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Jenkins DJA, Mejia SB, Chiavaroli L, Viguiliouk E, Li SS, Kendall CWC, et al. Cumulative meta-analysis of the soy effect over time. J Am Heart Assoc. 2019;8:8:e012458.

What We Know, Think We Know, or Are Starting to Know

In a previous Deepdive we covered the associations between nuts and cardiovascular disease risk, and identified that the phytosterol content of nuts may be a critical determinant of the effect of nuts on cardiovascular risk, specifically due to their cholesterol-lowering effect. Soy protein has attracted interest as an adjuvant cholesterol-lowering food, in addition to nuts, fibre, and plant sterols [(1)]. The US Food and Drug Administration [FDA] had, in 1999, approved the following health claim based on a meta-analysis of 43 studies: "Diets low in saturated fat and cholesterol that include 25g of soy protein a day may reduce risk of heart disease" [(2)].

In the early 2000' s, David Jenkins and colleagues at the University of Toronto developed the 'Portfolio Diet' pattern, a dietary pattern designed with the specific aim of containing cholesterol-lowering foods in physiologically relevant amounts: soluble fibres, plant sterols, and soy protein [(1)]. Early interventions yielded promising results, equivalent to the effect of statin therapy [at the time]. In one intervention, the Portfolio Diet resulted in a 28.6% decrease in LDL-cholesterol compared to the 30.9% reduction with lovastatin [(3)]. While the soy protein component was substantial at ~21g per 1,000kcal, the effects of the intervention were a composite of all cholesterol-lowering foods.

Recently, the Food and Drug Administration [FDA] proposed to revoke its position on soy protein, stating that the magnitude of effect of soy protein on LDL-cholesterol was not of clinical relevance [(4)]. This provoked a response from the Portfolio Diet research group, beginning with a meta-analysis of the 46 studies the Federal Drug Administration proposed to rely on, which indicated that a majority of studies demonstrated a modest benefit to soy protein on blood cholesterol levels [(5)].

The present study was conducted with the same studies, albeit using a cumulative meta-analysis* statistical approach.

*Geek Box: Cumulative Meta-Analysis

You'll be familiar with the concept of a meta-analysis, in which multiple studies are included and the results combined to obtain a single summary estimate of the effects of an intervention or exposure of interest. So, what is a "cumulative" meta-analysis? The term appears to have first been used in a 1992 paper led by Fred Mosteller and Tom Chalmers analysing the effects of various interventions for myocardial infarction [(6)]. In effect, the cumulative meta-analysis approach retrospectively calculates a summary estimate every time a new trial published in a specific time frame became available. For example, let's say in that in 2010 there were 15 studies available on the effects of a drug on blood glucose levels, and a meta-analysis of all 15 indicated an overall 20% reduction in blood glucose levels. Then in 2011, 3 more studies on the same question are published, followed by 2 in 2012, and 5 in 2013. A cumulative meta-analysis would examine the effects of these subsequent published studies on the original overall effect size, to see if whether the summary available to base conclusions upon at a given time would have changed. For example, adding the 3 studies in 2011 may have increased the effect size to 22%, while the 2 added in 2012 altered the effect size again to 19%. A cumulative meta-analysis therefore allows researchers to demonstrate how the available evidence evolved over time, and what the strength of evidence was at any given time. It provides a means of assessing accumulating evidence over time: hence the term 'cumulative'. An example of how cumulative meta-analysis can be important for public health policy may be seen in the example of Sudden Infant Death Syndrome (SIDS). In New Zealand in the 1980's, a case-control study suggested that lying in the prone position was a significant risk factor for SIDS. This prompted a public health campaign which led to profound reductions in the incidence of SIDS. However, a 2005 cumulative analysis of observational evidence from 1940 demonstrated that if the evidence had been analysed as it was accumulating, the risk of lying prone could have been identified at least 10yrs earlier, preventing thousands of deaths [(7)]. Thus, by updating the pool of evidence each time new studies emerge, it is possible to retrospectively quantify the strength of evidence at a certain time, and to continually update the strength of evidence as new studies are published.

