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Continuous Dose-Response Relationship of the LDL-Cholesterol–Lowering Effect of Phytosterol Intake[1,2]

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Abstract

Phytosterols (plant sterols and stanols) are well known for their LDL-cholesterol (LDL-C)–lowering effect. A meta-analysis of randomized controlled trials in adults was performed to establish a continuous dose-response relationship that would allow predicting the LDL-C–lowering efficacy of different phytosterol doses. Eighty-four trials including 141 trial arms were included. A nonlinear equation comprising 2 parameters (the maximal LDL-C lowering and an incremental dose step) was used to describe the dose-response curve. The overall pooled absolute (mmol/L) and relative (%) LDL-C–lowering effects of phytosterols were also assessed with a random effects model. The pooled LDL-C reduction was 0.34 mmol/L (95% CI: −0.36, −0.31) or 8.8% (95% CI: −9.4, −8.3) for a mean daily dose of 2.15 g phytosterols. The impacts of subject baseline characteristics, food formats, type of phytosterols, and study quality on the continuous dose-response curve were determined by regression or subgroup analyses. Higher baseline LDL-C concentrations resulted in greater absolute LDL-C reductions. No significant differences were found between dose-response curves established for plant sterols vs. stanols, fat-based vs. non fat-based food formats and dairy vs. nondairy foods. A larger effect was observed with solid foods than with liquid foods only at high phytosterol doses (>2 g/d). There was a strong tendency ($P = 0.054$) towards a slightly lower efficacy of single vs. multiple daily intakes of phytosterols. In conclusion, the dose-dependent LDL-C–lowering efficacy of phytosterols incorporated in various food formats was confirmed and equations of the continuous relationship were established to predict the effect of a given phytosterol dose. Further investigations are warranted to investigate the impact of solid vs. liquid food formats and frequency of intake on phytosterol efficacy. J. Nutr. 139: 271–284, 2009.

Introduction

Elevated plasma total cholesterol (TC)[5] and LDL-cholesterol (LDL-C) are a major risk factor for coronary heart disease (CHD). Phytosterols (plant sterols and stanols) are among the dietary options available to lower elevated plasma TC and LDL-C concentrations. The cholesterol-lowering properties of phytosterols were observed in humans already in the early 1950s (1). Since then, a vast number of human trials have shown that phytosterols, mainly in the form of plant sterols or stanols esterified to vegetable oil fatty acids (mainly C18), significantly lower TC and LDL-C when incorporated into various food products (2,3). The most recent meta-analysis including 41 trials with mainly fat-based foods like spreads, margarine, mayonnaise, or salad dressings enriched with phytosterol esters has shown a nonlinear dose-response relationship between the daily dose of phytosterols consumed and their cholesterol-lowering efficacy (3). On average, 2 g/d phytosterols (the equivalent dose expressed as free sterols based on 3.3 g/d phytosterol esters) lowered LDL-C concentrations by ~10% (3). The effect appeared to taper off at intakes of ~2 g/d or more, with little additional benefit at intakes higher than 2.5 g/d. As a consequence, several dietary recommendations now include the daily consumption of 2 g of phytosterols as an additional dietary option to lower elevated LDL-C concentrations (4–7). The main mechanism of action responsible for the cholesterol-lowering effect of phytosterols is the inhibition of intestinal cholesterol absorption (8). The recommended daily intake of 2 g of phytosterols reduces cholesterol absorption by 30–40% (3,9).

To date, additional evidence for the cholesterol-lowering efficacy of esterified or free phytosterols incorporated in a wide variety of food formats, including low-fat or fat-free foods such as milk (10–12), yogurt (10,11,13–16), fruit or vegetable juices

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[5] Abbreviations used: CHD, coronary heart disease; HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; TC, total cholesterol.

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(17–19), and single daily dose food formats such as yogurt drinks (13,16,20–24), has become available. Although some of these trials suggested that phytosterols incorporated in these food formats lower LDL-C to an extent similar to that observed with fat-based food formats, the impact of food format on the LDL-C–lowering efficacy had not been systematically evaluated. In addition, the most recent meta-analysis (3) pooled together trials in which different phytosterol doses were used and the cholesterol-lowering efficacy was reported for ranges of doses (0.7–1.1, 1.5–1.9, 2.0–2.4, ≥2.5 g/d). Using this approach, it was not possible to predict the cholesterol-lowering effect for a given dose of phytosterols.

