Original Article

The effects of phytosterols/stanols on blood lipid profiles: a systematic review with meta-analysis

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The objective of this work is to conduct a systematic review that investigates the efficacy of phytosterols/stanols in lowering lipid concentration in individuals with non-familial hypercholesterolemia. Randomized controlled intervention trials were identified through selected international journal databases and reference lists of relevant publications. Two researchers extracted data from each identified trial and only trials of sufficient quality were included in the review. Main outcomes of interest were differences between treatment and control groups in terms of low density lipoprotein cholesterol, total cholesterol, high density lipoprotein cholesterol and triacylglycerol. Of the studies reviewed, 20 out of 76 studies were of sufficient quality. The results of the systematic review indicated that phytosterols/stanols could significantly decrease low density lipoprotein cholesterol, total cholesterol and triacylglycerol in treatment groups compared with control groups and that the mean differences were [-0.35 mmol/L, 95%CI(-0.47, -0.22), p<0.00001], [-0.36 mmol/L, 95%CI(-0.46, -0.26), p<0.00001] and [-0.1 mmol/L, 95%CI(-0.16, -0.03), p=0.004] respectively. Foods enriched with 2.0 g of phytosterols/stanols per day had a significant cholesterol lowering effect.

Key Words: phytosterol, plant stanol ester, lipids, system review, meta-analysis

INTRODUCTION

According to World Health Organization (WHO) estimates, 17.5 million people died of cardiovascular disease (CVD) in 2005. This accounts for 30 percent of all deaths globally, of which 7.6 million deaths were the result of Coronary Heart Disease (CHD). It is estimated that over the next 10 years (2006-2015), China will lose $558 billion in foregone national income due to the combination of heart disease, stroke and diabetes. Hyperlipidemia, especially when linked to other metabolic abnormalities, is an emerging target for CHD prevention. A series of more recent trials have demonstrated conclusively that lowering total cholesterol and low density lipoprotein (LDL) cholesterol reduces the chance of having a heart attack, needing bypass surgery or angioplasty, and dying of CHD related causes. Data from drug trails indicate that reduction in LDL cholesterol levels by about 10% could be expected to reduce the incidence of ischemic heart disease by about 12% to 20% over a5 year peroid.[1]

Dietary therapy is the cornerstone of strategies to lower serum LDL cholesterol level and reduce the risk for CHD or CVD. Incorporating foods fortified with plant sterol and stanol esters into the daily diet can substantially enhance the cholesterol lowering effect of the diet. This is also applicable for patients already taking statins. Adding stanols and sterols appears somewhat more effective than doubling the statin dose. Thus, the recent introduction of stanol and sterol enriched food in many parts of the world is an important development because CHD/CVD is the leading cause of morbidity and mortality worldwide. Over the past ten years, many studies have been published regarding the cholesterol lowering effect of plant sterols/stanols, each proposing specific recommendation for the intake of plant sterols/stanols. In order to better determine the exact level at which plant sterols/stanols are most effective and provide stronger scientific support, we conducted a systematic review with a meta-analysis of the available literature to quantify the effects of dietary plant sterols/stanols on serum blood lipid profiles in adults.

MATERIALS AND METHODS

Identification of Literature

Studies were included in the systematic review if they had a randomized parallel controlled study design and the primary objective was to investigate the effects of phytosterols/stanols on total cholesterol (TC), LDL cholesterol, High density lipoprotein (HDL) cholesterol, and triacylglycerol (TG) concentrations in individuals 16 years or older without familial hypercholesterolemia, severe hepatic or renal diseases, and diabetes mellitus.

The literature search included studies published between 1980 and 2007. The studies were identified through international journal databases such as Medline, EMbase, IPA, CBMdisc, VIP and CNKI. Key words used were: “plant

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sterol* or phytosterol* or plant stanol* or sterol ester or stanol ester" and "cholesterol* or lipid* or LDL English and Chinese. A further search was done by scanning the reference lists of original and review publications. Although the search was not limited to English, all identified studies were published in English. Figure 1 illustrates the study selection process. Main targets for analysis were TC, LDL cholesterol, TG and HDL cholesterol. Other targets such as Apolipoprotein B (ApoB), Apolipoprotein A-I (ApoA1), TC/HDL cholesterol and LDL cholesterol/HDL cholesterol were also included.

Extraction of Data and Quality Assessment

Two independent researchers extracted the relevant data from the publications using an standardized form. Furthermore, the two researchers independently assessed the quality of the research methodology according to Cochrane Reviewer's Handbook and using a list of quality criteria items extracted from a modification of The Jadad List[2] in Table 1. Only the studies with a quality score of ≥4 were included in the systematic review.

