

## Brief Review

# Nutrition and Cardiovascular Disease

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**A message from Dr. Mark Taubman, Editor in chief:** The following brief review is part of an international initiative, termed the “Global Theme Issue on Poverty and Human Development.” On October 22, 2007, at least 231 science journals throughout the world will simultaneously publish papers related to the topic of poverty and human development to raise awareness and stimulate research. These various papers will take the form of original research, review articles, editorials, perspectives, news stories, and other types of articles, with a common print or on-line release date of Monday, October 22, 2007. This date coincides with a “Global Theme Issue” event, sponsored by the Fogarty International Center, the National Library of Medicine, and the Council of Science Editors, held on the campus of the US National Institutes of Health to promote the Global Theme Issue and to highlight some of the articles published. In keeping with the spirit of this international event, the Editors of *Arteriosclerosis, Thrombosis, and Vascular Biology* asked Dr. Godfrey S. Getz, an internationally-recognized authority on atherosclerosis and nutrition, to write a brief review on this subject. We present this excellent review as a cautionary tale of the potential danger that can befall populations “emerging” from poverty. The availability to such populations of relatively inexpensive, high caloric, but atherogenic foods may provide the cure for a variety of “deficiency” diseases associated with poverty, but may also increase the incidence of diabetes, obesity, hypertension and atherosclerotic vascular disease. It behooves us to learn from past experiences and to provide the support and guidance that will assure that such populations emerge into health.

**Abstract**—The major cardiovascular diseases affecting the developed world have at their core atherosclerosis and hypertension, both of which are profoundly affected by diet and can be approached, at least in part, from a nutritional point of view, as can the increasing “epidemic” of obesity. Diet is a multi-component mixture of many nutrients, which may interact with one another. The definitive study of nutrients and their impact on cardiovascular disease can be a daunting enterprise. Many dietary risk factors contribute to these diseases in various environmental and ethnic settings. These risk factors are often in evidence in youth so that preventive measures must be initiated early in life. Although most of the information about nutritional risk factors and cardiovascular disease derives from studies in the developed world, the situation is rapidly evolving toward epidemic proportions in the developing world where a major burden on the economy and health services will be imposed. (*Arterioscler Thromb Vasc Biol.* 2007;27:2499-2506.)

**Key Words:** nutrition ■ atherosclerosis ■ hypertension ■ obesity ■ underdeveloped world

The major cardiovascular diseases affecting the developed world have at their core atherosclerosis and hypertension, both of which are profoundly affected by diet and can be approached, at least in part, from a nutritional point of view. Diet is a multi-component mixture of many nutrients, which may interact with one another. The definitive study of nutrients and their impact on cardiovascular disease can be a daunting enterprise. The population being studied is often quite heterogeneous as is the diet that serves as the baseline for interventions. Many approaches have been used to examine the influence of nutrition on atherosclerosis: cross population comparisons, nutritional questionnaires administered to large population groups, and interventional studies. Some of these approaches can be very informative about individual nutrients. However, metabolic ward studies in which the nutrients are varied in a specific fashion without changing total calories or nutrient balance aside from the variable being

studied are most likely to yield relatively definitive answers. Yet these are not close to the real lives of free living peoples. The methodological problems may sometimes account for the variability in results reported in the literature.

The pathobiology of cardiovascular disease is complex, resulting from the interaction of genetics and the environment. Of the environmental mechanisms, few are more influential than the diet.

### Atherosclerosis-Related Diseases

Atherosclerosis underlies much of the cardiovascular disease encountered in the developed world. It can be assessed at 2 distinct levels. First, at the preclinical level the lesion itself can be monitored most directly in autopsy studies or alternatively by high resolution imaging of lesion size in the living person.<sup>1,2</sup> The second is when the disease has progressed to the point at which the consequences of atherosclerosis and its

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complications are manifest in clinical cardiovascular disease eg, angina, coronary thrombosis, or sudden death, each of which is used frequently as the surrogate measure of the underlying atherosclerosis. As many changes affect lesion evolution late in its progression, these latter measures may not be accurate assessments of the extent of underlying vascular disease. Thus these 2 measures are not the same from the point of view of atherogenesis, where many of the traditional risk factors are thought to operate. However the distinction is often not quite so clear cut as the atherosclerotic lesion progresses in part by the extension of lipid deposition particularly at the shoulders of the lesion which may be the site of instability and clinically relevant complications. This extension simulates some of the early stages of atherogenesis. Not surprisingly the thorough autopsy studies of human atherogenesis are few in number. Hence the importance of the Pathobiological Determinants of Atherosclerosis in Youth (PDAY) studies.<sup>3</sup>