The main objective of the present systematic review with meta-analysis was to establish a continuous dose-response relationship that would allow predicting the LDL-C–lowering efficacy of different phytosterol doses using an equation that would take into account the saturable nature of the cholesterol absorption process (25). Another objective was to evaluate the impact of different treatment characteristics such as phytosterol type (plant sterols vs. stanols) and the impact of food format (fat-based vs. non fat-based, dairy vs. non-dairy, and liquid vs. solid food formats) on the dose-response curve. As part of the investigation of heterogeneity between trials, the effect of subject characteristics (age, BMI, gender, baseline LDL-C concentrations) and study quality was also evaluated. Finally, because the TC:HDL-cholesterol (TC:HDL-C) ratio is a strong predictor of CHD mortality (26) and is affected, but not solely, by changes in LDL-C concentrations, we attempted to determine the dose-response effect of phytosterol intake on this ratio.

Methods

Search strategy. Five databases (MEDLINE, Cab Abstracts, Biological Abstracts, Web of Science, and the Cochrane Library) were searched in July 2007 for articles on phytosterols, with no specification for date of publication. The Medical Subject Headings (terms) phytosterols, lipids, and cholesterol were used, as well as the following search terms: (plant sterol* or plant stanol* or phytosterol* or phytostanol* or sitosterol* or sitostanol* or campesterol* or campestanol* or stigmasterol* or brassicasterol*) and (cholesterol* or blood lipid* or LDL cholesterol* or HDL cholesterol* or triglyceride*), limited to human and clinical trials whenever possible. There was no language restriction.

Inclusion and exclusion criteria. A first selection was made by screening the title and abstract of the publications based on the inclusion criteria (**Table 1**). Because the cholesterol-lowering effect of phytosterols is additive to that of statins (27,28) or "heart healthy" diets (low in total, saturated fat, and cholesterol content) (29–32), they were not considered as a co-intervention as long as they were present in both the control and the treatment groups/phases. The use of a vegetable oil-rich diet as background diet was not considered as co-intervention as long as the background diet was the same in all treatment groups/phases. Because most phytosterol esters result from the esterification of phytosterols to vegetable oil fatty acids, the use of vegetable oil fatty acid esters of phytosterols was not considered as a co-intervention. However, the use of novel, non-vegetable esters of phytosterols such as fish oil fatty acid esters was considered as a co-intervention, because fish oil fatty acids may have a moderate impact on LDL-C (33–35). This could not be distinguished from the usual phytosterol or phytosterol ester effect and it was not known whether this effect was additive to that of phytosterols or whether some interactions could exist between fish oil fatty acids and phytosterols.

After the full publications were read, trials were excluded based on the exclusion criteria (Table 1). Ferulated phytosterols were excluded, because these phytosterols are not commonly used for food/supplement enrichment and there is no consensus on whether they have a cholesterol-lowering effect (36,37). Although phytosterols are thought to exert their mechanism of action in the upper gastrointestinal tract (8), colectomized patients were excluded, because the possibility that colectomy could have consequences in the upper tract could not be completely discarded.

TABLE 1 Inclusion and exclusion criteria used to select the clinical trials

Inclusion criteria used when screening titles and abstracts
1) Randomized controlled trial within human adults (parallel-arm or cross-over trials)
2) Treatment with ``usual'' phytosterols, where ``usual phytosterols'' was defined as 4-desmethylsterols and/or 4-desmethylstanols extracted from vegetable or plant oils such as soybean oil, rapeseed oil and tall oil
3) Blood lipids as primary or secondary outcomes
4) Absence of a co-intervention from which consumption of phytosterol-enriched foods or supplements could not be isolated
Exclusion criteria used when reading the full publications
1) Not a randomized controlled trial
2) Relevant blood lipid data missing
3) Phytosterols consumed for less than 2 wk
4) Phytosterol dose higher than 10 g/d
5) Control group did not receive a placebo
6) Ferulated phytosterols such as rice bran oil and shea nut oil sterols were used
7) Colectomised patients were part of the study

