

Cumulative Meta-Analysis of the Soy Effect Over Time

David J. A. Jenkins, MD, PhD; Sonia Blanco Mejia, MD, MSc; Laura Chiavaroli, MSc, PhD; Effie Viguiliouk, MSc; Siying S. Li, MD, MSc; Cyril W. C. Kendall, PhD; Vladmir Vuksan, PhD; John L. Sievenpiper, MD, PhD

Background—Soy protein foods have attracted attention as useful plant protein foods with mild cholesterol-lowering effects that are suitable for inclusion in therapeutic diets. But on the basis of the lack of consistency in significant cholesterol reduction by soy in 46 randomized controlled trials, the US Food and Drug Administration (FDA) is reassessing whether the 1999 heart health claim for soy protein should be revoked.

Methods and Results—We have, therefore, performed a cumulative meta-analysis on the 46 soy trials identified by the FDA to determine if at any time, since the 1999 FDA final rule that established the soy heart health claim, the soy effect on serum cholesterol lost significance. The cumulative meta-analysis for both total cholesterol and low-density lipoprotein cholesterol demonstrated preservation of the small, but significant, reductions seen both before and during the subsequent 14 years since the health claim was originally approved. For low-density lipoprotein cholesterol, the mean reduction in 1999 was -6.3 mg/dL (95% Cl, -8.7 to -3.9 mg/dL; *P*=0.00001) and remained in the range of -4.2 to -6.7 mg/dL (*P*=0.0006 to *P*=0.0002, respectively) in the years after 1999. At no time point did the total cholesterol or low-density lipoprotein cholesterol reductions lose significance or were the differences at individual time points in the cumulative meta-analysis significantly different from those seen in 1999 when the health claim was approved.

Conclusions—A cumulative meta-analysis of the data selected by the FDA indicates continued significance of total cholesterol and low-density lipoprotein cholesterol reduction after soy consumption and supports the rationale behind the original soy FDA heart health claim. (*J Am Heart Assoc.* 2019;8:e012458. DOI: 10.1161/JAHA.119.012458.)

Key Words: cholesterol reduction • US Food and Drug Administration heart health claim • soy protein

T he US Food and Drug Administration (FDA) has proposed to revoke the heart health claim status for soy protein foods¹ that it originally granted in $1999.^2$ For almost 40 years, there has been interest in soy protein as

Correspondence to: David J. A. Jenkins, MD, Department of Nutritional Sciences, Faculty of Medicine, University of Toronto, Medical Sciences Bldg, Floor 5, Room 5336B, 1 King's College Cir, Toronto, Ontario, Canada M5S 1A8. E-mail: david.jenkins@utoronto.ca

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a food source with cholesterol-lowering properties, starting with the large reductions in serum cholesterol, as seen in the early feeding studies of hypercholesterolemic patients by Sirtori et al.³ Later, this cholesterol-lowering effect of soy was explored in a meta-analysis by Anderson and colleagues in 1995 that demonstrated a dramatic 13% reduction in low-density lipoprotein cholesterol (LDL-C).⁴ Subsequent meta-analyses have shown more moderate LDL-C reductions, but overall the reductions have remained significant.^{5–7} Concern has been expressed that the effects of soy on LDL-C are too modest to be clinically significant.⁸ However, trials that have combined several cholesterol-lowering foods that included soy in a "portfolio" provided under metabolically controlled conditions have achieved statin-like LDL-C reductions.⁹

Nevertheless, the FDA, without a formal meta-analysis, concluded that the variability in the results of soy trials was too great.¹ Further trials demonstrating a significant LDL-C reduction were too few. As a result, the FDA proposed that, subject to comment, the health claim should be revoked.¹

We have, therefore, performed a cumulative meta-analysis to demonstrate whether, and if so when, a significant effect of soy on cholesterol was lost.