Atherosclerosis is a chronic inflammation at hemodynamically determined sites of large and medium-sized arteries. It is characterized by the vessel wall accumulation of cholesterol and its esters, either in the large lipid droplets of macrophage foam cells or as extracellular lipids, including crystals of free cholesterol. Thus, it is to be expected in studies of atherogenesis that cholesterol receives pride of place. At least in experimental animals, hypercholesterolemia or lipoprotein dysfunction is requisite for the development of atherosclerosis. This is probably also the case in humans, though what is the normal plasma cholesterol level may still be a subject for debate.<sup>3</sup> The early and profound atherosclerosis in patients with homozygous familial hypercholesterolemia serves to reinforce the focus on cholesterol. Atherogenesis begins quite early in life as is demonstrated by the PDAY studies showing that by age 15 one frequently sees early lesions at sites where more advanced lesions are observed later in life. Thus, whatever preventive strategies are recommended, ultimately they must be initiated early in life. Among the risk factor determinants of atherosclerosis even in these young subjects is hypercholesterolemia. Indeed, it has been shown that maternal hypercholesterolemia may influence development of hypercholesterolemia and atherosclerosis in offspring.<sup>4</sup>

The primary dietary determinants of hypercholesterolemia are fats, particularly saturated fats, and dietary cholesterol. Unlike dietary fat which is almost completely absorbed in the intestinal tract, the absorption of cholesterol is incomplete and is regulated at the intestinal epithelium. The evolution of our thinking about the link between hypercholesterolemia and atherosclerosis has been excellently described by Daniel Steinberg in his recent thematic reviews on the pathogenesis of atherosclerosis.<sup>5-7</sup> Summarized in these reviews are the epidemiological studies of the 7 countries by Keys,<sup>8,9</sup> the Framingham studies,<sup>10</sup> as well as the changes in plasma cholesterol and cardiovascular disease in Japanese individuals migrating from Japan to Hawaii to the mainland United States.<sup>11</sup> The results from the latter study were further reinforced by studies of Indonesian natives migrating from Indonesia to Holland.<sup>12</sup> All of these investigations demonstrate the primacy of the environment in regulating plasma

cholesterol levels, particularly the impact of the relative levels of saturated versus unsaturated fatty acids in the diet. These conclusions were strongly reinforced by carefully controlled dietary interventions using liquid formula diets in which saturated and unsaturated fats were substituted for one another. Intervention studies were also strongly supportive of the role of fatty acids in controlling plasma cholesterol levels when experimental diets were used in which polyunsaturated fats were substituted for saturated fat while keeping the rest of the diet the same over a period of years. Those consuming the experimental high polyunsaturated fat diet had lower blood cholesterol levels and reduced rate of repeat myocardial infarctions and death.<sup>13,14</sup>

### Dietary Fatty Acids

The above studies point to the importance of decreasing the ratio of saturated to unsaturated fats in the diet. In many developing countries, oils rich in saturated fats, may constitute a major component of their diet, although it is worth noting that in many of these countries the total daily consumption of fat is significantly less than the average consumption in the industrialized countries.

Unsaturated fatty acids fall into several different categories; monounsaturated fatty acids as found predominantly in olive oil, n-6 polyunsaturated fatty acids, n-3 polyunsaturated fatty acids, and trans fatty acids. Each is functionally distinct, with respect to hypercholesterolemia and cardiovascular disease.

The predominant n-6 polyunsaturated fatty acid in the diet, linoleic acid, is found in many plant oils, notably corn oil or safflower oil. The effects of n-6 polyunsaturated fatty acids on lowering blood cholesterol was most clearly demonstrated in the liquid formula diet experiments of Kinsell and Ahrens,<sup>15,16</sup> which did not involve changing the rest of the diet. In contrast when saturated fat was used in the liquid formula diet, blood cholesterol rose. Linoleic acid is the precursor of arachidonic acid and arachidonic acid in the 2 position of phospholipids is the source of both leukotrienes and prostanooids. These molecules have a variety of effects on the cardiovascular system, some beneficial (eg, prostacyclin) and others not (eg, thromboxane).<sup>17</sup> The network of interactions of these inflammation related molecules can be quite complex, and it is not clear that this network is regulated in a major way by the dietary availability of fatty acid. The net effect of the long term consumption of diets rich in n-6 polyunsaturated fatty acids is a reduction in blood cholesterol and in atherosclerosis related cardiovascular disease such as myocardial infarction.

