographically defined coronary atherosclerosis were randomly assigned to usual care or multifactor risk reduction. Patients assigned to risk reduction were instructed to consume <20% fat (<6% from saturated fat) and <75 mg of cholesterol per day. Physical activity was recommended, consisting of an increase in daily activities such as walking, climbing stairs, and household chores and a specific endurance exercise training program. Intensive risk reduction resulted in improvements in LDL-C, ApoB (both ~22%), high-density lipoprotein cholesterol (HDL-C) (+12%), triglycerides (TG) (-20%), body weight (-4%), and exercise capacity (+20%) compared with the usual-care group. The intervention group also exhibited a 47% reduced rate of narrowing of diseased coronary artery segments, with some showing regression (136). In the Lifestyle Heart Trial, 48 patients were randomized to either intensive dietary and lifestyle changes, including a whole-food vegetarian diet with 10% of energy from fat, aerobic exercise, stress management training, smoking cessation, and group social support, or usual care, consisting of an NCEP Step I diet (282). After 1 yr, the experimental group showed more favorable changes in angina frequency and quantitative coronary arteriography. After 5 yr of follow-up, the experimental group exhibited a relative reduction in diameter stenosis of 7.9% compared with a 27.7% progression in the control group (281). The risk ratio for a cardiac event in the control group compared with the experimental group was 2.47.

One intervention that has been studied extensively is the Pritikin residential lifestyle intervention, designed to achieve changes in lifestyle that are very extensive in each subject. Participants undergo a complete medical history and physical examination, before a 26-day (more recently 21-day or 11-day) physical activity and diet intervention. Meals are served buffet style, and all participants are allowed unrestricted eating except for the meals when 3½ oz. of fish or fowl are provided. Prepared meals contain 10–15% of calories from fat, 15–20% of calories from protein, and 65–75% of calories from carbohydrates, primarily unrefined, according to analysis by computer dietary analysis software. Carbohydrates are in the form of high-fiber whole grains (≥5 servings/day), vegetables (≥4 servings/day), and fruits (≥3 servings/day). Protein is primarily derived from plant sources with small amounts of nonfat dairy (up to 2 servings/day) and fish or chicken. The diet contains <100 mg of cholesterol, and alcohol, tobacco, and caffeinated beverages are not served during the program. Before starting the exercise training, subjects undergo a graded treadmill stress test according to a modified Bruce protocol to determine the appropriate individual level of exercise intensity. On the basis of the results, the subjects are provided with an appropriate training heart rate value and given an individualized aerobic exercise program. The exercise regimen consists of daily treadmill walking at the training heart rate for 45–60 min. The training heart rate is defined as 70–85% of the maximal heart rate attained during the treadmill test. Additionally, the subjects perform flexibility and resistance exercise.

Early studies documented that this combined physical activity and diet intervention decreased all serum lipids and angina in patients, the majority of whom had a prior myocardial infarction and/or multiple vessel disease and all of whom had been recommended for bypass surgery. The majority were taken off cardiac and/or blood pressure-lowering drug therapy.

The durability of the changes were evidenced by a 5-yr follow-up, which documented that adherence to the program resulted in maintenance of the changes and dramatically reduced the need for bypass surgery (25). The 4,587 men and women who completed the 26-day physical activity and diet intervention from 1977 to 1988 revealed an average Total-C reduction of 23%, from 234 to 180 mg/dl. LDL-C decreased by 23%, from 151 to 116 mg/dl, with male subjects exhibiting a greater reduction in Total-C (24 vs. 21%) and LDL-C (25 vs. 19%) compared with female subjects. HDL-C was reduced by 16%, but the ratio of Total-C to HDL-C was reduced by 11%. Serum TG decreased 33%, from 200 to 135 mg/dl, with male subjects showing a greater reduction than female subjects (38% vs. 23%) (21). Figure 1 indicates the effect of combined lifestyle modification vs. diet modification, as tested by using an NCEP Step I or Step II diet, and suggests that more intensive dietary changes and the addition of exercise increase lipid reductions. Body weight was also reduced, 5.5% for male subjects and 4.4% for female subjects. Follow-up studies for 18 mo on a subgroup documented that continued compliance with the program led to maintained Total-C values, documenting that reductions were not transient. The drop in HDL-C is consistent with Brinton et al. (56) using a low-saturated fat, low-cholesterol diet, who suggested that diet-induced reductions in HDL-C changing from a high-fat to a low-fat diet does not carry the same risk as low HDL-C within a given diet. In the context of absolute lipid levels, one with a lower Total-C, LDL-C, HDL-C, and Total-C-to-HDL-C ratio would be at lower risk (249) than one with elevated levels, and given that diet affects numerous other cardiovascular variables (see below), a high-fiber, low-fat diet would be more appropriate. Additionally, it is well established that polyunsaturated fats decrease heart disease risk; however, this has led some to suggest that polyunsaturated fats should replace carbohydrate in the diet, citing increases in TG (85, 324), an effect that does not occur when high-fiber-containing carbohydrates are consumed (11). Furthermore, the beneficial effects of polyunsaturates can be largely attributed to omega-3 fatty acids in nuts (2) and fish (1, 156).

This lifestyle intervention has also been documented to improve coronary flow reserve. In 1995, Czernin et al. (73) measured myocardial blood flow at rest and after dipyridamole-induced hyperemia quantified with [<sup>13</sup>N]ammonia and positron emission tomography in 13 individuals undergoing

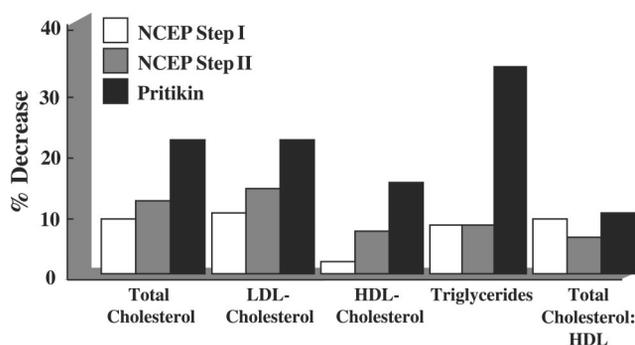


Fig. 1. Analysis of lipid reductions with National Cholesterol Education Program (NCEP) diet interventions vs. Pritikin combined lifestyle intervention. LDL, low-density lipoprotein; HDL, high-density lipoprotein. (Data from Refs. 21, 420).

6-wk outpatient lifestyle modification. Resting rate-pressure product decreased ( $8,859 \pm 2,128$  vs.  $7,450 \pm 1,496$ ), and the metabolic equivalent (METs) during an exercise task improved from  $10.0 \pm 3.0$  to  $14.4 \pm 3.6$  METs. Coronary resting blood flow decreased ( $0.78 \pm 0.18$  vs.  $0.69 \pm 0.14 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ ), whereas hyperemic blood flow increased ( $2.06 \pm 0.35$  vs.  $2.25 \pm 0.40 \text{ ml} \cdot \text{g}^{-1} \cdot \text{min}^{-1}$ ), resulting in an improved myocardial flow reserve ( $2.82 \pm 1.07$  vs.  $3.39 \pm 0.91$ -fold).

It is now clear that, in addition to the level of a given lipoprotein, its properties (HDL-inflammatory/anti-inflammatory properties, LDL size, and susceptibility to oxidation) may be critical to the atherogenic process. During an acute phase response, HDL is proinflammatory, independent of the level of HDL-C (271, 272, 393). In a study of 27 patients with normal levels of plasma HDL and yet with angiographically documented coronary atherosclerosis, who were not diabetic, who did not smoke, and who were not taking hypolipidemic medications, Navab and coworkers (271, 272, 393) studied the ability of the patients' HDL to inhibit LDL oxidation. This assay is performed using cocultures of human aortic endothelial cells and smooth muscle cells treated with native LDL and patient HDL. After an incubation period, the supernatant is removed and tested for monocyte chemotactic activity as a result of stimulation by the oxidized LDL. These investigators observed that the HDL from the patients was not protective against LDL oxidation (270). This group went on to document the same effect in patients with very high HDL-C (mean HDL-C 85 mg/dl) (12). Roberts et al. (unpublished data) documented in subjects at risk for CAD that, despite a lifestyle modification-induced reduction in HDL-C concentration, the ability of HDL to protect against LDL oxidation improved, supporting the contention of a complex relationship between HDL, diet, and physical activity. Although at a population level higher plasma HDL-C levels are associated with lower risk for CAD, at an individual level, HDL function may well be more important than plasma HDL-C levels.

Increasing evidence indicates that oxidative stress, for example the oxidation of apolipoprotein-B-containing lipoproteins, may play an integral role in lipoprotein atherogenicity (235). For example, 8-isoprostane  $\text{PGF}_{2\alpha}$  (8-iso- $\text{PGF}_{2\alpha}$ ) has been shown to be elevated in individuals at risk for cardiovascular events (295). Beard et al. (39) investigated the effects of physical activity and diet on LDL quality as well as its susceptibility to *in vitro* oxidation in men and women. The mean particle diameter of LDL increased, correlated with the reduction in serum TG, and LDL oxidation decreased 21%. Parks et al. (294) also addressed the issue of whether physical activity and diet can affect LDL oxidation. Twenty-five patients with documented CAD underwent a 3-mo treatment, and although two indexes of oxidizability, LDL particle size and fatty acid composition, were not affected by the treatment, it did increase the vitamin E and  $\beta$ -carotene contents of LDL and reduced the *in vitro* oxidizability of LDL. These data were corroborated in a group of postmenopausal women (27) and suggest that lifestyle modification may reduce LDL oxidizability. Others have noted decreases in LDL size on lower fat diets (85), which would increase LDL susceptibility to oxidation and may be related to the use of refined carbohydrates, which affects hepatic lipid metabolism.

Lifestyle modification has also documented significant improvement in plasma lipids in patients undergoing cholesterol-

lowering drug therapy. In a group of 93 subjects, before drug therapy, mean Total-C was  $276 \pm 5$  mg/dl and was reduced by 20% to  $220 \pm 4$  mg/dl (24). Total-C dropped an additional 19% to  $178 \pm 4$  mg/dl with the diet and exercise intervention. LDL-C decreased an additional 20% ( $126 \pm 4$  to  $101 \pm 3$ ) and TG were reduced by 29% ( $195 \pm 10$  to  $139 \pm 6$ ) with combined drug therapy and lifestyle modification. Patient query revealed that 51% percent of the primary care physicians had not used diet therapy before initiating drug therapy and 29% did not use diet therapy along with the drugs as recommended by the NCEP. Benefits have also been noted in postmenopausal women on hormone replacement therapy (27). More recently, Jenkins et al. (176, 177) used the whole-diet approach in hyperlipidemic patients to compare the effects of diet to those of lipid-lowering therapy. The diet, which was low in saturated fat and included viscous fibers, almonds, soy protein, and plant sterols, induced reductions in lipids that were comparable to statin therapy, independent of changes in body weight. Total-C decreased from 268 to 209 mg/dl on the diet vs. 256 to 197 mg/dl on lovastatin, LDL-C 178 to 126 mg/dl vs. 172 to 117 mg/dl on the statin, HDL-C from 45.9 to 42.8 mg/dl vs. 45.5 to 44.0 mg/dl on the statin, and TG from 219 to 202 mg/dl vs. 196 to 180 mg/dl on the statin. In the Dietary Approaches to Stop Hypertension (DASH) trial, the effect of a diet alone on plasma lipids was tested in 436 participants, who increased consumption of fruits, vegetables, and low-fat dairy products and reduced saturated fat, total fat, and cholesterol. Relative to the control diet, the DASH diet decreased Total-C (13.7 mg/dl), LDL-C (10.7 mg/dl), and HDL-C (3.7 mg/dl) with no change in TG or body weight (280).

