

META-ANALYSIS OF THE EFFECTS OF SOY PROTEIN INTAKE ON SERUM LIPIDS

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Abstract *Background.* In laboratory animals, the consumption of soy protein, rather than animal protein, decreases serum cholesterol concentrations, but studies in humans have been inconclusive. In this meta-analysis of 38 controlled clinical trials, we examined the relation between soy protein consumption and serum lipid concentrations in humans.

Methods. We used a random-effects model to quantify the average effects of soy protein intake on serum lipids in the studies we examined and used hierarchical mixed-effects regression models to predict variation as a function of the characteristics of the studies.

Results. In most of the studies, the intake of energy, fat, saturated fat, and cholesterol was similar when the subjects ingested control and soy-containing diets; soy protein intake averaged 47 g per day. Ingestion of soy protein was associated with the following net changes in serum lipid concentrations from the concentrations reached with the control diet: total cholesterol, a decrease of 23.2 mg per deciliter (0.60 mmol per liter; 95

percent confidence interval, 13.5 to 32.9 mg per deciliter [0.35 to 0.85 mmol per liter]), or 9.3 percent; low-density lipoprotein (LDL) cholesterol, a decrease of 21.7 mg per deciliter (0.56 mmol per liter; 95 percent confidence interval, 11.2 to 31.7 mg per deciliter [0.30 to 0.82 mmol per liter]), or 12.9 percent; and triglycerides, a decrease of 13.3 mg per deciliter (0.15 mmol per liter; 95 percent confidence interval, 0.3 to 25.7 mg per deciliter [0.003 to 0.29 mmol per liter]), or 10.5 percent. The changes in serum cholesterol and LDL cholesterol concentrations were directly related to the initial serum cholesterol concentration ($P < 0.001$). The ingestion of soy protein was associated with a nonsignificant 2.4 percent increase in serum concentrations of high-density lipoprotein (HDL) cholesterol.

Conclusions. We found that the consumption of soy protein rather than animal protein significantly decreased serum concentrations of total cholesterol, LDL cholesterol, and triglycerides. (*N Engl J Med* 1995;333:276-82.)

INGESTION of vegetable protein in place of animal protein appears to be associated with a lower risk of coronary heart disease^{1,2}; this effect may reflect decreases in serum cholesterol concentrations.³ The cholesterol-lowering effects of soy protein as compared with animal protein have been recognized in animals for more than 80 years.⁴ Carroll reviewed the evidence that soy protein produced less hypercholesterolemia and less atherosclerosis in laboratory animals than animal protein.⁵ Although many clinical investigators have examined the effects of soy protein on serum lipids in humans, the results have not been consistent⁶; consequently, the Nutrition Committee of the American Heart Association recently concluded that soy protein decreases serum cholesterol concentrations in rabbits but not in humans.⁷

Clinical investigators have used a variety of soy products, differing amounts of soy protein, differing criteria for selecting subjects, and a variety of protocols. We performed a meta-analysis of these studies, since combining the results of multiple studies of small or moderate size increases the statistical power brought to bear on the research question and thus greatly enhances the precision of estimates of effect. Our analysis indicated that the effects of soy protein in lowering serum cholesterol concentrations were significantly related to the initial serum cholesterol values. The substitution of soy protein for animal protein produced significant decreases in serum concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol,

and triglycerides without significantly affecting high-density lipoprotein (HDL) cholesterol concentrations.

METHODS

Identification and Selection of Studies

We searched the medical literature for studies of the effects of soy protein on serum cholesterol concentrations in humans; 37 articles containing primary reports were identified.⁸⁻⁴⁴ Studies were selected for analysis if they had used isolated soy protein or textured soy protein; if they were controlled and had either a crossover or a parallel design; and if they provided initial (base line) values so that changes for each study group could be calculated. Studies were excluded if there was no control group^{8,11,14,25,27}; if they used several sources of vegetable protein²⁶; if whole soybeans rather than soy protein were used³⁰; or if base-line values were not provided.²² After these 8 articles were excluded, 29 articles remained in the analysis.

