SUPPLEMENTARY DATA

Supplemental Table 1: *A priori* sensitivity analysis by the systematic removal of each trial on circulating LDL-C and TC concentrations in adults.

Study, year (reference)	Soy, *n*	Comparator, *n*	Weight	MD [95% CIs][1]	*P*[1]	*I*[2][1]	*P*-heterogeneity[1]
Overall effect on circulating LDL concentration in adults	**1,661**	**1,567**	**100%**	**-4.76 [-6.71, -2.80]**	**<0.0001**	**55%**	**<0.0001**
Bakhit et al. 1994 (12)- Cotyledon	21	21	2.2%	-4.90 [-6.87, -2.92]	<0.0001	55%	<0.0001
Bakhit et al.1994 (12)- Cellulose	21	21	2.0%	-4.70 [-6.68, -2.71]	<0.0001	56%	<0.0001
Blum et al. 2003 (13)	24	24	1.7%	-4.93 [-6.89, -2.97]	<0.0001	55%	<0.0001
Bosello et al. 1988 (14)	12	12	1.3%	-4.60 [-6.56, -2.64]	<0.0001	55%	<0.0001
Chen et al. 2006 (16)	13	13	0.9%	-4.58 [-6.51, -2.65]	<0.0001	55%	<0.0001
Cuevas et al. 2003 (17)	18	18	1.4%	-4.81 [-6.79, -2.84]	<0.0001	56%	<0.0001
Evans et al. 2007 (18)	22	22	2.2%	-4.93 [-6.89, -2.96]	<0.0001	55%	<0.0001
Gardner et al. 2001 (20)	64	30	3.0%	-4.96 [-6.93, -3.00]	<0.0001	54%	<0.0001
Gardner et al. 2007 (19)	28	28	2.6%	-4.64 [-6.64, -2.65]	<0.0001	56%	<0.0001
Goldberg et al. 1982 (21)- Hypercholesterolemics	12	12	1.6%	-4.67 [-6.65, -2.70]	<0.0001	56%	<0.0001
Goldberg et al. 1982 (21)- Normolipidemics	4	4	0.4%	-4.79 [-6.75, -2.82]	<0.0001	56%	<0.0001
Greany et al. 2004 (23)	72	71	2.8%	-4.76 [-6.76, -2.76]	<0.0001	56%	<0.0001
Harrison et al. 2004 (24)	103	110	0.9%	-4.91 [-6.85, -2.98]	<0.0001	55%	<0.0001
Higashi et al. 2001 (25)	14	14	1.4%	-4.79 [-6.77, -2.82]	<0.0001	56%	<0.0001
Hoie et al. 2005 (26)	78	38	3.3%	-4.41 [-6.32, -2.50]	<0.0001	51%	<0.0001
Hoie et al. 2005 (27)	78	39	3.2%	-4.52 [-6.49, -2.55]	<0.0001	54%	<0.0001
Hoie et al. 2006 (28)- Active treatment 1	20	20	3.2%	-4.98 [-6.94, -3.02]	<0.0001	54%	<0.0001
Hoie et al. 2006 (28)- Active treatment 2	20	20	2.9%	-4.76 [-6.77, -2.76]	<0.0001	56%	<0.0001
Hoie et al. 2007 (29)	60	28	3.4%	-4.53 [-6.51, -2.56]	<0.0001	54%	<0.0001
Hori et al. 2001 (30)	14	7	0.6%	-4.45 [-6.21, -2.69]	<0.0001	45%	<0.001
Jayagopal et al. 2002 (31)	31	31	1.4%	-4.58 [-6.54, -2.63]	<0.0001	55%	<0.0001
Jenkins et al. 2000 (33)	24	24	0.8%	-4.73 [-6.70, -2.76]	<0.0001	56%	<0.0001
Jenkins et al. 2002 (32)	41	41	1.4%	-4.92 [-6.87, -2.97]	<0.0001	55%	<0.0001
Jenkins et al.1989 (34)	11	11	0.4%	-4.68 [-6.63, -2.72]	<0.0001	56%	<0.0001
Kohno et al. 2006 (35)-Test 1	59	55	2.5%	-5.11 [-7.00, -3.23]	<0.0001	51%	<0.0001
Kohno et al. 2006 (35)-Test 2	42	46	2.3%	-4.85 [-6.83, -2.86]	<0.0001	56%	<0.0001
Lichenstein et al. 2002 (36)- Isoflavones	42	42	1.3%	-4.74 [-6.72, -2.76]	<0.0001	56%	<0.0001
Lichenstein et al. 2002 (36)- No Isoflavones	42	42	1.4%	-4.78 [-6.76, -2.80]	<0.0001	56%	<0.0001
Liu et al. 2012 (37)	60	120	3.0%	-4.80 [-6.80, -2.79]	<0.0001	56%	<0.0001
Ma et al. 2005 (38)	81	78	3.0%	-4.95 [-6.92, -2.98]	<0.0001	54%	<0.0001

SUPPLEMENTARY DATA

Study, year (reference)	Soy, *n*	Comparator, *n*	Weight	MD [95% CIs][1]	*P*[1]	*I*[2][1]	*P*-heterogeneity[1]
Maesta et al. 2007 (39)- Soy	10	11	1.7%	-4.59 [-6.56, -2.63]	<0.0001	55%	<0.0001
Maesta et al. 2007 (39)- Soy + resistance exercise	14	11	0.9%	-4.74 [-6.71, -2.77]	<0.0001	56%	<0.0001
Mangano et al. 2013 (40)- Soy + isoflavone	25	26	2.3%	-4.78 [-6.78, -2.79]	<0.0001	56%	<0.0001
Mangano et al. 2013 (40)- Soy + placebo	24	22	2.1%	-4.82 [-6.81, -2.84]	<0.0001	56%	<0.0001
Matthan et al. 2007 (41)	28	28	2.6%	-4.80 [-6.80, -2.80]	<0.0001	56%	<0.0001
McVeigh et al. 2006 (42)	35	35	3.7%	-4.60 [-6.61, -2.59]	<0.0001	55%	<0.0001
Murkies et al. 1995 (44)	23	24	0.8%	-4.80 [-6.77, -2.83]	<0.0001	56%	<0.0001
Murray et al. 2003 (45)	16	14	0.5%	-4.73 [-6.70, -2.77]	<0.0001	56%	<0.0001
Santo et al. 2008 (47)	21	9	0.5%	-4.80 [-6.77, -2.84]	<0.0001	56%	<0.0001
Steinberg et al. 2003 (48)	24	24	2.7%	-4.81 [-6.81, -2.81]	<0.0001	56%	<0.0001
Takatsuka et al. 2000 (49)	27	25	2.5%	-4.68 [-6.67, -2.68]	<0.0001	56%	<0.0001
Teede et al. 2001 (50)	86	93	3.4%	-4.74 [-6.76, -2.71]	<0.0001	56%	<0.0001
Teixeira et al. 2004 (52)	14	14	3.6%	-4.82 [-6.85, -2.79]	<0.0001	56%	<0.0001
Van Horn et al. 2001 (53)- Oats	32	32	1.4%	-4.80 [-6.78, -2.82]	<0.0001	56%	<0.0001
Van Horn et al. 2001 (53)- Wheat	31	32	1.4%	-4.84 [-6.81, -2.87]	<0.0001	56%	<0.0001
van Raaij et al. 1981 (54)	20	25	4.1%	-4.71 [-6.79, -2.62]	<0.0001	56%	<0.0001
Washbum et al. 1999 (55)	42	42	2.0%	-4.70 [-6.69, -2.72]	<0.0001	56%	<0.0001
West et al. 2005 (56)	32	32	2.5%	-4.85 [-6.84, -2.86]	<0.0001	56%	<0.0001
Wong et al.1998 (57)- Hypecholesterolemic	13	13	0.9%	-4.72 [-6.69, -2.75]	<0.0001	56%	<0.0001
Wong et al.1998 (57)- Normocholesterolemic	13	13	1.6%	-4.70 [-6.68, -2.72]	<0.0001	56%	<0.0001
Overall effect on circulating TC concentration in adults	**1,691**	**1,599**	**100%**	**-6.41 [-9.30, -3.52]**	**<0.0001**	**74%**	**<0.0001**
Bakhit et al. 1994 (12)- Cotyledon	21	21	2.2%	-6.59 [-9.53, -3.65]	<0.0001	74%	<0.0001
Bakhit et al.1994 (12)- Cellulose	21	21	2.2%	-6.38 [-9.33, -3.43]	<0.0001	75%	<0.0001
Blum et al. 2003 (13)	24	24	1.8%	-6.57 [-9.50, -3.64]	<0.0001	74%	<0.0001
Bosello et al. 1988 (14)	12	12	1.6%	-6.19 [-9.10, -3.29]	<0.0001	74%	<0.0001
Chen et al. 2006 (16)	13	13	1.4%	-6.00 [-8.85, -3.15]	<0.0001	73%	<0.0001
Cuevas et al. 2003 (17)	18	18	1.6%	-6.47 [-9.40, -3.54]	<0.0001	75%	<0.0001
Evans et al. 2007 (18)	22	22	2.1%	-6.67 [-9.59, -3.76]	<0.0001	74%	<0.0001
Gardner et al. 2001 (20)	64	30	2.5%	-6.68 [-9.60, -3.75]	<0.0001	74%	<0.0001
Gardner et al. 2007 (19)	28	28	1.0%	-6.44 [-9.35, -3.52]	<0.0001	75%	<0.0001
Goldberg et al. 1982 (21)- Hypercholesterolemics	12	12	1.9%	-6.38 [-9.32, -3.45]	<0.0001	75%	<0.0001
Goldberg et al. 1982 (21)- Normolipidemics	4	4	1.4%	-6.48 [-9.40, -3.55]	<0.0001	75%	<0.0001
Greany et al. 2004 (23)	72	71	2.3%	-6.47 [-9.43, -3.51]	<0.0001	75%	<0.0001