Physical activity and/or dietary intervention can also reduce the risk for CAD by other mechanisms, and attention has recently focused on the involvement of inflammation in CAD, with multiple prospective studies suggesting that elevated C-reactive protein (CRP) is a sensitive predictor of myocardial infarction, stroke, peripheral arterial disease, and sudden cardiac death. When considered in conjunction with plasma Total-C, CRP serves as a better predictor of CAD risk than Total-C alone (328), may be a stronger predictor of cardiovascular events than LDL-C, and adds prognostic information at all levels of the metabolic syndrome (326). These data suggest that atherothrombosis, in addition to being a disease of lipid accumulation, also represents a chronic inflammatory process. Wegge et al. (404) demonstrated that the Pritikin combined physical activity and diet intervention decreased CRP by 45%, serum amyloid A by 37%, and soluble ICAM-1 in postmenopausal women on hormone replacement therapy with risk factors for CAD. Heilbronn et al. (143) reported that CRP decreased when obese women underwent a 12-wk low-fat, 1,400 kcal diet (14% fat, 61% carbohydrate, 23% protein), whereas Ziccardi et al. (421) noted decreases in P-selectin and ICAM-1 and improvement in vascular response to L-arginine, after 1 yr of a 1,300 kcal diet (23% fat, 55% carbohydrate, 22% protein) and exercise (encouraged to walk 1 h 3 days/wk) intervention in obese women. In the aforementioned study by Jenkins et al. (177), after 1 mo CRP decreased 28% in the diet group and 33% in the lovastatin group, suggesting that the ability of diet to reduce CRP was comparable to statin therapy. Elevated CRP is associated with decreased nitric oxide (NO) bioavailability in human endothelial cells (395, 396), induces plasminogen activator inhibitor (82), and is independently

related to insulin (316). Along these lines, Barnard et al. (26) documented reduced platelet aggregation and thromboxane formation and Mehrabian et al. (250) noted a reduction in plasminogen activator inhibitor after the Pritikin physical activity and diet intervention. The mechanisms responsible for the observed reductions in inflammation may be related, in part, to attenuation of oxidative stress, as flavonoids and other antioxidants present in fruits and vegetables have been demonstrated to possess anti-inflammatory activities (255). The addition of vegetables to the diet has been shown to reverse the increase in sICAM-1 and sVCAM-1 induced by high-fat meal consumption (121). Consumption of an array of phytonutrients may be optimal, as the effect of individual supplements on inflammatory markers is not consistent (389). Liu et al. (229) have shown that glycemic load is associated with increased plasma CRP concentration, and epidemiological studies indicate that regular physical activity can also reduce inflammation (108), suggesting that both physical activity and diet may contribute to reduced inflammation.

The mechanisms for the benefits of physical activity in reducing CAD risk are numerous and include effects on plasma lipids (202), endothelial function (127), insulin sensitivity (172), inflammation (108), and blood pressure (100). For example, Oscai et al. (285) reported a normalization of elevated TG levels and very-low-density lipoprotein patterns after 7 days of 45-min daily walking or jogging. Exercise enhances levels of antioxidant enzymes superoxide dismutase and glutathione peroxidase (315). Smith et al. (355) documented that mononuclear cell production of atherogenic cytokines [interleukin (IL)-1 $\alpha$ , tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ ] and CRP fell by 58 and 35%, respectively, after the exercise program, whereas the production of atheroprotective cytokines (IL-4, IL-10, and transforming growth factor- $\beta_1$ ) rose by 36%. Changes in transforming growth factor- $\beta_1$  and cytokine production after the exercise program were proportionate to the time subjects spent performing lower body exercise. In a series of studies, Hambrecht and colleagues (128, 130) established that exercise training improves endothelium-dependent vasodilation in patients with CAD and chronic heart failure and provided evidence that improvement of endothelial function is associated with increased endothelial NO synthase (NOS), Akt phosphorylation, and endothelial NOS Ser<sup>1177</sup> phosphorylation by Akt (127). Recently, this group provided evidence that event-free survival was superior with 1 yr of exercise training compared with percutaneous coronary angioplasty, and this occurred at a lower financial cost secondary to reduced rehospitalizations and repeat revascularizations (129).

Additionally, it is important to point out that, although obesity contributes to atherosclerosis progression, mediated by effects related to visceral obesity, inflammatory cytokines produced in adipocytes, among other potential causes, the benefits of physical activity and diet modification may be accrued independent of significant weight loss. Evidence comes from Ehnholm et al. (90), who placed 54 subjects on a low-fat (~24% of total calories) diet for 6 wk. Total-C decreased from 263 to 201 mg/dl in men and from 239 to 188 mg/dl in women; however, body weight only decreased 2 lb. When the subjects resumed their usual diet (including ~39% calories from fat), Total-C increased back to baseline levels, despite no change in body weight. Just as risk factors for heart disease can be affected by changes in lifestyle independent of

changes in body weight, the actual disease itself can be as well. Applegate et al. (14) evaluated coronary angiograms of more than 4,500 men and women and noted that the risk of atherosclerosis actually decreased as body weight increased. The large-scale International Atherosclerosis Project analyzed over 23,000 sets of coronary arteries obtained at autopsy and found no relation between body weight or body fat and degree of CAD (115). In the Cholesterol Lowering Atherosclerosis Study, 82 moderately overweight men with CAD underwent a 2-yr program. Men who improved their diets showed no new fatty deposits in their coronary vessels, determined by coronary angiography. However, men who failed to make significant dietary changes all showed evidence of new lesions. Neither group lost any weight during the 2-yr study, suggesting that the appearance of new lesions can be influenced without weight change (47).

**Summary.** Physical inactivity and dietary factors both contribute vitally to atherosclerosis and consequent CAD. Studies indicate that inactivity may be as predictive of CAD risk as conventional risk factors, exercise training may improve endothelial function and is superior to percutaneous angioplasty for short-term survival. Additionally, several dietary factors such as fiber, fat (amount and type), glycemic load, and fruit and vegetable consumption appear to significantly modulate CAD risk. Combined exercise and diet interventions mitigate atherosclerosis progression and may in fact induce plaque regression and/or improve myocardial flow reserve. These benefits are, at least in part, due to reductions in plasma lipids, lipid oxidation, and inflammation. Improvements in risk factors with diet may, in some instances, be as great as with statin therapy, and lifestyle interventions combined with statin therapy possess additive effects on lipid lowering. Moreover, although obesity contributes to CAD, risk can be modified independent of large changes in weight.

## HYPERTENSION

Hypertension (systolic blood pressure >140 mmHg and/or diastolic >90 mmHg) is a hallmark risk factor for CAD, stroke, congestive heart failure, and end-stage renal disease. Presently, it has been estimated that hypertension affects as many as 56 million adults in the United States, and an additional 23 million have high-normal blood pressure (130–139 mmHg systolic or 85–89 mmHg diastolic), accounting for approximately one-third of all US adults (62, 372). Additionally, one-half of all individuals over the age of 60 have hypertension in the United States and only 47% of all adults have optimal blood pressure (<120/80) (62). The National High Blood Pressure Education Program includes in its recommendations for primary prevention of hypertension to engage in moderate physical activity and consume a diet rich in fruits, vegetables, and low-fat dairy products and reduced in saturated and total fat (410). Several cohort and epidemiologic studies document that both physical activity and diet have blood pressure-lowering effects. For example, studies of migrants suggest that diet can affect blood pressure (138, 313). In the Yi People Study in China (138), blood pressure rose very little with age after puberty in Yi farmers living in remote villages but increased in Yi migrants and Han (local residents). The proportion of energy from fat ranged from <10% among Yi farmers to almost 40% among Yi migrants and Han, and,

compared with Yi farmers, Yi migrants consumed less potassium, calcium, and magnesium. Population studies (335, 336) and clinical trials (243, 334) have suggested that vegetarian diets are associated with lower blood pressure. For example, the association between blood pressure and a vegetarian diet was studied in Seventh-Day Adventist lacto-ovo vegetarians and omnivores and in Mormon omnivores. Mean blood pressures adjusted for age, height, and weight were significantly lower in vegetarians than in Mormon omnivores (115.6/68.7 vs. 121.2/72.2, in men and 109.1/66.7 vs. 114.9/72.6, in women). The prevalence of hypertension was 10 and 8.5% in Mormon and Seventh-Day Adventist omnivores, respectively, and <2% in Seventh-Day Adventist vegetarians. Analysis of diet records showed that vegetarians consumed significantly more dietary fiber, polyunsaturated fat, magnesium, and potassium and significantly less total fat, saturated fat, and cholesterol than did Mormon omnivores (333). Ascherio et al. (19) examined prospectively the relation between nutritional factors and blood pressure among 30,681 predominantly US male health professionals, without hypertension. During 4 yr of follow-up, 1,248 men were diagnosed with hypertension, and, in men with a fiber intake of <12 g/day, the relative risk of hypertension was 1.57 compared with an intake of >24 g/day. This group subsequently looked at the effects of dietary factors on blood pressure levels among 41,541 female nurses, and after a 4-yr follow-up, 2,526 women reported a diagnosis of hypertension (18), and intakes of fiber, fruits, and vegetables were inversely associated with systolic and diastolic pressures.

For physical activity, Blair et al. (43) measured physical fitness in over 6,000 men and women with no history of cardiovascular disease and who were normotensive at baseline. After an average 4-yr follow-up, those with low levels of physical fitness (72% of the group) had a relative risk of 1.52 for the development of hypertension when compared with highly fit persons, and the risk of developing hypertension also increased substantially with increased baseline blood pressure. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, individuals with low fitness had a relative risk of 2.59 for hypertension compared with those with high fitness, as determined by duration on a maximal treadmill test (65). Additionally, Harvard alumni who did not engage in vigorous sports play were at 35% greater risk of hypertension (288), and vigorous sports participation was inversely related to hypertension (287). Hypertension is also less frequent in master's athletes (146). Previous meta-analyses have estimated that regular physical activity decreases blood pressure by an average of 7.4/5.8 mmHg (100), and both aerobic (190, 411) and resistance exercise training (191) have the ability to lower blood pressure, effects of which are largely independent of weight loss (17, 411).

*Intervention studies and mechanisms.* The DASH clinical trial tested a diet high in fruits and vegetables (~10 servings/day), low-fat dairy (2 servings/day), and reduced red meat, sugar, and refined carbohydrates on blood pressure (13). Significant reductions in blood pressure were noted within 2 wk, and by 8 wk diet reduced blood pressure by 5.5/3.0 mmHg in individuals with normal blood pressure and by 11.4/5.5 mmHg in patients with hypertension, with 70% of hypertensive patients exhibiting normal blood pressure after 8 wk. Such reductions are similar to that achieved with single-drug therapy in individuals with mild hypertension. The blood pressure-

lowering effects of DASH were correlated with blood pressure at randomization (367), occurred independent of body weight changes, and were enhanced with sodium reduction (337). Subsequently, the DASH diet reduced systolic blood pressure in patients with stage 1 isolated systolic hypertension (defined as a systolic blood pressure 140 to 159 mmHg, diastolic blood pressure <90 mmHg) (265).

