Meta-analysis

Plant sterols/stanols as cholesterol lowering agents: A meta-analysis of randomized controlled trials

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Abstract

***Background*:** Consumption of plant sterols has been reported to reduce low density lipoprotein (LDL) cholesterol concentrations by 5–15%. Factors that affect plant sterol efficacy are still to be determined. ***Objectives*:** To more precisely quantify the effect of plant sterol enriched products on LDL cholesterol concentrations than what is reported previously, and to identify and quantify the effects of subjects' characteristics, food carrier, frequency and time of intake on efficacy of plant sterols as cholesterol lowering agents.
***Design*:** Fifty-nine eligible randomized clinical trials published from 1992 to 2006 were identified from five databases. Weighted mean effect sizes were calculated for net differences in LDL levels using a random effect model.
***Results*:** Plant sterol containing products decreased LDL levels by 0.31 mmol/L (95% CI, −0.35 to −0.27, $P = <0.0001$) compared with placebo. Between trial heterogeneity was evident (Chi-square test, $P = <0.0001$) indicating that the observed differences between trial results were unlikely to have been caused by chance. Reductions in LDL levels were greater in individuals with high baseline LDL levels compared with those with normal to borderline baseline LDL levels. Reductions in LDL were greater when plant sterols were incorporated into fat spreads, mayonnaise and salad dressing, milk and yoghurt comparing with other food products such as croissants and muffins, orange juice, non-fat beverages, cereal bars, and chocolate. Plant sterols consumed as a single morning dose did not have a significant effect on LDL cholesterol levels.
***Conclusion*:** Plant sterol containing products reduced LDL concentrations but the reduction was related to individuals' baseline LDL levels, food carrier, and frequency and time of intake.

Keywords: *meta-analysis*; *plant sterols*; *LDL cholesterol*; *intake frequency*; *single dose*; *food carrier*

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Dietary incorporation of plant sterols and stanols is recommended for blood cholesterol reduction (1, 2). Berger et al. reviewed clinical trials on efficacy of plant sterols as cholesterol lowering agents and reported that the consumption of plant sterols/stanols have been reported to reduce low density lipoprotein (LDL) cholesterol levels by 5–15% (3). Reasons for such large variations need to be investigated.

Earlier studies that have tested the efficacy of plant sterols/stanols as cholesterol lowering agents incorporated plant sterols/stanols into either regular or low fat spreads (8–13). Since it appears counterintuitive to use a high fat food product to deliver a cholesterol lowering agent, clinical trials have been conducted to test the efficacy of plant sterols/stanols incorporated into low fat products (14). A number of clinical trials have tested the efficacy of plant sterols/stanols incorporated into low fat foods including low fat milk (15, 16), low fat yoghurt (16–20), bakery products (21), orange juice (22, 23), cereal bars (24) and low and non-fat beverages (25–27). However, although plant sterols/stanols that are incorporated into low fat food have been shown to reduce blood cholesterol (24, 27, 28), the same food carrier tested in different trials gave different magnitude in LDL cholesterol reduction. Plant sterol/stanol enriched yoghurt and milk drinks have resulted in LDL cholesterol reduction in the range of 5–14% in various clinical trials (29). The study by Clifton et al. (30) compared the effect of plant stanol esterified to fatty acids and incorporated in a number of food matrices including bread, breakfast cereal, milk and yoghurt on plasma lipids. Plant stanol esters in low fat milk were almost three times more effective than in bread and cereal

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in lowering plasma cholesterol levels. Whether all plant sterols/stanols enriched low fat food matrices are efficacious as plant sterol/stanol enriched spread carrier in lowering blood cholesterol has not been studied thoroughly. It remains to be determined which food matrices are viable carriers to deliver an effective dose of plant sterols/stanols.

The optimal number of servings per day of plant sterol/stanol containing products was addressed in only one study. Plat et al. (31) showed that 2.5 g of plant stanols in margarines and shortenings consumed for four weeks once per day at lunch or divided over three meals, lowered LDL cholesterol levels to a similar extent, about 10%. The intake of a single dose of plant sterol/stanol enriched products is thought to increase consumers' compliance and adds convenience. However, further studies using a single dose of plant sterols/stanols consumed either at breakfast (18, 19, 32), or with lunch or the principal meal (19, 31, 33, 34) yielded conflicting results. For example, when plant sterol enriched margarine was consumed with breakfast, no reduction in cholesterol levels was observed (32), in spite of the previously demonstrated efficacy as a single serving at lunch (31). In another study, intake of the single dose of plant sterols provided in yoghurt drinks with lunch resulted in a larger decrease in LDL levels than the intake of same dose of plant sterols provided 30 min before breakfast (19). Since plant sterol/stanol products are being marketed for consumption once a day, it remains to be investigated whether the effect of single dose of plant sterols/stanols consumed at different time of the day is comparable to that consumed as multiple dosages throughout the day.

Several potential modifiers for the effect of plant sterol/stanol supplementation on reduction of LDL levels were studied in some trials, including age and gender, baseline LDL levels, and genetic profile. Again, results from various studies are inconsistent. For example, baseline LDL levels have been shown to modify the effect of plant sterols/stanol in some (35, 36), but not other studies (8, 37, 38). Furthermore, identification of effect modifiers in the cholesterol lowering action of plant sterols/stanol will help target individuals who may benefit more from such an intervention.

Accordingly, instead of conducting additional randomized clinical trials to resolve the disagreement surrounding the influence of the aforementioned factors on the cholesterol lowering action of plant sterols/stanols, it was considered that an appropriate meta-analysis could be used as an alternative novel approach. Previous meta-analyses have studied the efficacy of plant sterols/stanols as cholesterol lowering agents. The first (4) looked at the cholesterol lowering action of plant sterols/stanols added to fat spreads mostly in the form of margarines. Another (5) looked at the efficacy and safety of plant sterols/stanols as cholesterol lowering agents, but since 2003 a number of clinical trials have examined the efficacy of low fat foods containing plant sterols/stanols and observed substantially weaker effects. A recent meta-analysis (6) sought to investigate effects of plant sterols/stanol in lowering total and LDL cholesterol levels of familial hypercholesterolemia subjects. Two previous meta-analyses conducted on plant sterols/stanols were non-systematic reviews (4, 5), which failed to describe how reviewers searched, selected and evaluated the quality of studies. Narrative reviews are qualitative summaries of a certain topic (7). While systematic meta-analyses include a comprehensive search of the primary studies on a specific clinical question, selection of studies by using clear eligibility criteria, critical evaluation of the quality of studies, and generating results using a pre-specified method (7).

Meta-analysis is a statistical tool that generates pooled estimates of effects from the results of randomized controlled trials (7). It is an unbiased tool to assess an intervention and may lead to resolution of controversy. Therefore, a systematic meta-analysis could resolve the apparent controversy concerning the influences of food carrier, frequency and time of intake, as well as subjects' baseline characteristics on cholesterol lowering action of plant sterols/stanols.

The objectives of the present meta-analysis were to more precisely quantify the effect of plant sterol/stanol enriched products on LDL cholesterol concentrations and to identify and quantify the effect of subjects' characteristics, food carrier, frequency and time of intake.