From the Departments of Nutritional Sciences (D.J.A.J., S.B.M., L.C., E.V., S.S.L., C.W.C.K., V.V., J.L.S.) and Medicine (D.J.A.J., V.V.), Faculty of Medicine, University of Toronto, Ontario, Canada; Clinical Nutrition and Risk Factor Modification Centre (D.J.A.J., S.B.M., L.C., C.W.C.K., V.V., J.L.S.), Division of Endocrinology and Metabolism (D.J.A.J., V.V., J.L.S.), and Li Ka Shing Knowledge Institute (D.J.A.J., V.V., J.L.S.), St. Michael's Hospital, Toronto, Ontario, Canada; College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon, Saskatchewan, Canada (C.W.C.K.); School of Medicine, Faculty of Health Sciences, Queen's University, Kingston, Ontario, Canada (S.S.L.); and Toronto 3D Knowledge Synthesis and Clinical Trials Unit, St. Michael's Hospital, Toronto, Ontario, Canada (D.J.A.J., S.B.M., L.C., E.V., C.W.C.K., J.L.S.).

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Clinical Perspective

What Is New?

 The 1999 US Food and Drug Administration heart health claim for soy is now challenged despite the fact that similar heart health claims are allowed for nuts and viscous fibers (ie, oats, barley, and psyllium), with equally modest cholesterol-lowering ability, and also despite the fact that all these foods have entered dietary guidelines for cholesterol control in other jurisdictions.

What Are the Clinical Implications?

• We, therefore, assessed, using a cumulative meta-analysis, whether at any time point since 1999 had soy foods failed to lower serum cholesterol and found that LDL cholesterol reductions for soy protein have consistently been between -4.2 and -6.7 mg/dL (*P*<0.006), with no loss of significance at any time point, so justifying the continued use of soy for health and therapeutic purposes as part of cholesterol-lowering diets.

Methods

This cumulative meta-analysis was conducted according to the *Cochrane Handbook for Systematic Reviews and Interventions*.¹⁰ Standard meta-analysis, heterogeneity, sensitivity, and risk of bias analysis are reported elsewhere.¹¹ This report focuses on the cumulative meta-analysis¹² to answer the question of if and when the soy effect on total cholesterol (TC) and LDL-C was lost. Results have been reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses¹³ guidelines. The authors declare that all supporting data are available within the article or within the online supplementary files of the standard meta-analysis referred to above.¹¹

Data Sources and Study Selection

We included all 46 trials $^{\rm 14-59}$ that the FDA selected $^{\rm 1}$ for the reanalysis.

Data Extraction

Data were extracted by at least 2 independent reviewers (S.B.M., L.C., E.V., or S.S.L.) and entered on a standard proforma. The outcome data included the mean difference between test and control in LDL-C and TC. Plot Digitizer, version 2.6.8,⁶⁰ was used to extract data from graphs, where numerical data were not available and we were unable to obtain original data from authors. Discrepancies in data extraction were resolved through consensus.

Statistical Analysis

A cumulative meta-analysis was performed to monitor the evidence over time and to detect whether the results were influenced by a particular study.^{12,61} We used Review Manager, version 5.3, for analyses. Pooled estimates of the treatment effect were updated every time the result of a new study was published. We tracked the progression of evidence on the effect of soy protein intake on lipid markers to pinpoint if there was a change in outcome since 1999 when the FDA published the final rule for the soy protein heart health claim. The principal effect measure was the mean pairwise difference in change from baseline (or, when not available, the posttreatment value) between the soy intervention arm and the comparator arm. We extracted the mean differences and corresponding 95% CIs for each outcome. Change from baseline differences was preferred over end differences, and paired analyses were applied to all crossover trials with the use of a within-individual correlation coefficient between treatments of 0.5, as described by Elbourne and colleagues.⁶² Data were pooled in a cumulative manner using the generic inverse variance method with a random-effects model and expressed as cumulative mean differences with 95% Cls.