The Study

The researchers conducted a cumulative meta-analysis of all 46 trials which the FDA had selected for its review of the health claim regarding soy protein and cardiovascular health. This allowed the researchers to investigate whether at any point in time from the original 1999 health claim approval to date, the effect of soy protein on total cholesterol [TC] and LDL-cholesterol [LDL-C] was not longer significant. By looking at the accumulation of evidence over time, it was also possible to identify whether a particular study influenced the results.

The main exposure of interest was the difference between the change in TC and LDL-C from baseline in the soy intervention diet vs. control diet. The mean difference and associated 95% confidence intervals for each included study were extracted from the primary paper. The data was then pooled cumulatively over the time period from 1999 onwards, adding new studies published in chronological order.

Results: Of the 46 studies identified by the FDA, 43 contained sufficient data to include in the analysis. The average age of participants in the studies was 55yo, 37% men and 63% women, and nearly half [49%] of participants had high cholesterol, defined as >6.2mmol/L [240mg/dL] for TC and >4.1mmol/L [160mg/dL] for LDL-C. The average study duration was 6-weeks, and the average dose of soy protein was 25g per day.

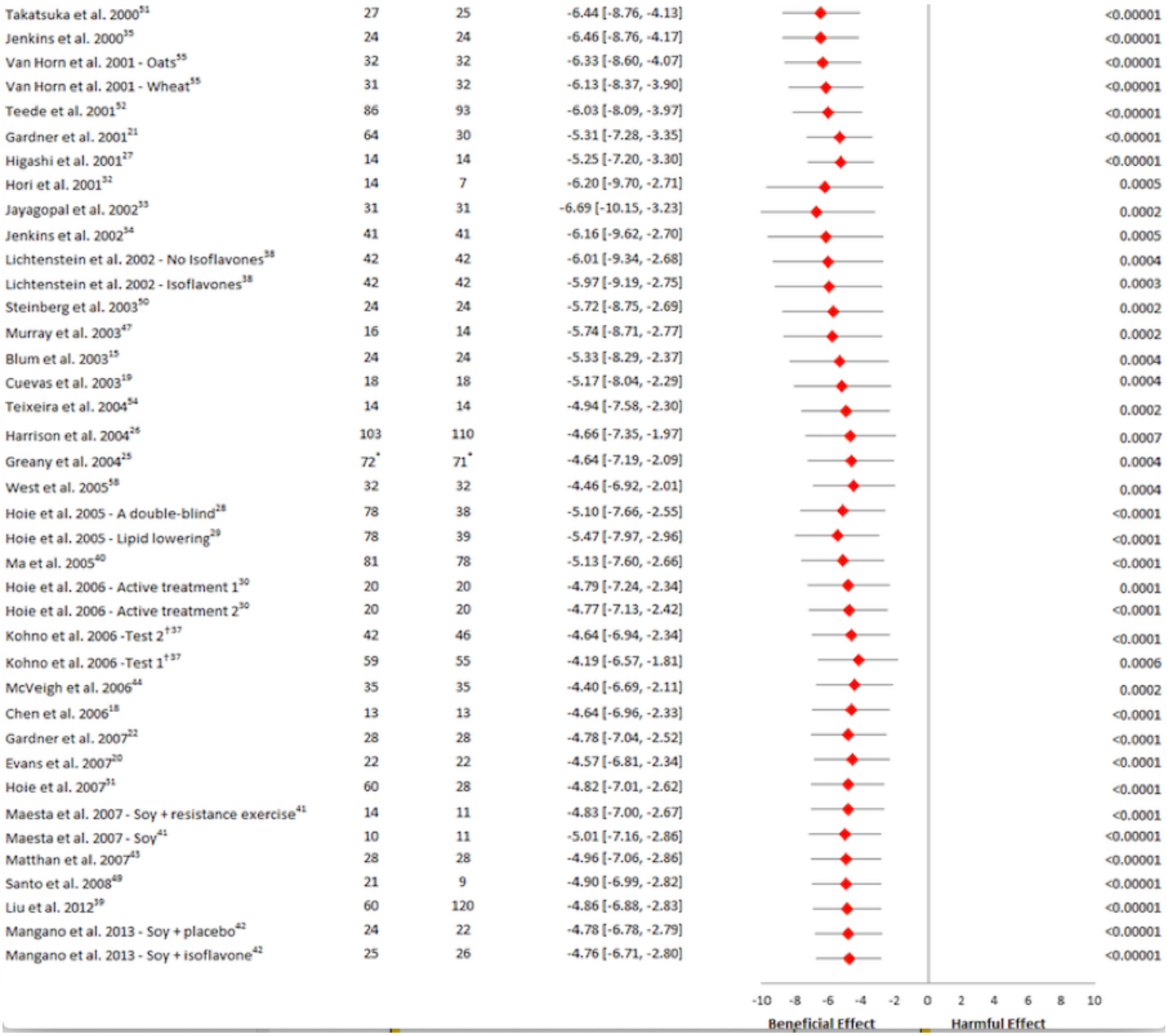
- ***1999 Results:***
  - **TC:** Average reduction of 0.11mmol/L [4.5 mg/dL] in the soy group compared to control group.
  - **LDL-C:** Average reduction of 0.16mmol/L [6.3mg/dL] in the soy group compared to control group.