Materials and methods

Literature search

Studies that examined the efficacy of plant sterols/stanols as cholesterol lowering agents in humans were identified by searching five databases PubMed, Embase, Medline, Cochrane Library and Web of Science using the terms "plant sterol", "plant stanol" "phytosterol" and "phytostanol" as words in the title, abstract or keywords. When available, the search was restricted to clinical trials. In addition, a manual search using reference lists of review articles (3–5, 39) was performed. For non-English language literature, if available, the abstract written in English was used to extract the required information; otherwise the trial was not included in the analysis. All citations were exported into reference manager software (EndNote version 8.0.2) and studies on plant sterols/stanols and cholesterol metabolism were identified. Fifty nine eligible randomized clinical trials published from 1992 to 2006 were identified from the five databases.

Selection criteria

Randomized placebo controlled studies conducted to test the efficacy of plant sterols/stanols incorporated into

food matrices on circulating cholesterol levels in adults were included in this meta-analysis. Therefore, studies were first excluded from the meta-analysis for not measuring circulating LDL levels as a primary or secondary outcome, for having duration of intervention of less than two weeks, for examining children or adults who were homo- or heterozygote for sitosterolemia or who possessed a history of cardiovascular disease. Studies were also excluded for having a co-intervention that could not be separated from plant sterol/stanol treatment, for incorporating plant sterols/stanols in the form of capsule or tablets, or for not having a control group or an appropriate control /placebo. In addition, studies were excluded if lipid profiling was done on non-fasting blood samples or if lipid profile data were published elsewhere. A total of 84 clinical trials met the first inclusion criteria and were then screened for the quality criteria (Fig. 1).

Quality assessment of trials

Randomized controlled studies were assessed for methodological quality with the Jadad score as described in Table 1 (40). A Jadad score of three or above, out of a maximum of five, was used to indicate that a study is of reasonable quality to be included in the meta-analysis (41).

Data abstraction

All data were abstracted from the original articles. No data were directly obtained from the original authors. For studies that met the inclusion criteria and that possessed a Jadad score of equal or more than three, data were extracted for parameters related to (i) trial design; (ii) type of plant sterols/stanols; (iii) dose (g/day) and duration of plant sterol/stanol treatment; (iv) frequency and time of intake of plant sterols/stanols; (v) food carrier, to which plant sterols/stanols were incorporate; (vi) characteristics of the study population; (vii) the mean values and the standard deviations (SD) of LDL cholesterol levels; and (viii) sample size. Two reviewers (SSA and RB) independently identified articles for inclusion, assessed quality and extracted data.

Quantitative data synthesis

For studies that reported multiple time points for the same subjects, only endpoints for the longest duration of the intervention were used. For studies in which the outcomes were presented as percentage change from baseline, and no endpoint data were available (37, 42, 43), endpoint data were imputed using the baseline values and percentage change from baseline and the SD of the baseline data for the endpoint SD. Where studies

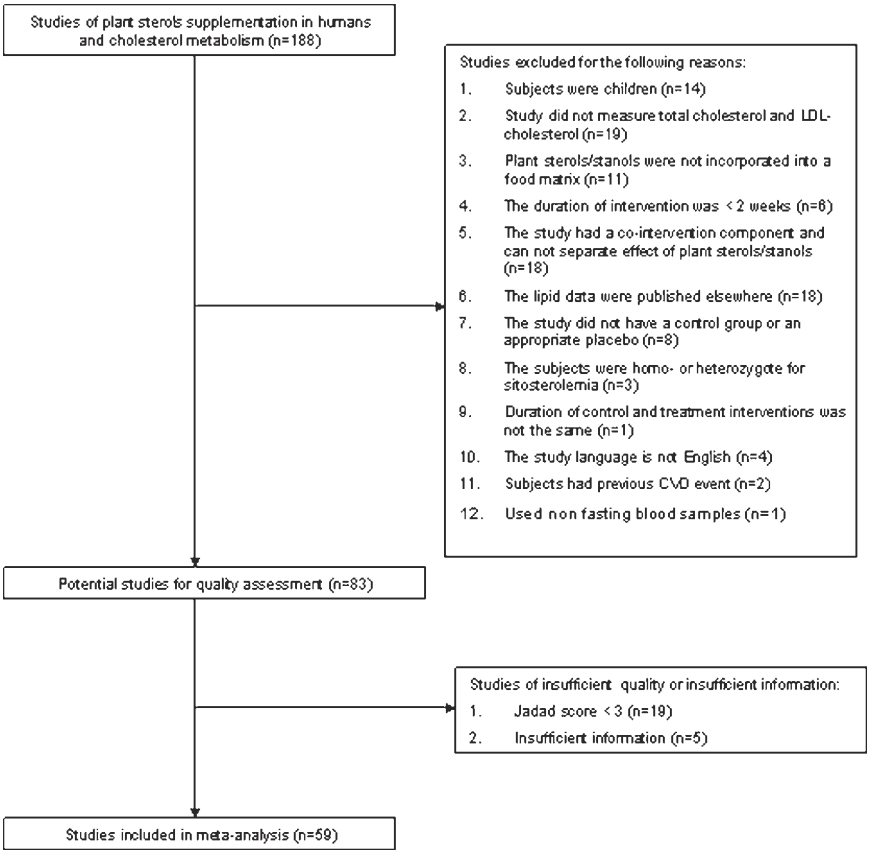

Fig. 1. Selection of randomized placebo controlled studies for meta-analysis of plant sterols and circulating cholesterol levels.

Table 1. Calculation of Jadad score to assess study quality[1]

Criterion	Score
If study was described as randomized (this includes words such as randomly, random, and randomization)	0/1
If the method used to generate the sequence of randomization was described and was appropriate (table of random numbers, computer-generated, etc.)	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)	0/−1
If the study was described as double blind	0/1
If the method of double blinding was described and was appropriate (identical placebo, active placebo, dummy, etc.)	0/1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet versus. injection with no double dummy).	0/−1
If there was a description of withdrawals and dropouts	0/1

[1]Adapted from Jadad et al. (40).

reported absolute change from baseline and no endpoint data were available (26, 44, 45), we imputed endpoints using baseline plus change for the mean and using the SD of the baseline data for the endpoint SD.

The primary outcome for this meta-analysis was the difference in LDL cholesterol levels, reported in mmol/L, due to plant sterol/stanol treatment. For parallel arm designed trials, endpoint LDL cholesterol in the treatment group was subtracted from endpoint LDL cholesterol in the control group (46). We did not use differences in changes from baseline as the primary outcome because this would imply imputing SDs for changes from baseline for the majority of parallel studies, which is not recommended (46). For crossover trials, the LDL cholesterol value at the end of the treatment period was subtracted from that at the end of the control period (46). Within-individual changes were used when presented; otherwise, group means were used. SDs were extracted from the studies or, if not reported, derived from standards errors (SDs) of mean, confidence intervals (CIs), paired t-value or *P*-value as provided (46). If different treatments were tested within the same trial, they were evaluated as separate strata, as is described by "a, b, c and d" suffixes in Tables and Figures. To obtain the pooled treatment effect size (ES), estimates and SE were entered into RevMan 4.2 under the "generic inverse variance" outcome. Heterogeneity between trial results was tested for using a standard chi-squared test. A *P*-value <0.1 was used to indicate that significant heterogeneity was present (46).