Subgroup Analyses

Changes in serum lipid concentrations were analyzed in relation to the initial serum lipid values, the types of soy protein used (isolated soy protein, textured soy protein, or a combination), the amount of soy protein ingested (in grams per day), the type of diet (usual Western diet or low-fat and low-cholesterol diet), the age group of the subjects (adults or children), and the similarity of the control diet and the soy-containing diet (specifically, regarding weight change in the subjects and dietary intake of fat, saturated fat, and cholesterol). Study diets were considered to be similar in terms of weight change if the subjects' change in weight during consumption of the two diets did not differ significantly. Study diets were considered to be similar in terms of the intake of total dietary fat, saturated fat, and cholesterol if the reported values for the soy-containing and control diets differed by less than 10 percent. When values were not reported for weight change, dietary fat, or cholesterol intake, these variables were assumed not to be similar.

Meta-Analysis

Summary results of each clinical trial and selected characteristics of the study were tabulated for analysis. The estimate of the principal effect was defined as the mean difference (in milligrams per deciliter) between the change in lipid concentrations when the subjects ingested the soy-containing diet (final value minus initial value) and the change when they ingested the control diet (final value minus initial value). This difference is referred to as the net change. In additional meta-analyses we used only the mean difference attributed to the in-

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gestion of soy protein. For the computation of pooled effects, each study was assigned a weight consisting of the reciprocal of its variance. When raw data were available, the variance for each study was calculated separately by computing the standard deviation of the differences between paired observations for the change during the soy-containing diet and the change during the control diet; the standard error of the differences was then calculated. When raw data were unavailable, the variances of the difference were based on the reported standard deviations for each measure and on either reported correlation coefficients or reported results of paired t-tests for the changes during the two diets.

Estimates of the average effect of soy protein on lipid values and 95 percent confidence intervals were calculated with models based on both fixed-effects and random-effects assumptions.^{45,46} Because substantial variability between observations was indicated by preliminary tests for homogeneity, we have presented the results of random-effects models calculated according to the method of DerSimonian and Laird.⁴⁷ The assumption of heterogeneity implied by the use of random-effects models is plausible because of the diverse clinical settings and groups of subjects analyzed.

Predictive models were also developed to examine characteristics of the studies that were hypothesized to influence the observed treatment effects. For this purpose, two-stage mixed regression models (fixed-effects and random-effects) were used.^{48,49} Predictive models were estimated by hierarchical linear modeling.⁵⁰ This approach models variation among studies as a function of the characteristics of the study that are hypothesized to affect the response to treatment and a two-stage random component. Both net and unadjusted effects of the substitution of soy protein for animal protein served as outcome variables in alternative models. The set of predictors used for testing hypotheses in regression models was defined at the outset and was based on a preliminary review of the literature. Several alternative coding strategies were evaluated in preliminary analyses. Our final models included the set of predictors specified above for subgroup analyses. To establish overall levels of variability in treatment effects, our regression analysis began with the estimation of unconditional random-effects regression models without predictors. In a second phase, predictors were entered into the models in bivariate and multiple-regression analyses. The degree of reduction in variance associated with each predictor was calculated by comparing the components of variance in unconditional models with those in conditional models containing predictors.⁵⁰

RESULTS

Characteristics of the Studies

Table 1 shows selected characteristics of the studies that met the criteria for analysis. The 29 articles chosen included the findings of 38 clinical studies; some articles reported data for different subgroups of subjects from one study (e.g., those with normal and those with high cholesterol concentrations); others reported on two different clinical studies. The 38 clinical studies were analyzed independently. In 4 studies the subjects were children, whereas in 34 they were adults. Most studies included both men and women, but the data necessary to analyze effects of soy protein according to sex were not available. Most studies used random assignment with crossover design. Twenty studies used isolated soy protein, 15 used textured soy protein, and 3 used a combination of the two. Soy protein intake averaged 47 g per day (range, 17 to 124); in 14 studies (37 percent) intake was ≤ 31 g per day.

