Citation:

Weggemans RM, Trautwein EA. Relation between soy-associated isoflavones and LDL and HDL cholesterol concentrations in humans: a meta-analysis. *European Journal of Clinical Nutrition* 2003. 57: 940-994.

PubMed ID: 12879088

Study Design:

Meta-analysis

Class:

M - Click here for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To analyze the independent effects of changes in soy-associated isoflavones on plasma cholesterol and lipoprotein concentrations in 10 well-controlled trials that substituted soy protein with dairy or animal protein.

Inclusion Criteria:

Seventy-two abstracts were examined for compliance with the following inclusion criteria:

- Within a study, the composition of the experimental diets should differ only in the amount of soy and animal proteins and in the amount of soy-associated isoflavones
- The subjects needed to be weight-stable throughout the study; average change in weight should be between 2kg and +2kg
- The design had to eliminate the effect of non-specific drifts of the outcome variable with time; this is accomplished by either feeding
- Different groups of volunteers, different diets side by side (parallel design) or by feeding each volunteer several diets in random order (crossover or Latin square design)
- The feeding periods had to last at least two weeks in order to attain equilibrium in the concentration of blood cholesterol
- Studies had to report fasting concentrations of total cholesterol and lipoproteins
- Initially, two additional criteria were used. One was that in parallel studies each treatment group needed to have a control or run-in period of at least two weeks and the other was that only isolated or textured soy protein should be used. These were considered too rigid (only five studies met them) and these criteria were dropped.

Exclusion Criteria:

Studies with before and after designs or linear designs without a control group were excluded, as

they do not adjust for non-specific drifts of the outcome variable with time or do not adjust for differences in baseline diets between treatment groups.

Description of Study Protocol:

Search Procedures

Authors screened PubMed for studies on the effect of soy protein and isoflavones on blood cholesterol concentrations.

- Search criteria were soy OR isoflavones AND cholesterol
- Publication years ranged from January 1, 1995 to June 6, 2002
- Human studies
- Published in English.

Quality Assessment of Studies

Quality assessment of studies was completed, although more rigorous selection criteria were downgraded to 'general criteria' (above) and authors did not perform an evidence-based evaluation of the studies.

Interventions

In addition to the inclusion criteria for study design mentioned above (soy vs. animal or dairy protein, weight stable subjects, minimum two weeks feeding trial, parallel or Latin Square X-over design), the following interventions were comparable between studies:

- During the soy treatment period, subjects were provided with isolated soy protein, a soy protein supplement, textured soy protein or tofu
- During the control treatment period, casein, dry milk, a milk protein supplement, dairy and egg protein or cooked lean meat were given, if necessary, in combination with other foods to balance the change in macronutrient intake
- The change in soy protein intake ranged from 19 to 60g per day
- The change in isoflavones ranged from one to 95mg per day as compared to the control group or treatment.

Outcomes

Before and after treatment TC, LDL-C, HDL-C.

Populations

- The 10 studies included 959 subjects (336 men and 623 women). Number of subjects ranged from 15 to about 90 per study.
- Average age of the volunteers ranged from 41 to 63 years
- Mean BMI ranged from 24 to 28kg per m^2
- Mean baseline cholesterol concentration ranged from 5.42 to 6.60mmol per L, except in one with baseline TC less than 4.21mm per L
- All studies used free-living subjects.

Data Collection Summary:

- The 10 studies yielded 21 dietary interventions that compared the effect of soy protein with that of dairy or animal protein on blood cholesterol levels
- Authors calculated Pearson's correlation coefficients to study the crude relation between changes in soy-associated isoflavones, soy protein and changes in plasma cholesterol and lipoproteins
- Linear regression models were used to study the independent effects of isoflavones and soy protein, respectively, on total cholesterol and lipoproteins. In the model, they adjusted also for differences between studies and checked whether there was statistical interaction between changes in isoflavones or soy protein and differences between studies.
- They also used a model in which soy protein and isoflavones and their interaction term were explanatory variables. There was no collinearity problem in this analysis because the correlation between changes in soy protein and soy-associated isoflavones was R=0.29 (P=0.21).
- **To account for different sample size between studies**, each study was weighted by the number of subjects, which is inversely proportional to the squared standard error
- Analysis of residuals was performed to check the appropriateness of each model
- **To detect publication bias**, heterogeneity in funnel plots was explored. The response of plasma cholesterol and lipoproteins to soy-associated isoflavones was plotted against the sample size by study. In the absence of bias, the plots will resemble a symmetrical funnel, as results of small studies will scatter at the left side of the plot with the spread narrowing among the larger studies on the right side of the plot. When all papers were included in the plot, the resulting funnel shape indicated no publication bias was found.