SUPPLEMENTARY DATA

Study, year (reference)	Soy, *n*	Comparator, *n*	Weight	MD [95% CIs][1]	*P*[1]	*I*[2][1]	*P*-heterogeneity[1]
Harrison et al. 2004 (24)	103	110	2.5%	-6.73 [-9.63, -3.83]	<0.0001	73%	<0.0001
Higashi et al. 2001 (25)	14	14	1.7%	-6.42 [-9.36, -3.49]	<0.0001	75%	<0.0001
Hoie et al. 2005 (26)	78	38	2.5%	-6.11 [-8.99, -3.22]	<0.0001	73%	<0.0001
Hoie et al. 2005 (27)	78	39	2.6%	-6.24 [-9.19, -3.29]	<0.0001	74%	<0.0001
Hoie et al. 2006 (28)- Active treatment 1	20	20	2.4%	-6.65 [-9.58, -3.72]	<0.0001	74%	<0.0001
Hoie et al. 2006 (28)- Active treatment 2	20	20	1.5%	-6.36 [-9.29, -3.44]	<0.0001	75%	<0.0001
Hoie et al. 2007 (29)	60	28	2.3%	-6.05 [-8.92, -3.18]	<0.0001	73%	<0.0001
Hori et al. 2001 (30)	14	7	1.3%	-5.94 [-8.75, -3.12]	<0.0001	73%	<0.0001
Jayagopal et al. 2002 (31)	31	31	1.8%	-6.26 [-9.18, -3.34]	<0.0001	74%	<0.0001
Jenkins et al. 2000 (33)	24	24	1.2%	-6.40 [-9.32, -3.48]	<0.0001	75%	<0.0001
Jenkins et al. 2002 (32)	41	41	2.3%	-6.34 [-9.29, -3.39]	<0.0001	74%	<0.0001
Jenkins et al.1989 (34)	11	11	1.7%	-6.34 [-9.27, -3.41]	<0.0001	75%	<0.0001
Kohno et al. 2006 (35)-Test 1	59	55	2.2%	-6.67 [-9.59, -3.75]	<0.0001	74%	<0.0001
Kohno et al. 2006 (35)-Test 2	42	46	2.1%	-6.57 [-9.51, -3.64]	<0.0001	74%	<0.0001
Lichenstein et al. 2002 (36)- Isoflavones	42	42	1.5%	-6.41 [-9.33, -3.48]	<0.0001	75%	<0.0001
Lichenstein et al. 2002 (36)- No Isoflavones	42	42	1.5%	-6.45 [-9.38, -3.53]	<0.0001	75%	<0.0001
Liu et al. 2012 (37)	60	120	2.5%	-6.53 [-9.50, -3.56]	<0.0001	74%	<0.0001
Ma et al. 2005 (38)	81	78	2.5%	-6.53 [-9.50, -3.56]	<0.0001	74%	<0.0001
Maesta et al. 2007 (39)- Soy	10	11	2.1%	-6.09 [-8.98, -3.20]	<0.0001	73%	<0.0001
Maesta et al. 2007 (39)- Soy + resistance exercise	14	11	1.6%	-6.60 [-9.52, -3.69]	<0.0001	74%	<0.0001
Mangano et al. 2013 (40)- Soy + isoflavone	25	26	2.1%	-6.44 [-9.38, -3.49]	<0.0001	75%	<0.0001
Mangano et al. 2013 (40)- Soy + placebo	24	22	2.1%	-6.42 [-9.36, -3.47]	<0.0001	75%	<0.0001
Matthan et al. 2007 (41)	28	28	2.3%	-6.50 [-9.46, -3.54]	<0.0001	75%	<0.0001
McVeigh et al. 2006 (42)	35	35	2.3%	-5.47 [-7.91, -3.02]	<0.0001	62%	<0.0001
Mitchell and Collins 1999 (43)	4	6	0.2%	-6.40 [-9.30, -3.50]	<0.0001	75%	<0.0001
Murkies et al. 1995 (44)	23	24	1.3%	-6.48 [-9.40, -3.56]	<0.0001	75%	<0.0001
Murray et al. 2003 (45)	16	14	1.7%	-6.58 [-9.50, -3.66]	<0.0001	74%	<0.0001
Sagara et al. 2004 (46)	25	25	1.6%	-6.36 [-9.29, -3.43]	<0.0001	75%	<0.0001
Santo et al. 2008 (47)	21	9	0.9%	-6.74 [-9.60, -3.88]	<0.0001	74%	<0.0001
Steinberg et al. 2003 (48)	24	24	2.3%	-6.45 [-9.40, -3.49]	<0.0001	75%	<0.0001
Takatsuka et al. 2000 (49)	27	25	2.3%	-6.29 [-9.23, -3.34]	<0.0001	74%	<0.0001
Teede et al. 2001 (50)	86	93	2.5%	-6.43 [-9.41, -3.45]	<0.0001	75%	<0.0001
Teixeira et al. 2004 (52)	14	14	2.5%	-6.45 [-9.43, -3.47]	<0.0001	75%	<0.0001