In most studies the investigators attempted to provide similar amounts of total fat and saturated fat in the control and soy-containing diets. In 14 studies the diets were similar to conventional Western diets in fat and cholesterol content (these were termed "usual" diets), and in 18 studies the diets were low in fat content

(≤ 30 percent of energy) and low in cholesterol content (≤ 200 mg per day). In 29 studies the amounts of total fat and saturated fat were similar in the control and soy-containing diets (i.e., they differed by less than 10 percent); 8 other studies were designed to provide similar total fat and saturated fat intake but the similarity of the diets was not documented. In 20 studies cholesterol intake was similar in the two diets; 9 other studies were designed to provide similar cholesterol intake but similarity was not documented.

All the studies except one³⁷ were designed to maintain weight; 34 studies reported similar weight changes for subjects ingesting the control and soy-containing diets. In all, 19 studies had control and soy-containing diets that were similar with respect to intake of dietary fat (total and saturated), intake of dietary cholesterol, and weight change. These 19 studies are listed as "similar" in each of the last three columns of Table 1.

Changes in Serum Lipid Concentrations

The ingestion of diets containing soy protein, as compared with the control diets, was accompanied by a significant reduction in serum concentrations of total cholesterol, LDL cholesterol, and triglycerides (Table 2). The net change (change during the soy diet minus change during the control diet) in serum cholesterol concentrations was a decrease of 23.2 mg per deciliter (0.60 mmol per liter; 95 percent confidence interval for the decrease, 13.5 to 32.9 mg per deciliter [0.35 to 0.85 mmol per liter]), or 9.3 percent. Of 38 studies, 34 (89 percent) reported a net decrease and 4 (11 percent) reported a net increase in serum cholesterol concentrations.

The net change in serum LDL cholesterol concentrations was a decrease of 21.7 mg per deciliter (0.56 mmol per liter; 95 percent confidence interval for the decrease, 11.2 to 31.7 mg per deciliter [0.30 to 0.82 mmol per liter]), or 12.9 percent. Figure 1 illustrates the net effects of the consumption of soy protein on serum LDL cholesterol concentrations as reported in 31 studies. Twenty-six studies (84 percent) reported a net reduction, four studies (13 percent) reported an increase, and one study (3 percent) reported no change.

Soy protein intake did not significantly affect serum HDL cholesterol concentrations, but the net change was an increase of 2.4 percent. Serum very-low-density lipoprotein (VLDL) cholesterol concentrations were not significantly altered by soy protein. The consumption of soy protein significantly decreased serum triglyceride concentrations, by 13.3 mg per deciliter (0.15 mmol per liter; 95 percent confidence interval for the decrease, 0.3 to 25.7 mg per deciliter [0.003 to 0.29 mmol per liter]), or 10.5 percent. Of 30 studies, 22 (73 percent) reported a net decrease in serum triglyceride concentrations, whereas 8 (27 percent) reported an increase.

Effect of Initial Serum Lipid Concentrations

Table 3 summarizes the effects of various factors on changes in serum cholesterol concentrations. In the complete regression model, the initial serum cholesterol concentration was the only significant predictor of the change in the serum cholesterol concentration