Data Analysis

The Cochrane Collaboration Review Manager 5.0 software package (Oxford, England) was used to perform the meta-analysis. For each trial, standard deviation of treatment for the outcome measures (TC, LDL cholesterol, HDL cholesterol and TG) were estimated using methods described by Follman et al.[3] Total cholesterol, LDL cholesterol, HDL cholesterol and TG were expressed in mmol/L, and ApoB, ApoA1 were expressed in g/L. Variables expressed in mg/dL were converted to mmol/L by using the following conversion factors: for TC, LDL cholesterol and HDL cholesterol the value was multiplied by 0.0258, and for TG the value was divided by 88.2.The meta-analysis for TC included 20 trials,[4-23] and that for LDL cholesterol, HDL cholesterol included 19 trials.[8-26] For TG, the meta-analysis was performed from data collected from 17 trials.[7-23] The differences between trials included in the meta-analysis were checked for heterogeneity by χ^2 test and by using I^2. If the *p* values from the chi-square test was ≥ 0.05 or if I^2 was ≤ 50%, meta-analysis was car-

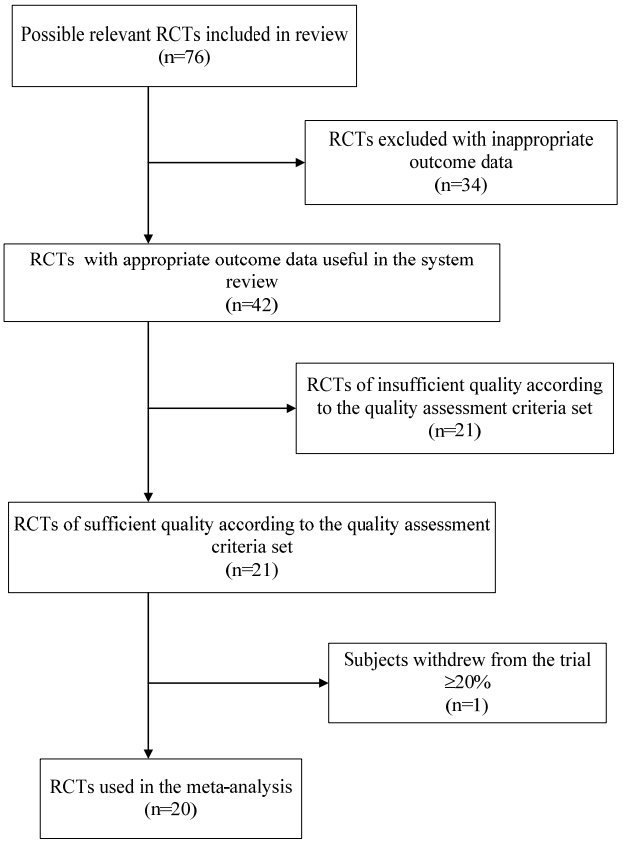

Fig. 1. Study Selection Process

Table 1. Quality Criteria List for Randomized Controlled Trials

Domain	Description	Score
Sequence generation	Appropriate (method used to generate the sequence of randomisation was described and appropriate, e.g., table of random numbers, computer generated, etc.)	2
	Unclear (randomisation stated but no information on method used is available)	1
	Inappropriate (method of randomisation was inappropriate, e.g., patients were allocated alternately, or according to date of birth, hospital number, etc.)	0
Allocation Concealment	Appropriate (randomisation method described that would not allow investigator/participant to know or influence the intervention group before eligible participant entered in the study)	2
	Unclear (randomisation stated but no information on method used is available)	1
	Inappropriate (method of randomisation used such as alternate medical record numbers or unsealed envelopes; any information in the study that indicated that investigators or participants could influence the intervention group)	0
	Not use	0
Blinding	Appropriate (the method of blinding was described and it was appropriate, e.g., identical placebo, active placebo, dummy, etc.)	2
	Unclear (blinding stated but no information on method used is available)	1
	Inappropriate (no blinding was used or the method of blinding was inappropriate, e.g., comparison of tablet vs. injection with no double dummy)	0
Withdrawals and dropouts	Described the participants who were included in the study but did not complete the observation period or who were not included in the analysis, and stated the number as well as the reasons for withdrawal in each group. If there were no withdrawals, it should be stated in the article.	1
	No statement on withdrawals	0

ried out using the 'fixed effect' statistical model, otherwise the 'random effects' statistical model was used.

RESULTS

Literatures searching and characteristics of the studies

The literature search yielded 76 studies of which 21 trials qualified to be used in the systematic review and finally 20 in the meta-analysis (Figure 1). Basic information from the 20 studies that met the selection criteria is shown in Table 2. Overall, 1273 subjects (613 subjects from the treatment arm and 660 subjects from the control arm) were included in the meta-analysis. All studies were conducted on subjects 20 to 70 years old, with or without dyslipidemia. Duration of the trials ranged from 3 weeks to 1 year. There were no differences in terms of baseline concentrations for TC, LDL cholesterol, HDL cholesterol, and TG between the treatment- and control arms. The trials were carried out under free living conditions and used plant sterols, plant stanols or plant stanols ester. Fat

Table 2. Basic information of the original studies.