It is commonly believed that when LDL becomes oxidized it plays an important role in the initiation of atherosclerosis.<sup>5</sup> Because it is the unsaturated fatty acids (eg, linoleic acid) in the lipids in the LDL particles that make them susceptible to oxidation, it could be argued that lipids enriched in these fatty acids would be proatherogenic. Yet there is no evidence that diets enriched in n-6 fatty acids promote lipid oxidation.

Although the conclusions that consumption of polyunsaturated fatty acid in place of saturated fat reduces blood cholesterol and atherosclerosis is quite robust, mechanisms by which this reduction occurs is less clear-cut. The more

profound is the understanding of the mechanism of action of a particular intervention the greater is the confidence in its use. This has been clearly shown by the seminal work of Brown and Goldstein in defining the mechanism of action of the statins.<sup>18</sup> These two investigators have also offered explanations for the action of the unsaturated fatty acids in lowering plasma cholesterol. Sterol response element binding proteins (SREBP) are transcription factors that increase fatty acid, cholesterol, and LDL receptor biosynthesis. One mechanism of action of unsaturated fatty acids is that they reduce the transcription of the SREBP genes as well as the processing of the SREBP precursor proteins.<sup>19</sup> Unsaturated fatty acids and sterols appear to potentiate one another in this downregulation. Other mechanisms may also be operative. Unsaturated fatty acids promote fatty acid oxidation which can contribute to lowering plasma lipids,<sup>20–22</sup> and they may also influence lipoprotein catabolism independently of the LDL receptor.<sup>23</sup> At least 3 other mechanisms have been proposed for polyunsaturated fatty acid–mediated decrease in plasma lipids.<sup>24–26</sup> This is not necessarily a complete list of the possible mechanisms by which polyunsaturated fatty acids participate in the suppression of lipoprotein levels and atherosclerosis.

A second class of polyunsaturated fatty acids are the n-3 polyunsaturated fat acids, which are mostly derived from fish oil. They are produced by further desaturation and chain elongation of the plant fatty acids present in the plankton and algae consumed by the fish. The major n-3 polyunsaturated fatty acids in fish oil are eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. They are derived from  $\alpha$ -linolenic acid, an n-3 unsaturated fatty acid. Observation of low cardiovascular mortality in communities that consume large quantities of fish has suggested that n-3 fatty acids are cardioprotective.<sup>27</sup> Indeed the American Heart Association has advised patients at risk of cardiovascular disease to eat 35 g of fatty fish twice a week.<sup>28</sup> The precursor  $\alpha$ -linolenic acid is also found in oils derived from flaxseed, canola, soybeans, and walnuts. Studies of the effect of the intake of  $\alpha$ -linolenic acid, as distinct from EPA and DHA, on sudden cardiac death have yielded variable outcomes.<sup>29,30</sup>

Although the n-3 fatty acids share some of the actions of n-6 fatty acids on lipoprotein metabolism (eg, <sup>26</sup>), they also appear to exert different actions. The high consumption of the n-3 fatty acids can lower plasma triglyceride levels, blood pressure, platelet aggregation, and inflammation, and increase vascular relaxation.<sup>31</sup> A major beneficial effect of n-3 fatty acids appears to be in the decrease of fatal arrhythmias rather than on the underlying atherosclerosis. Intervening with fish oil supplements for myocardial infarction survivors showed the maximum benefit by 9 months,<sup>32</sup> whereas a secondary prevention with statin treatment had its effectiveness only after 1 to 2 years with an effect mainly on nonfatal recurrent myocardial infarction. This suggests a different mode of action between n-3 fatty acids and statins. The effect on arrhythmias may be accounted for by inhibition of sodium and calcium currents in the myocardium.