Table 1. Characteristics of the 38 Studies.*

STUDY	NO. OF SUBJECTS	MALE/FEMALE (%)†	CHARACTERISTICS OF SUBJECTS‡	STUDY DESIGN§	SOY PREPARATION¶	AMOUNT OF SOY (g/day)	TYPE OF DIET	DIETARY FAT**	DIETARY CHOLESTEROL**	WEIGHT CHANGE**
Bakhit et al. ⁴⁴	21	100/0	Free-living, NC and HC	RC, MD	ISP	25	LFC	Similar	Similar	Similar
Bakhit et al. ⁴⁴	11		Free-living, HC	RC, MD	ISP	25	LFC	Similar	Similar	Similar
Carroll et al. ¹⁰	6	0/100	Free-living, NC	FC, MD	ISP, TSP	47	Usual	Similar	Decreased	Decreased
Carroll et al. ¹⁰	10	0/100	Free-living, NC	RC, MD	ISP, TSP	44	Usual	Similar	Similar	Similar
Descovich et al. ¹²	127	53/47	Free-living, HC	FC	TSP	47	LFC	NA	NA	Similar
Fumagalli et al. ¹⁸	4	75/25	HC	FC, RW	TSP	39	LFC	Similar	Similar	Similar
Fumagalli et al. ¹⁸	3	67/33	HC	FC, RW	TSP	39	LFC	Similar	Similar	Similar
Gaddi et al. ³³	16	56/44	Children, free-living, HC	FC	TSP	56	LFC	NA	NA	Similar
Gaddi et al. ³⁹	20	40/60	Free-living, HC	FC	TSP	75	LFC	Similar	Decreased	Similar
Giovannetti et al. ³¹	12	0/100	Free-living, NC	RC, MD	ISP	71	Usual or LFC	Similar	Similar	Similar
Goldberg et al. ¹⁹	12	58/42	Free-living, HC	RC	ISP	90	Usual	Similar	Similar	Similar
Goldberg et al. ¹⁹	4	75/25	Free-living, NC	RC	ISP	90	Usual	Similar	Similar	Similar
Holmes et al. ¹³	12	75/25	Free-living, HC	FC	TSP	27	LFC	Similar	Similar	Similar
Holmes et al. ¹³	10	60/40	Free-living, HC	RC	TSP	62	LFC	Similar	Similar	Similar
Huff et al. ²⁴	5	100/0	Free-living, HC	RC	TSP, ISP	41	LC	Similar	Increased	Similar
Jenkins et al. ³⁷	11	0/100	Free-living, obese	RC	ISP	28	Hypocaloric	Increased	Decreased	Decreased
Laurin et al. ⁴⁰	9	60/40	Children, free-living, HC	RC	ISP	31	LFC	—	—	—††
Lovati et al. ³⁴	12	42/58	Free-living, HC	RC	TSP	64	LFC	Similar	Similar	Similar
Meinertz et al. ³⁶	10	50/50	Free-living, NC	RC, LFD	ISP	113	LFC	Similar	Increased	Similar
Meinertz et al. ³⁸	11	45/55	Free-living, NC	RC, LFD	ISP	124	LF	Similar	Similar	Similar
Mercer et al. ³⁵	5	Unknown	Free-living, HC	RC	ISP	17	Usual	Similar	Similar	Similar
Potter et al. ⁴²	25	100/0	HC	RC, RW	ISP	50	LFC	Similar	Similar	Similar
Sacks et al. ²³	13	69/31	Free-living, NC, V	RC	ISP	27	Vegetarian	Similar	NA	NA
Shorey et al. ¹⁵	24	100/0	Free-living, HC	RP	ISP	55	Usual	Similar	Similar	Similar
Sirtori et al. ⁹	20	50/50	HC	RC, RW	TSP	47	LC	NA	NA	Similar
Sirtori et al. ²⁸	65	45/55	Free-living, HC	FC	TSP	47	LFC	Similar	Decreased	Similar
Sirtori et al. ²⁸	65	45/55	Free-living, HC	FC	TSP	23	LFC	Similar	Decreased	Similar
Steele ⁴¹	14	NR	Free-living, NC and HC; O, LOV, and V	RC	ISP	21	Usual	NA	NA	Similar
Steele ⁴¹	18	NR	Free-living, NC and HC; O, LOV, and V	RC	ISP	26	Usual	NA	NA	Similar
van Raaij et al. ¹⁶	24	NR	Free-living, NC and HC	RP	ISP	54	Usual	Similar	Similar	Similar
van Raaij et al. ²⁰	20	NR	Free-living, NC and HC	RP	ISP	53	Usual	Similar	Similar	Similar
van Raaij et al. ²⁰	20	NR	Free-living, NC and HC	RP	TSP	55	Usual	Similar	Similar	Similar
Verrillo et al. ²⁹	19	42/58	Free-living, HC	RC	TSP	31	Usual	Similar	Similar	Similar
Verrillo et al. ²⁹	38	50/50	Free-living, HC	RC	TSP	31	Usual	Similar	Decreased	Similar
Vessby et al. ²¹	6	67/33	HC	FC, RW	TSP	37	LC	Similar	Decreased	Similar
Widhalm ³²	11	64/36	Children, free-living, HC	FC	ISP	20	LFC	NA	NA	Similar
Widhalm et al. ⁴³	23	52/48	Children, free-living, HC	FC	ISP	18	LFC	NA	NA	NA
Wolfe et al. ¹⁷	7	100/0	Free-living, HC	RC	ISP	47	LC	NA	NA	Similar