The effect of the Pritikin combined lifestyle modification on blood pressure was measured in 268 hypertensive patients (35). Of 216 who entered the program on medication, blood pressure was reduced from  $134 \pm 2/77 \pm 1$  (blood pressure measured on drug therapy) to  $130 \pm 2/73 \pm 1$  mmHg (measured off in 83% and on in 17%), with 83% taken off medication and the majority of others having their dosages reduced. Barnard et al. (30) studied hypertensive, diabetic patients going through the 26-day intervention and noted reductions in blood pressure of  $141 \pm 2/81 \pm 2$  to  $127 \pm 2/75 \pm 1$  mmHg, with 37 of the 61 patients taking antihypertensive medications having discontinued their medications. In a study of 652 diabetics, lifestyle modification reduced both systolic and diastolic blood pressure (28). Overall, the combined effect of lifestyle modification on blood pressure over seven studies and 1,117 subjects is displayed in Fig. 2 (22, 26, 28, 30, 33, 35, 329). In all of the above studies, if the subject entered the program on antihypertensive medication, the preintervention recording was measured while on medication; if medication was discontinued, the postintervention recording was made off drug therapy; and if the subjects' dose was reduced, the patient was designated "on medication post."

Gordon et al. (122) compared the effects of single vs. combined physical activity and diet (kcal restriction) intervention and found no significant additive effect of both interventions; however, the combined intervention induced an average of  $12.5 \pm 6.3/7.9 \pm 4.3$  reductions in blood pressure. The Diet, Exercise, and Weight Loss Intervention Trial investigated the effects of lifestyle on blood pressure and other cardiovascular disease risk factors (257). For 9 wk, 44 hypertensive, overweight adults on a single blood pressure medication were fed a hypocaloric version of the DASH diet and participated in a supervised, moderate-intensity exercise program 3 times/wk. Noted were significant reductions in daytime systolic (12.1 mmHg) and diastolic (6.6 mmHg) blood pressures as well as Total-C (-25 mg/dl), LDL-C (-18 mg/dl), and HDL-C (-5 mg/dl), net of control. In the PREMIER trial, a comprehensive lifestyle intervention, including implementation of the DASH diet, a minimum of 180 min/wk of physical activity, and weight loss resulted in a 53% risk reduction in hypertension after 6 mo (416). Additionally, Dengel et al. (81) noted decreases in systolic ( $14 \pm 3$  mmHg) and diastolic ( $10 \pm 2$  mmHg) blood pressure after a combined aerobic exercise and weight loss intervention.

Exercise interventions have also been documented to reduce blood pressure. Ishikawa et al. (170) noted significant reductions in blood pressure in both young (~15/12 mmHg) and older (~10/5 mmHg) hypertensive subjects after a multifaceted physical activity intervention. Seals et al. (348) found similar reductions after 12 wk of training in both resting (10/7 mmHg) and submaximal exercise (21/8 mmHg) systolic and diastolic blood pressure in postmenopausal women with high-normal blood pressure or hypertension. Walking only 3-4 days/wk has been shown to reduce blood pressure, increase

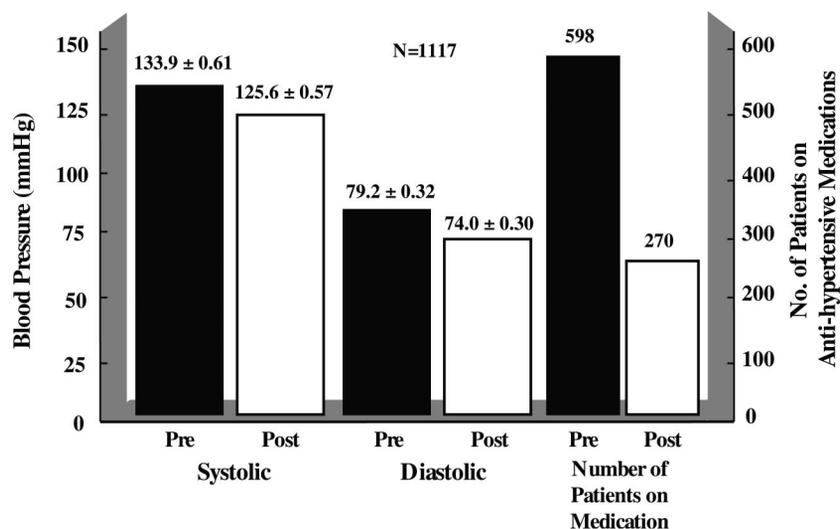


Fig. 2. Combined effect of Pritikin lifestyle intervention on systolic and diastolic blood pressure and need for anti-hypertensive medication. (Data from Refs. 22, 26, 28, 30, 33, 35, 329.)

forearm blood flow measured by venous occlusion plethysmography, and increase peak limb vascular conductance (a measure of arterial structure) in hypertensive patients (369).

Endothelium-mediated vasodilation is impaired in patients with essential hypertension (291), and improving endothelial function may lower blood pressure. Higashi et al. (148) documented that patients with mild hypertension who underwent a walking intervention for 12 wk decreased both systolic and diastolic blood pressure (8/4 mmHg) and demonstrated an improvement in ACh-mediated forearm blood flow, which was blocked by the NOS inhibitor  $N^G$ -monomethyl-L-arginine. They also noted that walking 5–7 times/wk for 12 wk increased maximal forearm blood flow response during reactive hyperemia from  $38.4 \pm 4.6$  to  $47.1 \pm 4.9$  ml/min per 100 ml tissue. Changes in forearm blood flow after sublingual nitroglycerin did not change, and intra-arterial infusion of the NOS inhibitor  $N^G$ -monomethyl-L-arginine abolished the enhancement of reactive hyperemia (149). In African-American men with hypertension and treated with antihypertensive therapy, 32 wk of exercise training led to decreases in resting, submaximal, and maximal exercise blood pressure, with reductions in interventricular septum thickness and left ventricular mass compared with those on medication only; these changes occurred despite significant reductions in dose of antihypertensive medication (200). Acute exercise may also possess antihypertensive effects, as Pescatello et al. (298, 299) noted that postexercise hypotension occurs for several hours after cycling exercise.

Several mechanisms may explain the blood pressure-lowering effect of physical activity and diet, including reduction of oxidative stress and amelioration of insulin resistance/hyperinsulinemia. Isoprostanes are a family of eicosanoids produced mainly through nonenzymatic oxidation of arachidonic acid by reactive oxygen species. Consequently, their production is increased in the presence of oxidative stress. 8-Iso-PGF<sub>2α</sub> is a potent vasoconstrictor (295), which increased in various conditions associated with oxidative stress (74, 75, 266). Thompson et al. (373) documented a 35% reduction in urinary 8-iso-PGF<sub>2α</sub> and 8-hydroxy-deoxyguanosine, a sensitive marker of DNA oxidation, and increased plasma carotenoids (i.e., cryptoxanthin, lutein, β-carotene) after 14 days of fruit and vegetable consumption; they suggested that consum-

ing an array of fruits and vegetables was important for maximizing exposure to a variety of beneficial phytochemicals, many of which remain undefined. Miller et al. (256) used diets containing fruits and vegetables or both of these in combination with low-fat dairy products and documented protection against lipid peroxidation and augmented serum radical-absorbing capacity. Ide et al. (168) have shown that vitamin E and vitamin C supplementation for 4 wk decreased urinary 8-iso-PGF<sub>2α</sub>. This may contribute to an increase in NO availability and a decrease in other oxidative processes that contribute to hypertension and other chronic diseases. To examine this possibility, Roberts et al. (329) tested whether lifestyle modification affected oxidative stress and NO bioavailability in 11 men with elevated blood pressure. Significant reductions in both systolic ( $137.8 \pm 4$  to  $119.0 \pm 3$ ) and diastolic ( $81.4 \pm 2$  to  $73.4 \pm 2$ ) blood pressure, fasting 8-iso-PGF<sub>2α</sub>, as well as increased 24-h urinary NO metabolite (NO<sub>2</sub>, NO<sub>3</sub>) excretion, a surrogate marker for NO availability, were noted after 3 wk. At the beginning of the study, 7 of the 11 subjects were clinically hypertensive, and at the end none had hypertension.

Hyperinsulinemia/insulin resistance impairs NO synthesis and may contribute to the development of hypertension (344). In the aforementioned study by Roberts et al. (329), the relationship between NO and insulin was examined. Insulin and homeostasis model assessment for insulin resistance, an index of insulin sensitivity, decreased, and there was a significant correlation between the decrease in serum insulin and the increase in urinary NO metabolite excretion ( $r^2 = 0.68$ ). These data suggested that physical activity and diet may mitigate oxidative stress and improve NO availability and that the improvement in NO availability may be related to insulin sensitivity. Petrie et al. (301) have shown that insulin sensitivity is related to endothelial function, and insulin and the insulin-to-glucose ratio have been documented to predict development of hypertension (137). Exercise training has been shown to increase NO production via vascular wall shear stress, which is a stimulus for NO production (116, 195, 223) and may contribute to improvements in endothelial function discussed earlier (148). Aerobic exercise training has also been documented to reduce plasma endothelin-1 concentration and

blood pressure from  $127 \pm 4/79 \pm 2$  to  $112 \pm 3/65 \pm 2$  in older women (237).

Increased intake of unrefined, high-fiber carbohydrates, antioxidants, and other phytochemicals as well as reduced fat consumption most likely contribute to diet-induced reductions in blood pressure. Katz et al. (185) documented that oatmeal consumption, containing high levels of the soluble fiber  $\beta$ -glucan, reversed the impairment in brachial artery endothelium-dependent dilation noted during a high-fat meal in healthy subjects. Soluble fiber attenuates postprandial elevations of plasma glucose, insulin, and TG, which may contribute to its beneficial effects (123). Whole grain consumption results in a reduction in 8-iso  $\text{PGF}_{2\alpha}$  (175). Vogel et al. (399) demonstrated that a single high-fat meal impairs endothelial function in healthy individuals, and this response was blocked by pretreatment with antioxidant vitamins C and E, suggesting an oxidative mechanism (308). Title et al. (378) reported an impairment in endothelium-dependent flow-mediated dilation in healthy subjects after an oral glucose load, which was also prevented with antioxidant pretreatment. Additionally, Block et al. (49) used ascorbic acid depletion and documented that plasma ascorbic acid was inversely correlated with blood pressure. They suggested that vitamin C may be, in part, responsible for the effectiveness of fruits and vegetables in the reduction in blood pressure. Antioxidants have also been shown to improve endothelium-dependent vasodilation in hypercholesteremic patients (377). Ingesting diets high in fruits and vegetables, offering an array of phytochemicals, may be more effective in mitigating oxidative stress, as opposed to consuming supplements, which have not been shown to be effective in some studies (321). Other dietary components may also be important, such as potassium, magnesium, calcium, and protein (70).

