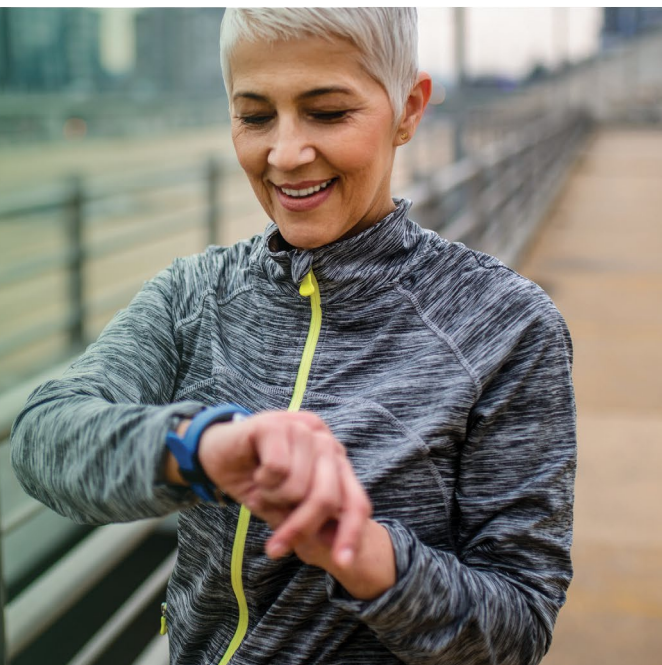




SOY + HEART HEALTH



CVD STATISTICS AND RISK FACTORS

EFFECTS OF SOY PROTEIN ON CIRCULATING LIPID LEVELS

EFFECTS OF SOY CVD MARKERS INDEPENDENT OF LIPID LEVELS

EFFECTS OF SOY FAT ON CHD RISK

Soy foods can make important contributions to heart-healthy diets, including high-quality protein and ample amounts of omega-6 and omega-3 essential fatty acids.

INTRODUCTION

Coronary artery disease and stroke, the two primary diseases comprising cardiovascular disease (CVD), account for over 20 percent of deaths worldwide, but there are striking variations in age-adjusted CVD mortality rates among countries.¹ 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.² In the most recent year (2015) for which data are available, an estimated 17.9 million Americans were affected by CVD.



Heart disease strikes someone in the U.S. every 40 seconds and kills over 367,000 Americans each year.³



Approximately one in seven deaths in the U.S. is caused by coronary heart disease (CHD), making CHD the number one killer of Americans.³



720,000 Americans have a new coronary attack (defined as first hospitalized myocardial infarction or CHD death) each year.³



335,000 Americans have a recurrent coronary attack annually.³

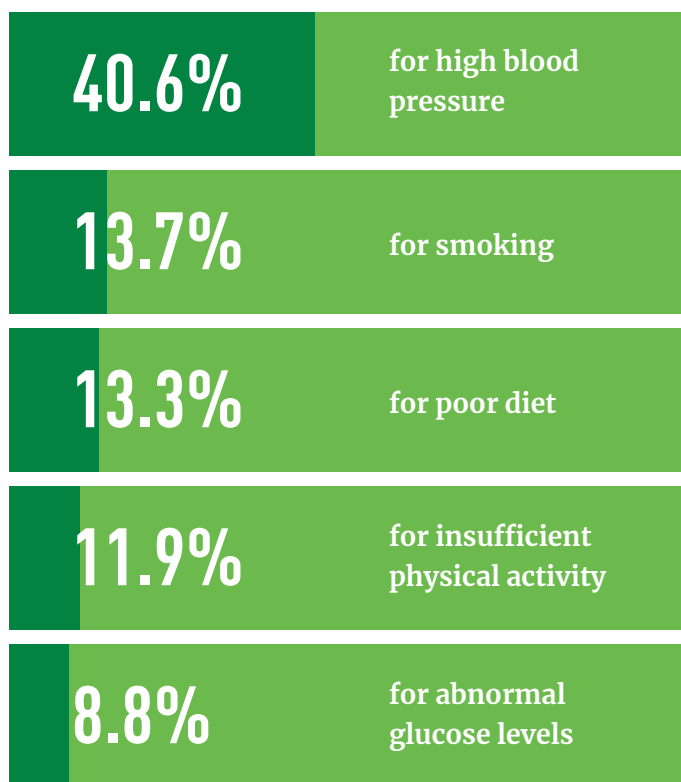


160,000 Americans experience a silent first myocardial infarction each year.³

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.³ On the other hand, risk factors such as high blood pressure and diabetes increase heart attack risk in women more severely than in men.

According to the American Heart Association (AHA), in addition to age and gender, risk is primarily determined by total cholesterol level, high-density-lipoprotein cholesterol (HDL-C) level, systolic blood pressure, and whether one smokes and has diabetes.