Calculations used in this meta-analysis are presented in the Appendix. Estimates of the pooled treatment ES of plant sterol/stanol containing food on LDL cholesterol levels and 95% CIs were calculated by using both fixed effect and random effect models. If the test for heterogeneity was significant, we presented the results of the random effect models. Otherwise, estimated results based on a fixed effect model are presented. We presented the ES as mmol/L, and not as percentage difference, as most of the studies did not report the SD of the percentage difference in LDL values between the control and the treatment group or phases. The presence of publication bias was examined for using a funnel plot, in which the SEs of the studies were plotted against their corresponding ES.

Results

Fifty-nine studies comprising 95 relevant strata were assessed as eligible for meta-analysis with >4500 subjects. A summary of trial design and characteristics is shown in Table 2 and Table 3. Twenty-nine studies utilized a crossover design while 30 used a parallel design. Sample sizes ranged from 8 to 185 subjects.

Individual trial results and the pooled ES for all trials are shown in Fig. 2. In the overall pooled estimate, plant sterol/stanol consumption decreased LDL levels by 0.31 mmol/L (95% CI, −0.35 to −0.27, $P=<0.0001$) compared with placebo. Between- trial heterogeneity was evident (Chi-square test, $P=<0.0001$; $I^2=65\%$). It was estimated that as 65% of the variability in the ES is due to heterogeneity between the trials (clinical and methodological diversity) rather than chance. Thus, we performed a subgroup analysis according to predefined criteria by subjects' characteristics and study design features as summarized in Table 4. Initial serum LDL cholesterol levels had a powerful effect on changes in lipid concentrations. Therefore, subjects were grouped into two groups, one included subjects with high baseline levels of LDL and the other group included subjects with low baseline levels of LDL, as defined according to ATPIII (85). A greater decrease in LDL levels was observed in subjects with optimal to borderline high levels of baseline LDL. The LDL cholesterol levels of the former decreased by 0.37 mmol/L (95% CI: −0.42, −0.31) and those of the latter decreased by 0.28 mmol/L (95% CI: −0.31, −0.25). The placebo adjusted reduction in LDL levels produced by consumption of plant sterols was the same across all age groups.

There was evidence of a dose response effect. The minimum (−0.25 mmol/L; 95% CI: −0.32, −0.18) and the maximum (−0.42 mmol/L; 95% CI: −0.46, −0.39) reductions in LDL cholesterol levels were achieved by the intake of <1.5g/ day and >2.5 g/ day of sterols/stanols, respectively. The reductions in LDL were −0.29 mmol/L (95% CI: −0.34, −0.24) and −0.32mmol/L (95% CI: −0.36, −0.28) for intakes of 1.5–2.0 g/d and 2.1–2.5 g/d, respectively.

Table 2. Design and subject characteristics of randomized controlled studies of plant sterols/stanols

Study ID	Reference	Design	Duration weeks	*n*	Subjects[1]	Sex [2]	Age years	BMI[3] kg/m^2
AbuMweis et al. (2006a)	(32)	crossover	4	30	borderline high	NR	59	25–29.9
AbuMweis et al. (2006b)	(32)	crossover	4	30	borderline high	NR	59	25–29.9
Algorta Pineda et al. (2005)	(34)	parallel	3	32	high	50–95% males	42	25–29.9
Alhassan et al. (2006)	(60)	parallel	5	26	near or above optimal	5–50% males	53Tx 52Co	25–29.9
Andersson et al. (1999)	(13)	parallel	8	40	high	5–50% males	55	25–29.9
Ayesh et al. (1999)	(61)	parallel	3 & 4	21	optimal	5–50% males	36	<24.9
Cater et al. (2005a)	(62)	crossover	6	8	NR	50–95% males	58	25–29.9
Cater et al. (2005b)	(62)	crossover	6	8	NR	50–95% males	58	25–29.9
Cater et al. (2005c)	(62)	crossover	6	8	NR	50–95% males	58	25–29.9
Cater et al. (2005d)	(62)	crossover	8	10	near or above optimal	>95% males	66	25–29.9
Christiansen et al. (2001a)	(63)	parallel	26	92	high	NR	51	<24.9
Christiansen et al. (2001b)	(63)	parallel	26	89	high	NR	51	25–29.9
Cleghorn et al. (2003)	(64)	crossover	4	50	borderline high	5–50% males	47	25–29.9
Davidson et al. (2001a)	(28)	parallel	8	42	borderline high	50–95% males;	46	NR
Davidson et al. (2001b)	(28)	parallel	8	40	borderline high	50–95% males;	46	NR
Davidson et al. (2001c)	(28)	parallel	8	44	borderline high	50–95% males;	46	NR
De Graaf et al. (2002)	(47)	parallel	4	62	high	50–95% males;	56 Tx 58 Co	25–29.9
Deavarj et al. (2006)	(22)	parallel	8	72	borderline high	5–50% males	44 Tx 48 Co	<24.9
Devaraj et al. (2004)	(23)	parallel	8	72	borderline high	5–50% males	41 Tx 44 Co	25–29.9
Doornbos et al. (2006a)	(19)	parallel	4	72	borderline high	5–50% males	57	25–29.9
Doornbos et al. (2006b)	(19)	parallel	4	71	borderline high	5–50% males	57	25–29.9
Doornbos et al. (2006c)	(19)	parallel	4	69	borderline high	5–50% males	57	25–29.9
Doornbos et al. (2006d)	(19)	parallel	4	71	borderline high	5–50% males	57	25–29.9
Gylling et al. (1994)	(65)	crossover	6	11	NR	>95% males	58	25–29.9
Gylling et al. (1999)	(66)	crossover	5	21	borderline high	<5% males	53	25–29.9
Hallikainen et al. (1999a)	(10)	parallel	8	37	high	5–50% males	41 Tx 46 Co	<24.9 Tx 25–29.9 Co
Hallikainen et al. (1999b)	(10)	parallel	8	35	high	5–50% males	43 Tx 46 Co	25–29.9
Hallikainen et al. (2000a)	(67)	crossover	4	34	high	NR	49	<24.9
Hallikainen et al. (2000b)	(67)	crossover	4	34	high	NR	49	<24.9
Hendriks et al. (1999a)	(12)	crossover	3.5	80	near or above optimal	5–50% males	37	<24.9
Hendriks et al. (1999b)	(12)	crossover	3.5	80	near or above optimal	5–50% males	37	<24.9
Hendriks et al. (1999c)	(12)	crossover	3.5	80	near or above optimal	5–50% males	37	<24.9
Hendriks et al. (2003)	(68)	parallel	52	185	borderline high	5–50% males	48	<24.9
Hyun et al. (2005)	(18)	parallel	4	51	near or above optimal	50–95% males;	29	<24.9
Jakulj et al. (2005)	(69)	crossover	4	39	very high	50–95% males;	56	25–29.9
Jones et al. (1999)	(54)	parallel	4.3	32	high & very high	>95% males	NR	NR
Jones et al. (2000a)	(50)	crossover	3	15	high	>95% males	NR	NR
Jones et al. (2000b)	(50)	crossover	3	15	high	>95% males	NR	NR
Jones et al. (2003a)	(27)	crossover	3	15	borderline high	50–95% males	NR	NR
Jones et al. (2003b)	(27)	crossover	3	15	borderline high	50–95% males	NR	NR
Judd et al. (2002)	(70)	crossover	3	53	borderline high	5–50% males	47	25–29.9
Jauhianen et al. (2006)	(49)	parallel	5	67	borderline high	5–50% males	43	NR
Lau et al. (2005a)	(71)	crossover	3	15	borderline high	5–50% males	55	25–29.9
Lau et al. (2005b)	(71)	crossover	3	14	borderline high	5–50% males	55	30–34.9