Source	Participant Characteristics† in terms of cholesterol	Intervention	Outcome				Score
			TC	LDL choles-terol	HDL choles-terol	TG	
Polagruto JA, J Am DietAssoc,2006 (P4)	hyper	PS‡: 1.5g/d; 6w	p<0.01	p<0.01	NO	NO	4
Devaraj S, Am J Clin Nutr, 2006 (P5)	borderline	PS: 2.0g/d; 8w	p<0.01	p<0.01	Increased p<0.02		4
Jauhiainen T, Eur J Clin Nutr, 2006 (P8)	borderline	PSE§: 2.0g/d; 5w	p<0.001	p<0.001	NO	NO	4
Goldberg AC, Am J Cardiol, 2006 (P11)	hyper	PS: 1.8g/d; 6w	p=0.03	p=0.007			4
Korpela R, Eur J Clin Nutr, 2006 (P12)	hyper	PS: 2g/d; 6w	p<0.0005	p<0.00005	NO	NO	4
Doornbos AM, Eur J Clin Nutr, 2006 (P13)	borderline-hyper	PS: 2.8g/d ; 4w	p<0.05	p<0.05			4
Devaraj S, Arterioscler Thromb Vasc Biol, 2 2004 (P27)	borderline	PS: 2g/d ; 8w	p<0.01	p<0.01	NO	NO	4
Seki S, Asia Pac J Clin Nutr, 2003 (P29)	normal	PSE: 0.45g/d; 12w	p<0.05	p<0.05	NO	NO	4
De Graaf J, Br J Nutr, 2002 (P35)	hyper	PS/PSE: 1.8g/d; 4w	p<0.005	p<0.005	NO	NO	4
Matvienko OA, Am J Clin Nutr, 2002 (P39)	borderline	PS: 2.7g/d; 4w	p<0.001	p<0.001		NO	4
Mensink RP, Atherosclerosis, 2002 (P44)	normal	PSE: 3g/d ; 4w	p<0.001	p<0.001	NO		4
Maki KC, Am J Clin Nutr, 2001 (P49)	borderline	PSE: 2.2g/d ; 5w	p<0.001	p<0.001		p<0.001	4
Jones PJ, Am J Clin Nutr, 1999 (P54)	hyper	PS: 1.7g/d; 4 w	p<0.05	p<0.01	NO	NO	4
Miettinen TA, N Engl J Med, 1995 (P58)	borderline	PSE: 1.8g/d; 1y	p<0.001	p<0.001	NO	NO	4
Hallikainen MA, Am J Clin Nutr, 1999 (P63)	borderline-hyper	PSE: 2.16g/d ; 8w	p<0.05	p=0.072	NO	NO	4
Quilez J, J Nutr, 2003 (P69)	normal	PSE: 3.2g/d ; 8w	p<0.01	p<0.005	NO		4
Hallikainen M, Atherosclerosis, 2006 (P76)	borderline	PSE: 1.93-1.98g/d; 10w	p<0.05	p<0.05	NO	NO	4
Niinikoski H, Scand J Nutr, 1997 (C3)	normal	PSE: 3g/d; 5w		p=0.03	NO		4
Woodgate D, Lipids, 2006 (E4)	hyper	PSE: 1.6g/d; 4w	p<0.05	p<0.05	NO	NO	5
Yae J.H, NutrRes, 2005 (E5)	normal	PS: 2g/d; 4w	p=0.001	p<0.001	NO	NO	5

† Participant characteristics: Participants were divided into 3 groups (normal, borderline, and hypercholesterolemia) according to their serum cholesterol levels.
‡ PS: phytosterol, plant sterol, plant stanol
§ PSE: phytosterol sterol ester
¶ NO: this outcome was not included in the trail