Data extraction. The data were independently extracted by 2 investigators (R.R. and L.M.) using a custom-made database. Codings were defined for the descriptive variables to ensure consistency in recording. In case of discrepancy or indecisiveness, consensus was reached by verbal discussion among the authors. We collected the following data: *1*) study identification (author, publication year, country); *2*) study design (parallel-arm or cross-over); *3*) subject characteristics (number of subjects, gender, age, BMI, body weight, health status, ethnicity); *4*) background diet (free living conditions or diet provided by the investigators, typical or "healthy" diet); *5*) treatment characteristics [phytosterol dose, phytosterol type (plant sterols or stanols), phytosterol esterification (in free form or esterified), source of phytosterols, source of fatty acids used for esterification, food format, intake occasion (with or without a meal), frequency of intake (number of portions during the day), and treatment duration]; *6*) blood lipid outcomes (LDL-C, HDL-C, and TC); *7*) variance measures for these outcomes; and *8*) study quality. When required, the original authors were contacted to obtain missing information.

Quality assessment. Trial quality was assessed using a custom-designed tool (Supplemental Appendix 1) adapted from the Delphi Consensus (38) and the method by Chalmers et al. (39). Consensus was reached among the authors for the inclusion of the following criteria in the tool due to their high potential to affect the estimate of the treatment effect: random sequence generation, blinding of the subjects, blinding of the investigators, eligibility criteria specified, compliance, and carryover effects taken care of in case of cross-over trials. For each study or trial arm, the overall quality score was calculated by adding the individual criteria scores. The maximal quality score that could be ascribed to a parallel trial was 7. Parallel trials deserving less than 5.5 points were classified as low quality trials, while trials given 5.5 points or more were judged to be of good quality. In case of cross-over trials, the maximal quality score was 8; trials given 6.0 points or less were considered of low quality, and those provided more than 6.0 points were classified as being of good quality.

The quality scores were not used to exclude lower quality trials from the meta-analysis or to weigh the trials, because there is no consensus on which scoring system is the best and hence the use of such a system, which is intrinsically subjective, could have biased the outcome of the meta-analysis (40). The quality scores were used only for performing subgroup analyses to determine whether the overall quality as well as 2 major quality criteria (randomization and compliance) considered separately could affect the dose-response curves.

Statistical analysis. The main outcome variable was the absolute net change (mmol/L) in LDL-C due to the phytosterol treatment. When the outcome variable was measured at various time points during the intervention, the value corresponding to or closest to the 4-wk time point was taken for the analysis. The absolute net change in LDL-C was calculated according to the formulas described in Supplemental Appendix 2. When only relative outcomes were provided in the publications, they were first converted to absolute outcomes using, as the 100% value, the baseline lipid value of the corresponding group for parallel trials and the endpoint lipid value of the control phase for cross-over trials. Absolute changes in the TC:HDL-C ratio were also estimated. Because not all publications reported the ratio, it was calculated from the reported means of TC and HDL-C.

The results of the meta-analysis were also expressed in terms of relative (%) change in LDL-C. When relative net changes were reported, these values were collected. For trials in which relative net changes were not reported, the relative changes were calculated as described in Supplemental Appendix 2.

The within-trial variance measures for the absolute net changes in LDL-C were obtained as standard errors (SE) or derived from SD or 100(1-α) % CI. To derive SE from SD and CI, we used the equations described (Supplemental Appendix 2). If not provided, the within-trial variance measures of the absolute net changes were estimated according to the equations provided in Supplemental Appendix 2.

Pooled estimates of the absolute LDL-C–lowering effect of phytosterols and of the LDL-C concentration at baseline were calculated using a random-effects model according to the method described by DerSimonian and Laird (41) using the inverse of the variance ($1/SE^2$) as weighing factor. A similar weighing factor was used for calculating the pooled estimate of the relative LDL-C–lowering effect. Heterogeneity between studies was assessed by calculating the DerSimonian and Laird Q statistic (41,42) and by looking at the funnel plot in which weights ($1/SE^2$) had been plotted against the absolute net changes in LDL-C (43). The funnel plot symmetry was examined as an indicator for absence of potential publication bias. The absence of publication bias was also verified with a probability plot of the ranked changes in LDL-C plotted against the normal deviates.