SUPPLEMENTARY DATA

Study, year (reference)	Soy, *n*	Comparator, *n*	Weight	MD [95% CIs][1]	*P*[1]	I^2[1]	*P*-heterogeneity[1]
Van Horn et al. 2001 (53)- Oats	32	32	2.0%	-6.57 [-9.50, -3.64]	<0.0001	74%	<0.0001
Van Horn et al. 2001 (53)- Wheat	31	32	2.0%	-6.55 [-9.49, -3.62]	<0.0001	74%	<0.0001
van Raaij et al. 1981 (54)	20	25	2.8%	-6.60 [-9.60, -3.60]	<0.0001	73%	<0.0001
Washbum et al. 1999 (55)	42	42	2.1%	-6.32 [-9.26, -3.38]	<0.0001	74%	<0.0001
West et al. 2005 (56)	32	32	2.4%	-6.52 [-9.48, -3.56]	<0.0001	74%	<0.0001
Wong et al.1998 (57)- Hypecholesterolemic	13	13	1.4%	-6.41 [-9.33, -3.48]	<0.0001	75%	<0.0001
Wong et al.1998 (57)- Normocholesterolemic	13	13	1.5%	-6.42 [-9.34, -3.49]	<0.0001	75%	<0.0001

[1]Data values post removal of that specific study. For the pooled effect estimates, $P<0.05$ is considered significant. $I^2>50\%$ is considered evidence of substantial heterogeneity. *P*-heterogeneity <0.10 is considered significant.

SUPPLEMENTARY DATA

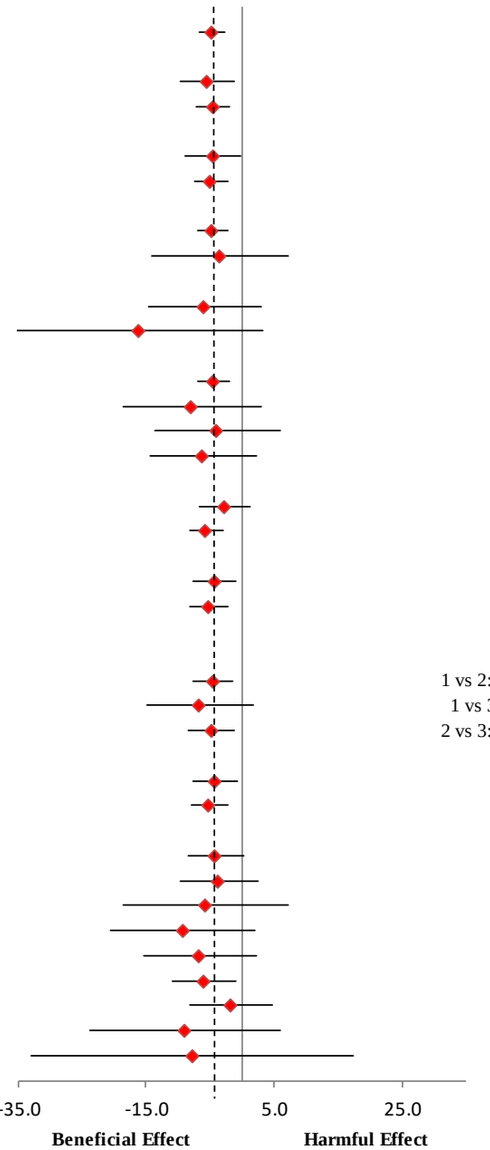
Study, year (reference)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personnel and outcome assessors	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Bakhit et al., 1994 (12)- Cellulose	?	?	?	−	+
Bakhit et al., 1994 (12)- Cotyledon	?	?	?	−	+
Blum et al., 2003 (13)	?	?	+	?	+
Bosello et al., 1988 (14)	?	?	+	?	+
Chen et al., 2006 (16)	?	?	+	?	+
Cuevas et al., 2003 (17)	?	?	+	+	?
Evans et al., 2007 (18)	?	+	+	?	+
Gardner et al., 2001 (20)	+	+	+	+	+
Gardner et al., 2007 (19)	+	+	+	+	+
Goldberg et al., 1982 (21)- Hypercholesterolemics	+	?	+	+	+
Goldberg et al., 1982 (21)- Normolipidemics	+	?	+	+	+
Greany et al., 2004 (23)	?	?	?	?	+
Harrison et al., 2004 (24)	+	+	+	+	+
Higashi et al., 2001 (25)	?	?	?	?	?
Hoie et al., 2005 (26)	+	?	+	?	+
Hoie et al., 2005 (27)	+	?	+	+	+
Hoie et al., 2006 (28)- Active treatment 1	?	?	+	+	+
Hoie et al., 2006 (28)- Active treatment 2	?	?	+	+	+
Hoie et al., 2007 (29)	+	?	+	+	+
Hori et al., 2001 (30)	?	+	+	?	?
Jayagopal et al., 2002 (31)	+	+	+	+	+
Jenkins et al.,1989 (34)	?	?	?	+	+
Jenkins et al., 2000 (33)	?	?	+	?	?
Jenkins et al., 2002 (32)	?	?	?	+	?
Kohno et al., 2006 (35)-Test 1	?	+	+	?	+
Kohno et al., 2006 (35)-Test 2	?	+	+	?	+

Study, year (reference)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants, personnel and outcome assessors	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Lichenstein et al., 2002 (36)- Isoflavones	?	?	+	?	?
Lichenstein et al., 2002 (36)- No Isoflavones	?	?	+	?	?
Liu et al., 2012 (37)	+	+	+	+	−
Maesta et al., 2007 (39)- Soy	?	?	+	?	+
Maesta et al., 2007 (39)- Soy + resistance exercise	?	?	+	?	+
Ma et al., 2005 (38)	?	?	+	+	+
Mangano et al., 2013 (40)- Soy + isoflavone	?	+	+	?	+
Mangano et al., 2013 (40)- Soy + placebo	?	+	+	?	+
Matthan et al., 2007 (41)	?	?	+	−	?
McVeigh et al., 2006 (42)	?	?	?	+	+
Mitchell and Collins 1999 (43)	?	?	+	?	?
Murkies et al., 1995 (44)	+	+	+	?	+
Murray et al., 2003 (45)	+	+	+	?	+
Sagara et al., 2004 (46)	?	+	+	+	?
Santo et al., 2008 (47)	?	?	+	−	+
Steinberg et al., 2003 (48)	?	?	+	+	?
Takatsuka et al., 2000 (49)	?	?	?	?	+
Teede et al., 2001 (50)	+	?	+	+	?
Teixeira et al., 2004 (52)	+	?	?	?	?
Van Horn et al., 2001 (53)- Oats	?	+	?	+	+
Van Horn et al., 2001 (53)- Wheat	?	+	?	+	+
van Raaij et al., 1981 (54)	?	?	+	−	?
Washburn et al., 1999 (55)	?	+	+	+	+
West et al., 2005 (56)	?	?	+	+	+
Wong et al.,1998 (57)- Hypecholesterolemic	?	?	+	+	+
Wong et al.,1998 (57)- Normocholesterolemic	?	?	+	+	+

Supplemental Figure 1. Risk of bias for the effect of soy protein on circulating LDL-C and TC concentrations in adults. Studies assess as low risk of bias are represented in green, unclear in yellow and high in red for the 5 domains of bias listed above.