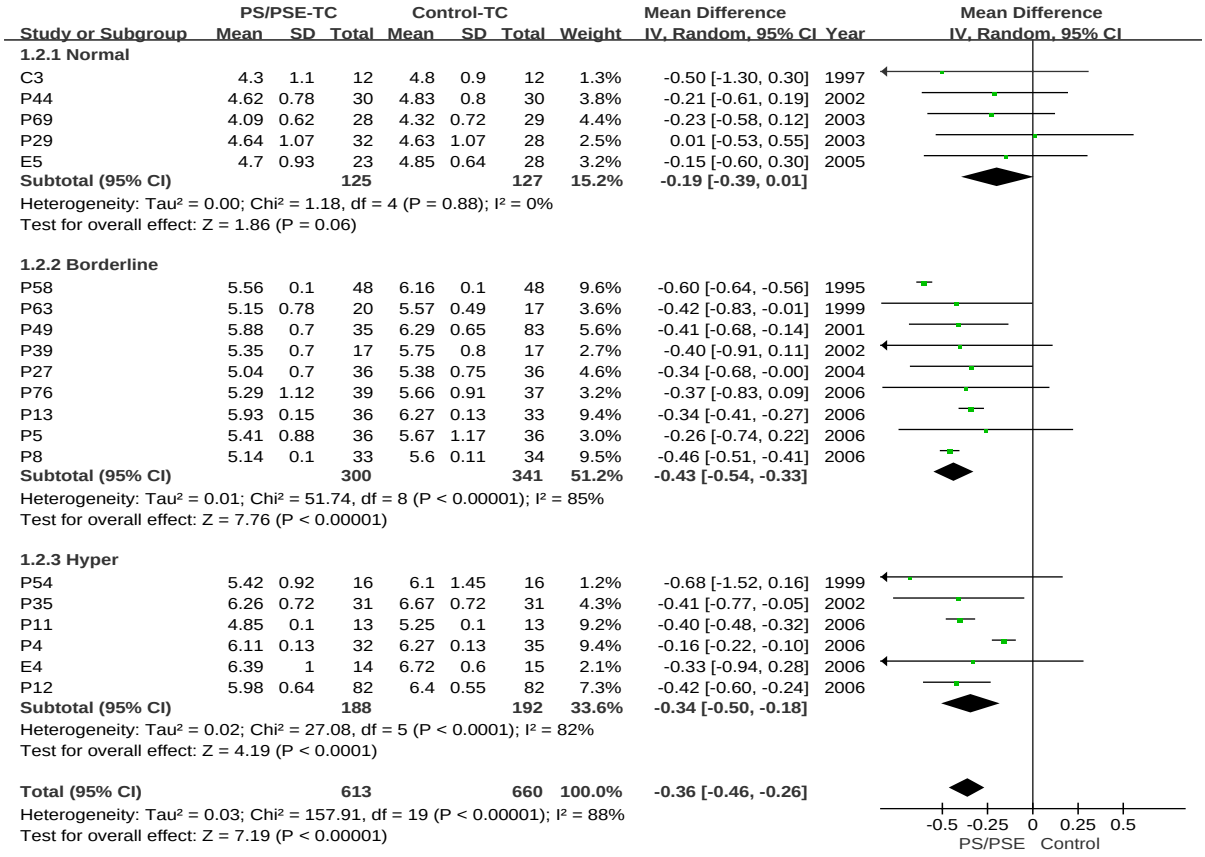

Fig.2. Effects of phytosterols/stanols on total cholesterol concentration of study subjects.

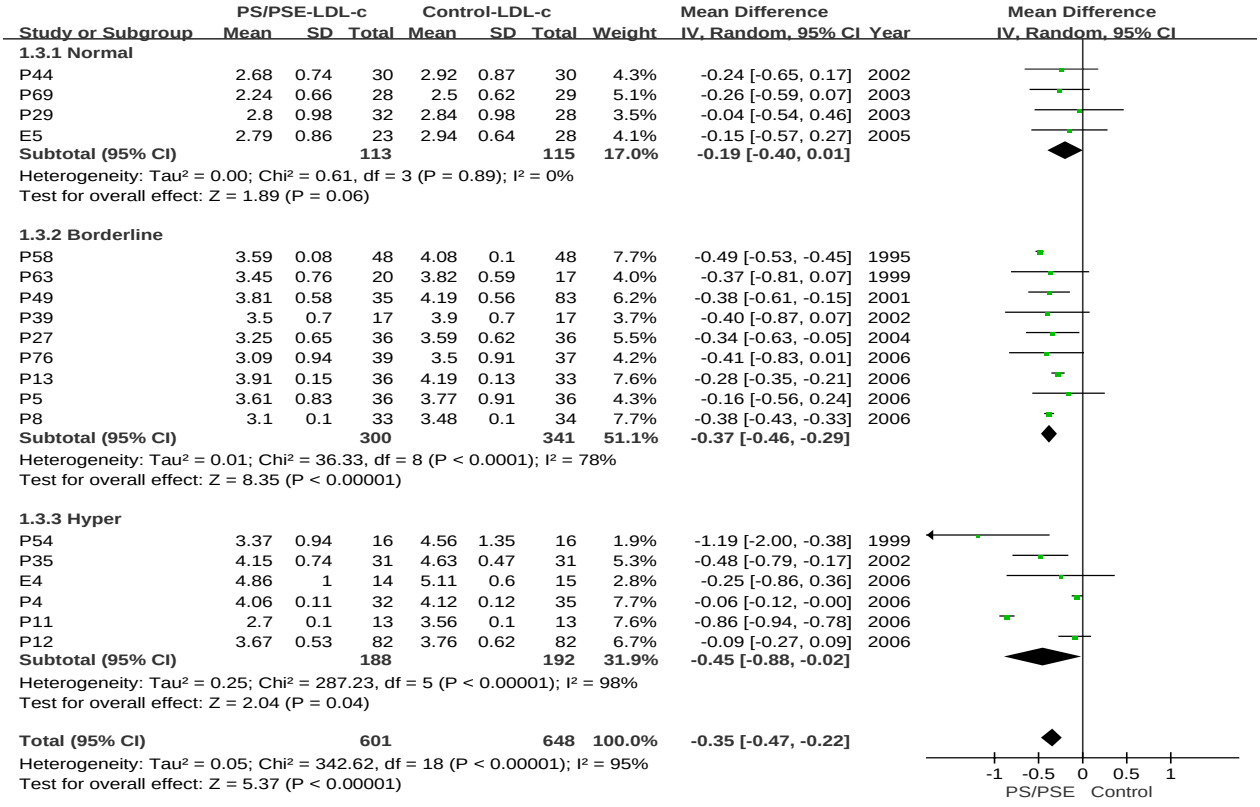

Fig.3. Effects of phytosterols/stanols on LDL cholesterol concentrations of study subjects.

spreads, bread, cream, beverages, yoghurt etc were used as vehicle for the sterols/stanols and the dose ranged from 0.45 to 3.2 g sterols/stanols per day, with a mean dose of 2.08 g/d.

The main reasons for the exclusion of 55 studies in the systematic review were that 34 reported inappropriate

outcome measures and 21 did not meet the quality criteria (scored less than 4). Characteristics of the studies that resulted in them not meeting the quality criteria include: not double blinded, not randomized, not controlled, or the method of randomisation was inappropriate. Studies with high withdrawal rate were also excluded.

Changes in serum lipid concentrations

Results of the meta-analysis on TC (Figure 2), LDL cholesterol (Figure 3), and TG (Figure 4) are presented in forest plots respectively. The forest plot presents the individual study effects with their confidence intervals as horizontal lines. The shorter the line, the more significant the results. The box in the middle of the horizontal line represents the mean effect, the size of the box represent the weight each study contributed to the analysis (presented as weighted mean difference, WMD). The vertical line at zero represents no effect. The diamond shaped indicator at the bottom of each graph represents mean overall difference between treatment and control. If this diamond shaped indicator does not touch the vertical line, the overall effect is statistically significant.