Table 2 (*Continued*)

Study ID	Reference	Design	Duration weeks	*n*	Subjects[1]	Sex [2]	Age years	BMI[3] kg/m^2
Lee et al. (2003)	(72)	parallel	12	81	high	5–50% males	60 TX 62 Co	25–29.9
Lottenberg et al. (2003)	(73)	crossover	4	60	very high	5–50% males	NR	NR
Maki et al. (2001a)	(37)	parallel	5	158	borderline high	5–50% males	59 Tx 58 Co	25–29.9
Maki et al. (2001b)	(37)	parallel	5	118	borderline high	5–50% males	60 Tx 58 Co	25–29.9
Matvienko et al. (2002)	(33)	parallel	4	34	borderline high	>95% males	22 Tx 22 Co	25–29.9
Mensink et al. (2002)	(20)	parallel	4	60	near or above optimal	5–50% males	36	<24.9
Miettinen and Vanhanen (1994a)	(45)	parallel	9	17	NR	50–95% males	45	25–29.9
Miettinen and Vanhanen (1994b)	(45)	parallel	9	15	NR	50–95% males	45	25–29.9
Miettinen and Vanhanen (1994c)	(45)	parallel	9	15	NR	50–95% males	45	25–29.9
Mussner et al. (2002)	(35)	crossover	3	63	borderline high	5–50% males	42	<24.9
Naumann et al. (2003a)	(36)	crossover crossover	3	42	near or above optimal	5–50% males	32 w 37 m	<24.9
Naumann et al. (2003b)	(36)	crossover	3	42	near or above optimal	5–50% males	32 w 37 m	<24.9
Neil et al. (2001)	(74)	crossover	8	29	very high	5–50% males	53 Tx 50 Co	25–29.9
Nguyen et al. (1999a)	(75)	parallel	8	159	borderline high	5–50% males	53	25–29.9
Nguyen et al. (1999b)	(75)	parallel	8	157	borderline high	5–50% males	53	25–29.9
Nguyen et al. (1999c)	(75)	parallel	8	162	borderline high	5–50% males	53	25–29.9
Nigon et al. (2001)	(76)	crossover	8	53	borderline high & high	5–50% males	58	< 24.9
Noakes et al. (2002a)	(77)	crossover	3	46	high	5–50% males	58 w 55 m	25–29.9
Noakes et al. (2002b)	(77)	crossover	3	46	high	5–50% males	58 w 55 m	25–29.9
Noakes et al. (2002c)	(77)	crossover	3	35	high	50–95% males	56 w 58 m	25–29.9
Noakes et al. (2005a)	(16)	crossover	3	40	high	5–50% males	60	25–29.9
Noakes et al. (2005b)	(16)	crossover	3	40	high	5–50% males	60	25–29.9
Ntanios et al. (2002)	(38)	crossover	3	53	near or above optimal	5–50% males	45	<24.9
Plat and Mensink et al. (2000a)	(78)	parallel	8	78	near or above optimal	5–50% males	33	<24.9
Plat and Mensink et al. (2000b)	(78)	parallel	8	76	near or above optimal	5–50% males	33	<24.9
Plat et al. (2000a)	(31)	crossover	4	39	optimal	5–50% males	31	<24.9
Plat et al. (2000b)	(31)	crossover	4	39	optimal	5–50% males	31	<24.9
Polagruto et al. (2006)	(48)	parallel	6	67	high	5–50% males	49 Tx 56 Co	25–29.9
Quilez et al. (2003)	(21)	parallel	8	57	optimal	5–50% males	31	<24.9
Saito et al. (2006a)	(79)	parallel	4	33	borderline high	>95% males	38 Tx 39 Co	<24.9
Saito et al. (2006b)	(79)	parallel	4	33	borderline high	>95% males	39	<24.9
Saito et al. (2006c)	(79)	parallel	4	34	borderline high	>95% males	38 Tx 39 Co	<24.9
Seki et al. (2003)	(43)	parallel	12	60	borderline high	>95% males	39	<24.9
Sierksma et al. (1999)	(80)	crossover	3	75	NR	50–95% males	44	<24.9
Simons et al. (2002)	(42)	parallel	4	77	very high	50–95% males	58 Tx 60 Co	25–29.9
Spilburg et al. (2003)	(26)	parallel	4	24	borderline high	50–95% males	51	25–29.9
Temme et al. (2002)	(81)	crossover	4	42	high	50–95% males	55	25–29.9
Thomsen et al. (2004a)	(15)	crossover	4	69	high	5–50% males	60	25–29.9
Thomsen et al. (2004b)	(15)	crossover	4	69	high	5–50% males	60	25–29.9
Vanhanen et al. (1993)	(82)	parallel	6	67	borderline high	50–95% males	48 Tx 43 Co	25–29.9
Vanhanen et al. (1994)	(83)	parallel	6	14	borderline high	5–50% males	55	25–29.9
Vanstone et al. (2002a)	(51)	crossover	3	15	high	50–95% males	48	30–34.9
Vanstone et al. (2002b)	(51)	crossover	3	15	high	50–95% males	48	30–34.9

Table 2 (Continued)

Study ID	Reference	Design	Duration weeks	*n*	Subjects[1]	Sex [2]	Age years	BMI[3] kg/m^2
Vanstone et al. (2002c)	(51)	crossover	3	15	high	50–95% males	48	30–34.9
Vissers et al. (2000)	(84)	crossover	3	60	NR	5–50% males	NR	NR
Volpe et al. (2001)	(17)	crossover	4	30	high	50–95% males	NR	<24.9
Weststrate et al. (1998a)	(8)	crossover	3.5	95	borderline high	50% males	45	<24.9
Weststrate et al. (1998b)	(8)	crossover	3.5	95	borderline high	50% males	45	<24.9
Yoshida et al. (2006a)	(24)	crossover	3	16	high	5–50% males	55	25–29.9
Yoshida et al. (2006b)	(24)	crossover	3	13	borderline high	5–50% males	57	30–34.9

NR = not reported, NC = Not clear, Tx = treatment; Co = control; w = women; m = men.

[1] Subjects were classified according to total or LDL cholesterol baseline levels reported in baseline characteristic. Classification based on ATPIII (85).

[2] Predominant sex.

[3]Body Mass Index.

The effect of plantsterols//stanols on LDL cholesterol is influenced by the food carrier to which plant sterols/stanols are incorporated. We predefined the food product groups according to their fat content, i.e. low fat products contain 3 g or less fat per serving, as well as their physical form, i.e liquid versus solid. Therefore, we ended up with four groups, i.e. fat spreads, mayonnaise and salad dressing, milk and yoghurt, and other food group. Other food products subgroup included studies testing the efficacy of plant sterols/stanols incorporated in chocolate, cereal bars, beverages, juices, meat, and croissants and muffins. All these were included in one subgroup and not further analyzed because of an insufficient number of clinical trials.