Study, Year	Soy, N	Comparator, N	Cumulative mean difference [95% CI] in LCL-C [mg/dL]		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 - Normolipidemics[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
Jenkins et al.1989[36]	11	11	-6.83 [-9.60, -4.06]		<0.00001
Bakhit et al.1994 - Cellulose[14]	21	21	-6.89 [-9.57, -4.21]		<0.00001
Bakhit et al. 1994 - Cotyledon[14]	21	21	-6.36 [-9.76, -2.96]		0.0002
Murkies et al. 1995[46]	23	24	-6.15 [-8.71, -3.60]		<0.00001
Wong et al.1998 - Normocholesterolemic[59]	13	13	-6.23 [-8.73, -3.74]		<0.00001
Wong et al.1998 - Hypecholesterolemic[59]	13	13	-6.27 [-8.75, -3.79]		<0.00001
Washburn et al. 1999[57]	42	42	-6.33 [-8.74, -3.92]	Initial FDA Claim	<0.00001

Forest plot *from the paper illustrating the average effect of soy protein compared to the control diet on LDL-C in studies that were available for meta-analysis in 1999 [at the time of the initial FDA health claim approval]. As can be clearly seen from the the forest plot, the effect of soy protein on LDL-C was similar, and was evident in both participants with high cholesterol and with normal cholesterol levels.*

- ***2000-2013 Results:***
  - **TC:** The minimum effect size of a 0.11mmol/L [4.0mg/dL] reduction was evident in 2001; the maximum of 0.19mmol/L [7.7mg/dL] was evident in 2006.
  - **LDL-C:** The minimum effect size of a 0.10mmol/L [4.2mg/dL] reduction was evident in 2006; the maximum of 0.17mmol/L [6.7mg/dL] was evident in 2002.

At no point over the period from the initial health claim in 1999 did the level of statistical significance for the effect of either TC or LDL-C fall below p=0.002 [translation: very very significant].



Forest plot *from the paper illustrating the average effect of soy protein compared to the control diet on LDL-C in studies that were available for meta-analysis from the time of the initial FDA health claim approval onwards, i.e., a further 14yrs. As can be clearly seen from the the forest plot, the effect of soy protein on LDL-C remained similar, and remained highly significant compared to the control diets in each study.*

The Critical Breakdown

Pros: The study used the exact evidence base upon which the FDA based their initial decision in 1999, and intended to base the revised assessment of the health claim. A comprehensive total of number of studies was available for the analysis. The cumulative analysis allowed for the strength of the evidence to be assessed from the date of the first health claim in 1999 over a 14yr subsequent period, and minimum and maximum effects identified.

Cons: 79% of included studies used soy protein, often as soy protein isolate, and only a handful of studies reported on soy foods, i.e., soy milk or textured soy protein [e.g., tofu]. This may mean that the results from a food-based perspective lack some applicability. In addition, there was significant heterogeneity between the included studies, which varied in their control diets from dairy proteins, to meat proteins, or mixed sources. The heterogeneity was not explained by factors such as study design, source of soy protein, or baseline cholesterol levels, which implies the variability may be in the effect size [although the trend in the results was consistently toward reduced TC and LDL-C levels]. The study was also based on the FDA studies specifically, and therefore did not have leeway to use its own inclusion/exclusion criteria.