*The 38 studies were reported in 29 published articles. The pairs of studies reported together are listed separately in this table. The numbers of subjects shown are those for whom data were available for comparisons of total cholesterol concentrations.

†NR denotes not reported; both male and female subjects were included.

‡NC denotes subjects with normal cholesterol concentrations, HC those with hypercholesterolemia, V vegetarians, O omnivores, and LOV lacto-ovo-vegetarians.

§RC denotes randomized crossover, MD metabolic diet (i.e., with all food prepared in a metabolic kitchen), FC fixed-sequence crossover, RW research ward, LFD liquid formula diet, and RP randomized parallel.

¶ISP denotes isolated soy protein, and TSP textured soy protein.

||LFC denotes low fat and cholesterol, LC low cholesterol, and LF low fat.

**Similar indicates that the soy-containing and control diets were similar in terms of dietary fat intake, dietary cholesterol intake, or weight change in the subjects. Increased indicates significantly higher in the soy-containing diet than the control diet, and decreased significantly lower in the soy-containing diet. NA denotes that the information was not available.

††Dietary fat and cholesterol and weight change in subjects consuming the two diets were similar. However, only eight of the subjects received both diets. An additional subject received only the soy-containing diet, and a different subject received only the control diet.

($P < 0.001$). The relation between the initial serum cholesterol concentration and changes in serum cholesterol was modeled as a quadratic polynomial function. The proportion reduction in variance among studies between conditional and unconditional models indicated that the base-line cholesterol concentration accounted for approximately 77 percent of the overall variance. However, significant heterogeneity continued to be present

in the model even after adjustment for hypothesized predictors of variation (variance component = 0.134, $P < 0.001$).

Table 4 presents changes in serum cholesterol and LDL cholesterol concentrations according to quartiles of the initial cholesterol concentration. Subjects with normal cholesterol levels, who had initial values below 200 mg per deciliter, had nonsignificant reductions of 3.3

Table 2. Net Change in Serum Lipids and Lipoprotein Concentrations in Subjects Ingesting the Soy-Containing Diets, as Compared with the Control Diets.*

INDEX	NO. OF STUDIES	NO. OF SUBJECTS	CHANGE (mg/dl)†	95% CI	PERCENT CHANGE
Total cholesterol	38	730	-23.2	-32.9 to -13.5	-9.3
LDL cholesterol	31	564	-21.7	-31.7 to -11.2	-12.9
HDL cholesterol	30	551	+1.2	-3.1 to +5.4	+2.4
VLDL cholesterol	20	255	-0.4	-4.6 to +3.9	-2.6
Triglycerides	30	628	-13.3	-25.7 to -0.3	-10.5

*Net change is expressed as the change during the soy-containing diet minus the change during the control diet. VLDL denotes very-low-density lipoprotein, and CI confidence interval.

†To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.01129.

percent while receiving the soy protein diet. Those with mild hypercholesterolemia, who had initial values of 200 to 255 mg per deciliter (5.2 to 6.6 mmol per liter), had nonsignificant reductions of 4.4 percent. Subjects with moderate hypercholesterolemia, who had initial values of 259 to 333 mg per deciliter (6.70 to 8.61 mmol per liter), had significant decreases of 7.4 percent. Subjects with severe hypercholesterolemia, whose initial values were above 335 mg per deciliter (8.66 mmol per liter), had significant reductions of 19.6 percent.