The dose-response curve was determined using the PROC NLIN function of the SAS System (SAS version 8.2, SAS Institute). As a model for the dose-response curve, we used a first-order elimination curve frequently used in pharmacokinetics (44). The choice of this equation was based on the assumption that the cholesterol–lowering effect of phytosterols would reach a plateau with increasing doses due to the saturable nature of the processes involved in cholesterol transport and absorption (25):

$$\text{Change} = D\,(1-\exp[-K\text{dose}]),$$

where D = maximal reduction in LDL-C concentration and K = LDL-C reduction rate. We re-parameterized this equation into:

$$\text{Predicted LDL-C change} = a\left(1-\exp\left[-\frac{\text{dose}}{b/\ln(2)}\right]\right)$$

in order to obtain the maximal LDL-C reduction that can be achieved at high phytosterol doses (parameter a) and the incremental dose step needed to achieve an additional effect, which is one-half the size of the previous dose effect (parameter b). Both parameters were estimated using a non-linear, unweighed regression analysis.

When using data from studies in which different phytosterol treatments were administered, we conducted comparisons with a single placebo. Some correlations existed between strata belonging to the same study, but these correlations were not taken into account, because they should not have affected the overall (pooled) reduction in LDL-C but only the error variation of the pooled estimate. In addition, the potential effect of inter-trial correlations on the dose-response curve was expected to be minimal due to the large number of trials included in the meta-regression. To verify whether the nonlinear regression fitted better with the observed relative LDL-C changes than a simple linear relationship (without a maximal reduction estimate), we performed a post hoc analysis to compare the sum of the residuals between the observed and predicted LDL-C changes obtained with the curve vs. a linear fit crossing the y axis at 0.

To explore possible causes of heterogeneity between trials, predefined covariate analyses were performed with the dose-response curve. The predefined continuous covariates were baseline age, BMI, LDL-C concentrations, and gender, and the categorical covariates were phytosterol type (plant sterols vs. stanols), food format (fat-based vs. non fat-based foods, dairy vs. non-dairy foods, solid vs. liquid foods), and study quality (low vs. good study quality, well vs. poorly randomized strata, and high vs. low compliance strata). We performed post hoc analyses to evaluate the impact of study design (cross-over vs. parallel) on the dose-response curve as well as the impact of the inclusion of trials in which phytosterol doses $>$ 5 g/d were used. The criteria used for classification of the strata within different categories of treatment or study characteristics are provided (Supplemental Appendix 3). For the continuous covariates, residuals (differences between predicted LDL-C changes and observed LDL-C changes) were plotted against the covariates and PROC GLM was used to examine the correlation between the covariates and the residuals. For the categorical covariates, dose-response curves were established for the different subgroups and the differences in the parameters describing the curves were evaluated. $P \leq 0.05$ was considered significant. All analyses were performed with the SAS System.

Results

Overview of trials. A total of 601 articles were identified from the search strategy. Of these, only 165 met the inclusion criteria based on title and abstract content. After full papers were read for the 2nd selection step, 71 articles were excluded based on the exclusion criteria. Ten other articles were excluded because only abstracts could be obtained ($n = 2$) or the data presented were the same as in previous publications ($n = 8$), resulting in the inclusion in the meta-analysis of 84 trials/publications comprising 141 strata (phytosterol treatment vs. control) (**Fig. 1**): 73 strata were from parallel design studies (**Table 2**) and 68 were from cross-over design studies (**Table 3**).