Figures.2 and 3 summarises the treatment effect of the mean dose of 2.08 g phytosterols/stanols/day on TC and LDL cholesterol in 1273 subjects for 3 weeks to 1 year of intervention. Total cholesterol concentrations was significantly reduced by 0.36 mmol/L (95% CI: -0.46, -0.26, p<0.00001) and LDL cholesterol concentrations by 0.35mmol/L (95% CI: -0.47,-0.22, p<0.00001). Total triacylglycerols concentration was significantly decreased by 0.1mmol/L (95% CI: -0.16, -0.03; p=0.004), and that of ApoB by 0.0912 g/L (95% CI: -0.106, -0.076; p<0.00001). The results of TC, LDL cholesterol and TG were statistically heterogeneous as reflected by I^2 values of greater than 50% and p values from the chi-square test were less than 0.05, indicating that the studies included in the meta-analysis presented differences. So 'random effects' statistical model was used to carry out the meta-analysis for those outcomes. The results of ApoB were statistically homogeneous as reflected by p value of greater than 0.05 from chi-square test. This suggested that the studies in the meta-analysis presented similar results. As a result the 'fixed effects' statistical model was used to carry out the meta-analysis for ApoB. There were no effects seen on HDL cholesterol and ApoA1 concentrations (data not shown).

Subgroup analysis

Results of TC, LDL cholesterol, HDL cholesterol and TG were statistically heterogeneous as reflected by I^2 values of greater than 50% and p value of less than 0.05 from the chi-square test, the subgroup analysis was carried out according to the serum cholesterol level in order to find out what caused the heterogeneity. Based on the recommendation of NCEP/ATP III,[24] studies were categorised into 3 groups i.e. 'normal' (TC < 200 mg/dL or 5.12 mmol/L), 'borderline' (TC 200-239 mg/dL or 5.12-6.12 mmol/L)and 'hyper' (TC > 240 mg/dL or 6.14 mmol/L). The treatment effect of phytosterols/stanols on TC, LDL cholesterol and TG in the subgroups (normal, borderline

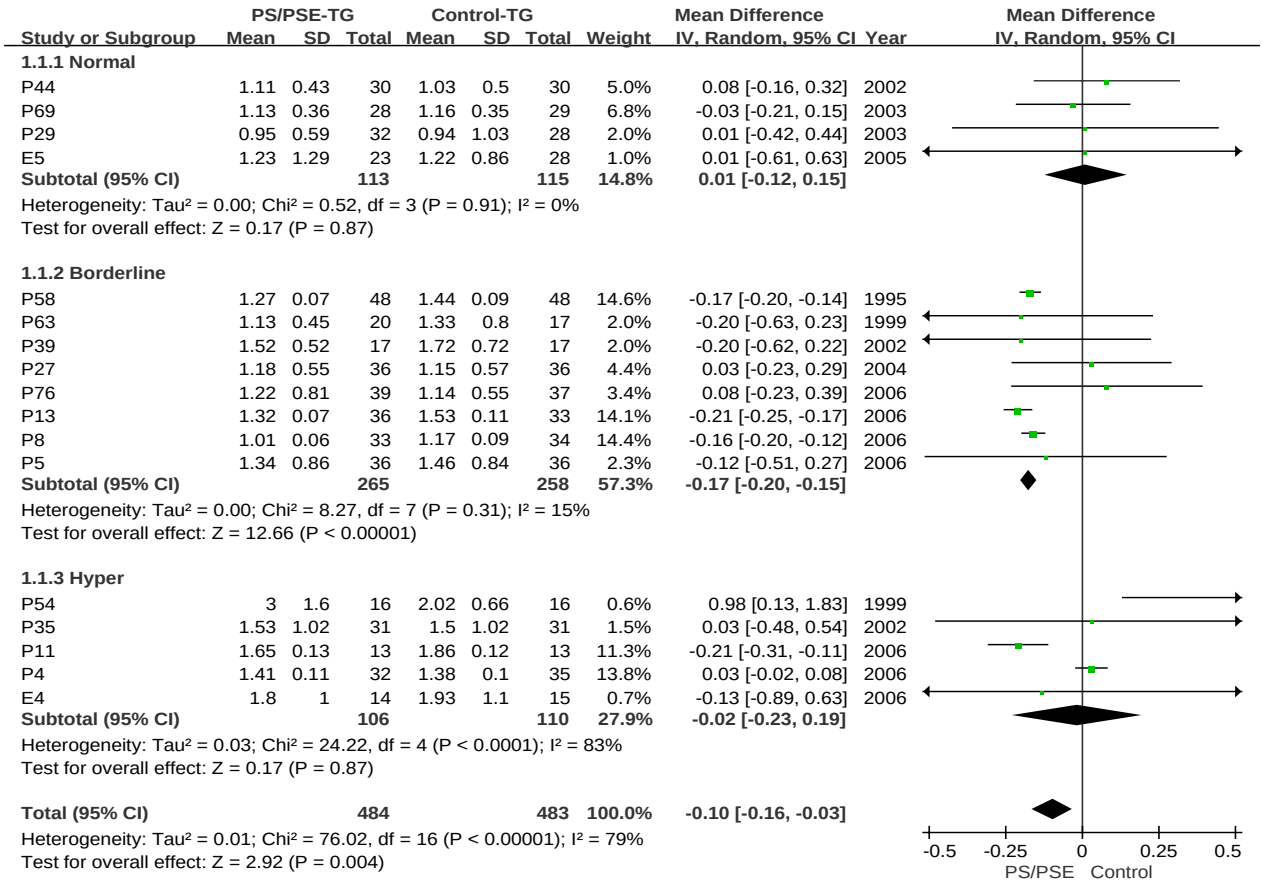

Fig.4. Effects of phytosterols/stanols on total triacylglycerols of subjects.