The pattern of changes in serum LDL cholesterol concentrations, according to quartiles of the initial serum cholesterol values, was similar to the pattern for serum cholesterol concentrations: first quartile, a decrease of 7.7 percent; second quartile, a decrease of 6.8 percent; third quartile, a decrease of 9.8 percent; and fourth quartile, a decrease of 24.0 percent. Changes in serum HDL cholesterol concentrations were similar for all quartiles. Changes in serum triglyceride concentrations were significantly related to the initial serum triglyceride concentrations ($P < 0.05$). However, changes in individual quartile groups were not statistically significant.

Effect of Other Variables

As shown in Table 3, the type of soy protein did not have a significant effect on the net change in serum cholesterol concentrations and accounted for only approximately 1.0 percent of the variance. The amount of soy protein in the diet was also not significant ($P = 0.39$) when net changes were assessed. The type of diet, although not statistically significant, accounted for approximately 12.6 percent of the variance ($P = 0.07$); larger changes tended to occur when the control diets were "usual" diets rather than low-fat and low-cholesterol diets. The results of studies of adult subjects did not differ significantly from those of the four studies of children; the age group of the subjects thus had a negligible effect on variance. The changes in the 19 studies with similar diets in terms of fat and cholesterol intake and weight change did not differ significantly from the changes in the remaining studies, in which the diets were not similar; this factor accounted for negligible variance.

To examine the effects of the type and amount of soy

protein further, we performed a complete regression analysis using changes observed with the soy diet alone instead of net changes (soy diet minus control diet) as the outcome variable. In this model, significant effects were obtained for the initial serum cholesterol concentration ($P < 0.001$; proportion of reduction accounted for, 0.69) and the amount of soy protein ($P = 0.02$; proportion of reduction, 0.13). This model predicted that soy protein intake would be associated with the following decreases in serum cholesterol concentrations, after adjustment for the initial values and other variables: 25 g per day of soy protein, a decrease of 8.9 mg per deciliter (0.23 mmol per liter); 50 g per day of soy protein, a decrease of 17.4 mg per deciliter (0.45 mmol per liter); and 75 g per day of soy protein, a decrease of 26.3 mg per deciliter (0.68 mmol per liter). The type of soy

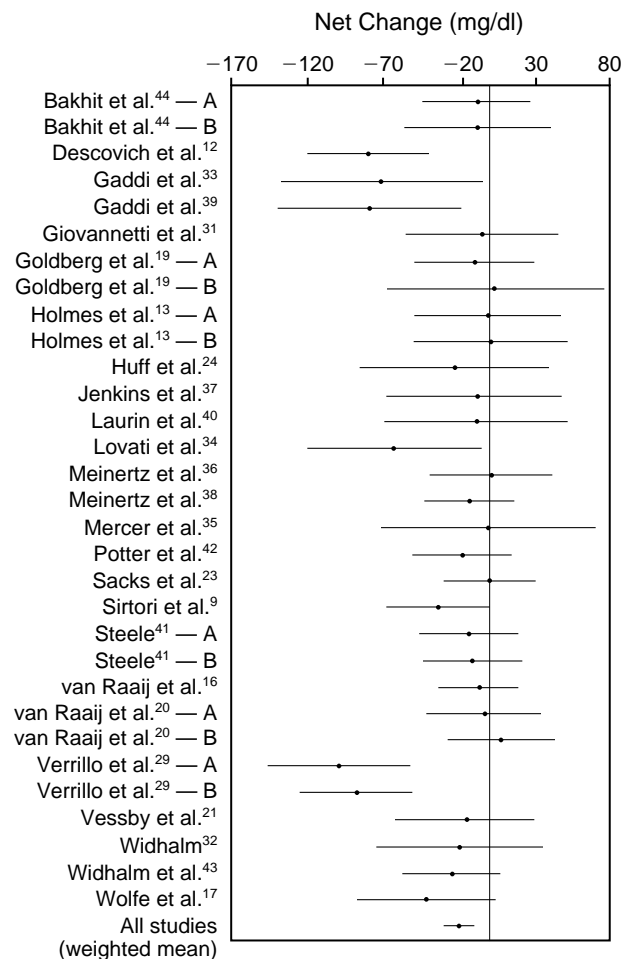


Figure 1. Net Changes in Serum LDL Cholesterol Concentrations in 31 Clinical Trials of the Effects of Soy Protein on Serum Lipids.