All of the natural unsaturated fatty acids discussed above are almost all *cis* unsaturated fatty acids. In natural foodstuffs there is a small amount of trans fatty acid especially in

ruminant fats including butter. The high presence of these fatty acids in the modern diet originates primarily from the industrial hydrogenation of unsaturated oils for ease of handling and storage. Trans fatty acids have physical properties intermediate between those of saturated and unsaturated fatty acids. Yet their effects on cardiovascular disease may be more adverse than those of saturated fatty acids.<sup>33,34</sup> Consumption of trans fatty acids increases blood cholesterol as much or more than saturated fats but unlike saturated fat decreases HDL cholesterol. Thus the ratio of LDL/HDL cholesterol is higher with trans fatty acid than with saturated fat feeding. This could well account for the good correlation between the increasing consumption of trans fatty acids and coronary heart disease. Thus the American Heart Association has issued a scientific statement making recommendations on lowering the use of trans fatty acids.<sup>28</sup> As a result of this and other information food manufacturers are now at pains to use hydrogenation procedures that do not generate trans unsaturated fatty acids.

### Dietary Cholesterol

Body cholesterol derives from 2 major sources—endogenous synthesis and absorption from the diet. Unlike triacylglycerol, the major form of dietary fat, which is almost completely absorbed, the fractional absorption of intestinal cholesterol is only about 50%, although there is a good deal of individual variability in absorption rates.<sup>35</sup> The cholesterol pool in the intestinal lumen is derived from 2 major sources; dietary cholesterol and the cholesterol excreted by the liver into the bile (about 800 to 1300 mg per day). The absorptive mechanisms do not distinguish between these 2 cholesterol sources. Like the role of dietary fat in regulating cholesterol levels, there is epidemiological, experimental, and clinical evidence for the importance of cholesterol absorption in regulating plasma and body cholesterol homeostasis. The National Cholesterol Education Program guidelines recommend a dietary cholesterol intake of less than 300 mg per day. Population groups consuming relatively low cholesterol (less than 100 mg per day) and low-fat diets have low plasma and LDL-cholesterol levels and virtually no coronary artery disease.<sup>36,37</sup>

Three intestinal proteins have received much attention in recent years with respect to their role in cholesterol absorption.<sup>38</sup> The adenosine triphosphate binding cassette transporters G5 and G8 (ABCG5/G8) in the intestine and the liver are mainly involved in the export of sterols into the intestinal lumen and bile respectively. The transporters are thought to be the major discriminators between cholesterol and noncholesterol sterols, most notably plant sterols, as they are very efficient in the export of the latter precluding significant accumulation of these plant sterols in the body. Plant sterols are similar but distinct from cholesterol and are present in fruit and vegetables and cannot be synthesized by mammalian tissues. The defective function of these transporters is associated with the accumulation of plant sterols in tissues<sup>39</sup> and increased cholesterol absorption.<sup>40,41</sup> Plant sterols at quite high levels are able to inhibit cholesterol absorption<sup>42</sup> though it is not clear that the ABC G5/G8 transporters participate in this reduction.<sup>43</sup>

Ezetimibe, a highly selective and potent inhibitor of cholesterol absorption, is able to effect a significant reduction in plasma and LDL cholesterol levels.<sup>42</sup> The specific target of this drug is the Niemann Pick C1 like 1 (NPC1L1) protein of the enterocyte.<sup>44</sup> The reduction of LDL cholesterol mediated by ezetimibe may be in part the result of the induction of the hepatic expression of the LDL receptor as a response to the lower delivery of cholesterol from the diet to the liver.<sup>45</sup> In any event, the efficacy of ezetimibe in reducing plasma cholesterol is indicative of the importance of cholesterol absorption in contributing to the body and plasma pool of cholesterol.