**Summary.** Hypertension is the most common cardiovascular disease in the United States and is a hallmark risk factor for CAD and stroke. Both physical activity and diet have been shown to affect the development of hypertension and can lower blood pressure even in those without clinically defined hypertension. The DASH trial documented that blood pressure reductions with dietary intervention may be comparable to single-drug therapy in the absence of weight loss. Exercise training has been shown in numerous studies to lower resting blood pressure, associated with improvements in endothelial function. Convincing as well are data from combined interventions that lower blood pressure, in part mediated by improved vascular function secondary to reductions in oxidative stress, augmented NO availability, and possibly increased insulin sensitivity.

## DIABETES

Normally over 75% of blood glucose is cleared into skeletal muscle by insulin (76), and insulin resistance in muscle is the primary defect leading to diabetes (225). Harris (135) noted that >40% of the elderly meet diagnostic criteria for diabetes or impaired glucose tolerance, an estimate matching those provided by the Centers for Disease Control, in which 40% of US adults have impaired fasting glucose and/or impaired glucose tolerance (320). In parallel, diabetes has increased dramatically and to epidemic levels in recent years. The estimated prevalence of diabetes increased 600% from 1958 to 1993 (7)

and has continued to increase in the last 10 years (261, 262). Currently, just under 20 million people in the United States have diabetes, with 18% of those 60 yr or older having the disease (8). Recently, Narayan et al. (268) estimated the lifetime risk of developing diabetes in individuals born in the year 2000 at 32.8% for men and 38.5% for women, with risk in Hispanic women exceeding 50%. Although traditionally diabetes was regarded as a chronic disease seen in older adults and was originally coined "adult-onset diabetes," evidence estimates that, before 1992, 4% of all newly diagnosed cases of diabetes occurred in those from birth to age 19, but in 1994 this age group accounted for 16% of all newly diagnosed cases (305), and an estimated 10-fold increase has occurred from 1982 to 1994. Those diagnosed in 1994 presented with diabetes at an average age under 14 and with an average BMI in excess of  $37 \text{ kg/m}^2$ . Impaired glucose tolerance was detected in 25 and 21% of obese children and adolescents, and insulin resistance was greater in those with impaired glucose tolerance (353). Thus diabetes is a good model of how lifestyle can reduce the time needed to present with chronic disease, independent of the increase in life expectancy.

As early as 1935, lifestyle factors were implicated to play a role in diabetes when Himsworth (151) reported that rates of diabetes were higher in those with higher fat intakes. Evidence that diabetes is primarily a lifestyle disease comes from Eaton and Konner (88, 89), who pointed out that hunter-gatherer societies exhibit a prevalence of diabetes at 1–2% vs. as high as 10% in industrialized nations. Additionally, migration studies demonstrated the role of lifestyle factors in chronic disease, as Japanese migrants living in Hawaii had an elevated risk of diabetes compared with their counterparts living in Hiroshima. Although caloric intake was not different, consumption of animal fat and simple carbohydrates was greater and high-fiber carbohydrates and physical activity were lower in the migrants (188). Studies in Seventh-Day Adventists have suggested that, compared with all US whites, Adventist whites have approximately a 50% reduced risk of diabetes and that vegetarian Adventists have a reduced risk compared with nonvegetarian Adventists (356). Gene-environment interaction in the pathogenesis of diabetes (317) is epitomized in studies comparing Pima Indians living in rural Mexico and following a traditional Pima lifestyle, with Pima Indians living in Arizona, consuming a Westernized diet, and maintaining a more sedentary lifestyle (206, 207). Despite the similarity in genetic background of these two Pima communities, the Arizona Pimas, living in an "affluent" environment, have markedly higher rates of obesity and diabetes than the Mexico Pimas, living a "traditional" lifestyle, characterized by a diet including less animal fat and more complex carbohydrates and by greater energy expenditure in physical labor (322). Other examples of populations exposed to a Westernized lifestyle and exhibiting high rates of diabetes include Micronesians in Nauru, Wanigela in New Guinea, and Australian Aborigines, among others (424).

In the Nurses' Health Study, 91% of diabetes cases observed over a 16-yr follow-up could be attributed to lifestyle factors, such as a poor diet and physical inactivity (158). In a prospective study of 42,504 male health professionals, a prudent diet, characterized by higher intakes of vegetables, fruits, fish, poultry, and whole grains, was associated with a lower risk of diabetes (relative risk 0.84), whereas a high Western diet, characterized by higher intakes of processed and red meat,

high-fat dairy, refined grains, sweets, and desserts, was associated with an increased risk (1.59). When the Western diet pattern was combined with low physical activity, risk increased further (1.96) (392). In Native Canadians, a higher prevalence of impaired glucose tolerance and diabetes is associated with consumption of foods high in simple sugar and fat and low in fiber (120). Regarding specific dietary components, dietary fiber consumption is associated with reduced diabetes risk (234, 254, 340) and lower fasting insulin (234). Whole grain consumption is inversely associated with risk of diabetes (233, 254), and substituting whole grain for refined grains is also associated with decreased risk (231). In the Nurses' Health Study, a higher consumption of refined grain foods such as white bread and rice, desserts, muffins, pancakes, and breakfast cereals was associated with an increased risk of diabetes (233). When data from several cohort studies are pooled (227), the estimated relative risk from high whole grain consumption is  $\sim 0.70$ . Fiber and whole grains may also explain, in part, the effect of glycemic load on diabetes risk. In both the Nurses' Health Study (340) and Health Professionals Follow-up Study (338), diabetes incidence increased with higher glycemic load. In addition, omega-3 fatty acids may affect diabetes risk. An association between the proportion of long-chain omega-3 fatty acids in skeletal muscle membrane phospholipids and insulin sensitivity has been noted (289). Fish consumption has been shown to reduce the risk of glucose intolerance (105) and to be inversely associated with 2-h postload glucose in a cohort of the Seven Countries Study (106). On the other hand, after 14 yr of follow-up, consumption of trans-fatty acids was associated with increased risk of diabetes in the Nurses' Health Study (339).

Several studies indicate that low fitness increases the risk of diabetes and increased physical activity is effective in preventing diabetes (144, 145). In men with diabetes, low cardiorespiratory fitness and physical inactivity independently predict mortality risk compared with fit men (405). In the CARDIA study, those not obese at the onset of the study with low fitness were 3.66 times more likely to develop diabetes compared with those with high fitness, and increasing fitness during the 7-yr study was associated with a reduced risk of diabetes (risk ratio of 0.4) (65). In the University of Pennsylvania Alumni Health Study, 5,990 men were surveyed and the amount of leisure-time physical activity was inversely related to the development of diabetes; each additional 500 kcal/wk of physical activity was associated with a decrease in risk of 6%. Manson et al. (242) examined the association between regular vigorous exercise and the subsequent incidence of diabetes in 87,253 US women aged 34–59 yr. During an 8-yr follow-up, 1,303 cases of diabetes were noted, and women who engaged in vigorous exercise at least once/wk had an age-adjusted relative risk of 0.67 compared with women who did not exercise weekly. The Physicians' Health Study followed 21,271 men 40–84 yr of age and free of diagnosed diabetes for 5 yr; men who exercised at least once/wk had an age-adjusted relative risk for diabetes of 0.64 compared with those who exercised less frequently. Among 6,815 Japanese-American men in the Honolulu Heart Program, 6-yr age-adjusted odds ratios for diabetes comparing the upper vs. the lower four quintiles of physical activity were 0.5 (60). The relative risk of diabetes decreased in male physicians with increasing frequency of exercise: 0.77 for once weekly, 0.62 for 2 to 4 times/wk, and 0.58 for 5 or more

times/wk (241). Hu et al. (165) demonstrated in over 14,000 Finnish men and women that occupational physical activity, leisure-time physical activity, and walking to and from work all significantly reduced the risk of developing diabetes over a 12-yr follow-up. Additional studies have demonstrated that there is a dose-dependent effect of physical activity on lowering risk of diabetes, even independent of BMI (160). Over 4,000 Finnish men and women were prospectively followed to investigate the relationship between physical activity and diabetes risk, and physical activity was inversely related to diabetes incidence in both normal weight and obese individuals (164). In addition, it is interesting to note that there is also a powerful effect of television watching on risk of diabetes, as it has been reported among 37,918 men that, compared with 0–1 h/wk,  $>21$  and  $>40$  h/wk of television watching are associated with relative risks of 2.16 and 2.87, respectively, for development of diabetes over a 10-yr period (155, 157). In fact, it has been estimated that average time viewing television for US men is  $\sim 29$  h/wk and for women  $\sim 34$  h/wk (279).

*Intervention studies and mechanisms.* Interventions incorporating physical activity, diet, or a combination of both have been documented to reduce progression to diabetes and reverse existing diabetes. Residents of Da Qing, China, were screened for impaired glucose tolerance and diabetes, and the 577 that were classified as having impaired glucose tolerance were randomized to control, diet, exercise, or diet plus exercise groups. After 6 yr, the interventions were associated with reductions in risk of developing diabetes of 31, 46, and 42%, respectively (290). In the Malmo Preventive Trial, 6,956 men underwent health screening at 48 yr of age, and 41 subjects with early-stage diabetes and 181 subjects with impaired glucose tolerance were selected for long-term lifestyle intervention. After the 5-yr protocol,  $\dot{V}O_{2\max}$  increased by 10–14% in the intervention group and decreased by 5–9% in the control group. Glucose tolerance was normalized in  $>50\%$  of subjects with impaired glucose tolerance, and  $>50\%$  of the diabetic patients were in remission after a mean follow-up of 6 yr (96). At 12-yr follow-up, the mortality rate in the intervention group was similar to those with normal glucose tolerance and 50% lower than those with impaired glucose tolerance given routine treatment (95). In an exercise-only intervention, resistance training decreased glycosylated hemoglobin levels, blood pressure and diabetes medication dose were lowered in 72% of trainees, whereas over the 16-wk study, blood pressure increased and medication dose increased by 42% in the control group (67).

Two large randomized intervention trials, the Finnish Diabetes Prevention Study and the Diabetes Prevention Program in the United States, both demonstrate that lifestyle change can significantly reduce the risk of developing diabetes in individuals with impaired glucose tolerance (198, 383). In the Finnish Diabetes Prevention Study, 522 subjects with impaired glucose tolerance were randomly assigned to either control or lifestyle intervention, including specific recommendations to increase fiber and decrease fat, via whole grains, vegetables, fruits, and low-fat dairy and meats, weight reduction, and daily exercise, including supervised, progressive resistance training and endurance exercise. After an average 3-yr follow-up, the risk of diabetes was reduced 58% in the intervention group, despite minimal weight loss (3.5 kg after 2 yr) (383). The authors also pointed out that a target of  $\sim 4$  h of exercise per week reduced

the risk of diabetes in those who did not lose weight. In the Diabetes Prevention Program, 3,234 individuals with elevated glucose were randomized to placebo, the insulin-sensitizing biguanide metformin, or lifestyle modification that included >150 min/wk of exercise and a low-fat diet (198). Over the 2.8-yr follow-up, metformin and lifestyle reduced diabetes by 31 and 58%, respectively, compared with controls.