Plant sterols/stanols incorporated into fat spreads, mayonnaise and salad dressing or milk and yoghurt reduced LDL cholesterol levels to a greater extent than plant sterols/stanols incorporated into other food products. Compared to control, LDL levels were reduced by 0.33 (95% CI, −0.38 to −0.28), 0.32 (95% CI, −0.40 to −0.25), −0.34 (95% CI, −0.40 to −0.28) and 0.20 (95% CI, −0.28 to −0.11) mmol/L in the fat spreads, mayonnaise and salad dressing, milk and yoghurt, and other food products, respectively. Other food product subgroups included studies testing the efficacy of plant sterols/stanols incorporated in chocolate (47, 48), orange juice (22, 23), cheese (49), non-fat beverage (26, 27), meat (33), croissants and muffins (21), oil in bread (43), and cereal bars (24).

The favorable effect of plant sterols/stanols on LDL cholesterol levels was also shown to be influenced by the frequency and time of intake of plant sterols. For instance, plant sterols/stanols consumed 2–3 times/day reduced LDL cholesterol levels by 0.34 mmol/L (95% CI: −0.38, −0.18) while plant sterols/stanols consumed once per day in the morning did not result in a significant reduction in LDL levels. On the other hand, plant sterols/stanols consumed once/day with lunch or the principal meal reduced LDL levels by 0.30 mmol/L (95%: −0.39, −0.21).

We found no evidence of publication bias in this meta-analysis, as indicated by the funnel plot symmetry (Fig. 3).

Discussion

The present meta-analysis is the first systematic quantitative review of randomized clinical trials yielding information on factors that might affect efficacy of plant sterols/stanols as cholesterol lowering agents. Since the meta-analyses of Law (4) and Katan et al. (5) examining plant sterol/stanol effects on circulating cholesterol levels, several studies have been conducted examining the action of various plant sterol/stanol containing products on blood cholesterol levels using different study designs. The present work shows that the intake of plant sterol/stanol containing food products was associated with a significant decrease in LDL cholesterol (−0.31 mmol/L). However, the substantial heterogeneity among individual trials indicates that the effects of plant sterols/stanols on LDL cholesterol levels are not uniform.

A larger reduction in LDL cholesterol levels was observed in subjects with a high to very high baseline levels of LDL, compared to those with optimal to borderline high baseline levels. Some previous (35, 36), but not other studies (8, 37, 38), have reported that the higher the baseline levels of LDL-cholesterol the more the reduction in LDL due to plant sterols consumption. The present meta-analysis has confirmed that baseline LDL cholesterol levels affect magnitude of reduction in LDL after plant sterol/stanol consumption which could explain the wide variation in responsiveness seen in previous studies. Nevertheless, plant sterols/stanols do reduce LDL levels in individuals with normal to high baseline LDL levels as well as in adults across different age groups. Therefore, everyone, excluding individuals

Table 3. Features of plant sterol intervention of randomized controlled studies of plant sterols/stanols

		Plant sterols/stanols				
Study ID	Reference	Carrier[1]	Type[2]	Dose g/day as free	Frequency	Time[3]
AbuMweis et al. (2006a)	(32)	margarine	free sterols	1.7	1	at breakfast
AbuMweis et al. (2006b)	(32)	margarine	sterol esters	1.7	1	at breakfast
Algorta Pineda et al. (2005)	(34)	yoghurt	stanol esters	2.0	1	with the main meal
Alhassan et al. (2006)	(60)	margarine	stanol esters	NR	NR	NR
Andersson et al. (1999	(13)	margarine	stanol esters	1.9	NR	NR
Ayesh et al. (1999)	(61)	margarine	sterol esters	8.6	2	breakfast+supper
Cater et al. (2005a)	(62)	margarine	stanol esters	2.0	3	with each meal
Cater et al. (2005b)	(62)	margarine	stanol esters	3.0	3	with each meal
Cater et al. (2005c)	(62)	margarine	stanol esters	4.0	3	with each meal
Cater et al. (2005d)	(62)	margarine	stanol esters	3.0	3	with each meal
Christiansen et al. (2001a)	(63)	margarine	free sterols	1.5	at least 2	NR
Christiansen et al. (2001b)	(63)	margarine	free sterols	3.0	at least 2	NR
Cleghorn et al. (2003)	(64)	margarine	sterol esters	2.0	NR	NR
Davidson et al. (2001a)	(28)	margarine	sterol esters	3.0	NR	NR
Davidson et al. (2001b)	(28)	salad dressing	sterol esters	6.0	NR	NR
Davidson et al. (2001c)	(28)	spread+salad dressing	sterol esters	9.0	NR	NR
De Graaf et al. (2002)	(47)	chocolate bars	free sterols	1.8	3	with each meal
Deavarj et al. (2006)	(22)	Orange juice	free sterols	2.0	2	breakfast+supper
Devaraj et al. (2004)	(23)	Orange juice	free sterols	2.0	2	NR
Doornbos et al. (2006a)	(19)	yoghurt	sterol esters	3.2	1	at breakfast
Doornbos et al. (2006b)	(19)	yoghurt	sterol esters	3.2	1	at lunch
Doornbos et al. (2006c)	(19)	yoghurt	sterol esters	2.8	1	at breakfast
Doornbos et al. (2006d)	(19)	yoghurt	sterol esters	2.8	1	at lunch
Gylling et al. (1994)	(65)	margarine	stanol esters	3.0	3	at breakfast+lunch +supper
Gylling et al. (1999)	(66)	dairy spread	stanol esters	2.5	NR	NR
Hallikainen et al. (1999a)	(10)	margarine	stanol esters	2.2	NR	NR
Hallikainen et al. (1999b)	(10)	margarine	stanol esters	2.3	NR	NR
Hallikainen et al. (2000a)	(67)	margarine	sterol esters	2.1	2 to 3	NR
Hallikainen et al. (2000b)	(67)	margarine	stanol esters	2.0	2 to 3	NR
Hendriks et al. (1999a)	(12)	margarine	sterol esters	0.8	2	at lunch and supper
Hendriks et al. (1999b)	(12)	margarine	sterol esters	1.6	2	at lunch and supper
Hendriks et al. (1999c)	(12)	margarine	sterol esters	3.2	2	at lunch and supper
Hendriks et al. (2003)	(68)	margarine	sterol esters	1.6	2	at breakfast+lunch or supper
Hyun et al. (2005)	(18)	yoghurt	stanol esters	2.0	1	at breakfast
Jakulj et al. (2005)	(69)	margarine	sterol esters	2.0	NR	NR
Jones et al. (1999)	(54)	margarine	free sterols	1.7	3	at breakfast+lunch+ supper
Jones et al. (2000a)	(50)	margarine	sterol esters	1.8	3	at breakfast+lunch+ supper

Table 3 (*Continued*)