SUPPLEMENTARY DATA

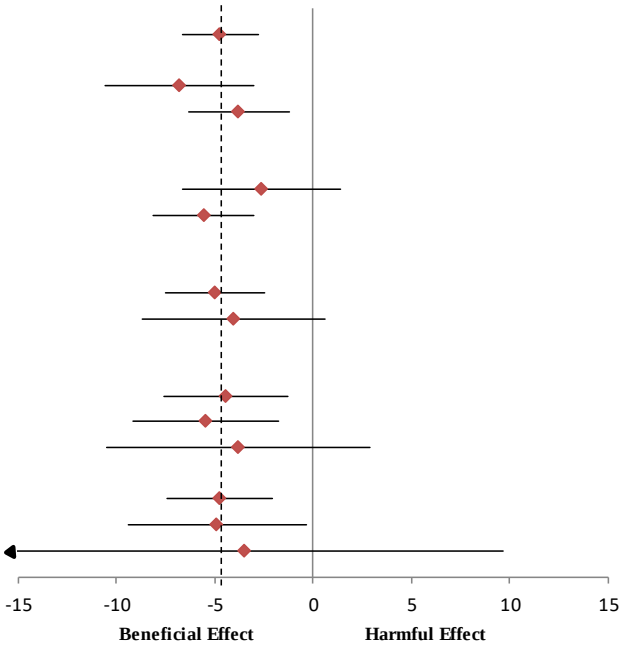
Subgroup	Level	Studies	*n*	Mean difference [95% CI] on circulating LDL-C concentration [mg/dL] in adults: Within subgroups	Between subgroups	Residual I^2	*P*
Total		**50**	**2,547**	**-4.75 [-6.68, -2.82]**	-	-	-
Baseline LDL-C							
	< 135 mg/dL	14	443	-5.39 [-9.57, -1.21]	0.89 [-4.04, 5.81]	55.9%	0.72
	≥ 135 mg/dL	36	2,104	-4.51 [-7.11, -1.89]			
Soy dose							
	< 25 g/d	12	795	-4.52 [-8.90, -0.13]	-0.32 [-5.40, 4.76]	55.8%	0.90
	≥ 25g/d	38	1,752	-4.84 [-7.40, -2.27]			
Soy protein food							
	Isolated soy protein (ISP) [1]	41	2,327	-4.57 [-6.95, -2.20]	See legend	57.0%	0.68
	Soy food [2]	3	100	-3.42 [-14.18, 7.34]			
	Soy milk [3]	0	-	-			
	Mixed [4]	5	96	-5.84 [-14.67, 2.98]			
	Texturized soy protein [5]	1	24	-16.00 [-35.34, 3.34]			
Comparator							
	Dairy protein [1]	35	2,006	-4.53 [-7.02, -2.05]	See legend	57.7%	0.92
	Meat protein [2]	4	42	-7.82 [-18.53, 2.90]			
	Mixed [3]	3	70	-3.82 [-13.62, 5.97]			
	Other [4]	8	429	-6.07 [-14.37, 2.22]			
Follow-up							
	< 6 wk	16	598	-2.72 [-6.79, 1.36]	-2.85[-7.67, 1.97]	55.4%	0.24
	≥ 6 wk	34	1,949	-5.56 [-8.14, -2.99]			
Study design							
	Crossover	24	531	-4.29 [-7.60, -0.99]	-0.83 [-5.29, 3.62]	56.1%	0.71
	Parallel	26	2,016	-5.13 [-8.11, -2.15]			
FDA categories							
Baseline TC or LDL-C							
	Desirable or borderline[1] [1]	25	1,217	-4.48 [-7.59, -1.38]	1 vs 2: -2.11 [-11.01, 6.78]	57.1%	0.89
	Normal, borderline, and high[2] [2]	5	79	-6.60 [-14.94, 1.74]	1 vs 3: -0.30 [-4.99, 4.40]		
	High[3] [3]	20	1,251	-4.78 [-8.31, -1.25]	2 vs 3: -1.82 [-10.87, 7.24]		
How soy protein was provided							
	Feeding or substitution	23	805	-4.18 [-7.63, -0.73]	-0.97 [-5.45, 3.52]	55.9%	0.67
	Added to diet	27	1,742	-5.15 [-8.02, -2.28]			
Baseline TC or LDL-C + how soy protein was provided							
	Desirable or borderline, added ISP [1]	14	844	-4.07 [-8.49, 0.35]	See legend	59.6%	0.95
	Desirable or borderline, feeding or substitution ISP [2]	6	211	-3.66 [-9.77, 2.45]			
	Desirable or borderline, added soy foods [3]	2	99	-5.67 [-18.62, 7.28]			
	Desirable or borderline, feeding or substitution soy foods [4]	3	63	-9.24 [-20.52, 2.03]			
	Normal, borderline, and high, feeding or substitution ISP [5]	5	79	-6.61 [-15.37, 2.15]			
	High, added ISP [6]	10	771	-5.96 [-10.87, -1.04]			
	High, feeding or substitution ISP [7]	8	427	-1.72 [-8.20, 4.77]			
	High, added soy foods [8]	1	28	-9.00 [-23.88, 5.88]			
	High, feeding soy foods [9]	1	25	-7.73 [-32.91, 17.44]			



Supplemental Figure 2. *A priori* subgroup analyses on circulating LDL-C concentration in adults. [1]Desirable or bordeline, TC <240 mg/dL or LDL-C <160 mg/dL. [2]Goldberg et al. 1982 - Normolipidemics comparison is in this category as the FDA listed the study with both comparisons (Normolipidemics and Normolipidemics). [3]High, TC>240 mg/dL or LDL-C>160 mg/dL. Pooled effect estimates for each subgroup level are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis of soy protein on LDL-C. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences [95%] CIs for soy protein food are as follows: 1 vs 2: 1.15 mg/dL [-9.87, 12.17]; 1 vs 3: - ; 1 vs 4: -1.27 mg/dL [-10.41, 7.87]; 1 vs 5: -11.43 mg/dL [-30.91, 8.05]; 2 vs 3: - ; 2 vs 4: 2.42 mg/dL [-11.49, 16.34]; 2 vs 5: 12.58 mg/dL [-9.55, 34.71]; 3 vs 4: - ; 3 vs 5: - ; 4 vs 5: 10.16 mg/dL [-11.10, 31.41]. Pairwise between-subgroup mean differences [95%] CIs for comparator are as follows: 1 vs 2: -3.29 mg/dL [-14.28, 7.71]; 1 vs 3: 0.71 mg/dL [-9.40, 10.81]; 1 vs 4: -1.54 mg/dL [-10.20, 7.12]; 2 vs 3: -3.99 mg/dL [-18.51, 10.52]; 2 vs 4: -1.75 mg/dL [-15.30, 11.80]; 3 vs 4: 2.25 mg/dL[-10.59, 15.08]. Pairwise between-subgroup mean differences [95%] CIs for baseline TC or LDL-C + how soy protein was provided are as follows: 1 vs 2: 0.41 mg/dL [-7.13, 7.95]; 1 vs 3: -1.59 mg/dL [-15.28, 12.09]; 1 vs 4: -5.17 mg/dL [-17.28, 6.94]; 1 vs 5: -2.54 mg/dL [-12.35, 7.28]; 1 vs 6: -1.89 mg/dL [-8.50, 4.72]; 1 vs 7: 2.36 mg/dL [-5.49, 10.20]; 1 vs 8: -4.93 mg/dL [-20.45, 10.60]; 1 vs 9: -3.66 mg/dL [-29.22, 21.90]; 2 vs 3: 2.00 mg/dL [-12.32, 16.32]; 2 vs 4: 5.58 mg/dL [-7.25, 18.41]; 2 vs 5: 2.95 mg/dL [-7.73, 13.63]; 2 vs 6: 2.30 mg/dL [-5.54, 10.14]; 2 vs 7:-1.95 mg/dL [-10.85, 6.96]; 2 vs 8: 5.34 mg/dL [-10.75, 21.43]; 2 vs 9: 4.07 mg/dL [-21.83, 29.98]; 3 vs 4: 3.58 mg/dL [-13.60, 20.75]; 3 vs 5: 0.94 mg/dL [-14.69, 16.58]; 3 vs 6: 0.29 mg/dL [-13.56, 14.15]; 3 vs 7: -3.95 mg/dL [-18.43, 10.53]; 3 vs 8: 3.33 mg/dL [-16.40, 23.06]; 3 vs 9: 2.07 mg/dL [-26.24, 30.38]; 4 vs 5: -2.63 mg/dL [-16.91, 11.65]; 4 vs 6: -3.28 mg/dL [-15.59, 9.02]; 4 vs 7: -7.53 mg/dL [-20.53, 5.48]; 4 vs 8: -0.24 mg/dL [-18.92, 18.43]; 4 vs 9: -1.51 mg/dL [-29.09, 26.08]; 5 vs 6: -0.65 mg/dL [-10.70, 9.40]; 5 vs 7: -4.89 mg/dL [-15.79, 6.00]; 5 vs 8: 2.39 mg/dL [-14.88, 19.66]; 5 vs 9: 1.12 mg/dL [-25.53, 27.78]; 6 vs 7: -4.24 mg/dL [-12.38, 3.89]; 6 vs 8: 3.04 mg/dL [-12.63, 18.72]; 6 vs 9: 1.78 mg/dL [-23.87, 27.42]; 7 vs 8: 7.29 mg/dL [-8.95, 23.52]; 7 vs 9: 6.02 mg/dL [-19.98, 32.01]; 8 vs 9: -1.27 mg/dL [-30.51, 27.98].