Evidence indicates that adjusted population attributable fractions for CVD mortality are as follows³:



From the information above, it is clear that dietary choices can significantly impact the risk of developing CVD. While markedly reducing CVD risk via dietary modification requires a comprehensive approach, there is little doubt that soy foods can play an important role in heart-healthy diets.



EFFECTS OF SOY PROTEIN ON CIRCULATING LIPID LEVELS

The first clinical trial demonstrating the cholesterol-lowering effect of soy protein was published in 1967.⁴ Throughout the 1970s and 1980s, Italian researchers were instrumental in showing that soy protein directly lowered blood cholesterol levels in very hypercholesterolemic patients.⁵⁻⁷ 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 (LDL-C) by approximately 13 percent.⁸

Four years after the meta-analysis, and after conducting its own analysis, the U.S. Food and Drug Administration (FDA) approved an "unqualified" health claim for soy foods and CHD based on the cholesterol-lowering effects of soy protein.⁹ An "unqualified" claim indicates that there was significant scientific agreement in support of it. The FDA established 25 g/d soy protein as the threshold intake of cholesterol reduction.

Despite the fact that claims similar to the FDA claim have subsequently been approved in >10 other countries¹⁰ including most recently Canada, which did so in 2015,¹¹ and that meta-analyses show soy protein statistically significantly lowers LDL-C approximately 4 to 6 percent,^{11–20} in October of 2017, the FDA announced its intention to revoke the existing “unqualified” claim citing inconsistency in the data.²¹ It is possible that soy protein will receive a “qualified” claim, but the FDA does not plan to make a final decision until September of 2019.

Some inconsistency in the literature is expected given that many trials involved relatively small sample sizes and that in general about 20 percent of individuals whose cholesterol levels are elevated do not respond to dietary changes.²² Such data inconsistency exists even for many well-accepted approaches for lowering elevated cholesterol including those for which an FDA-approved unqualified health claim exists. For example, this is the case for oat-glucan²³ and phytosterols/stanols.²⁴ Nevertheless, meta-analyses of the clinical studies show oatglucan²³ and phytosterols/stanols²⁴ statistically significantly lower LDL-C.

In the case of soy protein in its reevaluation of the data, the FDA found that of the 46 studies included in its analysis,¹⁹ 41 percent reported a statistically significant decrease in total cholesterol and/or LDL-C. In the view of the FDA, this percentage was too low for the health claim to be maintained. However, this binary approach (studies were either supportive or unsupportive of the health claim based on statistical significance) to interpreting the data can be called into question. To this point, in 2015, Health Canada also recognized that only a minority of studies (33 percent) reported a statistically significant reduction in LDL-C in response to soy protein.¹¹ Nevertheless, because Health Canada also found that 81 percent of the studies showed a reduction in LDL-C irrespective of whether the finding was statistically significant, the data were considered sufficiently consistent for a health claim to be

allowed. The FDA did not meta-analyze the data from the 46 studies included in its analysis. These data were meta-analyzed by Jenkins and colleagues with the results showing a statistically significant 3.2 percent reduction in LDL-C (approximately 75 percent of the studies showed a reduction). Although the magnitude of reduction is lower than past estimates, each 1 percent decrease in LDL-C is estimated to lower CHD risk by 1 to 3 percent, thus, in theory, incorporating soy protein into the diet can substantially reduce CHD morbidity and mortality.^{25,26}

Finally, research shows that soy protein modestly raises HDL-C and lowers circulating triglyceride levels.¹⁴ In addition, soy protein was found to decrease postprandial triglyceride levels, elevated levels of which are increasingly viewed as important for reducing CHD risk.²⁷



Fatty Acid Composition of Soybean Oil

FATTY ACID	SERVING SIZE	GRAMS OF SOY PROTEIN
Fortified Soymilk	1 cup	6-7
Soy Cereal	1 1/4 cup	7
Soy Yogurt, Vanilla	1 cup	6
Soy Breakfast Patty	2 patties	11
Soy Bar	1 bar	14
Soy Chips	1 bag	7
Soynut Butter	2 tbsp	7
Soynuts, Roasted, Unsalted	1/4 cup	11
Tofu	1/2 cup	10
Edamame	1/2 cup	11
Soy Burger	1 patty	13-14
Soy Pasta	1/2 cup (cooked)	13
Soy Pudding	1/2 cup	6

Source: United States Department of Agriculture Nutrient Database.