A total of 6805 participants were included in the trials. Most of the strata included European and North American participants who were apparently healthy regardless of baseline lipid levels. Mean age ranged from 22.7 to 66.0 y and mean BMI and body weight at baseline ranged from 22.0 to 31.0 kg/m^2 and 63.0 to 88.3 kg, respectively. Body weight did not change significantly during the intervention except in 9 strata, which reported small (<2 kg) but significant body weight changes. Baseline LDL-C concentrations were reported in 123 strata,

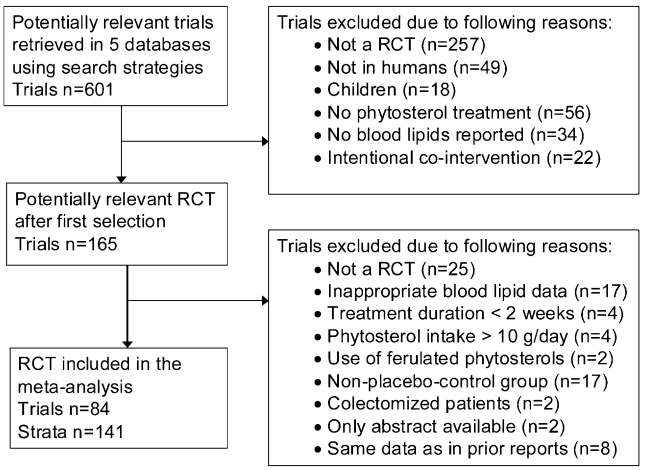

FIGURE 1 Flow diagram of the trial selection procedure starting with 601 trials and ending with 84 randomized controlled trials (RCT), including 141 strata with a phytosterol treatment.