### Obesity

Obesity is a nutritional disorder to the extent that it arises from an imbalance between energy intake and energy consumption, to which reduced physical activity contributes. The increasing "epidemic" of obesity is a cause for great concern in developed societies because it is associated with an increased morbidity and mortality from many diseases including cardiovascular disease, especially those related to atherosclerosis. The age-adjusted prevalence of obesity (defined as a body mass index [BMI] greater than 30 kg/m<sup>2</sup>) in the United States is 30.5% in the most recently reported survey.<sup>46</sup> Particularly disturbing is the fact that 17% of American children are overweight.<sup>47</sup> There are many cardiovascular risk factors associated with obesity, most importantly hypertension, dyslipidemia (increased triglycerides and reduced HDL), and insulin resistance. The presence of several of these risk factors is diagnostic of the metabolic syndrome. Not all obese subjects have the metabolic syndrome, yet the prevalence of the metabolic syndrome is said to be 20% to 25% of US adults over the age of 20.<sup>48</sup>

Obese individuals have increased amounts of atherosclerotic lesions. This was demonstrated in the right coronary artery of men aged 15 to 34 years in the PDAY study.<sup>49</sup> This relationship was not seen in premenopausal women of this age bracket. Only a relatively small proportion of this relationship between obesity and atherosclerosis (15%) was attributed to traditional risk factors. The risk relationship between obesity and atherosclerosis was also seen in an older autopsy sample (35 to 54 years old),<sup>50</sup> suggesting that these risk factors may operate continuously as atherosclerosis progresses. This relationship is complex and incompletely understood. Among the traditional risk factors, the dyslipidemia may in part be attributable to the increased release of free fatty acids from adipose tissue, which may in turn increase VLDL production and plasma triglycerides. This release of free fatty acid may also contribute to the insulin resistance,<sup>51,52</sup> which is associated with atherogenic proinflammatory and prooxidant vascular changes.

The fact that only a proportion of the relationship between obesity and atherosclerosis can be attributed to traditional risk factors implies that other factors associated with obesity might contribute to this proatherogenic effect. This could be the result of the proinflammatory state induced by the large visceral adipose tissue mass, represented for example by tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-6, and serum amyloid A levels in the plasma.<sup>53</sup> Adipokines such as leptin

and adiponectin, which are released in increased and decreased levels, respectively, from the enhanced adipose tissue mass,<sup>51,53</sup> may also contribute to increased atherosclerosis in obese individuals. Inasmuch as adiponectin increases the oxidation of fatty acids,<sup>54</sup> it could play a role in modulating the free fatty acid concentration and the insulin resistance. In this review it is not possible to deal with the mechanistic details thought to be involved in the relationship between obesity and atherosclerosis, but the reader is referred to the excellent reviews cited in this section.

Atherosclerosis is not the only cardiovascular consequence of obesity. There may also be a shift in cardiac metabolism favoring fatty acid oxidation.<sup>55</sup> Heart failure is also more prevalent among obese patients which could be related to the expansion of blood volume associated with the vasculogenesis of the expanded adipose tissue mass. From this might follow left ventricular hypertrophy and ultimately failure especially as hypertension is frequently found in association with obesity. There is clearly much to learn about the impact of an increased adipose tissue mass on cardiovascular pathophysiology. Indeed this impact is likely to vary with the distribution of the adiposity. It is known that visceral obesity represents a higher risk for atherosclerosis than peripheral obesity.<sup>52</sup>

The prevalence of obesity in different ethnic and socioeconomic classes will be discussed in a later section.

### Hypertension

Hypertension affects many cardiovascular diseases, including atherosclerosis, coronary heart disease, renal disease, and stroke. It is less frequently an isolated risk factor but rather is more often accompanied by a cluster of other risk factors as in the metabolic syndrome.<sup>56</sup> Indeed in overweight individuals the influence of hypertension on cardiovascular disease is more substantial than in normal weight individuals.<sup>57</sup> Hypertension is a powerful risk factor for atherosclerosis-based cardiovascular disease.<sup>58</sup> There is even an increase in the risk at prehypertensive levels (systolic BP 120 to 139 mm Hg and diastolic 80 to 89 mm Hg).<sup>59</sup> As with other determinants of atherosclerosis, hypertension is a risk factor for atherosclerosis in youth.<sup>60</sup> About 25% of the worldwide adult population has hypertension.<sup>61</sup>

