Coronary artery disease and stroke account for over 20% of deaths worldwide, but there are striking variations in age-adjusted cardiovascular disease (CVD) mortality rates among countries. These international variations are not due to genetic differences among populations. This is evident from trends in rates within countries and changes in rates among migrants moving from low-risk to high-risk countries.

The United States has one of the highest rates of CVD in the world. In the most recent year for which data are available, an estimated 15.5 million Americans were affected by coronary heart disease (CHD) alone, which includes myocardial infarction and angina pectoris.

- Heart disease strikes someone in the United States every 42 seconds and kills more than 370,000 Americans each year.
- Approximately one in seven deaths in the United States is from CHD, which makes it the number-one killer of Americans.
- 550,000 Americans have a new coronary attack (defined as first hospitalized myocardial infarction or coronary heart disease death) each year.
- 200,000 people have a recurrent coronary attack.
- 160,000 people experience silent first myocardial infarctions each year.

The number of coronary deaths divides approximately evenly between men and women, although the average age of a first heart attack is approximately 64 for men and 70 for women. On the other hand, risk factors such as high blood pressure and diabetes increase heart attack risk in women more severely than in men.

SOYFOODS CAN MAKE IMPORTANT CONTRIBUTIONS TO HEART-HEALTHFUL DIETS, INCLUDING HIGH-QUALITY PROTEIN AND AMPLE AMOUNTS OF OMEGA-6 AND OMEGA-3 ESSENTIAL FATTY ACIDS.

INTRODUCTION
In 2013, the American Heart Association (AHA) issued new guidelines for the assessment of CVD risk. According to the AHA, in addition to age and gender, risk is primarily determined by total cholesterol level, HDL-cholesterol, systolic blood pressure, and whether one smokes and has diabetes.

Evidence indicates that adjusted population attributable fractions for CHD mortality are as follows:

- 34.7% for high blood pressure
- 16.7% for smoking
- 20.6% for poor diet
- 7.8% for insufficient physical activity
- 7.5% for abnormal glucose levels

From the information above, it is clear that dietary choices can significantly impact the risk of developing CHD. While markedly reducing CHD risk via dietary modification requires a comprehensive approach, there is no doubt that soyfoods can play an important role in heart-healthy diets.

**CIRCULATING LIPID LEVELS**

Soyfoods have been recognized by nutritionists for decades as rich sources of high-quality protein, but over the past 20 years the effect of soy protein on blood cholesterol levels has attracted attention from the nutrition and medical communities. The first rodent studies showing that soy protein lowered cholesterol levels were published more than 60 years ago, and the first clinical trial demonstrating this effect was published in 1967. Throughout the 1970s and 1980s, Italian researchers were instrumental in showing that soy protein directly lowered blood cholesterol levels in very hyper-cholesterolemic patients. Nevertheless, it wasn’t until 1995 that the cholesterol-lowering effects of soy protein received widespread recognition.

In that year, a meta-analysis of the clinical data, which included 38 different comparisons, found that soy protein reduced low-density lipoprotein cholesterol (LDLC) by approximately 13 percent. This reduction was independent of the fatty acid content of soyfoods and, because statins were not yet widely used in clinical practice, the effect of soy protein was similar to that of the available cholesterol-lowering medications.

The results of the 1995 meta-analysis prompted much investigation into the cholesterol-lowering effects of soy protein. Some of this research has been directed at identifying the specific soybean components and mechanisms responsible for cholesterol reduction, whereas other research explored the responses to soy protein in different subpopulations such as hypercholesterolemic individuals and pre- and postmenopausal women. In regard to mechanism, some data suggest that cholesterol reduction is a result of the upregulation of hepatic LDL receptors by the peptides formed upon digestion of soy protein. Researchers also continue to explore whether isoflavones in soybeans impact the cholesterol-lowering effects of soy protein. Soyfoods are uniquely rich sources of these diphenolic compounds.

In 1999, the U.S. Food and Drug Administration (FDA) approved a health claim for soyfoods and CHD based on the cholesterol-lowering effects of soy protein. Claims similar to the FDA claim have been approved in >10 other countries, including most recently Canada, which did so in 2014. However, despite the large amount of research upon which the FDA health claim was based, the cholesterol-lowering ability of soy protein has been challenged in recent years. Some inconsistency in the literature is expected given that many trials involved relatively small sample sizes and that in general about 20% of individuals whose cholesterol levels are elevated do not respond to dietary changes.