TABLE 2 Overview of the parallel-arm design strata included in the meta-analysis

Author, publication year, and reference	Subject characteristics: Sample size Control	Treatment	Mean age	Mean BMI	Male	Treatment characteristics: Food format	Sterols or stanols	Ester or free	Duration	Dose free phytosterols[1]	Blood lipid outcomes: LDL cholesterol Mean baseline	NNet change[2]	95% CI	Overall quality score[3]
	n		*y*	*kg/m²*	*%*				*d*	*g/d*	*mmol/L*			
Algorta Pineda et al. 2005 (21)	15	17	42.0	26.0	59.4	Yogurt drink	Stanols	Ester	21	1.20	4.06	−0.34	(−0.66–0.01)	—[4]
Alhassan et al. 2006 (55)	9	17	52.7	26.6	53.8	Margarine	Stanols	Ester	28	3.00	3.31	−0.65	(−1.03–0.27)	6.5 (good)
Andersson et al. 1999 (56)	21	19	55.1	25.1	45.9	Margarine	Stanols	Ester	56	1.90	4.68	−0.29	(−0.61 0.03)	6.5 (good)
Ayesh et al. 1999 (57)	11	10	36.0	24.0	50.0	Margarine	Sterols	Ester	24	8.60	3.18	−0.58	(−0.77–0.39)	5.0 (low)
Beer et al. 2001 stratum 1 (58)[5]	33	33	54.8	27.5	—	Low-fat milk	Mix	Free	26	0.90	4.13	−0.33	(−0.57–0.08)	5.0 (low)
Beer et al. 2001 stratum 2 (58)	33	33	56.4	27.3	—	Low-fat milk	Mix	Free	26	1.80	4.16	−0.38	(−0.61–0.14)	5.0 (low)
Beer et al. 2001 stratum 3 (58)	33	33	53.3	27.6	—	Low-fat milk	Mix	Free	26	3.60	4.14	−0.57	(−0.82–0.33)	5.0 (low)
Blair et al. 2000 (114)	84	83	56.0	28.5	59.9	Margarine	Stanols	Ester	28	2.90	3.80	−0.36	(−0.52–0.21)	6.5 (good))
Blomqvist et al. 1993 (59)	33	34	45.5	25.5	70.1	Mayonnaise	Stanols	Ester	42	3.40	3.35	−0.33	(−0.54–0.12)	6.5 (good)
Clifton et al. 2007 stratum 1 (60)	39	37	55.2	26.8	56.6	Margarine	Sterols	Ester	21	1.60	4.35	−0.39	(−0.63–0.15)	5.5 (good)
Clifton et al. 2007 stratum 2 (60)	39	39	54.5	26.9	48.7	Margarine	Sterols	Ester	21	1.60	4.20	−0.45	(−0.67–0.23)	5.5 (good))
Clifton et al. 2007 stratum 3 (60)	39	36	54.2	26.7	56.0	Margarine	Sterols	Ester	21	1.60	4.39	−0.33	(−0.55–0.11)	5.5 (good)
Davidson et al. 2001 stratum 1 (61)	21	21	45.1	—	52.4	Spread and salad dressing	Sterols	Ester	28	3.00	3.40	−0.14	(−0.47 0.18)	5.0 (low)
Davidson et al. 2001 stratum 2 (61)	21	19	47.3	—	50.0	Spread and salad dressing	Sterols	Ester	28	6.00	3.36	−0.13	(−0.42 0.16)	5.0 (low)
Davidson et al. 2001 stratum 3 (61)	21	23	46.1	—	54.5	Spread and salad dressing	Sterols	Ester	28	9.00	3.37	−0.41	(−0.73–0.09)	5.0 (low)
de Graaf et al. 2002 (62)	31	31	57.0	25.4	48.4	Chocolate	Mix	Free	28	1.80	4.70	−0.61	(−0.81–0.41)	6.5 (good)
de Jong et al. 2008 stratum 1 (63)	11	15	58.1	26.8	46.2	Margarine	Sterols	Ester	112	2.50	3.57	−0.28	(−0.57 0.01)	6.5 (good)
de Jong et al. 2008 stratum 2 (63)	11	15	58.3	27.0	46.2	Margarine	Stanols	Ester	112	2.50	3.44	−0.43	(−0.78–0.08)	6.5 (good)
Devaraj et al. 2004 (17)	36	36	42.5	25.5	40.3	Orange juice	Sterols	Free	56	2.00	3.72	−0.44	(−0.62–0.26)	5.5 (good)
Devaraj et al. 2006 (18)	36	36	46.0	24.5	43.1	Orange juice	Sterols	Free	28	2.00	3.72	0.08	(−0.19 0.35)	5.5 (good)
Doornbos et al. 2006 (20)	33	38	56.8	25.2	44.0	Low-fat yogurt drink	Sterols	Ester	28	2.80	3.90	−0.37	(−0.49–0.25)	5.5 (good)
Earnest et al. 2007 (64)	29	25	50.5	26.3	53.7	Capsules	Sterols	Ester	84	1.56	4.27	−0.41	(−0.69–0.13)	6.5 (good)
Goldberg et al. 2006 (65)	13	13	59.5	27.2	34.6	Tablets	Stanols	Free	42	1.80	2.89	−0.32	(−0.58–0.05)	6.5 (good)
Hallikainen & Uusitupa 1999 stratum 1 (31)	17	18	44.6	25.6	40.0	Margarine	Stanols	Ester	56	2.31	4.54	−0.61	(−0.96–0.26)	6.5 (good)
Hallikainen & Uusitupa 1999 stratum 2 (31)	17	20	43.2	24.9	32.4	Margarine	Stanols	Ester	56	2.16	4.25	−0.35	(−0.71 0.01)	6.5 (good)
Hansel et al. 2007 (24)	99	95	48.9	23.6	67.0	Low-fat fermented milk	Sterols	Ester	42	1.60	4.09	−0.32	(−0.45–0.19)	6.5 (good)
Hironaka et al. 2006 stratum 1 (19)	51	50	43.7	23.9	50.5	Vegetable juice	Sterols	Free	28	0.80	3.68	−0.25	(−0.41–0.08)	—
Hironaka et al. 2006 stratum 2 (19)	51	54	43.2	24.0	47.6	Vegetable juice	Sterols	Free	28	1.60	3.70	−0.32	(−0.46–0.18)	—
Homma et al. 2003 stratum 1 (66)	34	33	46.5	23.5	33.3	Margarine	Stanols	Ester	28	2.00	3.96	−0.34	(−0.49–0.19)	3.0 (low)
Homma et al. 2003 stratum 2 (66)	34	34	47.5	24.0	38.0	Margarine	Stanols	Ester	28	3.00	3.96	−0.26	(−0.44–0.08)	3.0 (low)
Hyun et al. 2005 (13)	28	23	28.7	22.6	51.0	Yogurt	Stanols	Ester	28	2.00	3.08	−0.24	(−0.43–0.06)	5.0 (low)
Ishiwata et al. 2002 study 1 stratum 1 (67)[6]	19	21	48.2	23.5	22.5	Margarine	Stanols	Ester	28	2.00	4.01	−0.37	(−0.54–0.20)	2.0 (low)
Ishiwata et al. 2002 study 1 stratum 2 (67)	19	25	47.8	24.0	29.5	Margarine	Stanols	Ester	28	3.00	4.01	−0.35	(−0.57–0.13)	2.0 (low)
Ishiwata et al. 2002 study 2 stratum 1 (67)	11	10	42.6	23.0	61.9	Margarine	Stanols	Ester	28	2.00	3.83	−0.42	(−0.69–0.16)	2.0 (low)
Ishiwata et al. 2002 study 2 stratum 2 (67)	11	6	44.6	23.4	58.8	Margarine	Stanols	Ester	28	3.00	3.90	−0.25	(−0.53 0.03)	2.0 (low)
Jauhiainen et al. 2006 (68)	34	33	43.3	—	35.8	Hard cheese	Stanols	Ester	35	2.00	3.58	−0.36	(−0.53–0.18)	6.5 (good)
Jones et al. 1999 (29)	16	16	—	—	100.0	Margarine	Mix	Free	30	1.70	4.45	−0.64	(−1.22–0.06)	7.0 (good)
Korpela et al. 2006 study 1 (14)	25	25	57.3	27.0	21.3	Yogurt	Mix	Free	42	1.65	4.10	−0.32	(−0.58–0.06)	5.0 (low)
Korpela et al. 2006 study 2 (14)	29	33	57.3	27.0	21.3	Hard cheese	Mix	Free	42	2.00	4.10	−0.46	(−0.71–0.21)	5.0 (low)
Korpela et al. 2006 study 3 (14)	28	24	57.3	27.0	21.3	Fresh cheese	Mix	Free	42	2.00	4.10	−0.56	(−0.80–0.32)	5.0 (low)
Lagström et al. 2006 (69)	20	22	40.1	25.0	—	Capsules	Stanols	Ester	21	2.00	3.40	−0.20	(−0.46 0.06)	6.5 (high)
Lee et al. 2003 (70)	40	41	61.0	29.1	44.4	Margarine	Sterols	Ester	28	1.60	4.33	−0.36	(−0.61–0.11)	5.0 (low)
Li et al. 2007 stratum 1 (71)	99	102	44.5	26.0	35.3	Milk tea	Sterols	Ester	35	1.50	3.22	−0.15	(−0.32 0.02)	6.5 (good)