Diet is the most important environmental factor influencing hypertension,<sup>62</sup> with sodium and potassium being the most important dietary components. The high consumption of dietary sodium is a relatively recent phenomenon. Almost a third of the American population has hypertension and consumes an average of more than 6 g per day of sodium chloride. In isolated societies where the consumption of sodium is less than 1 g per day, the prevalence of hypertension is only 1% of that in industrialized communities. The regulation of sodium homeostasis in response to dietary sodium is effected at the kidney where the reabsorption of the increased sodium load results in a loss of potassium. An excess of sodium and depletion of potassium results in vascular wall smooth muscle cell contraction and reduced vasodilation by limiting the production of nitric oxide (NO) by endothelial nitric oxide synthase (eNOS).<sup>61,63</sup> There is a good deal of variability in the individual responses to sodium



overload frequently resulting in subjects being designated as salt sensitive or insensitive. This difference in salt sensitivity is likely attributable to multiple individual genes, though these have not been defined. Dietary potassium exhibits a dose-dependent inhibition of salt sensitivity. A number of recommendations for dietary modulation of hypertension have been made. This includes the Institute of Medicine recommendation<sup>64</sup> for a maximum salt (as NaCl) consumption of 3.8 g/d for those 50 years or younger to 2.9 g/d for those 71 years or older. Currently these recommendations are about one half the average consumption in industrialized societies. A potassium consumption of 4.7 g/d, which is about twice the current average, is also recommended. The American Heart Association has based its recommendations on the DASH study (Dietary Approaches to Stop Hypertension) which is a diet rich in fruits and vegetables, low-fat dairy products, grains, fish, and poultry (and hence low in sodium and high in potassium).<sup>65</sup> The DASH diet has been compared with the average American diet at 3 levels of sodium intake (average, intermediate, and low), and blood pressure was reduced in those consuming the DASH diet at each level of sodium intake.<sup>66</sup>

### Nutrient Determination of Vascular Responsiveness

Hypercholesterolemia is often associated with endothelial dysfunction which reflects a reduction in the bioavailability of NO, an important vasorelaxant. NO is produced in the vessel wall by 2 nitric oxide synthases (NOS)—eNOS characteristic of the endothelium and iNOS found in smooth muscle cells and macrophages. Many risk factors for atherosclerosis—hypercholesterolemia, hypertension, diabetes, and turbulent shear stress—reduce NOS activity, perhaps by increasing oxidant stress.<sup>67</sup> The substrate for NOS is arginine and reduced vasorelaxant activity of eNOS can be reversed by the administration of arginine.<sup>68</sup> An important determinant of endothelial NO formation depends on the intracellular availability of the arginine substrate which in turn may be regulated by arginine transport by the arginine cation transporter.<sup>69</sup> Oxidized LDL decreases arginine transport into cells,<sup>70</sup> and this may contribute to the proatherogenicity of oxidized LDL. Whereas eNOS activity is atheroprotective in part through its vasoreactive properties, iNOS is proatherogenic. The latter has a higher flux of NO than eNOS and in the presence of reactive oxygen species can lead to the formation of proinflammatory peroxynitrites. Also in atherosclerotic lesions there is an increase in the concentration of asymmetrical dimethyl arginine, a competitive inhibitor of NOS.<sup>71</sup> Thus the effects of arginine supplementation could be quite complex.<sup>72</sup> With oxidative stress, the cofactor for eNOS, tetrahydrobiopterin (BH4), is reduced. Under these circumstances superoxides are generated by eNOS, a process referred to as uncoupling, leading to the generation of peroxynitrites.<sup>67</sup> Oral BH4 supplementation may improve vascular reactivity and the recoupling of eNOS.<sup>73</sup>

An increase in arginine consumption may result in the formation of creatine by the methylation of guanidinoacetate. This reaction would consume S-adenosylmethionine, leading to increased levels of S-adenosylhomocysteine, which can in

turn be hydrolyzed to homocysteine.<sup>74</sup> Elevated homocysteine is a risk factor for atherothrombosis in some, but not all studies.<sup>75,76</sup> The supplementation of the diet with folic acid and vitamins B12 and B6, nutrients often removed during food processing, appears to improve vascular responsiveness and homocysteine levels,<sup>74</sup> but prospective clinical trials have not shown a positive effect of vitamin supplementation on cardiovascular disease.<sup>77,78</sup> Loscalzo has offered a number of possible explanations for this failure perhaps related to the increased methylation potential affecting other proatherogenic pathways.<sup>74</sup>

Other nutrients that have an impact on cardiovascular disease include thiamine deficiency, which is still endemic in certain parts of the world and is associated with beriberi cardiomyopathy.<sup>79</sup> In reviewing the women's health initiative vitamin D levels have also been considered in relation to cardiovascular diseases,<sup>80</sup> but no major effect was observed.