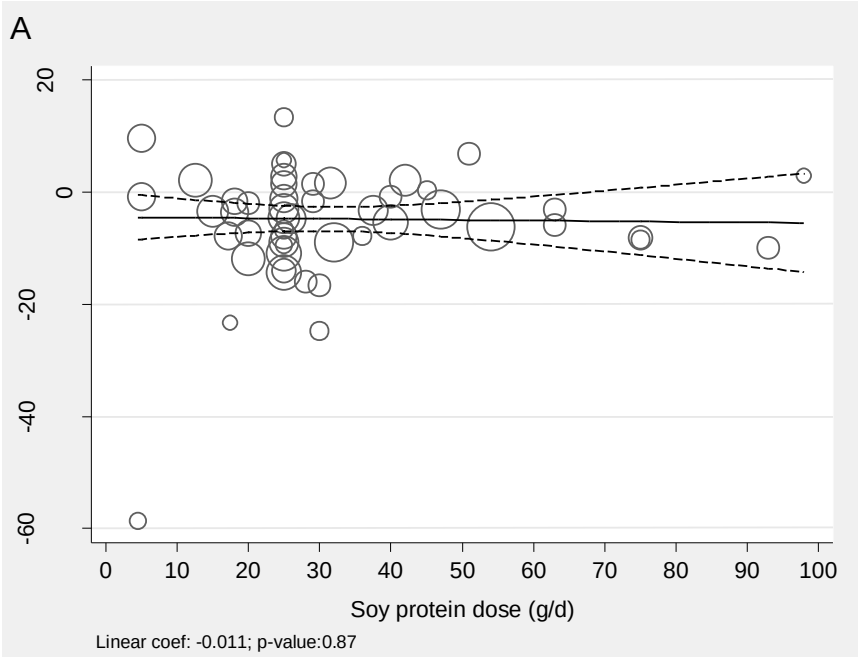
SUPPLEMENTARY DATA

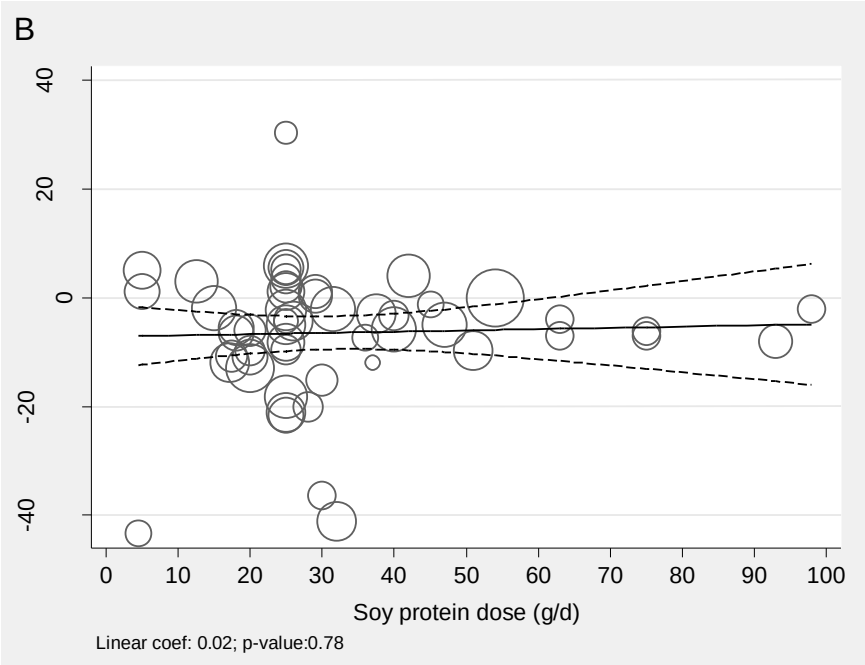
Subgroup	Level	Studies	*n*	Within subgroups	Between subgroups	Residual I^2	*P*-interaction
				Mean difference [95% CI] on circulating LDL-C concentration [mg/dL] in adults			
Total	**-**	**50**	**2,547**	**-4.75 [-6.68, -2.82]**	-	-	-
Sequence Generation							
	Low risk of bias [1]	14	1,153	-6.83 [-10.61, -3.05]	1 vs 2: -3.05 [-7.63, 1.53]	53.9%	0.19
	Unclear risk of bias [2]	36	1,394	-3.78 [-6.36, -1.20]	1 vs 3: -		
	High risk of bias [3]	0	-	-	2 vs 3: -		
Allocation Concealment							
	Low risk of bias [1]	16	1,153	-2.66 [-6.68, 1.35]	1 vs 2: 2.91 [-1.83, 7.67]	53.3%	0.22
	Unclear risk of bias [2]	34	1,394	-5.58 [-8.12, -3.04]	1 vs 3: -		
	High risk of bias [3]	0	-	-	2 vs 3: -		
Blinding of participants, personnel and outcome assessors							
	Low risk of bias [1]	39	2,195	-4.97 [-7.49, -2.45]	1 vs 2: 0.95 [-4.34, 6.23]	56.3%	0.72
	Unclear risk of bias [2]	11	352	-4.02 [-8.67, 0.62]	1 vs 3: -		
	High risk of bias [3]	0	-	-	2 vs 3: -		
Incomplete outcome data							
	Low risk of bias [1]	24	1541	-4.45 [-7.60, -1.31]	1 vs 2: -1.03 [-5.88, 3.82]	57.2%	0.87
	Unclear risk of bias [2]	21	858	-5.48 [-9.17, -1.79]	1 vs 3: 0.67 [-6.73, 8.07]		
	High risk of bias [3]	5	148	-3.78 [-10.48, 2.92]	2 vs 3: -1.70 [-9.35, 5.95]		
Selective outcome reporting							
	Low risk of bias [1]	37	1892	-4.76 [-7.42, -2.10]	1 vs 2: -0.15 [-5.39, 5.10]	57.1%	0.98
	Unclear risk of bias [2]	12	475	-4.90 [-9.43, -0.38]	1 vs 3: 1.28 [-12.09, 14.65]		
	High risk of bias [3]	1	180	-3.48 [-16.59, 9.63]	2 vs 3: -1.42 [-15.29, 12.44]		



Supplemental Figure 3. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis on circulating LDL-C concentration in adults. Pooled effect estimates for each subgroup level are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis of soy protein on plasma LDL-C concentration. The residual I^2 value represents unexplained heterogeneity for each subgroup.