These 31 trials presented data on LDL cholesterol for a total of 564 subjects. The values shown are the mean changes in LDL cholesterol concentrations while subjects received the diet containing soy protein minus the changes during the control diet, with 95 percent confidence intervals. A and B indicate separate studies reported in a single published article, listed here in the same order as in Table 1. To convert values to millimoles per liter, multiply by 0.02586.

protein ($P=0.16$), the type of diet ($P=0.11$), the age group of the subjects (adults or children) ($P=0.39$), and the similarity of the diets ($P=0.28$) did not have significant effects on this model.

DISCUSSION

This analysis of 38 controlled clinical studies reported in 29 scientific articles indicated that the replacement of animal protein in the diet with soy protein was associated with a significant decrease in serum cholesterol and LDL cholesterol concentrations. This was a fairly consistent finding, since decreases in serum cholesterol concentrations were reported in 34 of 38 studies; in the 4 studies^{13,20,23,36} that did not report such reductions, the subjects had fairly low initial serum cholesterol values (average, 185 mg per deciliter [4.78 mmol per liter]). Changes in serum lipid concentrations were independent of changes in body weight and dietary intake of total fat, saturated fat, and cholesterol.

The strength and consistency of these observations are surprising in the light of the conclusion of the Nutrition Committee of the American Heart Association that the "consumption of vegetable proteins leads to lower cholesterol levels than consumption of animal proteins in rabbits but not in humans."⁹⁷ This comment was supported by only one study.⁵¹

Initial serum cholesterol concentrations had a powerful effect on changes in serum cholesterol and LDL cholesterol concentrations and accounted for approximately 77 percent of the variance among studies. The amount of soy protein ingested had a significant effect on serum cholesterol concentrations when the effects of the soy diet were examined alone, without the effects of the control diet. Soy protein intake averaged 47 g per

Table 3. Fixed-Effects Estimates from the Regression Model Predicting Net Changes in Serum Cholesterol Concentrations as a Function of Characteristics of the Study.*

VARIABLE†	REGRESSION COEFFICIENT	STANDARD ERROR	PROPORTION REDUCTION IN VARIANCE	P VALUE
Intercept	0.194	0.381	—	—
Square of initial cholesterol value (mg/dl)‡	-0.020	0.005	0.773	<0.001
Type of soy protein	-0.115	0.133	0.010	0.27
Amount of soy protein (g/day)	-0.001	0.003	—	0.39
Type of diet	0.322	0.173	0.126	0.07
Age group of subjects	0.024	0.331	—	0.39
Similarity of diets	0.132	0.169	—	0.29

*Final estimate of random effects for net change: variance component=0.134; chi-square = 100.4; $P<0.001$.

†In the regression analysis, the following values were assigned to categorical variables: type of soy protein, 0=isolated soy protein, 1=isolated and textured soy proteins, and 2=textured soy protein; type of diet, 0=usual and 1=low fat and cholesterol; age group, 0=children and 1=adults; similarity, 0=not similar or data unavailable, and 1=similar.

‡Modeled as a quadratic polynomial function.

Table 4. Changes in Serum Cholesterol and LDL Cholesterol Concentrations According to Quartiles of the Study Group for Initial Cholesterol Concentration.*

VARIABLE	QUARTILE			
	1	2	3	4
Cholesterol (mg/dl)				
Initial range	127.1 to 197.8	201.2 to 255.4	259.3 to 332.8	>335
Change	-5.2	-10.1	-22.2	-71.5
95% CI	-17.1 to +6.7	-21.8 to +1.7	-37.3 to -7.1	-86.6 to -56.5
% Change	-3.3	-4.4	-7.4	-19.6
LDL cholesterol (mg/dl)				
Change	-7.1	-10.7	-18.3	-68.1
95% CI	-20.0 to +6.0	-24.3 to +2.9	-35.3 to -1.3	-90.2 to -45.9
% Change	-7.7	-6.8	-9.8	-24.0