### Socioeconomic Status, Ethnicity, and Cardiovascular Disease

With the exception of some epidemiological studies, the data on most of the risk factors for cardiovascular disease has been derived from well-fed Western populations. The discussion of obesity points to the importance of a positive energy balance. Although many endogenous factors may enhance this situation, the increased food availability and larger portion sizes especially in fast food restaurants plays a role in the increasing prevalence of obesity.<sup>81</sup> Despite studies suggesting that obesity may be associated with poverty, a review of the changes in obesity over 3 decades by Chang and Lauderdale<sup>82</sup> showed that among Black women obesity increased more in the middle income group than in the poor group, whereas among Black men it was the highest income group that showed the largest increase in obesity. The basis for the difference between men and women is not clear. Although obesity cannot be completely explained by socioeconomic status, poverty can impact on the healthiness of food choice. Foods of high density are often selected by the poor because of cost and availability, whereas fruit and vegetables are not readily available to the poor.<sup>83</sup> Comparing obesity trends in adult men and women between 1999 to 2000 with the National Health and Nutrition Examination Survey (NHANES III) of 1988 to 1994, there was an increase in the prevalence of obesity of both men and women of all age groups among non-Hispanic Whites, Blacks, and Mexican Americans.<sup>46</sup> Among women, the highest obesity prevalence was seen in Black women. No ethnic difference was observed for men. In the NHANES III cohorts of children and young adults, obesity and dietary fat intake was higher for Black and Mexican-American girls than for non-Hispanic White girls. Blood pressure was higher for Black girls than for non-Hispanic White girls and glycosylated hemoglobin (an indicator of hyperglycemia) was highest for Black and Mexican American boys and girls.<sup>84</sup> It has also been noted that Blacks are more sensitive to salt restriction to control blood pressure.<sup>66</sup> Heart disease is a leading cause of death among homeless people. They have higher rates of undiagnosed and untreated cardiovascular disease, hypercholesterolemia, and hypertension.<sup>85</sup> This is consistent with the association of a

lifetime accumulation of adverse socioeconomic positions with increased risk of myocardial infarction.<sup>86</sup>

Over the course of several centuries there have been recognizable transitions in the nutrition of humans, beginning with the hunter gatherer, when life expectancy was low and death was attributable to acute infections, to phase II with early agriculture, and phase III involving the second agricultural revolution and the Industrial Revolution associated with a mainly rural society and chronic infection such as tuberculosis.<sup>87</sup> In phase IV there is increased urbanization and increased consumption of fat, especially animal fat relative to vegetable fat, as well as increased sugar consumption and prevalence of obesity. These changes are largely associated with increasing average income, and have been aided by the globalization of food processing. This is the phase in which most newly developed societies find themselves and is associated with a predominance of chronic disease, including heart disease.<sup>87</sup> One of the features of the globalization of food processing is the proliferation of fast food restaurants, whose use appears to be associated with the increment in the body mass index.<sup>88</sup> The fifth phase of the nutritional transition is that of mature developed societies where health promotion is accentuated, and a further increase in life expectancy may occur along with the reduction in heart disease. The transition phases III and IV are seen throughout the developing world as exemplified in sub-Saharan Africa. For example, among rural Black South Africans in the 1970s to the early 1990s, myocardial infarction was almost nonexistent and was even rare in urban Black South Africans.<sup>89,90</sup> However, among the latter group the prevalence of risk factors such as hypertension, obesity, and hyperlipoproteinemia are rapidly increasing and, as expected, this is associated with the appearance of acute myocardial infarctions.<sup>91</sup> These changes are seen also in other developing societies such as China, India, and South America.<sup>92,93</sup> Thus there is an evolving epidemic of cardiovascular disease in the developing world<sup>94</sup> that will impose a major economic burden on their societies.

### Conclusion

Here we have shown the intimate relationship between nutrition and cardiovascular disease, well understood and studied in the developed world but evolving rapidly in the developing world. The prevalence of this environmentally determined disease imposes a major burden on both societies. Many of the underlying causes and risk factors begin in youth. Thus the challenge is to promote healthy nutrition and physically active lifestyles as early as possible in children and young adults throughout the world.

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### Disclosures

None.

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