Description of Actual Data Sample:

- Ten papers were included in this review
- Of 148 articles on soy and isoflavones founds
    - 72 studies were selected for abstract review based on title scan
    - 40 from the 72 abstracts were selected for a full text scan
    - Nine papers that met criteria were selected for review
    - One study in press at time of MS submission.

Summary of Results:

- Three of the 21 treatments increased and 18 treatments decreased LDL cholesterol
- 19 of the 21 treatments increased and the other two decreased HDL cholesterol concentrations
- Consuming on average 36±12g per day soy (mean±s.d.) in combination with 52±30mg per day isoflavones lowered LDL cholesterol by 0.17mmol per L (95% confidence interval (CI) 0.25 to 0.09mmol per L) and the ratio of total: HDL cholesterol by 0.26 (95% CI, 0.36 to 0.16)
- The treatments significantly increased HDL cholesterol by 0.03mmol per L (95% CI, 0.01-0.06) and the ratio of HDL: LDL cholesterol by 0.02 (95% CI, 0.01-0.03)
- By only looking at the five studies that fulfilled the very stringent selection criteria, there was a significant correlation between change in soy-associated isoflavones and change in LDL cholesterol (R¼_0.59, P¼0.03), but possibly due to publication bias in these results (separate analysis)

- There was no evidence of any dose-response relation between changes in the intake of soy-associated isoflavones with changes in LDL cholesterol when all ten studies were included (R= -0.33, P=0.14)
- There was also no significant correlation between changes in soy-associated isoflavone intake and changes in HDL cholesterol (R= -0.07, P=0.76)
- Correlations between changes in soy protein and blood cholesterol and lipoprotein concentrations were also not significant.

Author Conclusion:

" We found that replacing dairy and animal proteins with soy protein led to 4% lower LDL cholesterol concentra-tions and significantly increased HDL cholesterol concentrations by 3%."

Small changes in CVD risk reduction with soy on an indvidual level may be considerable at a population level.

"In conclusion, the present meta-analysis shows that changes in soy-associated isoflavones are not related to changes in LDL or HDL cholesterol."

Reviewer Comments:

- *This review focused on the effects pf soy isoflavones and less on the effects of soy protein in lowering TC and LDL and increasing HDL*
- *LDL decreases and HDL increases were variable between the studies, but generally small*
- *The authors are from the Unilever Health Institute which sells stanols and sterold in margarines. This potential bias may have colored their selection of studies to include in the meta-analysis.*
- *I am not sure how one selects abstracts based on a title scan alone.*

Research Design and Implementation Criteria Checklist: Review Articles

Relevance Questions		
1.	Will the answer if true, have a direct bearing on the health of patients?	Yes
2.	Is the outcome or topic something that patients/clients/population groups would care about?	Yes
3.	Is the problem addressed in the review one that is relevant to nutrition or dietetics practice?	Yes
4.	Will the information, if true, require a change in practice?	Yes

Validity Questions		
1.	Was the question for the review clearly focused and appropriate?	Yes
2.	Was the search strategy used to locate relevant studies comprehensive? Were the databases searched and the search termsused described?	Yes

3.	Were explicit methods used to select studies to include in the review? Were inclusion/exclusion criteria specified and appropriate? Were selection methods unbiased?	Yes
4.	Was there an appraisal of the quality and validity of studies included in the review? Were appraisal methods specified, appropriate, and reproducible?	Yes
5.	Were specific treatments/interventions/exposures described? Were treatments similar enough to be combined?	Yes
6.	Was the outcome of interest clearly indicated? Were other potential harms and benefits considered?	Yes
7.	Were processes for data abstraction, synthesis, and analysis described? Were they applied consistently across studies and groups? Was there appropriate use of qualitative and/or quantitative synthesis? Was variation in findings among studies analyzed? Were heterogeneity issued considered? If data from studies were aggregated for meta-analysis, was the procedure described?	Yes
8.	Are the results clearly presented in narrative and/or quantitative terms? If summary statistics are used, are levels of significance and/or confidence intervals included?	Yes
9.	Are conclusions supported by results with biases and limitations taken into consideration? Are limitations of the review identified and discussed?	Yes
10.	Was bias due to the review's funding or sponsorship unlikely?	Yes