and hyper) is also shown in Figures 2, 3 and 4, respectively. For subgroup normal, phytosterols/stanols presented no effects on all of the outcomes (p>0.05). For subgroup borderline, phytosterols/stanols presented effects on TC, LDL cholesterol and TG but no influence upon HDL cholesterol. For subgroup hyper, there were statistically significant effects seen on all of the outcomes except TG. Throughout tests of heterogeneity, subgroup normal was statistically homogenous for all the outcomes, but heterogeneity still existed in the rest of two subgroups for one or more outcomes.

Furthermore, an additional subgroup analysis was conducted, with groups defined according to the intervention dose. Using 2 g/d as the threshold, all the studies were divided in one of the two subgroups. In subgroup intervention dosage ≥ 2 g/d, there were statistically significant effects seen on TC, TG and LDL cholesterol. And in subgroup intervention dosage < 2 g/d, the levels of TC and LDL cholesterol were significantly lowered but no influence on TG were found. Neither intervention dosage ≥ 2 g/d nor < 2 g/d, phytosterols/stanols showed an effect on HDL cholesterol (data not shown).

DISCUSSION

All effort was made to find all the published studies that investigated the effect of phytosterols/stanols on lipid concentrations. In this regard, the search strategy included both computerized and manual search methods and several international databases were searched from 1980. Possible bias was further minimized by not limiting the search to English language publications but all the identified published studies were in English. Publication and citation bias can, however, not be excluded.

Furthermore, the studies included in the meta-analysis were heterogeneous, as indicated by I^2 values greater than 50% and p values of less than 0.05 for TC, LDL cholesterol , HDL cholesterol, TG and homogeneous for ApoA1 and ApoB. So the 'random effects' statistical model was used to carry out the meta-analysis for heterogeneous outcomes, and the 'fixed effects' statistical model for homogeneous ones. With the purpose of identifying the source of heterogeneity, subgroups analysis was done based on the serum cholesterol level and intervention dose, respectively. The results of the test of heterogeneity of subgroup analysis indicated that the serum cholesterol level and intervention dosage were the two factors that resulted in the heterogeneity. Moreover, when studies were classified by serum cholesterol level, the subgroup 'normal cholesterol' was statistically homogenous for all of the outcomes, but the heterogeneity still existed in the two other subgroups. This may be ascribed to the fact that there were other sources that contributed to the heterogeneity. It is suggested that regression analysis be carried out to identify all the possible factors that generate the heterogeneity next.

The results of this systematic review are in accordance with results from studies on subjects with familial hypercholesterolemia and non-familial hypercholesterolemia.[25] Some researchers concluded from their review that 1.5-3 g of phytosterols/stanols per day led to a 8-15% reduction in LDL cholesterol in normocholesterolemic, mildly HC and HC subjects with no effect on HDL cholesterol and TG..In this systematic review and meta-analysis, LDL cholesterol concentrations were reduced by 6-15 % with a mean reduction of 0.35 [-0.47, -0.22] mmol/L and TC concentrations were reduced by 5-10 % with a mean reduction of 0.36 [-0.46, -0.26] mmol/L, with intakes ranging from 0.45 to 3.2 g (average of 2.08 g/d) phytosterols/stanols per day. This is in line with the 2 g plant sterols/stanols per day recommended by the NCEP/ATP III.[24] One out of every 2 men and 1 out of every 3 women will develop heart disease sometime in their life. Reducing cholesterol concentrations is important in terms of cardiovascular disease risk reduction. The Framingham Heart Study established that high blood cholesterol is a risk factor for CHD. Results of the Framingham study showed that the higher the cholesterol level, the greater the CHD risk. At the other end of the spectrum, CHD is uncommon at total cholesterol levels below 1.7 mmol/L. A direct link between high blood cholesterol and CHD has been confirmed by the Lipid Research Clinics Coronary Primary Prevention Trial (1984) which showed that lowering total and LDL cholesterol levels significantly reduces CHD. Cholesterol is obtained by the body in two ways: through production by the liver (± 1 g a day) and the ingestion of cholesterol containing foods. Maintaining a healthy diet and lifestyle offers the greatest potential of all known approaches for reducing the risk for cardiovascular disease in the general population. This is still true in spite of major advances in clinical medicine. It is established that diet therapy is the cornerstone in lowering TC and LDL cholesterol concentrations and in reducing the risk of cardiovascular disease. Plant stanols/sterols lower LDL cholesterol levels by up to 15% and therefore are seen as a therapeutic option, in addition to an adjuvant to a healthy diet and lifestyle modification, for individuals with elevated LDL cholesterol levels.