Results

Of the 46 FDA-selected studies, 2 reported data on neither TC nor LDL-C^{17,24} and 1 was a substudy of a larger study already included,⁵³ leaving 43 trials (Figure S1). The median age of the 2607 participants included in the 43 trials for which TC or LDL-C was available was 55 years; 37% were men, and 49% had hypercholesterolemia. Hypercholesterolemia was defined by the FDA as >240 mg/L for TC or >160 mg/L for LDL-C.¹ The median soy protein dose was 25 g/d, with a median follow-up of 6 weeks.

The cumulative forest plots for both TC and LDL-C showed a similar pattern. A significant reduction in TC with soy protein was seen in 1999, at the time of the FDA heart health claim, of -4.5 mg/dL (95% Cl, -8.1 to -1.0 mg/dL; P=0.01). Significance was maintained over the following 14 years and ranged from a minimum reduction of -4.0 mg/dL (95% Cl, -6.7 to -1.3 mg/dL; P=0.004) in 2001 to a maximum reduction of -7.7 mg/dL (95% Cl, -11.2 to -4.3 mg/dL; P<0.0008) in 2006 (Figure 1). The corresponding effect estimate for LDL-C was -6.3 mg/dL (95% Cl, -8.7 to -3.9 mg/dL; P<0.00001) in 1999; and in the following 14 years, the estimates ranged from a minimum reduction of -4.2 mg/dL (95% Cl, -6.6 to -1.8 mg/dL; P=0.0006) in 2006 to a maximum reduction of -6.7 mg/dL (95% Cl, -10.2 to -3.2 mg/dL; P=0.0002)