In 2008, the American Heart Association (AHA) formally expressed their opposition to the existing soy health claim. In their 2006 position paper, the AHA acknowledged the important role soyfoods can have in heart-healthy diets because they are low in saturated fat and high in polyunsaturated fat (PUFA). However, the decrease in LDLC in
response to soy protein, which they estimated to be approximately 3%, based on the results of 22 studies, was insufficient in their view to warrant a health claim. The AHA endorsed the health claim in 2000 shortly after it was first issued.

Importantly, however, the AHA did not conduct a formal statistical meta-analysis of the 22 studies upon which they based their estimate of the potency of soy protein. When such an analysis was conducted, Jenkins et al. found that the AHA had considerably underestimated the hypocholesterolemic effects of soy protein since the analysis showed that soy protein lowered LDL by 4.3 percent. Furthermore, when the analysis was limited to the 11 studies that provided evidence that the control and soy diets were matched for nutrient content, soy protein was found to lower LDL by 5.2 percent. Over the past decade or so, all of the meta-analyses of the clinical data have found soy protein statistically significantly lowers LDL. A conservative estimate based on the results of these analyses is that soy protein lowers LDL approximately 4%, which is similar to the effects of soluble fiber, which also has a health claim. Since each 1% decrease in LDL lowers CHD risk by 1-3%, incorporating soy protein into the diet can substantially reduce CHD morbidity and mortality.

Finally, research shows that soy protein modestly raises high density lipoprotein cholesterol and lowers circulating triglyceride levels. In addition, soy protein was found to decrease postprandial triglyceride levels, elevated levels of which are increasingly viewed as important for reducing CHD risk.

EFFECTS OF SOY FAT ON CHD RISK

In contrast to other legumes which are nearly fat-free, approximately 40% of the calories from soybeans are comprised of fat. The fatty acid composition of soy is very heart-healthy as it is comprised of only 12% saturated fat, 29% monounsaturated fat and 59% PUFA (53% linoleic acid and 6% α-linolenic acid). The soybean is one of the few good sources of both essential fatty acids and, because of its widespread use in the United States, soy oil accounts for over 40% of the intake of both essential fatty acids. Although the omega-3 fatty acid α-linolenic acid (ALA) does not possess the same properties as the long-chain omega-3 fatty acids found in cold-water fish, evidence suggests that ALA has direct coronary benefits; the degree is a matter of some debate.

In 2010, using National Health and Nutrition Examination Survey III population data, Jenkins et al. estimated that as a result of differences in fatty acid intake, when soyfoods replace more traditional sources of protein in the Western diet, LDL is reduced by 3 to 6 percent. There was a 4% reduction in LDL when 24g soy protein – an amount similar to the 25g/day established by FDA as the threshold intake for cholesterol reduction – replaced a comparable amount of the more commonly consumed protein sources. Thus, as a result of the displacement of traditional sources of protein in Western diets (which tend to be high in saturated fat) by soyfoods and the direct effects of soy protein, soyfoods can be expected to decrease LDL by approximately 8 percent.

In recent years there has been considerable controversy about the impact of saturated fat on CHD risk with some analyses finding no relationship. Certainly, it is recognized that not all dietary saturated fatty acids exert the same effect on serum LDL. In addition, the impact of dietary saturated fatty acids on serum LDL depends upon the type and composition of food in which the saturated fat is consumed. For example, saturated fat in butter raises LDL to a much greater extent than saturated fat in cheese. This finding has been attributed to the high calcium content of cheese, which can form insoluble salts with the saturated fatty acids, preventing them from being absorbed.
While it is far beyond the scope of this review to examine the relationship between dietary fatty acid intake and CHD risk in depth, data indicate that the impact of saturated fat is dependent upon that which replaces it. To this point, a combined analysis of the Nurses’ Health Study (1980 to 2010, n=84,628) and the Health Professionals Follow-up Study (1986 to 2010, n= 42,908 men) found that replacing 5% of energy intake from saturated fats with equivalent energy intake from PUFA, monounsaturated fat, or carbohydrates from whole grains was associated with a 25%, 15%, and 9% lower risk of CHD, respectively, whereas replacing saturated fat with carbohydrates from refined starches/added sugars was not significantly associated with CHD risk.41 Interestingly, a recent analysis found that in many countries around the world inadequate intake of PUFA contributes much more to CHD mortality than an excess intake of saturated fat.42 Thus, full-fat soyfoods and soybean oil can markedly help to reduce risk of developing CHD.