Key Characteristic

By conducting a cumulative meta-analysis it was possible to examine the state of the evidence in 1999, and then whether the addition of studies published subsequent to that date influenced the results. Using a cumulative approach to the analysis provided rather unequivocal evidence that the evidential basis for the FDA purporting to revoke the health claim in relation to soy protein does not appear to support the decision. That, or the FDA was hasty in its approval in the first instance in 1999. Either way, it does appear that the effect of soy protein was consistent over time, and the strength of evidence is largely similar as it was in 1999. It appears the FDA concern is primarily due to inconsistency in the overall evidence base [(4)]. What could help to resolve this perceived inconsistency is if a meta-analysis was confined to whole-food sources of soy protein, given that 79% of studies included by the FDA used soy protein, often in isolate form. The reason is that a previous 2015 meta-analysis demonstrated that whole-food products [soyabeans, soy milk] led to significantly greater reductions in LDL-C: 0.28mmol/L [11.06mg/dL] [(8).] The minimum bound of the confidence intervals was 0.16mmol/L [6.3mg/dL] - the same as the average reduction in LDL-C in the present study. It it possible that whole-food sources exert greater biological activity: a common finding in nutrition science.

Interesting Finding

The fact that the lipid-lowering effect of the soy interventions is specific to the protein component is interesting, given the bioactive food components of soy that are often touted for their health effects. Soy is a rich source of isoflavones, in particular genistein, daidzin, and glycitin, which [similar to other phenolic compounds] are metabolised by the gut bacteria into equol and absorbed into circulation [9]. These compounds have long been a major focus of the potential health effects of soy, as equol acts as a potent antioxidant in addition to having an affinity for binding to oestrogen receptors, a mechanism implicated in reduced risk of hormone-dependent cancers from soy intake [10]. However, previous research on isoflavone supplementation has demonstrated that, while soy protein may reduce blood cholesterol levels, soy isoflavones do not [9]. Soy peptides from beta-conglycinin, which comprises up to 20% of soy protein, have been shown in animal models to influence cholesterol metabolism in the liver [11,12]. However, as noted under ***Key Characteristic*** above, if the effects of whole-food sources of soy have a greater effect on lowering cholesterol levels, this suggests a synergistic effect of the whole-food matrix. And isolated supplements of either protein or isoflavones may not have the same effect. Again, this is a fairly consistent theme we have seen before with other 'food vs. nutrient' examples, and with antioxidant supplements.

Relevance

The results of soy protein in isolation may be highly statistically significant in the included studies, and overall meta-analysis, but they have questionable clinical significance on their own. To be fair to the FDA, their reasoning is not unreasonable. That said, it is difficult to fathom how the effects of a single nutrient in isolation could be deemed clinically insignificant given that we consume total diets, and the effects of diet tends to be - excuse the pun on the study design - cumulative. The Portfolio Diet [1,3] focused specifically on achieving 22g soy protein per 1,000kcal, 2.5g plant sterols per day, 30-60g almonds per day, and 20g of soluble fibre from oat [beta-glucans] and psyllium - the composite effect of the diet is up to 15-30% reductions in LDL-C: these effects are clinically meaningful as well as statistically significant. The meta-analyses published by Jenkins et al., including the present study, have been to directly address the proposed revoking of the health claim for soy by the FDA. Being frank, one could care less about whether the food industry gets to slap a halo effect on every random soy-based junk product on supermarket shelves. Rather, what we should be considering is whether soy foods reliably reduce cardiovascular risk factors, and whether indeed it is the protein component which confers particular benefit. Is the addition of soy foods in a heart-healthy dietary pattern likely to confer some benefit? At this juncture, although the effect may be modest in itself, the direction of effect in every study is is clearly toward a reduction of cholesterol levels. When considered in the context of additional lipid-lowering foods, soy protein foods added into a total diet could result in clinically meaningful reductions in LDL-C [1,3].

Application to Practice

The caveat is that most interventions included used soy protein supplements, and the take-home message is not necessarily to load up on soy protein isolate. For people who use protein powders, this is of course an option. But for the majority, it could be more prudent to focus on whole-food sources: soy milk, tofu, tempeh, etc.

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