Study, real	50y, N	N	cunuativen		ing/utj P-value
van Raaij et al. 1981 ⁵⁶	20	25	-6.20 [-9.13, -3.27]	_	<0.0001
Goldberg et al. 1982 - Hypercholesterolemics ²³	12	12	-6.39 [-9.24, -3.54]		<0.0001
Goldberg et al. 1982 - Normolinidemics ²³	4	4	-6.30 [-9.14, -3.47]		<0.0001
Bosello et al. 1988 ¹⁶	12	12	-6.68 [-9.46, -3.90]		<0.00001
lenkins et al 1989 ³⁶	11	11	-6.83 [-9.60, -4.06]		<0.00001
Pathitist at 1004 Callulace ¹⁴	21	21	6 99 [9 57 . 4 21]		<0.00001
Bakhit et al. 1994 - Cellulose	21	21	-6.26 [-9.76, -2.96]		0.00001
Baknit et al. 1994 - Cotyledon	22	21	-6.15 [-8.71, -3.60]		<0.0002
Wang at al 1999 Normachalastaralamis ⁵⁹	13	13	-6.23 [-8.73 -3.74]		<0.00001
Wong et al. 1998 - Normocholesterolemic	13	12	6 27 [9 75 2 70]		<0.00001
wong et al. 1998 - Hypecholesterolemic	15	15	-0.27 [-8.73, -3.79]		<0.00001
Washburn et al. 1999"	42	42	-6.33 [-8.74, -3.92]		Initial FDA Claim <0.00001
Takatsuka et al. 2000 ⁵¹	27	25	-6.44 [-8.76, -4.13]		<0.00001
Jenkins et al. 2000 ⁵⁵	24	24	-6.46 [-8.76, -4.17]	_	<0.00001
Van Horn et al. 2001 - Oats ³³	32	32	-6.33 [-8.60, -4.07]	_	<0.00001
Van Horn et al. 2001 - Wheat ⁵⁵	31	32	-6.13 [-8.37, -3.90]		<0.00001
Teede et al. 2001 ⁵²	86	93	-6.03 [-8.09, -3.97]		<0.00001
Gardner et al. 2001 ²¹	64	30	-5.31 [-7.28, -3.35]		<0.00001
Higashi et al. 2001 ²⁷	14	14	-5.25 [-7.20, -3.30]		<0.00001
Hori et al. 2001 ³²	14	7	-6.20 [-9.70, -2.71]		0.0005
Jayagopal et al. 2002 ³³	31	31	-6.69 [-10.15, -3.23]		0.0002
Jenkins et al. 2002 ³⁴	41	41	-6.16 [-9.62, -2.70]	—	0.0005
Lichtenstein et al. 2002 - No Isoflavones ³⁸	42	42	-6.01 [-9.34, -2.68]		0.0004
Lichtenstein et al. 2002 - Isoflavones ³⁸	42	42	-5.97 [-9.19, -2.75]	—	0.0003
Steinberg et al. 2003 ⁵⁰	24	24	-5.72 [-8.75, -2.69]	_	0.0002
Murray et al. 200347	16	14	-5.74 [-8.71, -2.77]	_	0.0002
Blum et al. 2003 ¹⁵	24	24	-5.33 [-8.29, -2.37]	_	0.0004
Cuevas et al. 2003 ¹⁹	18	18	-5.17 [-8.04, -2.29]		0.0004
Teixeira et al. 2004 ⁵⁴	14	14	-4.94 [-7.58, -2.30]		0.0002
Harrison et al. 2004 ²⁶	103	110	-4.66 [-7.35, -1.97]	_	0.0007
Greany et al. 2004 ²⁵	72	71	-4.64 [-7.19, -2.09]	_	0.0004
West et al. 2005 ⁵⁸	32	32	-4.46 [-6.92, -2.01]	_	0.0004
Hoje et al. 2005 - A double-blind ²⁸	78	38	-5.10 [-7.66, -2.55]	_	<0.0001
Hole et al. 2005 - Linid Iowering ²⁹	78	39	-5.47 [-7.97, -2.96]		<0.0001
Ma et al. 2005 ⁴⁰	81	78	-5.13 [-7.60, -2.66]		<0.0001
Hole et al. 2005 - Active treatment 1 ³⁰	20	20	-4 79 [-7 24 -2 34]		0.0001
Hole et al. 2006 - Active treatment 1	20	20	-4.77 [-7.13, -2.42]		<0.0001
Kohno et al. 2006 - Test 2 ^{†37}	42	46	-4 64 [-6 94 -2 34]		-0.0001
Kohno et al. 2005 Test 1 ^{†37}	59	55	-4 19 [-6 57 -1 81]		<0.0001
Konno et al. 2006-rest 1	35	25	4.10 [-0.57, -1.81]		0.0008
Nicveign et al. 2006	35	55	-4.40 [-0.09, -2.11]		0.0002
Chen et al. 2006	13	13	-4.64 [-6.96, -2.33]		<0.0001
Gardner et al. 2007	28	28	-4.78 [-7.04, -2.52]		<0.0001
Evans et al. 2007	22	22	-4.57 [-6.81, -2.34]		<0.0001
Hoie et al. 2007	60	28	-4.82 [-7.01, -2.62]		<0.0001
Maesta et al. 2007 - Soy + resistance exercise ⁴¹	14	11	-4.83 [-7.00, -2.67]		<0.0001
Maesta et al. 2007 - Soy ⁴¹	10	11	-5.01 [-7.16, -2.86]		<0.00001
Matthan et al. 2007	28	28	-4.96 [-7.06, -2.86]		<0.00001
Santo et al. 2008"	21	9	-4.90 [-6.99, -2.82]		<0.00001
Liu et al. 2012 ⁵⁷	60	120	-4.86 [-6.88, -2.83]		<0.00001
Mangano et al. 2013 - Soy + placebo**	24	22	-4.78 [-6.78, -2.79]		<0.00001
Mangano et al. 2013 - Soy + isoflavone**	25	26	-4./0[-6./1, -2.80]		<0.00001
				-10 -8 -6 -4 -2 -4	2 4 5 9 10
				Reneficial Effect	Harmful Effect
				beneficial Effect	