		Plant sterols/stanols				
Study ID	Reference	Carrier[1]	Type[2]	Dose g/day as free	Frequency	Time[3]
Jones et al. (2000b)	(50)	margarine	stanol esters	1.8	3	at breakfast+lunch+supper
Jones et al. (2003a)	(27)	beverage	free sterols	1.8	3	at breakfast+lunch+supper
Jones et al. (2003b)	(27)	beverage	free sterols	1.8	3	at breakfast+lunch+supper
Judd et al. (2002)	(70)	salad dressing	sterol esters	2.2	2	at lunch and supper
Jauhianen et al. (2006)	(49)	soft cheese	stanol esters	2	1 or 2	at lunch or with the main meal
Lau et al. (2005a)	(71)	margarine	free sterols	1.8	1	at breakfast
Lau et al. (2005b)	(71)	margarine	free stanols	1.8	1	at breakfast
Lee et al. (2003)	(72)	margarine	sterol esters	1.6	2	breakfast+supper
Lottenberg et al. (2003)	(73)	margarine	sterol esters	1.7	3	at breakfast+lunch+supper
Maki et al. (2001a)	(37)	margarine	sterol esters	1.1	2	NR
Maki et al. (2001b)	(37)	margarine	sterol esters	2.2	2	NR
Matvienko et al. (2002)	(33)	meat	sterol esters	2.7	1	at lunch
Mensink et al. (2002)	(20)	yoghurt	stanol esters	3.0	2 or 3	with each meal or breakfast+supper
Miettinen and Vanhanen (1994a)	(45)	mayonnaise	free sterols	0.7	NR	NR
Miettinen and Vanhanen (1994b)	(45)	mayonnaise	free stanols	0.7	NR	NR
Miettinen and Vanhanen (1994c)	(45)	mayonnaise	stanol esters	0.8	NR	NR
Mussner et al. (2002)	(35)	margarine	sterol esters	1.8	2	breakfast+supper
Naumann et al. (2003a)	(36)	margarine	mixture of sterol and stanol esters	2.0	NR	NR
Naumann et al. (2003b)	(36)	margarine	mixture of sterol and stanol esters	2.0	NR	NR
Neil et al. (2001)	(74)	margarine	sterol esters	2.5	NR	NR
Nguyen et al. (1999a)	(75)	margarine	stanol esters	3.0	3	NR
Nguyen et al. (1999b)	(75)	margarine	stanol esters	3.0	3	NR
Nguyen et al. (1999c)	(75)	margarine	stanol esters	2.0	3	NR
Nigon et al. (2001)	(76)	margarine	sterol esters	1.6	3	at breakfast+lunch+supper
Noakes et al. (2002a)	(77)	margarine	sterol esters	2.3	3	at breakfast+lunch+supper
Noakes et al. (2002b)	(77)	margarine	stanol esters	2.5	3	at breakfast+lunch+supper
Noakes et al. (2002c)	(77)	margarine	sterol esters	2.0	3	at breakfast+lunch+supper
Noakes et al. (2005a)	(16)	yoghurt	sterol esters	1.8	2	NR
Noakes et al. (2005b)	(16)	yoghurt	stanol esters	1.7	2	NR
Ntanios et al. (2002)	(38)	margarine	sterol esters	1.8	2	at breakfast+lunch or supper
Plat and Mensink et al. (2000a)	(78)	margarine	stanol esters	3.8	3	at breakfast+lunch+supper
Plat and Mensink et al. (2000b)	(78)	margarine	stanol esters	4.0	3	at breakfast+lunch+supper

Table 3 (*Continued*)

Study ID	Reference	Plant sterols/stanols		Dose g/day as free	Frequency	Time[3]
		Carrier[1]	Type[2]			
Plat et al. (2000a)	(31)	margarine	stanol esters	2.5	1	at lunch
Plat et al. (2000b)	(31)	margarine + shortening in cakes and cookies	stanol esters	2.5	3	at breakfast + lunch + supper
Polagruto et al. (2006)	(48)	chocolate bars	sterol esters	1.5	2	between meals
Quilez et al. (2003)	(21)	croissants and muffins	sterol esters	3.2	2	NR
Saito et al. (2006a)	(79)	mayonnaise	sterol esters	0.3	1	NR
Saito et al. (2006b)	(79)	mayonnaise	sterol esters	0.4	1	NR
Saito et al. (2006c)	(79)	mayonnaise	sterol esters	0.5	1	NR
Seki et al. (2003)	(43)	vegetable oil	sterol esters	0.5	3	NR
Sierksma et al. (1999)	(80)	margarine	free sterols	0.8	NR	NR
Simons et al. (2002)	(42)	margarine	sterol esters	2.0	2	NR
Spilburg et al. (2003)	(26)	beverage	stanol lecithin	1.9	3	at breakfast + lunch + supper
Temme et al. (2002)	(81)	margarine	sterol esters	2.0	3	at breakfast + lunch + supper
Thomsen et al. (2004a)	(15)	milk	free sterols	1.2	2	at breakfast + lunch
Thomsen et al. (2004b)	(15)	milk	free sterols	1.6	2	at breakfast + lunch
Vanhanen et al. (1993)	(82)	mayonnaise	stanol esters	3.4	NR	NR
Vanhanen et al. (1994)	(83)	mayonnaise	stanol esters	1.5	NR	NR
Vanstone et al. (2002a)	(51)	dairy spread	free sterols	1.8	3	at breakfast + lunch + supper
Vanstone et al. (2002b)	(51)	dairy spread	free stanols	1.8	3	at breakfast + lunch + supper
Vanstone et al. (2002c)	(51)	dairy spread	mixture of free sterols and stanols	1.8	3	at breakfast + lunch + supper
Vissers et al. (2000)	(84)	margarine	free sterols	2.1	NR	NR
Volpe et al. (2001)	(17)	yoghurt	free sterols	1.0	1	NR
Weststrate et al. (1998a)	(8)	margarine	sterol esters	3.2	2	at lunch and supper
Weststrate et al. (1998b)	(8)	margarine	stanol esters	2.7	2	at lunch and supper
Yoshida et al. (2006a)	(24)	cereals bars	free sterols	1.8	3	between meals
Yoshida et al. (2006b)	(24)	cereals bars	free sterols	1.8	3	between meals

NR = not reported.
[1]Food carrier to which plant sterols/stanols were added.
[2]Type of plant sterols/ stanols.
[3]Time of consumption of plant sterol/stanol enriched products.

with β-sitosterolemia and heterozygote for the disease, can reduce his/her blood cholesterol levels by consuming plant sterols/stanols.

A positive dose response relationship was apparent with the greatest reduction in LDL levels obtained with intakes of 2.5 g/day of plant sterols/stanols. The meta-analysis by Katan et al. (5) showed that there is little additional effect of plant sterols/stanols at doses higher than 2.5 g/day. It should be noted that studies included in the subgroups with intakes $\geq$2.1 g/day incorporated plant sterols/stanols mainly in fat spreads, while the other subgroups included a variety of food products, which could explain why heterogeneity was absent with intakes of $\geq$2.1g/ day.