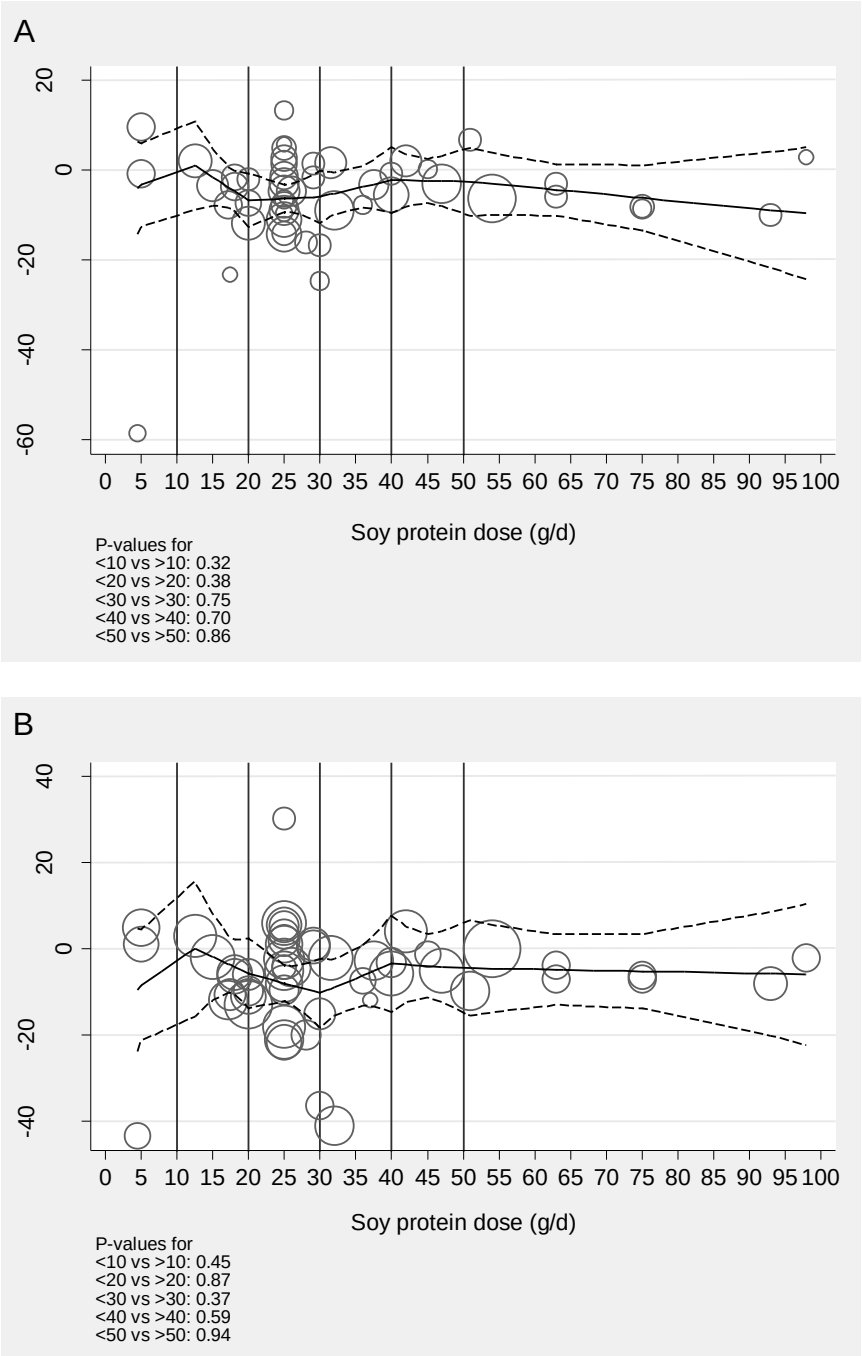
SUPPLEMENTARY DATA





Supplemental Figure 4. Linear meta-regression analyses for the effect of soy protein dose (g/d) on circulating LDL-C (A) and TC (B) concentrations in adults. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The straight line represents the estimate dose response for amount of soy protein consumed (g/d) and the dashed lines represent the upper and lower 95% Confidence Intervals.

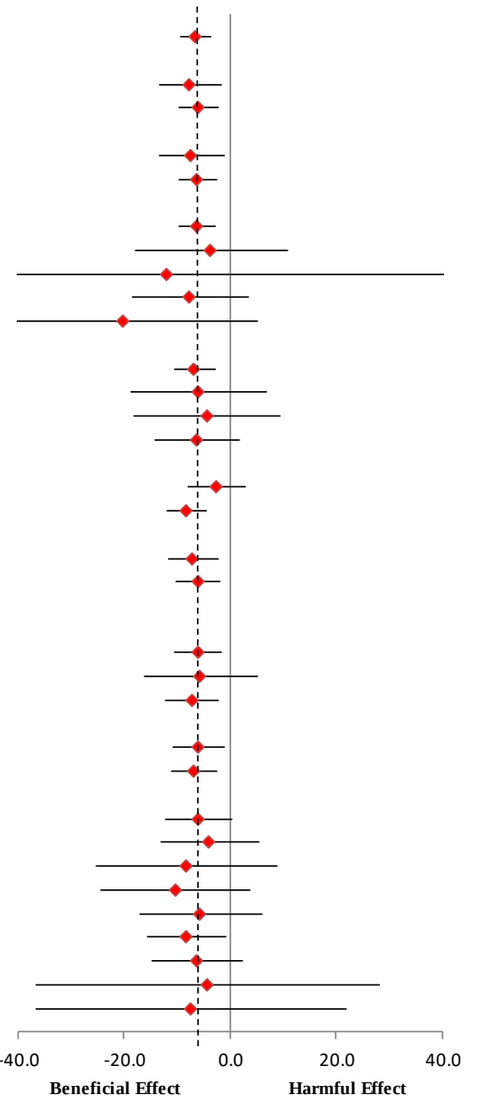
SUPPLEMENTARY DATA



Supplemental Figure 5. Piecewise linear meta-regression analyses for the effect of soy protein dose (g/d) on circulating LDL-C (A) and TC (B) concentrations in adults. Individual studies are represented by the circles, with their weight in the overall analysis represented by the size of the circles. The horizontal straight line represents the estimate dose response for amount of soy protein consumed (g/d), and the dashed lines represent the upper and lower 95% Confidence Intervals. The vertical straight lines represent the threshold knots.