Across two studies, Barnard et al. (29, 31) noted that diabetes may be controlled by lifestyle modification. In 129 patients with diabetes mellitus, 45 of 54 patients who were on oral hypoglycemic agents discontinued medication, 26 of 35 patients who were taking insulin were off medication at discharge, and most of the others had their dosage reduced. In the first of these studies (29), data were obtained from 60 patients; fasting blood glucose was reduced from  $194.9 \pm 10.1$  to  $144.6 \pm 7.1$  mg/dl and maximum work capacity increased from  $5.6 \pm 0.3$  to  $7.9 \pm 0.4$  METs. In the second (31), glucose decreased from  $180 \pm 11$  to  $134 \pm 4$ , and after a 2- to 3-yr follow-up blood glucose concentration was unchanged; however, in those who did not adhere to the program, oral agents were started. In 1992, Barnard et al. (33) documented that, in individuals with diabetes or insulin resistance, lifestyle modification significantly reduced hyperinsulinemia, blood pressure, and hypertriglyceridemia. In the diabetic patients, decreases were noted in glucose ( $200 \pm 17$  to  $144 \pm 14$  mg/dl), insulin ( $40 \pm 15$  to  $27 \pm 11$   $\mu$ U/ml), blood pressure ( $142 \pm 9$  to  $132 \pm 6$  mmHg systolic,  $83 \pm 3$  to  $71 \pm 3$  mmHg diastolic), and TG ( $353 \pm 76$  to  $196 \pm 31$  mg/dl), and significant reductions were also noted in insulin-resistant and normal groups (33). In a separate study (30), 70 hypertensive, diabetic patients had reductions in blood pressure of  $141 \pm 2/81 \pm 2$  to  $127 \pm 2/75 \pm 1$  mmHg, with 37 of the 61 patients taking antihypertensive medications having discontinued their medications. Glucose decreased from  $198 \pm 9$  to  $152 \pm 5$  with 20 of 28 discontinuing oral hypoglycemics and 12 of 27 discontinuing insulin therapy after the intervention.  $\dot{V}O_{2\max}$  increased, and blood pressure at the same relative work rate decreased from  $183 \pm 3/84 \pm 2$  to  $161 \pm 3/76 \pm 1$  mmHg. Of the 4,587 individuals previously discussed (21), 652 patients were identified with diabetes; 71% of 197 subjects taking oral hypoglycemic agents and 39% of 212 taking insulin were able to

discontinue their medication. Overall, the combined effect of lifestyle modification on diabetes over five studies (38, 39, 40, 41, 43) and 864 subjects is shown in Fig. 3. These data suggest the need to emphasize lifestyle modification early in the treatment of diabetes. It should be noted that these studies were performed when diabetes was defined as fasting glucose >140 mg/dl.

The major mechanism by which diet and physical activity decrease the risk for diabetes is by improvement in insulin sensitivity (245). In the British Regional Study, activity levels were inversely related to insulin sensitivity, and this was associated with development of diabetes (401). Heath et al. (139) noted exaggerated blood glucose and insulin responses to an oral-glucose tolerance test in subjects after 10 days of inactivity, documenting compromised insulin sensitivity in the absence of training, an effect related to reduced GLUT-4 content (400). Exercise training may ameliorate insulin resistance by direct effects on the muscle, such as enhancing insulin receptor autophosphorylation (417) and increasing GLUT-4 content (72, 79, 167, 351) and glucose transport-phosphorylation (297), by reducing visceral obesity (351), which is associated with a reduction in free fatty acid levels, and/or by improvement in insulin-stimulated limb blood flow (78). Additionally, muscle hypertrophy via resistance training, which increases the depot size available for glucose disposal, has also been documented to improve glycemic control in diabetes patients (93, 94). Reductions in insulin levels and plasma insulin response to a glucose challenge (259) and glucose utilization via the hyperinsulinemic-euglycemic clamp are improved by resistance training.

Diet also has direct effects on insulin sensitivity. Swinburn et al. (368) demonstrated deterioration in glucose tolerance during intravenous and oral glucose tolerance tests in both Pima Indians and Caucasians fed a modern Western diet, compared with a traditional Pima diet, and suggested that diet composition, by affecting glucose tolerance, may affect the prevalence of diabetes. Both high-complex-carbohydrate and Mediterranean diets conferred improvements in insulin sensitivity by glucose-suppression tests and insulin-stimulated glucose uptake in peripheral monocytes (296).

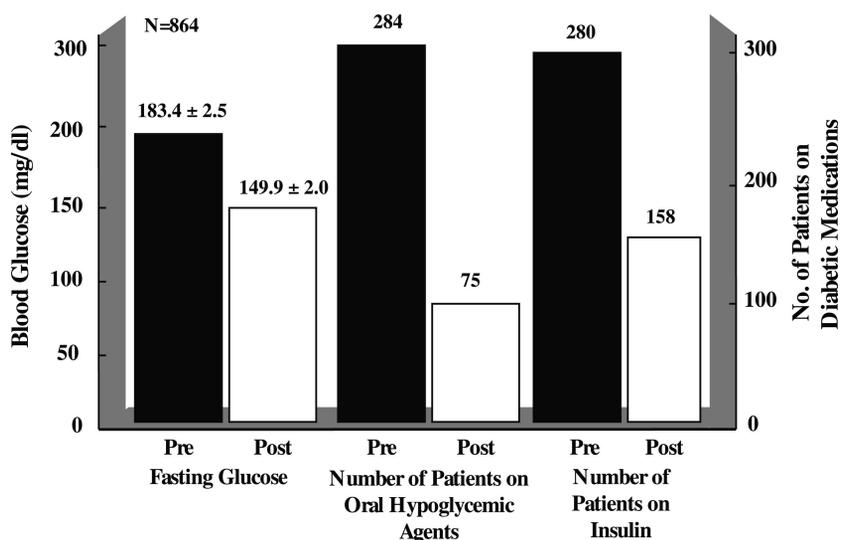


Fig. 3. Combined effect of Pritikin lifestyle intervention on blood glucose and need for oral hypoglycemic medication or insulin therapy. (Data from Refs. 38, 39, 40, 41, 43.)

**Summary.** Diabetes prevalence has increased dramatically over the past two decades, contributed to by changes in activity levels (exercise training, television viewing, computers/internet, etc.) and diet. This problem is exemplified by removal of “adult onset” from its description, given its prevalence in today’s children and adolescents, a group in whom this disease was essentially nonexistent previously. Exercise training (aerobic and/or resistance) has been shown to reduce progression to diabetes and reverse overt diabetes. Combined interventions have documented reversal of existing diabetes, even in those on insulin therapy, albeit less than with oral hypoglycemic therapy. Lifestyle interventions have been highlighted by the Finnish and Diabetes Prevention Program trials, which unequivocally document that progression to diabetes in those with elevated fasting glucose or impaired glucose tolerance can be mitigated by exercise and diet and are superior to drug therapy. The major mechanism for risk reduction appears to be improvement in insulin sensitivity.

### METABOLIC SYNDROME

One of the earliest references to the metabolic syndrome was in 1966 by Camus (64); however, it was not until 1988 when description of this syndrome began to receive more interest. At that time, Reaven (323) termed it “syndrome X,” and in 1989 Kaplan (183) called it “the deadly quartet,” referring to the aggregation of CAD risk factors, including insulin resistance/hyperinsulinemia, hypertension, hypertriglyceridemia, and visceral obesity (42). DeFronzo and Ferrannini (77) suggested that insulin resistance is the underlying factor, and once that developed, those with a genetic predisposition would develop other aspects; however, they pointed out that diet, physical exercise, and body weight could modify insulin resistance, suggesting that the final phenotypic expression involves both genetic and acquired influences. Additionally, Haffner et al. (126) renamed the syndrome the “insulin resistance syndrome” to highlight the fact that insulin resistance preceded other aspects of the syndrome. Because this array of factors is associated with abnormal carbohydrate and lipid metabolism, it is usually referred to as the “metabolic syndrome” (104). Subsequent to the initial list of risk factors, several additional characteristics have been suggested to be components of the syndrome, including dyslipidemia (including small, dense LDL particles and depressed HDL-C), enhanced clotting factor activity involving elevated levels of fibrinogen and tissue plasminogen activator inhibitor-1 (213), endothelial dysfunction (394), and inflammation (219, 419). The clustering of these risk factors in the same individual results in a highly atherogenic risk profile. Various population studies have revealed familial clustering of the aspects encompassing the metabolic syndrome (36, 54, 125, 199, 226, 275, 357, 363–365).

Currently, both the NCEP’s ATP III guidelines (98) and the WHO (3) have established criteria for diagnosis of metabolic syndrome. The prevalence of the metabolic syndrome is extremely high in Westernized societies. As defined by ATP III diagnostic criteria (abdominal obesity, hypertriglyceridemia, low HDL, hypertension, and fasting hyperglycemia), a multi-ethnic representative US sample of 12,363 men and women 20 yr and older from the Third National Health and Nutrition Examination Survey was evaluated, and the metabolic syndrome was present in 22.8 and 22.6% of US men and women,

respectively. Metabolic syndrome was present in 4.6, 22.4, and 59.6% of normal-weight, overweight, and obese men, respectively, and physical inactivity was associated with an increased risk (292). Additionally, of those >60 yr of age (109), it has been estimated that ~43% have the metabolic syndrome and ~80% of those with diabetes have the metabolic syndrome (171). Given that the estimated prevalence is based on the Third National Health and Nutrition Examination Survey (1988–1994), it is likely that prevalence of the metabolic syndrome is currently higher.

Those with the metabolic syndrome have a significantly higher risk of CAD and all-cause mortality, even in the absence of baseline cardiovascular disease and diabetes (166, 171, 210). For example, Lakka et al. (210) reported that middle-aged men with the metabolic syndrome exhibited a 4.26-fold risk of death over an 11-yr follow-up compared with healthy men. Sattar et al. (342) noted that men with four or five features of the syndrome have been estimated to have a 3.7-fold increase in risk for CAD and a 24.5-fold increased risk for diabetes compared with men with none, whereas Klein et al. (196) reported 2.5 and 1.1% incidence of cardiovascular disease and diabetes, respectively, in those with one component of the metabolic syndrome, whereas 14.9 and 17.9% developed these diseases in those with four or more components of the syndrome.