In this review, the result of reduced TG concentrations was different from other studies. Possible explanations include: (1). the heterogeneity of trails and (2). publication and citation bias. Statistical heterogeneity shows differences among studies included in the review, which could affect the final result. However, plant stanols/sterols could decrease TG level in subgroup borderline hypercholesterolemia, whereas no effects on TG in subgroup normal blood cholesterol. This may indicate the effect of plant stanols/sterols on TG is in relation to the primary lipid level of the subject. (Figure 4) Because carrying out meta- analysis with only positive studies may result in a higher estimation of the effects of plant stanols/sterols on TG.

In addition, ApoA1 and ApoB were also analyzed as an objective in the review. Apolipoprotein A1 is the most abundant protein component of HDL. This protein serves as an acceptor for cholesterol released from cells thus promoting efflux of cholesterol to HDL then to the liver for excretion from the body (reverse cholesterol transport). It also acts as a cofactor for lecithin cholesterol acyltransferase that forms cholesterol esters on the HDL particles. Apolipoprotein B is the major structural proteins of triacylglycerol rich lipoproteins. There are two forms, apolipoprotein B100 and apolipoprotein B48, both derived from a single gene. ApoB100 is expressed by the liver and found in LDL and VLDL. Apolipoprotein B48 is ex-

pressed by the intestine is found in chylomicrons. They are important in the biosynthesis, transport, and metabolism of triacylglycerol rich lipoproteins. A high ApoB plasma level is recognised as a risk factor for atherosclerosis, while a high ApoA1plasma level is a protective factor against atherosclerosis. The results of reduction in ApoB and no effects on ApoA1 were just in accordance with the results of LDL cholesterol and HDL cholesterol.

In conclusion, the incorporation of 2.0 g of phytosterols/stanols/sterols per day in different food vehicles such as margarine/fat spreads, butter, salad dressings, mayonnaise, low fat yogurt, and bakery products could significantly reduce TC and LDL cholesterol concentrations in subjects with and without hypercholesterolemia by 0.36 [-0.46, -0.26] mmol/L and 0.35 [-0.47, -0.22] mmol/L, respectively without causing any adverse side effects. This is similar to the recommendations of the NCEP/ATP III.[27] Compared to the literature on familial hypercholesterolemia subjects, phytosterol/stanol treatment were as effective in subjects with familial hypercholesterolemia as those with non-familial hypercholesterolemia. Phytosterols/stanols may be an effective and useful tool to contribute to cholesterol lowering in adults and as an supplement to a healthy diet, it has been proposed as functional food ingredients to be widely used in food industry. To sustain LDL cholesterol reductions from these products, individuals need to consume them daily, just as they would use lipid lowering medication.

AUTHOR DISCLOSURES

We declare that we have no conflict of interest. This work was supported by a grant 2006BAD27B01 from China's 11th Five-Year Scientific and Technical Plan: 'Research on evaluating procedures and techniques for functional foods' from January 2006.