Figure 1. Cumulative forest plot for the effect of soy protein intake on low-density lipoprotein cholesterol (LDL-C). Cumulative effect is represented by red diamonds. *Total n=37, but reported n=71 for soy protein diets and n=72 for milk protein diets. [†]Twelve subjects were excluded in data analysis in test 1 and 7 in test 2, but it was not specified from which arm; and a 50% dropout rate was taken from each. Data are expressed as cumulative mean differences with 95% Cls.

in 2002 (Figure 2). At no point over the 14 years since the initial FDA heart health claim did the significance level for either TC or LDL-C fall below P=0.002 (Figures 1 and 2),

nor was there a significant deviation at any time from the values of 1999, at the time when the FDA soy heart health claim was granted (Figures 1 and 2).

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Study, Year	Soy, N	Comparator, N	C	umulative mean difference [95% CI] in TC [mg/dL]	P-value
van Raaij et al. 1981 ⁵⁶	20	25	0.00 [-4.06, 4.06]	_	1.00
Goldberg et al. 1982 - Hypercholesterolemics ²³	12	12	-1.73 [-8.19, 4.73]		0.60
Goldberg et al. 1982 - Normolipidemics ²³	4	4	-0.82 [-4.59, 2.96]	• • • • • • • • • • • • • • • • • • •	0.67
Bosello et al. 1988 ¹⁵	12	12	-5.89 [-14.59, 2.80]	• • • • • • • • • • • • • • • • • • •	0.18
Jenkins et al.1989 ³⁶	11	11	-6.49 [-13.98, 1.01]		0.09
Bakhit et al. 1994 - Cellulose ¹⁴	21	21	-6.44 [-12.55, -0.32]	+	0.04
Bakhit et al. 1994 - Cotyledon ¹⁴	21	21	-4.82 [-9.92, 0.28]		0.06
Murkies et al. 1995 ⁴⁶	23	24	-4.32 [-8.92, 0.28]		0.07
Wong et al. 1998 - Hypecholesterolemic ⁵⁹	13	13	-4.16 [-8.34, 0.02]		0.05
Wong et al.1998 - Normocholesterolemic ⁵⁹	13	13	-3.84 [-7.59, -0.10]	_	0.04
Mitchell and Collins 1999 ⁴⁵	4	6	-3.27 [-6.59, 0.05]	Initial FDA Claim	0.05
Washburn et al. 1999 ⁵⁷	42	42	-4.53 [-8.08, -0.99]		0.01
Takatsuka et al. 2000 ⁵¹	27	25	-5.82 [-9.51, -2.13]		0.002
Jenkins et al. 2000 ³⁵	25	25	-5.62 [-9.07, -2.17]		0.001
Teede et al. 2001 ⁵²	86	93	-5.29 [-8.26, -2.33]		0.0005
Van Horn et al. 2001 - Wheat ⁵⁵	31	32	-4.84 [-7.64, -2.04]		0.0007
Van Horn et al. 2001 - Oats ⁵⁵	32	32	-4.45 [-7.13, -1.78]	_	0.001
Higashi et al. 2001 ²⁷	14	14	-4.17 [-6.63, -1.72]	_	0.0009