Several studies have clearly demonstrated that the pathogenesis of the metabolic syndrome is largely attributable to dietary factors and activity levels. Cross-sectional associations of leisure-time physical activity and cardiorespiratory fitness with the metabolic syndrome were investigated in a population-based sample of 1,069 middle-aged men without diabetes, cardiovascular disease, or cancer. Men who engaged in moderate-intensity leisure time physical activity  $\leq 1.0$  h/wk were 60% more likely to have the metabolic syndrome than those engaging in  $\geq 3.0$  h/wk. Men with a  $\dot{V}O_{2\max} \leq 29.1$  ml $\cdot$ kg $^{-1}\cdot$ min $^{-1}$  were approximately seven times more likely to exhibit metabolic syndrome than those with a  $\dot{V}O_{2\max} \geq 35.5$  ml $\cdot$ kg $^{-1}\cdot$ min $^{-1}$  (211). Across cardiorespiratory fitness quintiles, as measured by maximal treadmill exercise test, prevalence of the metabolic syndrome in a population of 7,104 women was lower as cardiorespiratory fitness increased, with prevalence ranging from 19.0% in the least fit quintile to 2.3% in the most fit quintile. Additionally, the prevalence of the metabolic syndrome in the different age groups for women who achieved a maximal MET level of 11 or higher was one-third to one-fourth that of women who achieved lower maximal MET levels (102). This relationship was extended to African-American and Native-American women, as the odds ratio for metabolic syndrome was 0.18 for women in the highest category of physical activity compared with the lowest, whereas the odds ratio was 0.07 comparing the duration of groups with the shortest to the longest maximal treadmill time (169). The odds of having risk factors for metabolic syndrome (elevated systolic blood pressure, serum TG, fasting glucose, and central adiposity) was reported as 3.0 and 10.1 for least fit men compared with moderately fit and most fit men, respectively (409). Furthermore, in the CARDIA study, low fitness predicted risk of metabolic syndrome as powerfully as conventional risk factors (65). Additionally, in a study of 5,159 men ages 40–59 yr, physical activity level was associated with metabolic syndrome factors, as well as risk of CAD and

diabetes (401). In 19,223 men 20–83 yr old, Katzmarzyk et al. (186) investigated the effects of cardiorespiratory fitness and mortality in healthy men and in those with the metabolic syndrome. Relative risk of all-cause and cardiovascular disease mortality were 1.29 and 1.89, respectively, for men with the metabolic syndrome compared with healthy men. However, after accounting for cardiorespiratory fitness, the associations were no longer significant (0.98 for all-cause and 1.23 for cardiovascular disease). The relative risks for all-cause mortality comparing unfit with fit men were similar in men deemed “healthy” and in men with the metabolic syndrome (2.18 vs. 2.01 in men), whereas the relative risk for cardiovascular disease mortality for unfit vs. fit men was actually greater in healthy men compared with men with metabolic syndrome (3.21 vs. 2.25). Additionally, a significant dose-response relationship between cardiorespiratory fitness and mortality was observed in men with the metabolic syndrome. These data provide compelling evidence for exercise providing a protective effect against mortality risk in men with the metabolic syndrome.

**Intervention studies.** An early review by Barnard and Wen (34) suggested that physical activity and diet could mitigate risk associated with metabolic syndrome and appear to be major factors in the progression of the metabolic syndrome. Early intervention studies previously discussed have noted significant reductions in metabolic risk factors associated with the metabolic syndrome including hyperinsulinemia, hyperlipidemia, and hypertension, although the studies were not designed to test effects of physical activity and diet on metabolic syndrome per se, given its more recent characterization. For example, in diabetic and insulin-resistant patients, combined physical activity and diet intervention resulted in decreases in glucose, insulin, blood pressure, and TG (33). Watkins et al. (402) studied 53 men and women with characteristics of metabolic syndrome. Subjects were randomly assigned to exercise (EX) only (3–4/wk 70–85% heart rate reserve 35 min), EX + weight loss (WL) (1,200–1,500 kcal and 15–20% fat), or control group for 6 mo. Hyperinsulinemic responses to glucose challenge were significantly reduced in both groups (EX + WL group, 47% reduction; EX-only group, 27% reduction). Diastolic blood pressure was significantly reduced in the EX + WL group ( $96 \pm 4$  to  $87 \pm 5$  mmHg) (402). The Oslo diet and exercise study randomized 219 men and women to a 1-yr participation in supervised exercise (aerobic exercise three times a week) and dietary changes (fish and reduced fat) and showed significant benefits in insulin sensitivity, especially using the combined approach (380). In subjects with the metabolic syndrome fed an ad libitum low-fat, complex-carbohydrate diet, improvements in Total-C, TG, and body weight were noted compared with control and low-fat, simple-carbohydrate diet (310).

Katzmarzyk et al. (187) investigated the efficacy of exercise training in treating the metabolic syndrome as defined according to the NCEP guidelines in 621 black and white participants from the HERITAGE Family Study. The presence of the metabolic syndrome and component risk factors were determined before and after 20 wk of supervised aerobic exercise training (3 days/wk at 55% of  $\dot{V}O_{2\max}$  for 30 min and progressing up to 75%  $\dot{V}O_{2\max}$  for 50 min). The prevalence of the metabolic syndrome was 16.9% in this sample (105/621) of apparently healthy participants. Of the 105 participants with

the metabolic syndrome at baseline, 30.5% were no longer classified as having the metabolic syndrome after the exercise training. Endothelial dysfunction, one critical factor of the metabolic syndrome (306), has been documented to be ameliorated by exercise training, independent of changes in BMI or blood pressure (215). In addition, as the metabolic syndrome is associated with inflammation (327), physical activity has been shown to decrease levels of the chemokines monocyte chem.attractant-1 and IL-8 (382). Finally, Barnard et al. (23) suggested that prostate cancer may be another manifestation of the metabolic syndrome.

**Summary.** The metabolic syndrome, although only more recently defined and investigated, exhibits a prevalence at nearly 25% of the US adult population and epitomizes the integrative nature of modern chronic disease, given its endocrine, metabolic, and cardiovascular underpinnings. Most notable is the relation between cardiovascular fitness and metabolic syndrome, given data that the mortality risk in unfit vs. fit men with the metabolic syndrome is similar to the same comparison in healthy men. Many of the studies discussed, although not designed to investigate the effect of exercise and/or diet on the metabolic syndrome per se, have shown amelioration of risk factors comprising the metabolic syndrome, including insulin resistance, blood pressure, lipid levels, inflammation, and endothelial dysfunction.

## CANCER

Cancer is the second leading killer in the United States accounting for ~23% of all deaths in 2001 (553,768) (15). Prostate cancer is the most common cancer in men, followed by lung and colon. For women, breast cancer is the most common, followed by lung and colorectal. However, it should be noted that lung cancer is the leading killer in both men and women (5). An abundance of evidence suggests that lifestyle factors, including exposure to chemical carcinogens (mainly from smoking), physical inactivity, and diet play major roles in the development of these common cancers. According to Ames (10), the current human diet contains a variety of mutagens and carcinogens that may act through the generation of reactive oxygen species and lead to the initiation of cancer and other chronic diseases. Diet has also been documented to affect reactive oxygen species generation (256, 373). For example, consumption of red meat is associated with cancers of the colon, breast, and prostate, as charbroiling and frying meats at high temperatures forms heterocyclic amines, which are potent carcinogens (362, 408). Evidence from cohort and case-control studies also indicates that physical activity protects against cancer risk, with a graded dose response (375).

Several potential mechanisms may contribute to the benefits of physical activity and diet on risk of lifestyle-related cancers. First, lifestyle modification may affect oxidant/antioxidant status. Diets high in whole grains, fruits, and vegetables contain a high amount of natural antioxidants that might play an important role in preventing cancer (10), and this type of diet combined with physical activity has been shown to reduce oxidative stress (329). Physical activity has also been shown to increase the body's antioxidant mechanisms (178). Second, physical activity and diet may induce reductions in free sex hormone levels (testosterone, estrogen, dihydrotestosterone) and/or may increase circulating sex hormone-binding globulin

(SHBG), which binds sex hormones and decreases their ability to interact with target tissues. Third, exercise and diet may reduce metabolic hormone levels (e.g., insulin) (118) and growth factors like IGF-I (418), which has been associated with increased risk of prostate (69), breast (133), and colorectal cancers (236). Additionally, moderate physical activity and diet improve immune function.

**Lung cancer.** The link between smoking and lung cancer was established in the first Surgeon General's Report in 1964 (388). However, a number of epidemiological studies have reported that exercise lowers the risk for lung cancer (218). The large Norwegian study of 81,516 men and women followed for 19 yr reported a 25% reduction in lung cancer risk for men who walked or cycled for at least 4 h/wk, after controlling for smoking habits and the number of cigarettes smoked (376). The mechanism by which exercise might reduce that risk for lung cancer has not been investigated, although Yu and Rohan (418) reported that IGF-1 is a risk factor for lung cancer. Greater consumption of vegetables, fruits, or both together has also been associated with a lower risk of lung cancer (423).

**Prostate cancer.** Prostate cancer is the most common male cancer in the United States but has a very low incidence in Asian men; this international variation in the death rate from prostate cancer, along with data from migration studies, suggests that lifestyle factors play an important role in the development of clinically significant prostate cancer (293, 350). When both Japanese and Chinese men migrate to the United States and adopt a Western lifestyle, the incidence of prostate cancer approaches that of US whites (350). In addition, as underdeveloped countries in the world adopt a more Western lifestyle, prostate cancer increases (154). A study of the risk for cancer among 44,788 pairs of twins in Sweden, Denmark, and Finland concluded that 42% of the prostate cancer cases were attributed to inheritance and the majority to lifestyle factors (224).

Of 28 published studies, 14 have demonstrated that physical activity decreases prostate cancer risk by 10–70%, with a dose-response relation observed in 10 of 19 studies (375). The international data show a positive correlation between dietary fat and prostate cancer mortality, with the lowest rates found in East Asian men and the highest rates found in US and European men (142). Most of the prospective cohort studies within a given population, however, have failed to show a relationship between dietary fat or fatty food consumption and prostate cancer risk (267). For example, a cohort study of 14,000 Seventh-Day Adventist men followed for 6 yr found no association between the consumption of animal fat and prostate cancer. However, they did find that the consumption of other foods such as lentils, beans, peas, and tomatoes was associated with a lower risk for prostate cancer (260). The Health Professionals Follow-up Study of 47,855 men found a positive but not statistically significant relationship with fat consumption and total prostate cancer, but the relationship was significant for advanced prostate cancer. They also found a relationship between red meat consumption and prostate cancer risk (119), which suggests that components other than fat in meat, for example heterocyclic amines formed during cooking of animal fat, may increase prostate cancer risk (366). One large prospective study has demonstrated a consistent, statistically significant relationship between the consumption of high-fat foods

and prostate cancer. This was a large cohort (20,316) of multiethnic men living in Hawaii with 9 to 14 yr of follow-up and 198 cases of prostate cancer (216). Exactly why prospective cohort studies have not confirmed the international data showing a strong relationship between fat consumption and prostate cancer is unclear but might relate to evidence that other dietary components such as fruits, vegetables, fiber, and cereals may have beneficial effects, independent of fat intake (132) and/or due to lack of variability in dietary fat consumption. Another possibility is a variation in the type of fat consumed. Current evidence from experimental and human studies implicates omega-6 polyunsaturated fatty acids in the promotion of cancers and omega-3 polyunsaturated fatty acids and omega-9 monounsaturated fatty acids as being protective (37, 407). Furthermore, it is possible that in the international data not only do men with a low incidence of prostate cancer mortality consume lower fat diets, consumption of other dietary components may be different, and they may be more physically active.

Tymchuk et al. (384) developed a bioassay using serum to stimulate prostate cancer cells in culture to examine the effects of lifestyle modification on serum changes in vivo and on LNCaP (an androgen-dependent cell line) cell growth in vitro. Eleven days of physical activity and diet reduced serum-stimulated LNCaP cell growth by 30%. Serum samples obtained from men who had adhered to the program for an average of 14 yr induced an additional 15% reduction in LNCaP cell growth. In a subsequent study, Ngo et al. (276) confirmed this reduction, using another androgen-dependent, patient-derived cell line, LAPC-4. Tymchuk et al. (386) reported a reduction in serum insulin concentration and increase in SHBG, contributing to lower free testosterone and estradiol, and potentially contributing to LNCaP cell growth reduction. This group confirmed the reduction in serum-free testosterone and reported that insulin, testosterone, and estradiol addition to the postintervention serum accounted for half of the reduction in LNCaP cell growth (384, 385).