Plant sterols/stanols reduce LDL cholesterol through interfering with cholesterol absorption (9, 50–52). Because of their inert crystalline structure, pure plant sterols/stanols are not consistently effective in lowering cholesterol absorption. Thus, plant sterols/stanols should be adequately formulated before use. The most accepted method used to optimize the effect of plant sterols/stanols on cholesterol absorption is esterification to fatty acids

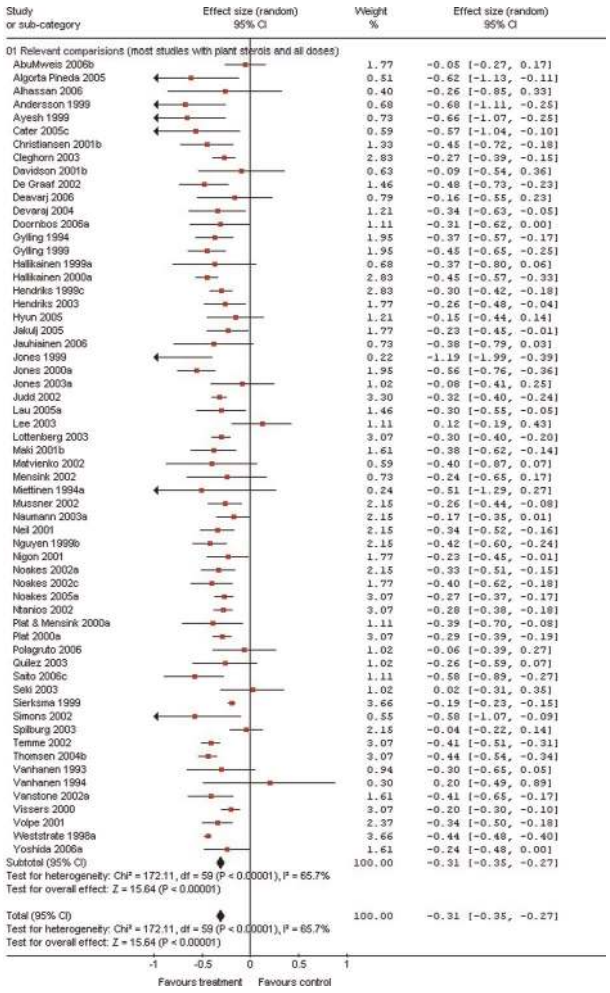

Fig. 2. Effect size and 95% CI in LDL cholesterol levels associated with consumption of plant sterol/stanol containing food products.

and dissolving plant sterols/stanols within food fats (53). Some studies have shown that free plant sterols/stanols when mixed with fat spread are also effective in reducing LDL cholesterol levels (51, 54). Later on, plant sterols/stanols were added to low and non- fat food products. The results presented here show that compared with plant sterol/stanol containing fat spreads, mayonnaise and salad dressing, and milk and yoghurt, other plant sterol/stanol containing food products, including chocolate (47, 48), orange juice (22, 23), cheese (49), non-fat beverage (26, 27), meat (33), croissants and muffins (21), oil in bread (43), and cereal bars (24) demonstrated less of a LDL-reduction efficacy. This finding highlights the importance of food carrier and proper formulation of plant sterols/stanols. Although milk and yoghurt drinks contain much less fat than fat spreads and mayonnaise, milk and yoghurt drinks demonstrated similar efficacy as of products with higher fat content. Thus, the food carrier to which plant sterols/stanols are added does not have to contain a high fat content to be an effective means of release of plant sterols/stanols to compete with cholesterol absorption, given that a proper plant sterol formulation is provided. Unfortunately, exact methods used to formulate plant sterols/stanols in the milk and yoghurt studies are not described in adequate detail. Studies were reported only if they used free (15, 17) or esterified (16, 18–20, 34) sterols or stanols. It is also possible that plant sterols/stanols in milk may be more readily incorporated into milk globule membranes, thus more readily compete with cholesterol for transfer into the micelles, while in the other low fat foods plant sterols/stanols may be trapped in the centre of the lipid droplets and not be available until the fat is digested (30). Future work is needed to identify proper formulation of plant sterols/stanols to improve their efficacy in food products other than those with high fat contents, i.e. vegetable and dairy spreads and mayonnaise, or milk and yoghurts.

In a previous study from our group, consumption of a single dose of different preparations of plant sterols in the morning failed to lower LDL levels (32). Some studies have shown that consumption of single dose of plant sterols/stanols with lunch lowered LDL levels (31, 33). One study has tested the efficacy of plant stanol consumed at different frequencies. In the study by Plat et al. (31) subjects consumed the plant stanol enriched margarine at breakfast and at lunch and ate a cake or cookie containing plant stanol-enriched shortening within one hour after supper. The higher portion of plant stanol during the 3 times/day phase was given using a different food carrier and was consumed without a meal in comparison to the single dose phase, thus, multiple factors might contribute to the differences in results obtained between the study phases. Additionally, the availability of plant stanol in the cakes and cookies might be affected by baking conditions. To what extent this affected the cholesterol lowering action of 3 times/day phase of plant stanol intake is unknown. To examine that question, we conducted a subgroup analysis looking at frequency and time of intake of plant sterols/stanols. The results of this meta-analysis show that the time of intake of a single dose of plant sterols/stanols may affect their cholesterol- lowering action as consumption of single dose with lunch or main meal, but not before or with breakfast, lowered LDL levels. The results of the subgroup analyses examining time of intake of plant sterols/stanols should be interpreted with caution, however. The number of subjects included in the individual subgroups was small and many of the included studies did not report data on time of intake, resulting in the potential to be misled by bias. The exact mechanisms responsible for the effects of plant sterols/stanols on LDL levels are still being investigated. Based on current knowledge, plant sterols/stanols reduce solubilization of cholesterol in micelles and also may affects the site of

Table 4. Pooled estimates of treatment effect on LDL cholesterol in subgroups of trials defined by subject characteristics and study design features

Variables	No. of trials, *n*	Effect size (95% CI) mmol/L	*P*	Test of heterogeneity, *P*
Age (years)				
20–39	10	−0.29 (−0.35, −0.23)	<0.0001	0.16
40–49	15	−0.32 (−0.41, −0.24)	<0.0001	<0.0001
50–60	21	−0.30 (−0.37, −0.23)	<0.0001	<0.0001
Baseline LDL cholesterol levels				
Optimal to border line high	33	−0.28 (−0.31, −0.25)	<0.0001	0.38
High to very high	22	−0.37 (−0.42, −0.31)	<0.0001	0.01
Plant sterol dose (g/day)				
<1.5	8	−0.25 (−0.32, −0.18)	<0.0001	0.05
1.5–2.0	35	−0.29 (−0.34, −0.24)	<0.0001	0.0003
2.1–2.5	9	−0.32 (−0.36, −0.28)	<0.0001	0.12
2.5	13	−0.42 (−0.46, −0.39)	<0.0001	0.57
Carrier				
Fat spreads	38	−0.33 (−0.38, −0.28)	<0.0001	<0.0001
Mayonnaise and salad dressing	6	−0.32 (−0.40, −0.25)	<0.0001	0.3
Milk and yoghurt	7	−0.34 (−0.40, −0.28)	<0.0001	0.18
Other than fat spreads, mayonnaise, salad dressing and milk and yoghurt	11	−0.20 (−0.28, −0.11)	<0.0001	0.21
Frequency of intake and time of intake				
2–3 times/day	38	−0.34 (−0.38, −0.18)	<0.0001	<0.0001
Once/day in the morning	4	−0.14 (−0.29, 0.00)	0.05	0.60
Once/ day in the afternoon or with main meal	3	−0.30 (−0.39, −0.21)	<0.0001	0.82

absorption and intra-cellular trafficking of cholesterol (55).