Nevertheless, despite soy’s cholesterol-lowering effect, some concerns have arisen that too much omega-6 PUFA and, in particular, linoleic acid, may increase CHD risk by increasing inflammation. However, the AHA has rejected concerns about the pro-inflammatory properties of linoleic acid and concluded that omega-6 PUFA plays a critically important role in heart-healthful diets.43 This position is supported by a comprehensive review by Johnson and Fritsche,44 published in 2012, which concluded that “virtually no evidence is available from randomized, controlled intervention studies among healthy, non-infant human beings to show that addition of LA [linoleic acid] to the diet increases the concentration of inflammatory markers.”

One reason for this lack of effect may be because, although linoleic acid is converted to arachidonic acid (AA) from which a number of pro-inflammatory eicosanoids are produced, tissue levels of AA don’t substantially increase because they are tightly regulated.45 Also, it is now recognized that not all of the eicosanoids produced from AA are pro-inflammatory; some in fact may be anti-inflammatory.46 Interestingly, in eight-week-old male C57Bl/6 mice, diets high in saturated and monounsaturated fat increased pro-inflammatory markers in the liver and adipose tissue whereas no such effects were noted in animals fed diets high in linoleic acid.4
BEYOND EFFECTS ON LIPID LEVELS

There is epidemiologic evidence that soyfoods exert coronary benefits independent of their effect on blood cholesterol levels. For example,

- In Shanghai, a prospective study involving nearly 65,000 postmenopausal women found after controlling for a variety of factors that soy protein intake was associated with an 86% reduction in the risk of non-fatal myocardial infarction.\(^48\)

- In China, a cross-sectional study involving 406 adults ages 40 to 65 years old (134 males, 272 females) without confirmed relevant diseases, found that soyfood intake was inversely related to bifurcation intima-media thickness, although the association was more apparent in men than women.\(^49\)

- In Japan, a prospective study involving 40,462 participants, ages 40 to 59 years old without cardiovascular disease or cancer at baseline, found that when comparing women with frequent (≥5x/week) versus infrequent (≤2x/week) soy consumption, the multivariable hazard ratios were 0.64, 0.55 and 0.31 for risk of the incidence of cerebral infarction, myocardial infarction and CHD mortality, respectively.\(^50\) However, there was only a non-significant trend toward a protective effect of soy among men.

In contrast to the above studies, in Singapore, a prospective study involving 63,257 Chinese adults aged 45-74 years, found soy intake was unrelated to mortality in either men or women after 890,473 person-years of follow-up.\(^51\) Also, a large prospective study from Shanghai found that over the 5.4-year follow-up period, soy intake was associated with an increased risk of CHD among men.\(^52\) This finding comes from a study that was published as a letter to the editor and is inconsistent with the prospective studies from Japan\(^50\) and Singapore;\(^51\) nevertheless, this result warrants additional investigation.

For at least two reasons, it is highly unlikely that the cholesterol-lowering effects of soyfoods were primarily responsible for the protective effects observed in the prospective studies from Japan\(^50\) and Shanghai\(^48\) and the cross-sectional study from China.\(^49\) First, soy protein consumption in the upper intake categories was between eight and 16g/day, which, based on the results from the clinical studies, is likely too little to lower cholesterol. Second, the protective effects were far greater than could be expected from the cholesterol reduction typically associated with soy protein. Perhaps the explanation is a “healthy user effect,” i.e., that soyfood consumption is associated with an overall healthier lifestyle. This explanation is unlikely, however, because most of the studies controlled for a wide range of potentially confounding variables. Also, soy consumption in Asia is much less reflective of an overall lifestyle than it is in countries where soyfoods have not been part of the traditional diet.
BLOOD PRESSURE

In support of the epidemiologic studies, which found inverse relationships between CHD risk and soy intake, are various clinical studies that show soyfoods, soy protein or soybean isoflavones favorably affect a number of biological measures that impact heart disease risk. For example, four recently published meta-analyses concluded that soy modestly lowers blood pressure. In the largest of these, which included 27 studies, soy lowered systolic and diastolic blood pressure by 2.21 and 1.44 mgHg, respectively. Reducing systolic blood pressure by just 2-5mmHg may reduce stroke and CHD disease by 6-14% and 5-9%, respectively.