In contrast to other legumes which are nearly fat-free, approximately 40% of the calories from soybeans are comprised of fat.²⁸ The fatty acid composition of soybean oil is very hearthealthy as it is comprised of approximately 12% saturated fat, 29% monounsaturated fat, and 59% polyunsaturated fat (PUFA, ~53% linoleic acid and ~6% -linolenic acid).²⁹ Not surprisingly, given its composition, soybean oil has been shown to lower LDL-C.³⁰ In fact, the hypocholesterolemic effect has been demonstrated so convincingly that the FDA recently approved a very strong qualified health claim for soybean oil and CHD.³¹ Although saturated fat is typically discussed more in relation to CHD risk, 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.³²

The essential omega-3 fatty acid-linolenic acid (ALA) does not possess the same properties as the long-chain omega-3 fatty acids found in cold-water fish; nevertheless, evidence suggests that ALA has direct coronary benefits, although there is disagreement on this point.³³⁻³⁶ Notable in this regard is the recent conclusion by the AHA that ALA may reduce risk of fatal CHD.³⁷ Other evidence supports this conclusion as well.³⁸ In recent years, controversy has risen about the impact of saturated fat on CHD risk with some analyses finding no relationship.³⁹ Certainly, it is recognized that not all dietary saturated fatty acids exert the same effect on serum LDL-C.⁴⁰ Also, the impact of dietary saturated fatty acids on serum LDL-C may depend upon the type and composition of food in which the saturated fat is consumed. For example, saturated fat in butter raises LDL-C to a much greater extent than saturated fat in cheese.^{41,42} This difference 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.⁴³

More importantly, the failure of some observational studies to show saturated fat intake is associated with an increased risk of CVD isn't because saturated fat doesn't raise risk, but rather, because the impact of saturated fat is dependent upon the macronutrient that replaces it.³⁷ 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 fat 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.⁴⁴ Similar findings exist for total mortality and for CHD-specific mortality.⁴⁵

BLOOD PRESSURE

Four meta-analyses have concluded that soy modestly lowers blood pressure.^{18,46-48} In the largest of these, which included 27 studies, soy lowered systolic and diastolic blood pressure by 2.21 and 1.44 mgHg, respectively.⁴⁶ Reducing systolic blood pressure by just 2–5 mmHg may reduce stroke and CHD disease by 6 to 14 percent and 5 to 9 percent, respectively.⁴⁹ Despite the intriguing data, no conclusions about the hypotensive effects of soy protein can be made because in most of the trials included in the meta-analyses, blood pressure was not the primary outcome of interest.

INFLAMMATION

Despite its cholesterol-lowering effect, some concerns have been raised 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 play a critically important role in heart-healthy diets.⁵⁰ This position is supported by a comprehensive review by Johnson and Fritsche⁵¹ that concluded that “virtually no evidence is available from randomized, controlled intervention studies among healthy, non-infant human beings to show that addition of LA to the diet increases the concentration of inflammatory markers.”⁵² More recently, in the Kuopio



Ischaemic Heart Disease Risk Factor Study, Virtanen et al.⁵² found that serum linoleic acid levels were strongly inversely related to serum C-reactive protein, which is a general marker of inflammation. This study involved 1,287 generally healthy men aged 42 to 60 years.

There are several reasons why omega-6 PUFA are not pro-inflammatory as commonly thought. One is that 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 in response to linoleic intake because they are tightly regulated.⁵³ Also, it is now recognized that not all of the eicosanoids produced from AA are pro-inflammatory; some in fact may be anti-inflammatory.⁵⁴

ENDOTHELIAL FUNCTION (VASODILATION)

Two meta-analyses have found that soybean isoflavones improved endothelial function in postmenopausal women.^{55,56} 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 found only in those women who had impaired endothelial function at baseline.⁵⁵ The fat in soy foods may also favorably affect endothelial function. British researchers recently found that, when compared to saturated fat, unsaturated fat increased the number of endothelial progenitor cells, which are cells that play a role in regenerating the lining of the endothelium. In this cross-over trial, men and women consumed three diets containing different amounts of saturated and unsaturated fat for 16-week periods.⁵⁷



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, which is predictive of future cardiovascular events.⁵⁸ In 2011, a systematic review by Pase et al.⁵⁹ concluded on the basis of five studies⁶⁰⁻⁶⁴ that isoflavones reduce arterial stiffness although one of the four that reported benefit intervened with an isoflavone metabolite.⁶⁴ Three additional studies not reviewed by Pase et al.⁵⁹ are supportive of the ability of isoflavones to improve arterial compliance in postmenopausal women.⁶⁵⁻⁶⁷ Conversely, no differences in arterial compliance were noted in a small group of hypercholesterolemic men and women when comparing a soymilk/soy yogurt intervention to a dairy milk/yogurt intervention.⁶⁸

EFFLUX CAPACITY

Efflux capacity, which refers to the ability to remove cholesterol from lipid-laden macrophages, is inversely related to CHD risk.⁶⁹ Recent data show that in comparison to saturated fat, unsaturated fat can enhance cholesterol efflux capacity.⁷⁰ This effect on efflux capacity may represent another mechanism by which unsaturated fat reduces CHD risk.

SUMMARY AND CONCLUSIONS

Soy foods 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 HDL-C and decreases triglyceride levels. Furthermore, soy foods may favorably affect CHD risk factors independent of lipid levels — for example, by improving endothelial function and systematic arterial compliance and lowering blood pressure. Given all of these attributes, it is not surprising that soy foods and soy protein are important components of the portfolio diet, a diet which has been shown to markedly lower LDL-C and blood pressure.⁷¹

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