The efficacy of plant sterols/stanols as a cholesterol-lowering agent may demonstrate a time-of-day variation, possibly coinciding with the diurnal rhythm of cholesterol metabolism. Diurnal rhythm in cholesterol synthesis has been shown in humans (56–58), where cholesterol fractional synthetic rate values peaked at 6:00 h and were lowest during the daytime period. Moreover, bile acid synthesis in humans has also a diurnal rhythm that is opposite from the diurnal rhythm of cholesterol synthesis (59). Therefore, until mechanisms have been elucidated by which plant sterols/stanols and in particular single dose of plant sterols/stanols reduce LDL levels, and until there are more studies on consumption of plant sterols/stanols as single dose; plant sterols should be consumed in two to three portions per day.

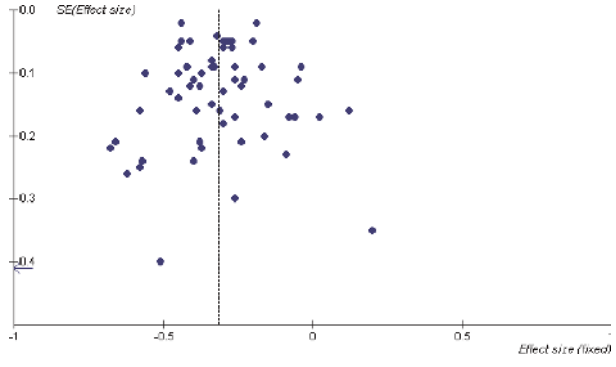

Fig. 3. Funnel plots of SE versus effect size for LDL cholesterol levels.

In conclusion, plant sterol/stanol containing products significantly reduced LDL concentrations but the reduction was related to individuals' baseline LDL levels, food carrier, frequency and time of intake.

Conflict of Interest and Funding

The contribution of the authors were as follow: SSA designed and implemented the search strategy, assessed study quality, extracted data, performed statistical analysis, interpreted the results and wrote and edited the manuscript. RIB was involved in literature search, study selection and quality assessment, and data extraction. PJHJ provided guidance and critical revision of the manuscript. We would like to thank Mrs Mary Cheang, a statistical consultant at the Department of Community Health Sciences, University of Manitoba, for reviewing

the method section and providing statistical advice. SSA and RIB have no conflict of interest. PJHJ is a consultant for Danone, Unilever, Forbes Meditech, Whitewave and Enymotec Inc.

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Appendix: Calculations used in the meta-analysis of plant sterols and LDL-cholesterol levels

Effect size (ES)

For parallel trials, endpoint LDL cholesterol in the treatment group was subtracted from endpoint LDL cholesterol in the control group (46). For crossover trials, LDL cholesterol values at the end of the treatment period were subtracted from LDL cholesterol values at the end of the control period (46). Within-individual changes were used when presented; otherwise, group means were used. In symbols, the estimates of effect size (ES) are:
– For parallel trials: $ES_{II} = T_f - C_f$

where
ES_{II} = the effect size of a parallel design trial,
T_f = final LDL cholesterol mean in the treatment group
C_f = final LDL cholesterol mean in the control group
– For crossover trials: $ES_x = T - C$

where
ES_x = the effect size of a crossover design trial

T = LDL cholesterol mean at the end of the treatment period
C = LDL cholesterol mean at the end of the control period

Standard Error (SE) of effect size (ES)

– For parallel trials:
The SE of ES for a parallel study was calculated as follows

$$SE_{II} = \sqrt{(SD_T)^2/n_T + (SD_C)^2/n_C}$$

where
SE_{II} = SE of effect size for a parallel study
SD_T = standard deviation of LDL-cholesterol endpoints in the treatment group
SD_C = standard deviation of LDL-cholesterol endpoints in the control
n_T = sample size of the treatment group
n_C = sample size of the control group
SDs were extracted from the studies or, if not reported, derived from SE of mean or CI for group mean, (46) as follows:

– From SE:
Standard error of group mean = SD $/\sqrt{N}$

– From CI for group mean:
SD = $\sqrt{N} \times$ (upper limit − lower limit)/2* $t_{(1\text{-confidence level, degree of freedom})}$

where
$t_{(1\text{-confidence level, degree of freedom})}$ is the *t* -value associate with study confidence level, usually 95%, and sample size of group

– For crossover trials (46, 86):
The SE of ES for a crossover study was calculated as follows

$$SE_x = SD_{(diff)}/\sqrt{n}$$

where
SE_x = standard error of effect size for a crossover study
$SD_{(diff)}$ = Standard deviation of difference between the treatment period and the control period
n = sample size
or

SE_x was extracted from reported statistical values in the trial, paired t-value or *P*-value, CI from a paired analysis or imputed from a number of studies as follows:

– From *t* or *P*-value:
t = diff/ SE_x

where
diff is mean of difference between control period and treatment period

If only the exact *P*-value or the upper bounded *P*-value of the paired *t*-test was reported, then the correspondent *t*-value for that *P*-value was calculated by entering the *P*-value and the degree of freedom into a spreadsheet as follows: $= tinv_{(P\text{-value, degree of freedom})}$

– From CI:
SE_x = (upper limit − lower limit)/2* $t_{(1\text{-confidence level, degree of freedom})}$

where
$t_{(1\text{-confidence level, degree of freedom})}$ is the *t* -value associate with study confidence level, usually 95%, and degree of freedom

– From imputed $SD_{(diff)}$:
Imputed $SD_{(diff)} = \sqrt{(SD_T^2 + SD_C^2 - (2 \times R \times SD_T \times SD_C))}$

where
$SD_{(diff)}$ = standard deviation of difference between the treatment period and the control period
SD_T^2 = LDL-cholesterol variance at the end of the treatment period
SD_C^2 = LDL-cholesterol variance at the end of the control period
R = 0.81 which is within-individual correlation between the treatment and control periods that was calculated from a number of studies.

Pooled effect size (ES) estimate
Treatment ES and its SE were calculated for every trial as described above. To obtain the pooled treatment effect size, the effect size estimates and standards error were entered into RevMan 4.2 under the "Generic inverse variance" outcome. In the inverse variance method the weight given to each study is chosen to be the inverse of the variance of the effect estimate.
A fixed effect meta-analysis using the inverse variance method calculates a weighted average as follows:

$$\text{Generic inverse variance weighted average} = \frac{\Sigma(ES_i/SE_i^2)}{\Sigma(1/SE_i^2)}$$

where
ES_i is the effect size in study *i,* SE_i is the standard error of that estimate and the summation is across all studies.

Calculation of within-individual correlation between the treatment and control periods for crossover studies

	SD (mmol/L)			
Study ID	Control	Treatment	Difference	*R*
AbuMweis 2006a (32)	0.93	1.01	0.51	0.87
AbuMweis 2006b (32)	0.93	1.06	0.59	0.83
Noakes 2005a (16)	0.74	0.71	0.32	0.91
Noakes 2005b (16)	0.74	0.76	0.32	0.91
Jones 2003a (27)	0.89	1.08	0.64	0.81
Jones 2003b (27)	0.89	0.81	0.51	0.83
Judd 2002 (70)	0.28	0.28	0.28	0.50
Jones 2000a (50)	0.70	0.59	0.40	0.82
Jones 2000b (50)	0.70	0.74	0.39	0.86
			Average =	0.81

where

$R =$ within-individual correlation between the treatment and control periods and was calculated as follows:

$$R = \frac{(\text{Control SD})^2 + (\text{Treatment SD})^2 - (\text{Difference SD})^2}{2 \times (\text{Control SD}) \times (\text{Treatment SD})}$$