ENDOTHELIAL FUNCTION (VASODILATION)

Two meta-analyses have found that soybean isoflavones improved endothelial function in postmenopausal women. Endothelial cells line the blood vessels and their functioning can impact CHD risk. When the data from one of these meta-analyses were sub-analyzed, the improvement was only found in those women who had impaired endothelial function at baseline. Of course, these women are at greater risk of having or developing CHD. This finding provides an explanation for the inconsistent literature in that some studies included women with both impaired endothelial function and others with normal endothelial function. It may also be that some of the observed anti-inflammatory effects of isoflavones occur only in people at risk of CHD who have elevated levels of inflammatory markers.
ARTERIAL COMPLIANCE

Unlike endothelial-mediated vasodilation (primarily nitric oxide-dependent), arterial compliance relates to the constriction and dilation of arteries associated with systole and diastole. Arterial compliance is determined by components of the artery wall, such as elastin, proteoglycans and smooth muscle cell function. The most straightforward, valid, and reliable measure of arterial stiffness is pulse wave velocity (PWV), which is predictive of future cardiovascular events.61

In 2011, a systematic review by Pase et al.62 concluded on the basis of five studies63-67 that isoflavones reduce arterial stiffness, although one of the four that reported benefit intervened with an isoflavone metabolite.67 Three additional studies not reviewed by Pase et al.62 are supportive of the ability of isoflavones to improve arterial compliance in postmenopausal women.68-70 Conversely, no differences in arterial compliance were noted in a small group of hypercholesterolemic men and women when comparing a soymilk/soy yogurt intervention with a dairy milk/yogurt intervention.71

CAROTID INTIMA-MEDIA THICKNESS

Subclinical atherosclerosis can be assessed using ultrasound to measure the thickness of the carotid arteries, which are located on both sides of the neck beneath the jawline and provide the main blood supply to the brain. The thickness of the carotid artery is referred to as carotid intima-media thickness or CIMT. Typically, CIMT increases or progresses over time; the extent of progression reflects risk of future coronary events.

An important clinical trial to evaluate the impact of soy on CIMT is the Women’s Isoflavone Soy Health (WISH) study, a 3-year study involving 350 healthy postmenopausal women ages 45 to 92. Based on changes in CIMT, this study found that isoflavone-rich soy protein inhibited the progression of subclinical atherosclerosis.72 Participants in the WISH study were randomly assigned to groups consuming either 25g of isolated soy protein or 25g of milk protein per day. The soy protein provided 91mg of isoflavones (expressed in aglycone equivalent weight).

At study termination, progression among the women consuming soy was 16% lower than in the milk group. Furthermore, the difference between groups increased steadily over the 3-year study period. This suggests that after a longer period of soy exposure, progression would have been reduced to an even greater extent, and with it, risk of coronary events. Additionally, subanalysis of the results revealed that among women who were fewer than five years, five to 10 years, and more than 10 years postmenopause, CIMT progression was reduced by 68 (p=0.05), 17 (p=0.51) and 9% (p=0.77), respectively. That progression was reduced so significantly in early postmenopausal women is notable for two reasons.

First, it adds substantially to the biologically plausibility of the findings and second, it provides clear insight into the soy component responsible for the beneficial effects. The pronounced effect in early menopausal women suggests isoflavones were primarily responsible for the reduced CIMT progression because over the past 15 years a hypothesis has emerged, referred to as the “estrogen timing hypothesis,” which maintains that exposure to estrogen-like compounds leads to dramatic coronary benefits when begun soon after menopause, but has less effect in later years.72

SUMMARY AND CONCLUSIONS

In summary, soyfoods can make important contributions to heart-healthy diets through several different mechanisms. They provide high-quality protein but minimal amounts of saturated fat. They provide ample amounts of omega-6 and omega-3 essential fatty acids. Soy protein directly lowers blood LDL-C levels, modestly elevates high density lipoprotein cholesterol levels and decreases triglyceride levels. Furthermore, soyfoods appear to favorably affect CHD risk factors independent of lipid levels; for example, improving endothelial function and systematic arterial compliance and lowering blood pressure.
the value of U.S. soy meal and oil, to ensure U.S. soybean farmers and their customers have the freedom and infrastructure to operate, and to meet the needs of U.S. soy’s customers.

The 70 farmer-directors of USB oversee the investments of the soy checkoff to maximize profit opportunities for all U.S. soybean farmers. These volunteers invest and leverage checkoff funds to increase

References

For more information, please visit SoyConnection.com.