SUPPLEMENTARY DATA

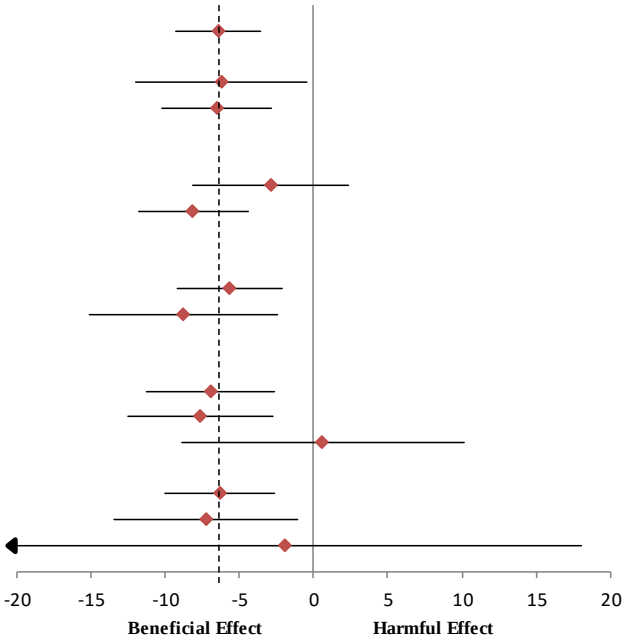
Subgroup	Level	Studies	*n*	Mean difference [95% CI] on circulating TC concentration [mg/dL] in adults: Within subgroups	Between subgroups	Residual I^2	*P*
Total		**52**	**2,607**	**-6.41 [-9.30, -3.52]**	-	-	-
Baseline LDL-C							
	≤ 135 mg/dL	16	503	-7.52 [-13.26, -1.78]	1.55 [-5.26, 8.37]	74.5%	0.65
	> 135 mg/dL	36	2,104	-5.97 [-9.65, -2.29]			
Soy dose							
	< 25 g/d	13	845	-7.24 [-13.24, -1.23]	1.11 [-5.90, 8.12]	74.5%	0.75
	≥ 25g/d	39	1,762	-6.13 [-9.75, -2.50]			
Soy protein food							
	Isolated soy protein [1]	42	2,377	-6.21 [-9.64, -2.78]	See legend	75.5%	0.84
	Soy food [2]	3	100	-3.56 [-17.90, 10.79]			
	Soy milk [3]	1	10	-11.99 [-76.73, 52.76]			
	Mixed [4]	5	96	-7.55 [-18.51, 3.41]			
	Texturized soy protein [5]	1	24	-20.00 [-45.02, 5.02]			
Comparator							
	Dairy protein [1]	36	1,994	-6.67 [-10.40, -2.93]	See legend	75.5%	0.99
	Meat protein [2]	4	42	-5.97 [-18.70, 6.75]			
	Mixed [3]	3	70	-4.31 [-18.08, 9.45]			
	Other [4]	9	501	-6.22 [-14.09, 1.64]			
Follow-up							
	< 6 wk	18	658	-2.39 [-7.78, 3.00]	-5.82 [-12.30, 0.67]	71.3%	0.08
	≥ 6 wk	34	1,949	-8.21 [-11.82, -4.60]			
Study design							
	Crossover	24	531	-6.94 [-11.56, -2.32]	0.94 [-5.30, 7.17]	74.1%	0.76
	Parallel	28	2,076	-6.00 [-10.18, -1.81]			
FDA categories							
Baseline TC or LDL-C							
	Desirable or borderline[1] [1]	27	1,277	-6.03 [-10.35, -1.71]	1 vs 2: 0.53 [-11.06, 12.11]	75.1%	0.93
	Normal, borderline, and high[2] [2]	5	79	-5.51 [-16.25, 5.24]	1 vs 3: -1.14 [-7.77, 5.50]		
	High[3] [3]	20	1,251	-7.17 [-12.20, -2.13]	2 vs 3: 1.66 [-10.21, 13.53]		
How soy protein was provided							
	Feeding or substitution	21	805	-5.86 [-10.61, -1.11]	-0.91 [-7.34, 5.51]	74.9%	0.78
	Added to diet	29	1,802	-6.77 [-11.10, -2.45]			
Baseline TC or LDL-C + how soy protein was provided							
	Desirable or borderline, added ISP [1]	15	894	-5.91 [-12.05, 0.23]	See legend	77.1%	1.00
	Desirable or borderline, feeding or substitution ISP [2]	6	211	-3.80 [-12.96, 5.36]			
	Desirable or borderline, added soy foods [3]	3	109	-8.10 [-25.13, 8.93]			
	Desirable or borderline, feeding or substitution soy foods [4]	3	63	-10.26 [-24.35, 3.83]			
	Normal, borderline, and high, feeding or substitution ISP [5]	5	79	-5.51 [-16.89, 5.88]			
	High, added ISP [6]	10	771	-8.11 [-15.44, -0.78]			
	High, feeding or substitution ISP [7]	8	427	-6.30 [-14.77, 2.17]			
	High, added soy foods [8]	1	28	-4.20 [-36.63, 28.23]			
	High, feeding soy foods [9]	1	25	-7.35 [-36.48, 21.79]			



Supplemental Figure 6. *A priori* subgroup analyses on circulating TC concentration in adults. [1]Desirable or bordeline, TC <240 mg/dL or LDL-C <160 mg/dL. [2]Goldberg et al. 1982 - Normolipidemics comparison is in this category as the FDA listed the study with both comparisons (Normolipidemics and Normolipidemics). [3]High, TC>240 mg/dL or LDL-C>160 mg/dL. Pooled effect estimates for each subgroup level are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis of soy protein on plasma TC. The residual I^2 value represents unexplained heterogeneity for each subgroup. Pairwise between-subgroup mean differences [95%] CIs for comparator are as follows: 1 vs 2: -5.50 mg/dL [-14.29, 3.29]; 1 vs 3: -1.23 mg/dL [-20.38, 17.92]; 1 vs 4: 1.41 mg/dL [-7.44, 10.26]; 1 vs 5: -1.54 mg/dL [-10.08, 7.00]; 2 vs 3: -4.26 mg/dL [-24.19, 15.66]; 2 vs 4: -6.91 mg/dL [-17.33, 3.52]; 2 vs 5: -3.96 mg/dL [-14.12, 6.21]; 3 vs 4: -2.64 mg/dL [-22.60, 17.31]; 3 vs 5: 0.31 mg/dL [-19.51, 20.12]; 4 vs 5: 2.95 mg/dL [-7.26, 13.16]. Pairwise between-subgroup mean differences [95%] CIs for baseline TC or LDL-C + how soy protein was provided are as follows: 1 vs 2: 2.12 mg/dL [-8.90, 13.13]; 1 vs 3: -2.19 mg/dL [-20.30, 15.92]; 1 vs 4: -4.33 mg/dL [-19.70, 11.03]; 1 vs 5: 0.41 mg/dL [-12.52, 13.34]; 1 vs 6: -2.19 mg/dL [-11.74, 7.37]; 1 vs 7: -0.33 mg/dL [-10.60, 9.95]; 1 vs 8: 1.72 mg/dL [-31.35, 34.79]; 1 vs 9: -1.43 mg/dL [-31.25, 28.38]; 2 vs 3: 4.31 mg/dL [-15.03, 23.65]; 2 vs 4: 6.45 mg/dL [-10.35, 23.25]; 2 vs 5: 1.71 mg/dL [-12.90, 16.32]; 2 vs 6: 4.31 mg/dL [-7.42, 16.03]; 2 vs 7: 2.45 mg/dL [-9.87, 14.77]; 2 vs 8: 0.4 mg/dL 0 [-33.36, 34.16]; 2 vs 9: 3.55 mg/dL [-27.03, 34.13]; 3 vs 4: 2.14 mg/dL [-19.97, 24.25]; 3 vs 5: -2.60 mg/dL [-23.09, 17.89]; 3 vs 6: -0.01 mg/dL [-18.55, 18.54]; 3 vs 7: -1.86 mg/dL [-20.79, 17.07]; 3 vs 8: -3.91 mg/dL [-40.60, 32.78]; 3 vs 9: -0.76 mg/dL [-34.55, 33.03]; 4 vs 5: - mg/dL 4.74 [-22.86, 13.37]; 4 vs 6: -2.15 mg/dL [-18.03, 13.73]; 4 vs 7: -4.01 mg/dL [-20.33, 12.32]; 4 vs 8: -6.05 mg/dL [-41.47, 29.37]; 4 vs 9: -2.90 mg/dL [-35.30, 29.50]; 5 vs 6: 2.59 mg/dL [-10.95, 16.13]; 5 vs 7: 0.74 mg/dL [-13.32, 14.80]; 5 vs 8: -1.31 mg/dL [-35.74, 33.12]; 5 vs 9: 1.84 mg/dL [-29.48, 33.16]; 6 vs 7: -1.86 mg/dL [-12.89, 9.17]; 6 vs 8: -3.90 mg/dL [-37.21, 29.41]; 6 vs 9: -0.75 mg/dL [-30.84, 29.33]; 7 vs 8: -2.05 mg/dL [-35.57, 31.48]; 7 vs 9: 1.10 mg/dL [-29.22, 31.42]; 8 vs 9: 3.15 mg/dL [-40.52, 46.82].