IGF is a potent mitogenic factor in tissues including prostate (221, 418). Barnard et al. (23) developed a model (Fig. 4) and subsequently investigated the role of IGF-I and its binding proteins. Ngo et al. (278) demonstrated that the Pritikin physical activity and diet intervention decreased fasting insulin and IGF-I while increasing IGF binding protein (IGFBP)-1 but did not affect the more abundant IGFBP-3. The changes in IGF-I and IGFBP-1 may be due to changes in serum insulin and its impact on the liver, where 90% of circulating IGF-I is produced (217), as Phillips et al. (302) reported that insulin stimulated the production of IGF-I by hepatocytes. When IGF-I was added back to postintervention serum, the reduction in LNCaP cell growth was eliminated, and when IGFBP-1 was added to the baseline serum, LNCaP cell growth decreased (277). In addition to being a regulator of cell growth, IGF-I suppresses apoptosis (124). Ngo et al. (278) studied apoptosis in their culture system using Annexin-V and terminal deoxynucleotidyltransferase-mediated deoxy-UTP nick-end labeling (TUNEL) staining, and noted increased Annexin-V and TUNEL staining in cultures exposed to postintervention samples.

Barnard et al. (32) investigated the individual effects of long-term exercise (EX) vs. diet and exercise (DE) using serum from the aforementioned study by Tymchuk et al. (384) and

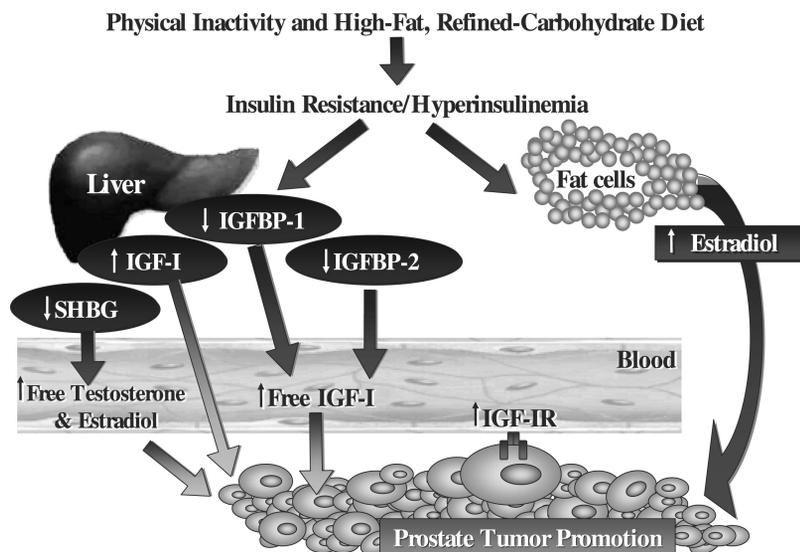


Fig. 4. Hypothesized mechanisms by which physical inactivity and diet can induce prostate cancer tumor promotion. SHBG, sex hormone-binding globulin; IGFBP, IGF binding protein; IGF-IR, IGF-I receptor.

serum from men in the University of Nevada, Las Vegas Adult Fitness Program (average duration 14.7 yr, 5 days/wk for 1 h). Serum insulin and IGF-I were lower and IGFBP-1 was higher in both EX and DE compared with age-matched controls (Table 1). When the serum was used to stimulate the LNCaP cells in culture, growth was reduced in both the EX (65% of control) and DE (55% of control) compared with controls. Annexin-V and TUNEL staining demonstrated increased apoptosis in both EX and DE, with staining being greater in DE compared with EX. Subsequently, Leung et al. (222) investigated the potential involvement of the p53 gene in the protective effects of EX. IGF-I suppresses the action of p53, which plays a role in cell cycle arrest, DNA repair, and induction of apoptosis, and defects in the p53 gene have been reported in end-stage prostate cancer (124). Protein expression of p53 and one of its downstream effectors, p21, was significantly increased in lysates from the EX-serum-stimulated LNCaP cells. Furthermore, PCNA, a marker for cell cycling, was reduced by 33% in the EX-serum-stimulated LNCaP. They also utilized the LN-56 cell line, in which p53 is rendered nonfunctional by expression of a dominant negative fragment of p53, genetic suppressor element 56, in LNCaP cells and noted no significant difference in growth between the control and EX serum and less apoptosis in EX vs. control (222). Additionally, when IGF-I receptor blockers (an IGF-I receptor antibody or a kinase inhibitor) were added to the control serum, LNCaP cell growth was reduced and apoptosis increased to levels observed with

the DE or EX alone groups. However, when the IGF-I receptor kinase blocker was added to the EX serum, no additional changes in LNCaP cell growth or apoptosis was noted (222, 277). These results also demonstrate that the LNCaP cells have an intact p53 pathway that is suppressed with control serum and provide a possible mechanism to explain, in part, the epidemiological data showing a reduction in prostate cancer risk in men who exercise regularly (375).

A few recent studies have investigated lifestyle modification and/or supplementation in men with documented prostate cancer before prostatectomy to evaluate serum biomarkers and tissue histopathology. Ornish and colleagues (284) randomized men with prostate cancer on “watchful waiting” to control or to diet and exercise intervention. After 1 yr, changes in serum prostate-specific antigen were small, but statistically significant, with the control group showing an increase and the diet and exercise group exhibiting a drop. Compared with baseline, serum samples from these patients exhibited a 9% reduction in in vitro cell growth in the control group and a 60% reduction in the diet and exercise group. Additionally, after 1 yr, 6 of 43 in the control group had progressed to conventional treatment, owing to rising prostate-specific antigen, whereas none of the 41 in the diet and exercise group had treatment. The value of lycopene supplementation, before radical prostatectomy, was investigated by Kucuk et al. (209). Twenty-six men with clinically localized prostate cancer were randomized to lycopene (15 mg, twice daily) or control for 3 wk before surgery. Prostate-specific antigen fell by 18% in the supplementation group and increased 14% in the control group. Demark-Wahnefried et al. (80) investigated a low-fat diet (20% kcal) combined with flaxseed supplementation (30 g/day) for 30 days before surgery. Although serum prostate-specific antigen values did not change, histological analyses of the prostate specimens indicated a lower mean proliferation index and a higher apoptosis score, suggesting possible clinical benefits from following a low-fat, high-omega-3 fatty acid diet. Other studies also suggest that omega-3 fatty acids from fish may suppress tumor growth in general, whereas omega-6 may encourage tumor growth (332).

Table 1. Effect of exercise or combined diet and exercise on serum factors of the IGF axis

	Control (n = 14)	Diet and Exercise (n = 8)	Exercise (n = 12)
Insulin, $\mu$ IU/ml	17 $\pm$ 4.6	5.4 $\pm$ 0.5	6.9 $\pm$ 1.0
IGF-I, ng/ml	315 $\pm$ 31	143 $\pm$ 13	128 $\pm$ 12
IGFBP-1, ng/ml	22 $\pm$ 4	69 $\pm$ 12	42 $\pm$ 8
IGFBP-3, ng/ml	2,606 $\pm$ 243	2,662 $\pm$ 201	2,610 $\pm$ 238

Values are means  $\pm$  SE; n, no. of subjects. IGFBP, IGF binding protein. All diet and exercise as well as exercise values were significantly different ( $P < 0.05$ ) from control. IGFBP-1 was significantly higher in diet and exercise compared with the exercise group. Data from Barnard et al. (32).

**Breast cancer.** Breast cancer is the most common cancer in US women (6) and like prostate cancer is hormone dependent. Although breast cancer is estrogen dependent, most breast cancer occurs in postmenopausal women in whom estrogen levels are low; however, elevated serum estradiol has been shown to be a risk factor for breast cancer in postmenopausal women (134). The influence of lifestyle factors in breast cancer is supported by cross-cultural variation and migration studies (16, 422). For example, breast cancer incidence and mortality for Asian immigrants in the United States is intermediate between US white women and Asian women who live in Japan or China, and these differences have been attributed in part to adoption of Western diets among Asian immigrants (319). Fat intake has been suggested as a contributor to breast cancer, with reports of a positive correlation between per capita fat consumption and both incidence and mortality from breast cancer (16). In a large retrospective study of 2,599 breast cancer patients and 2,588 controls, Favero et al. (103) found that increased consumption of calories, saturated fat, sugar, and alcohol all significantly correlated with increased risk for breast cancer. However, several studies of Westernized societies have not shown a relation of fat intake to breast cancer risk, possibly owing to the lowest percentage intake being above a threshold for benefits to be noted (267). The low breast cancer incidence in East Asian women is associated not only with dietary fat, but also with diets high in omega-3 fatty acids (i.e., fish oil) and fiber (330). In addition, Asian women may be more physically active. Friedenreich and Orenstein (112) stated that 32 of the 44 studies to date have observed a reduction in breast cancer risk in women who were most physically active, and of the 32 studies that observed a decrease, the average risk reduction was 30–40%. Additionally, a dose-response relation between increasing activity and decreased risk was noted in 20 of 23 studies.

Physical activity may modulate the production, metabolism, and excretion of sex hormones, as sedentary, postmenopausal women have higher serum estradiol and estrone (273) and lower SHBG concentrations (274). Additionally, increased body fat, present in sedentary women (208), is a location of increased aromatization of steroid hormones. Sedentary women also have high insulin, which may be a promoter of breast tumor development (180).

Heber et al. (140) reported a 50% reduction in estradiol in postmenopausal women after lifestyle modification (exercise and high-fiber, low-fat diet) and subsequently noted reductions of 25 and 22% during the follicular and luteal phases, respectively, in premenopausal women after 2 mo of high-fiber, low-fat diet intervention carried out at the UCLA Clinical Research Center (20). Serum estrone also decreased by 19 and 18%, respectively, during the two phases. In a more recent study in postmenopausal women, serum insulin decreased 39% and SHBG increased 39% in women on hormone replacement therapy; in those not on hormone replacement therapy, insulin decreased 19% and SHBG increased 42% in response to the Pritikin diet and exercise intervention (387). Additionally, this intervention results in reductions in insulin (pre:  $14.5 \pm 2$  vs. post:  $9.1 \pm 1$   $\mu$ U/ml) and IGF-I (pre:  $170 \pm 22$  vs. post:  $142 \pm 13$  pg/ml), while increasing IGFBP-1 (pre:  $55 \pm 8$  vs. post:  $71 \pm 10$  pg/ml) in postmenopausal women on hormone replacement therapy (Barnard RJ, Liva M, and Ngo TH, unpublished data). Kaaks et al. (181) noted reductions in fasting

serum testosterone and insulin area after a glucose tolerance test and increases in SHBG, IGFBP-1, IGFBP-2, and growth hormone-binding protein. Other more recent studies have also reported reductions in serum estradiol by adopting a low-fat diet by both pre- and postmenopausal women (318, 331, 415). Insulin (152) and IGF-I have been reported to be risk factors for breast cancer, and cross talk occurring between the IGF-I and estrogen receptor pathways in breast cancer has been reported (131, 418).