*Exact ranges are given for cholesterol and total cholesterol concentrations in the quartiles. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. CI denotes confidence interval.

day, and 37 percent of the studies used 31 g per day or less. These observations suggest that the daily consumption of 31 to 47 g of soy protein can significantly decrease serum cholesterol and LDL cholesterol concentrations. After adjustment for initial serum cholesterol concentrations and other variables, the ingestion of 25 or 50 g of soy protein per day was estimated to decrease serum cholesterol concentrations by 8.9 or 17.4 mg per deciliter, respectively. Persons with moderate or severe hypercholesterolemia (>250 mg per deciliter [6.46 mmol per liter]) should have even larger decreases in serum cholesterol concentrations when soy protein replaces animal protein in the diet.

Soy protein products are widely available in supermarkets, and lower-fat soy products are easily obtainable. Persons with hypercholesterolemia can achieve an intake of more than 30 g of soy protein per day by consuming two to three servings of soy products daily. The amount of soy protein in a single serving of various soy products is as follows: 8 oz (226 g) of soy milk contains 4 to 10 g of soy protein; 4 oz (113 g) of tofu, 8 to 13 g; 1 oz (28 g) of soy flour, 10 to 13 g; 1 oz (28 g) of isolated soy protein, 23 g; 1/2 cup (113 g) of textured soy protein, 11 g; and 3.2 oz (91 g) of meat analogue, 18 g.⁵² Thus, substituting two cups (473 ml) of soy milk for regular milk and consuming one serving of meat analogue would provide approximately 30 g of soy protein per day.

The mechanisms responsible for the effects of soy protein on serum lipoproteins are unknown^{6,44} and were not addressed in this study. Carroll⁶ recently reviewed and discussed various hypotheses. In experiments in animals, the amino acid composition of the diet affects serum cholesterol concentrations; increases in arginine are accompanied by decreases in serum cholesterol concentrations.⁶ Although some studies suggest that alterations in bile acid or cholesterol absorption may contribute to altered cholesterol homeostasis,⁶ Fumagalli et al.¹⁸ found no differences in the fecal excretion of bile acids or sterols by human subjects. Some observers, as discussed by Carroll,⁶ suggest that alterations in the ratio of serum glucagon to serum insulin may affect hepatic cholesterol synthesis; others^{6,44} suggest that serum free thyroxine concentrations may

be higher when the diet contains soy protein. Huff and colleagues²⁴ suggest that turnover of VLDL apoprotein B is increased in humans when soy protein is substituted for meat and dairy protein. Lovati and colleagues³⁴ report that the LDL-receptor activity of monocytes is eight times greater in human subjects receiving soy protein than in those eating control diets.

Setchell⁵³ suggests that soy estrogens may contribute to the cholesterol-lowering effects of soy protein. Most soy protein products contain soy estrogens (isoflavones or phytoestrogens),⁵⁴ which have weak estrogenic effects under certain circumstances and antiestrogenic effects under others.⁵⁵ The administration of oral estrogens⁵⁶ or the synthetic antiestrogen tamoxifen⁵⁷ decreases serum cholesterol and LDL cholesterol concentrations; soy estrogens may have similar actions. This suggestion is supported in studies by Anthony and colleagues.⁵⁸⁻⁶⁰ In three studies using cynomolgus or rhesus monkeys, soy protein rich in soy estrogens favorably affected serum lipids, whereas soy protein from which the soy estrogens had been extracted had a minimal effect. These primate studies suggest that soy estrogens may account for 60 to 70 percent of the hypocholesterolemic effects of soy protein.

In summary, this meta-analysis of 38 studies indicates that the consumption of soy protein is associated with significant decreases in serum cholesterol, LDL cholesterol, and triglyceride concentrations and with a nonsignificant increase in serum HDL cholesterol concentrations. The decreases in serum cholesterol and LDL cholesterol concentrations were strongly related to the subjects' initial serum cholesterol concentrations. Soy estrogens may be responsible for most of the hypocholesterolemic effects of soy protein.

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