Gardner et al. 2001	64	30	-3.99 [-6.70, -1.27]	_	0.004
Hori et al. 2001 ³²	14	7	-5.85 [-9.52, -2.17]		0.002
Lichtenstein et al. 2002 - Isoflavones ³⁸	42	42	-5.83 [-9.38, -2.29]	_	0.001
Lichtenstein et al. 2002 - No Isoflavones ³⁸	42	42	-5.72 [-9.14, -2.29]		0.001
Jayagopal et al. 2002 ³³	31	31	-6.12 [-9.52, -2.72]		0.0004
Jenkins et al. 2002 ³⁴	41	41	-6.30 [-9.56, -3.05]	—	0.0001
Steinberg et al. 2003 ⁵⁰	24	24	-6.16 [-9.24, -3.08]		<0.0001
Murray et al. 2003 ⁴⁷	16	14	-5.86 [-8.88, -2.84]		0.0001
Blum et al. 2003	24	24	-5.58 [-8.52, -2.63]		0.0002
Cuevas et al. 2003 ¹⁹	18	18	-5.48 [-8.34, -2.62]		0.0002
Teixeira et al. 2004 ⁵⁴	14	14	-5.38 [-8.07, -2.70]		<0.0001
Sagara et al. 200448	25	25	-5.46 [-8.09, -2.84]		<0.0001
Greany et al. 2004 ²⁵	72	71	-5.35 [-7.85, -2.85]		<0.0001
Harrison et al. 2004 ²⁶	103	110	-4.86 [-7.45, -2.26]		0.0002
West et al. 2005 ⁵⁸	32	32	-4.69 [-7.17, -2.21]		0.0002
Hoie et al. 2005 - Lipid lowering ²⁹	78	39	-5.25 [-7.79, -2.70]		<0.0001
Hoie et al. 2005 - A double-blind ²⁸ Ma et al. 2005 ⁴⁰	78 81	38 78	-5.91 [-8.60, -3.23] -5.73 [-8.31, -3.15]		<0.0001 <0.0001
Malerian 2005		25	746[40.52, 2.01]		-0.0001
Chap at al. 2006	30	35	-7.10 [-10.52, -3.81]		<0.0001
Kabas at al. 2006 Tast 2 ^{†37}	15	15	-7.75 [-11.15, -4.50]		0.0001
Kohno et al. 2006 - Test 2	59	55	-7.35 [-10.73, -3.97]		<0.0001
Nonno et al. 2006 - Test 1	42	40	-7.12 [-10.43, -3.80]		<0.0001
Hole et al. 2006 - Active treatment 1	20	20	-6.80 [-10.06, -3.55]		<0.0001
Matthan et al. 2007 ⁴³	28	28	-6.73 [-9.85, -3.61]		<0.0001
Gardner et al. 2007 ²²	28	28	-6 70 [-9 79 -3 60]		<0.0001
Evans et al. 2007 ²⁰	22	20	-6.39 [-9.45, -3.33]	_	<0.0001
Maesta et al. 2007 - Soy ⁴¹	10	11	-6.76 [-9.83, -3.69]		<0.0001
Maesta et al. 2007 - Soy + resistance exercise ⁴¹	14	11	-6.55 [-9.58, -3.51]	_	<0.0001
Hoie et al. 2007 ³¹	60	28	-6.93 [-9.98, -3.87]	_	<0.00001
Santo et al. 200849	21	9	-6.56 [-9.65, -3.48]	_	<0.0001
Liu et al. 2012 ³⁹	60	120	-6.44 [-9.44, -3.44]	_	<0.0001
Mangano et al. 2013 - Soy + placebo ⁴²	24	22	-6.44 [-9.38, -3.49]	_	<0.0001
Mangano et al. 2013 - Soy + isoflavone ⁴²	25	26	-6.41 [-9.30, -3.52]		<0.0001
				-14 -12 -10 -8 -6 -4 -2 0 2 4 6 8 10 12 14 Beneficial Effect Harmful Effect	1