**Colon cancer.** Cancer of the colon and/or rectum is the second leading cause of cancer deaths and is the third most common cancer in both men and women in the United States (6). Over the years there has been a lot of controversy regarding the involvement of lifestyle factors in colon cancer. According to Friedenreich and Orenstein (112), the most definitive evidence for an association between physical activity and cancer exists for colon cancer. Of 51 studies on colon or colorectal cancer, 43 demonstrated a reduction in risk in the most physically active men and women with an average reduction of 40–50%. Of the 29 studies in which a dose-response has been investigated, 25 documented that increasing levels of activity were associated with decreasing risk. Others have suggested that physical activity is the most important risk factor associated with colon cancer (379). Colorectal cancer shows a large international variation that Armstrong and Doll (16) attributed to the variation in dietary fat consumption. Additionally, the European Cancer Prevention Consensus Panel concluded in 1998 that there was good evidence to support the protective effect of fiber against colon and breast cancer (150).

Several potential mechanisms have been purported to explain how physical inactivity and diet affect colon cancer. For example, Burkitt (61) noted a high incidence of colon cancer in British subjects living in Uganda; however, he rarely saw this in native Africans. He noted that the Africans consumed large amounts of fiber and suggested that fiber played an important role in colorectal cancer and that removal of fiber by refining carbohydrates reduced stool bulk and increased gastrointestinal transit time as well as adversely affected intestinal flora. Second, alterations in insulin may affect colonic epithelial cell growth. It has recently been suggested that hyperinsulinemia resulting from consumption of high-fat, refined-carbohydrate diets may play a role in the etiology of colorectal cancer (117, 201), and, as discussed, insulin sensitivity is improved by exercise training (172). Third, physical activity and diet may alter bile acid metabolism. Reddy et al. (325) studied colon cancer risk factors in eight women who underwent lifestyle modification and noted increases in stool weight and decreases in total stool bile acids and secondary bile acids deoxycholic and lithocholic acid, the latter two of which are thought to be the most carcinogenic bile acids (87). Slattery et al. (354) examined the relationship of lifestyle factors to p53 mutations in colon tumors and concluded that a Western diet high in glycemic load and red meat was correlated with p53 mutations. Red meat consumption also appears to affect colon cancer, as 19 of 33 cohort and case-control studies have reported an association between red meat and colon cancer (379), with the relative risk being ~2.5-fold higher for women who consumed animal fat in the form of beef, lamb, or pork at least once per day compared with those at once per month (412). How much of the association between red meat and colon cancer is due to

total fat or saturated fat and how much is due to other constituents of meat or the diet is presently unknown (312). Increased fruits and vegetables are also protective against colon cancer (360). A protective effect of vegetable intake was noted in a cohort study of over 760,000 adults, which documented a 40% decrease in women and a 20% decrease in men in the highest vs. lowest quintile of vegetable intake (374). The benefits may be independent of fiber, as Steinmetz and Potter (361) have suggested that vegetables contain an “anticarcinogenic cocktail” of substances (i.e., carotenoids, vitamins C and E, selenium, dithiolthiones, glucosinolates and indoles, isothiocyanates, flavonoids, plant sterols) that inhibit carcinogenesis by a variety of mechanisms. Increased vegetable consumption may also increase stool bulk and decrease transit time, thereby minimizing contact between the colon and potential carcinogens (361).

Adenomas are precursor lesions of colorectal cancer and are informative endpoints for assessing risk. Ten case-control studies reviewed by Peters et al. (300) showed inverse associations between fiber intake and colorectal adenoma. On the other hand, large cohort studies have been less convincing. Studies in the United States, Finland, and Sweden reported no protective effect of fiber (113, 304, 371). Intervention trials with bran, soluble fiber, or vegetables have not reduced the recurrence rates of adenomatous colorectal polyps (4, 50, 343). One large cohort study in US men, the Health Professionals Follow-up Study, did find a significant inverse association of distal adenomas and soluble but not insoluble fiber intake (307). The exact reason for the inconsistency in the cohort studies is not known but may be due to the fact that the populations have been rather homogeneous with relatively low fiber intakes or may be due to the inability of food questionnaires to accurately predict habitual fiber intake. In Burkitt’s original work, not only did the African natives have a very low incidence of colorectal cancer with a high fiber intake, they also consumed a low-fat diet and were physically active, suggesting that comprehensive lifestyle modification is required to reduce cancer risk. The recent European Prospective Investigation into Cancer and Nutrition study involved 519,978 individuals and had a fiber intake that ranged from 13 g/day for the lowest quintile to 34 g/day for the highest quintile (41). Comparing the highest to the lowest quintile of fiber intake, the investigators found a relative risk for large bowel cancer of 0.75. Even this intake of 34 g/day was lower than the 50+ g/day originally described by Burkitt.

**Summary.** Several forms of cancer are influenced by lifestyle factors, and cancers of the prostate, breast, and colon are significantly affected by exercise and diet. Several dietary factors can affect cancer progression, including fiber, fat (amount and type), and meat intake. Exercise has been documented to be associated with reduced risk of developing several forms of cancer. Antioxidant, growth factor, and hormonal effects appear to mediate in large part the benefits noted with exercise and/or diet intervention. Extensive research has been carried out for prostate cancer, and lifestyle modification induces reductions in prostate tumor growth and increases tumor cell apoptosis, mediated, at least in part, by changes in the IGF-I axis and its regulation of prostate cell signal transduction.

## CONCLUSION AND FUTURE DIRECTIONS

Given that >55% of US adults do not engage in regular physical activity and >75% do not consume at least five fruits and vegetables a day (261), it is no surprise that chronic diseases are the most common cause of preventable death in the United States. The evidence is overwhelming that physical activity and diet can reduce the risk of developing numerous chronic diseases, including CAD, hypertension, diabetes, metabolic syndrome, and several forms of cancer, and in many cases in fact reverse existing disease. Furthermore, risk of several other chronic diseases may be ameliorated by physical activity and diet, including musculoskeletal diseases such as sarcopenia (352), osteoporosis (398), and arthritis (253), as well as stroke and congestive heart failure (238), chronic renal failure (66), Alzheimer’s disease (182), and erectile dysfunction (97). For instance, it has been reported that only 16% of American women aged 45–64 and <10% of women >65 yr of age report ever engaging in strengthening activities (345). As discussed, especially in the case of hypertension and metabolic syndrome, several studies have shown that physical activity favorably affects chronic disease, but relatively few trials have simultaneously examined both dietary modification and physical activity. Consequently, further studies using combined interventions that attempt to maximize benefits are warranted, as recommended by the ATP III guidelines (98). Additionally, the molecular mechanisms by which physical activity and diet protect against chronic disease are not completely understood, and future studies using translational paradigms should be utilized. Figure 5 summarizes various potential mechanisms by which physical activity and diet may ameliorate cardiovascular-associated chronic disease risk.

Many of the studies discussed applied a whole-diet approach, and it cannot be determined whether the benefits noted are due to a higher intake of antioxidants, phytochemicals, minerals, and/or fiber, a lower intake of fat, and/or changes in the dietary fatty acid composition, in carbohydrate type, and/or protein source; however, most likely all of these factors contribute. For example, when one macronutrient is removed, another is added, and whether the benefit is due to the added nutrient, the removed nutrient, or a combination of both is

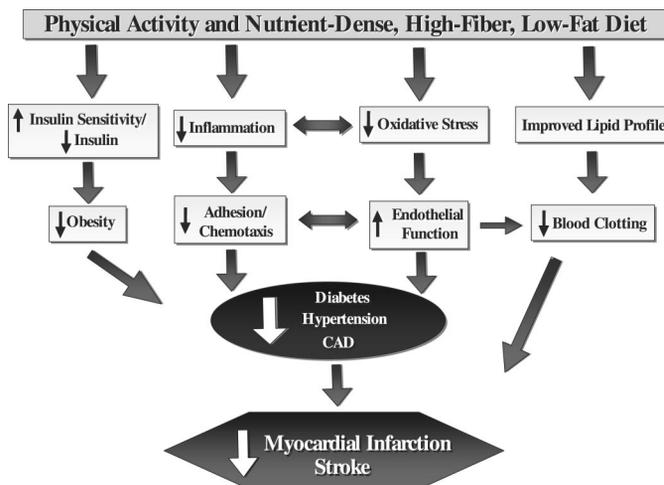


Fig. 5. Hypothesized mechanisms by which physical activity and diet reduce the risk of coronary artery disease (CAD), hypertension, and diabetes.

unknown. However, the evidence suggests that numerous dietary changes contribute to the reduction in chronic disease risk, including elimination of refined carbohydrates and fatty foods, such as fast food and sugar-containing beverages, and substitution with a diet based largely on whole foods high in fiber and nutrient density. For example, processing whole grains increases caloric density by ~10% and decreases fiber and protein by ~80 and 30%, respectively (86).

A concerted effort to increase primary prevention of chronic disease through the translation of research data on the value of exercise and diet to the general public and legislation to urge implementation of primary prevention strategies as opposed to opportunistic care are essential (99). It is commonly argued that it is difficult to change the lifestyle of obese and sedentary people, but such pessimism may not be justified. For a successful public health approach to chronic disease prevention, we cannot rely on pharmaceuticals but must implement long-term, sustainable behaviors that encourage healthy lifestyles. It is possible to achieve primary prevention of chronic disease by means of a nonpharmacological intervention that can be implemented in a primary health care setting. Chronic disease not only impacts life expectancy but also may significantly blunt quality of life years (268). Additionally, recommendations have been questioned on the basis of their practicality. For example, the Institutes of Medicine recommendation for physical activity of 60 min/day has been questioned on the basis of its feasibility. It is known that 30 min provides important benefits; however, this may be inadequate for maximal health benefits. Similarly, diets recommending higher fruit and vegetable intakes ( $\geq 7$ ) (13, 21, 269) and lower fat consumption have been criticized as a result of the perceived inability of patients to adhere to more intensive guidelines. We feel it is essential to make recommendations that are effective and to strive to achieve them, knowing that even some modification, i.e., performing 30 min of activity per day and consuming five fruits and vegetables, will possess important health benefits. In addition, weight loss is a beneficial side effect of diet and exercise, and focus should be shifted to chronic disease reduction because many patients will experience modest weight loss (2–5%) and in the majority of cases still be classified as overweight or obese, yet will significantly reduce their chronic disease risk profile independent of significant weight loss.

Finally, as we look to the role of diet and physical activity in preventing chronic disease in the future, modifying the lifestyle of children is paramount to reducing chronic disease risk. Most children consume diets high in fat, especially saturated fat (189), refined sugar (194), including fast food (55, 111), soft drinks, and high-calorie fruit juices, and there are known interactions between diet and activity patterns (244) and between in utero and postnatal lifestyle influences and risk of future metabolic disease (397). Furthermore, children are performing less activity as computers, televisions, and video games become more commonplace, combined with elimination of school physical education programs (101, 197). Encouraging healthy diets and activity in our nation's children is critical to winning the war against chronic disease.

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