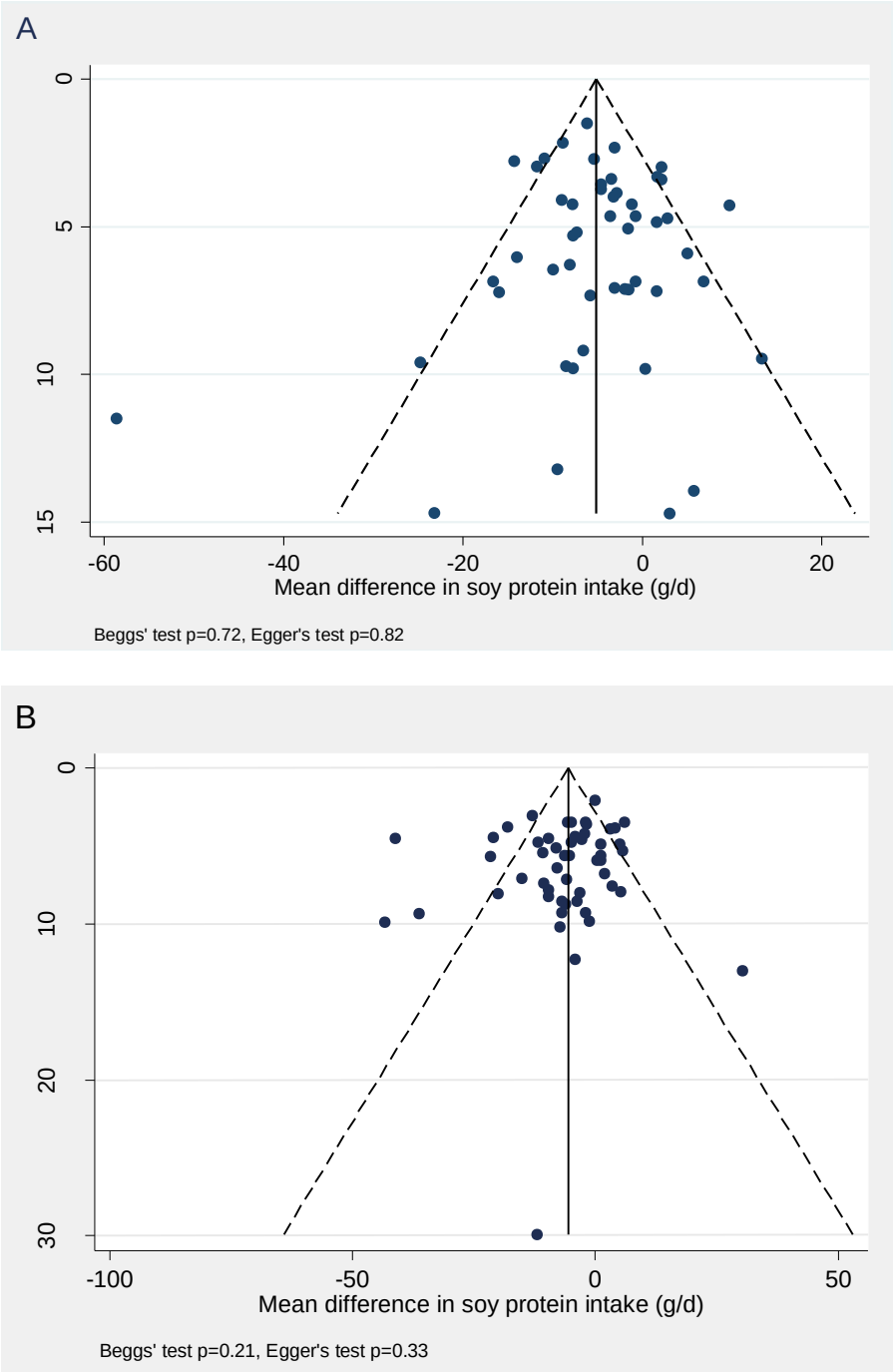
SUPPLEMENTARY DATA

Subgroup	Level	Studies	*n*	Within subgroups	Between subgroups	Residual I^2	*P*-interaction
Total	-	**52**	**2,607**	**-6.40 [-9.26, -3.54]**	-	-	-
Sequence Generation							
	Low risk of bias [1]	14	1,153	-6.20 [-11.98, -0.41]	1 vs 2: 0.32 [-6.54, 7.17]	74.5%	0.93
	Unclear risk of bias [2]	38	1,454	-6.52 [-10.20, -2.83]	1 vs 3: -		
	High risk of bias [3]	0	-	-	2 vs 3: -		
Allocation Concealment							
	Low risk of bias [1]	17	1,203	-2.90 [-8.16, 2.37]	1 vs 2: 5.21 [-1.21, 11.63]	72.1%	0.11
	Unclear risk of bias [2]	35	1,404	-8.11 [-11.79, -4.44]	1 vs 3: -		
	High risk of bias [3]	0	-	-	2 vs 3: -		
Blinding of participants, personnel and outcome assessors							
	Low risk of bias [1]	41	2,255	-5.68 [-9.21, -2.16]	1 vs 2: -3.12 [-10.37, 4.14]	73.5%	0.39
	Unclear risk of bias [2]	11	352	-8.80 [-15.14, -2.46]	1 vs 3: -		
	High risk of bias [3]	0	-	-	2 vs 3: -		
Incomplete outcome data							
	Low risk of bias [1]	25	1591	-6.94 [-11.24, -2.64]	1 vs 2: -0.68 [-7.19, 5.84]	73.6%	0.29
	Unclear risk of bias [2]	22	868	-7.62 [-12.51, -2.73]	1 vs 3: 7.57 [-2.87, 18.00]		
	High risk of bias [3]	5	148	0.63 [-8.88, 10.13]	2 vs 3: -8.25 [-18.94, 2.44]		
Selective outcome reporting							
	Low risk of bias [1]	37	1892	-6.29 [-9.98, -2.60]	1 vs 2: -0.96 [-8.19, 6.27]	74.7%	0.87
	Unclear risk of bias [2]	14	535	-7.25 [-13.47, -1.03]	1 vs 3: 4.36 [-15.93, 24.64]		
	High risk of bias [3]	1	180	-1.93 [-21.88, 18.01]	2 vs 3: -5.32 [-26.21, 15.57]		



Supplemental Figure 7. Risk of bias (using The Cochrane Collaboration Tool) subgroup analysis on circulating TC concentration in adults. Pooled effect estimates for each subgroup level are represented by diamonds. The dashed line represents the pooled effect estimate for the overall analysis of soy protein on TC. The residual I^2 value represents unexplained heterogeneity for each subgroup.

SUPPLEMENTARY DATA



Supplemental Figure 8. Publication bias funnel plots for the effect of soy protein intake on circulating LDL-C (A), and TC (B) concentrations in adults. The solid line represents the pooled effect estimate expressed as the weighted mean difference (MD) of each analysis, and dashed lines represent pseudo-95% confidence limits. Circles represent effect estimates of included trials.