Figure 2. Cumulative forest plot for the effect of soy protein intake on total cholesterol (TC). Cumulative effect is represented by red diamonds. *Total n=37, but reported n=71 for soy protein diets and n=72 for milk protein diets. [†]Twelve subjects were excluded in data analysis in test 1 and 7 in test 2, but it was not specified from which arm; and a 50% dropout rate was taken from each. Data are expressed as cumulative mean differences with 95% Cls.

Discussion

The FDA proposes to revoke the heart health claim status granted for soy in 1999^2 ; however, the cumulative meta-

analyses of the same data that the FDA is basing this decision on show no inflections that would suggest a significant departure from the effect present at the time when the FDA granted the original health claim for soy in 1999.² A major concern is that if the FDA is now to use this same approach (on the basis of its 2009 ruling)⁶³ for the remaining heart health claims, then the claims for nuts, viscous fibers (ie, oats, barley, and psyllium), and plant sterols could also be revoked because these effects on serum cholesterol are also modest and variable in terms of individual study statistical significance.

Such a move will reduce public awareness of useful foods for cholesterol control. We have shown that in combination under metabolically controlled conditions, as a dietary portfolio, these foods may reduce LDL-C and CRP (C-reactive protein) similarly to a statin (lovastatin) by ~30%.⁹ This dietary portfolio^{8,64,65} that specifically includes the FDA heart health claim approved foods has now entered the dietary guidelines of the Canadian Cardiovascular Society,⁶⁶ Heart UK,⁶⁷ and The European Atherosclerosis Society Guidelines for the Treatment of Statin Associated Muscle Symptoms⁶⁸ and was mentioned originally in the 2004 National Cholesterol Education Program Adult Treatment Panel-III update.⁶⁹

The FDA has, in fact, led the field internationally in providing cardiovascular disease risk reduction health claims. Agencies in other jurisdictions (eg, Health Canada and European Food Safety Authority) have followed the FDA's lead in initiating health claims for various foods or food components. Health Canada approved a cholesterol-lowering claim for soy as recently as 2016.⁷⁰

In taking its current action, the FDA found 238 intervention studies, of which it considered 58 to be well-designed studies, 12 that mentioned blood pressure and 46 that mentioned blood TC or LDL-C.¹ However, studies were eliminated if they had no control group, there was no statistical comparison between the test and control group, total fat intakes were different between treatments, or the saturated fat, dietary cholesterol, and fiber were not balanced between the test and control arms. The level of tolerance for differences between treatments in these nutrients was not defined, and it may be that otherwise reasonable studies with small treatment differences in fiber or dietary cholesterol might still have been acceptable and have strengthened the conclusions. Furthermore, some negative studies were included, such as the one by Jenkins et al,³⁵ in which soy flour was added to high-temperature extruded breakfast cereal, that may have resulted in possible damage to soy protein structure and the formation of browning reaction products between the starch and soy amino acids. These interactions may have reduced the effectiveness of soy protein. Nevertheless, despite inclusion of such studies, the overall soy effect persisted over time.

The soy health claims may be particularly important at a time when government agencies worldwide are suggesting more plant foods,^{71–74} and especially plant protein foods,⁷⁵ should be consumed. Soy provides an important plant protein source.

The weakness of this study is that it is not a systematic review (followed by a meta-analysis) because no systematic review of the literature was undertaken, but rather the 46 studies identified by the FDA for their determination were used without prior selection and comprehensive review of the literature by the authors. It may also be questioned how easy it is to consume 25 g of soy protein daily. A total of 7 g of soy protein can be obtained by a cup of most soy milks (some, such as Eden Soy, provide 12 g soy protein/cup), soy yogurts contain up to 9 g/cup and Greek-style soy yogurts even more, the average soy burger provides ≈ 12 g soy protein/patty, and extrafirm tofu has just >14 g soy protein in 3 oz, so the daily dose could be obtained from a cup of soy milk, half a cup of yogurt, and 3 oz of extrafirm tofu as a meat replacement.

The strength of this study is that it used the exact data on which the FDA is basing its judgment. Furthermore, a cumulative meta-analysis was undertaken to determine when, or if, the TC or LDL-C reductions lost significance.

We conclude that soy continues to have a significant, if modest, effect in reducing serum LDL-C as a cardiovascular disease risk factor. The effect of soy alone is modest, but it may produce a clinically meaningful reduction when combined in the diet with other FDA-approved cholesterol-lowering foods. Furthermore, at a time when plant protein sources are required, soy protein provides a useful plant protein source for the food industry, with a range of applications and with the production of heart healthy foods being one of them.

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Disclosures

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Supplemental Material

Figure S1. Study selection indicating the number of studies identified by the FDA and the number of studies included in the meta-analysis.



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