REFERENCES

1. Downs JR, Clearfiled M, Weis S, Whitney E, Shapiro DR, Beere PA, Langendorfer A, Stein EA, Kruyer W, Gotto AM Jr. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. JAMA. 1998;279:1615-22.
2. Jadad AR, Moore A, Carroll D, Jenkinson C, Reynolds JM, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trails: Is blinding necessary. Control Clin Trials. 1993,17:1-12.
3. Follman D, Elliot P, Suh I, Cutler, J. Variance imputation for reviews of clinical trials with continuous response. J Clin Epidemiol. 1992;45:769–73.
4. Niinikoski H, Viikari J.; Palmu T. Cholesterol-lowering effect and sensory properties of sitostanol ester margarine in normocholesterolemic adults. Scandinavian Journal of Nutrition. 1997; 41:9-12.
5. Maki KC, Davidson MH, Umporowicz DM, Schaefer EJ, Dicklin MR, Ingram KA et al. Lipid responses to plant-sterol-enriched reduced-fat spreads incorporated into a National Cholesterol Education Program Step I diet. Am J Clin Nutr. 2001;74:33-43.
6. Korpela R, Tuomilehto J, Högström P, Seppo L, Piironen V, Salo-Väänänen P et al. Safety aspects and cholesterol-lowering efficacy of low fat dairy products containing plant sterols. Eur J Clin Nutr. 2006;60:633-42.
7. Mensink RP, Ebbing S, Lindhout M, Plat J, van Heugten MM. Effects of plant stanol esters supplied in low-fat yoghurt on serum lipids and lipoproteins, non-cholesterol sterols and fat soluble antioxidant concentrations. Atherosclerosis. 2002;160:205-13.
8. Seki S, Hidaka I, Kojima K, Yoshino H, Aoyama T, Okazaki M, Kondo K. Effects of phytosterol ester-enriched vegetable oil on plasma lipoproteins in healthy men. Asia Pac J Clin Nutr. 2003;12:282-91.
9. Quílez J, Rafecas M, Brufau G, García-Lorda P, Megías I, Bulló M, Ruiz JA, Salas-Salvadó J. Bakery products enriched with phytosterol esters, alpha-tocopherol and beta-carotene decrease plasma LDL-cholesterol and maintain plasma beta-carotene concentrations in normocholesterolemic men and women. J Nutr. 2003;133:3103-9.
10. Hyun YJ, King OY, Kang JB, Lee JH, Jang Y, Liponkoski L, Salo P. Plant stanol esters in low-fat yogurt reduces total and low-density lipoprotein cholesterol and low-density lipoprotein oxidation in normocholesterolemic and mildly hypercholesterolemic subjects. Nutrition Research. 2005;25: 743-53.
11. Miettinen TA, Puska P, Gylling H, Vanhanen H, Vartiainen E. Reduction of serum cholesterol with sitostanol-ester margarine in a mildly hypercholesterolemic population. N Engl J Med. 1995;333:1308-12.
12. Hallikainen MA, Uusitupa MI. Effects of 2 low-fat stanol ester-containing margarines on serum cholesterol concentrations as part of a low-fat diet in hypercholesterolemic subjects. Am J Clin Nutr. 1999;69:403-10.
13. Matvienko OA, Lewis DS, Swanson M, Arndt B, Rainwater DL, Stewart J et al.. A single daily dose of soybean phytosterols in ground beef decreases serum total cholesterol and LDL cholesterol in young, mildly hypercholesterolemic men. Am J Clin Nutr. 2002;76:57-64.
14. Devaraj S, Jialal I, Vega-López S. Plant sterol-fortified orange juice effectively lowers cholesterol levels in mildly hypercholesterolemic healthy individuals. Arterioscler Thromb Vasc Biol. 2004;24:25-8.
15. Doornbos AM, Meynen EM, Duchateau GS, van der Knaap HC, Trautwein EA. Intake occasion affects the serum cholesterol lowering of a plant sterol-enriched single-dose yoghurt drink in mildly hypercholesterolaemic subjects. Eur J Clin Nutr. 2006;60:325-33.
16. Devaraj S, Autret BC, Jialal I. Reduced-calorie orange juice beverage with plant sterols lowers C-reactive protein concentrations and improves the lipid profile in human volunteers. Am J Clin Nutr. 2006;84:756-61.
17. Hallikainen M, Lyyra-Laitinen T, Laitinen T, Agren JJ, Pihlajamäki J, Rauramaa R, Miettinen TA, Gylling H. Endothelial function in hypercholesterolemic subjects: Effects of plant stanol and sterol esters. Atherosclerosis. 2006;188: 425-32.
18. Jauhiainen T, Salo P, Niittynen L, Poussa T, Korpela R. Effects of low-fat hard cheese enriched with plant stanol esters on serum lipids and apolipoprotein B in mildly hypercholesterolaemic subjects. Eur J Clin Nutr. 2006;60:1253-7.
19. Jones PJ, Ntanios FY, Raeini-Sarjaz M, Vanstone CA. Cholesterol-lowering efficacy of a sitostanol-containing phytosterol mixture with a prudent diet in hyperlipidemic men. Am J Clin Nutr. 1999;69:1144-50.
20. De GJ, De SNPRW, Van DM, Belsey EM, Kastelein JJP, Haydn PP, Stalenhoef AFH. Consumption of tall oil-derived phytosterols in a chocolate matrix significantly decreases plasma total and low-density lipoprotein-cholesterol levels. Br J Nutr. 2002;88:479-88.
21. Woodgate D, Chan CH, Conquer JA. Cholesterol-lowering ability of a phytostanol softgel supplement in adults with

mild to moderate hypercholesterolemia. Lipids. 2006;41:127-32.
22. Goldberg AC, Ostlund RE Jr, Bateman JH, Schimmoeller L, McPherson TB, Spilburg CA. Effect of plant stanol tablets on low-density lipoprotein cholesterol lowering in patients on statin drugs. Am J Cardiol. 2006;97:376-9.
23. Polagruto JA, Wang-Polagruto JF, Braun MM, Lee L, Kwik-Uribe C, Keen CL. Cocoa flavanol-enriched snack bars containing phytosterols effectively lower total and low-density lipoprotein cholesterol levels. J Am Diet Assoc. 2006;106:1804-13.
24. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285:2486–97.
25. Moruisi KG, Oosthuizen W, Opperman AM. Phytosterols/stnols lower choleaterol concentrations in familial hypercholesterolemic subjects:a system review with meta analysis. J Am Coll Nutr. 2006;25:41-48.

Original Article

The effects of phytosterols/stanols on blood lipid profiles: a systematic review with meta-analysis

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植物甾醇对非家族性高胆固醇血症人群血脂作用的系统评价

为了探讨植物甾醇对非家族性高胆固醇血症人群的降脂作用，本研究通过全面检索 Medline、EMbase 等国际期刊数据库和相关出版物的参考文献，选择人体随机对照介入试验，以血浆低密度胆固醇、总胆固醇、高密度胆固醇和甘油三酯水平为分析指标进行系统评价。由两位评价者独立阅读相关文献并提取数据，只有文献质量达到要求的研究才被纳入评价。最后在 76 篇相关文献中共纳入 20 项研究进行评价。结果显示，与对照组相比，植物甾醇能显著降低试验组的血浆低密度胆固醇、总胆固醇和甘油三酯水平，其平均效应值分别为[-0.35 mmol/L, 95%CI(-0.47, -0.22), p<0.00001]、[-0.36 mmol/L, 95%CI(-0.46, -0.26), p<0.00001]和[-0.1 mmol/L, 95%CI(-0.16, -0.03), p=0.004]。系统评价的结果表明每日随食物摄入 2 g 植物甾醇对非家族性高胆固醇血症人群有良好的降低血浆胆固醇作用。

关键词：植物甾醇，植物甾烷醇酯，脂质，系统评价，統合分析