(Continued)

TABLE 2 *Continued*

Author, publication year, and reference	Subject characteristics: Sample size: Control	Sample size: Treatment	Mean age	Mean BMI	Male	Treatment characteristics: Food format	Sterols or stanols	Ester or free	Duration	Dose free phytosterols[1]	Blood lipid outcomes: LDL cholesterol: Mean baseline	NNet change[2]	95% CI	Overall quality score[3]
Li et al. 2007 stratum 2 (71)	99	100	44.5	26.0	37.2	Milk tea	Sterols	Ester	35	2.30	3.08	−0.17	(−0.35 0.00)	6.5 (good)
Maki et al. 2001 stratum 1 (72)	83	75	58.1	27.5	44.0	Margarine	Sterols	Ester	30	1.10	4.08	−0.31	(−0.45–0.17)	4.5 (low)
Maki et al. 2001 stratum 2 (72)	83	35	58.4	27.3	42.4	Margarine	Sterols	Ester	30	2.20	4.03	−0.33	(−0.48–0.17)	4.5 (low)
Matsuoka et al. 2004 (45)	23	23	48.0	25.8		Mayonnaise	Sterols	Free	28	0.80	3.78	0.01	(−0.23 0.25)	—[4]
Matvienko et al. 2002 (73)	17	17	22.9	26.4	100.0	Beef	Sterols	Ester	28	2.70	4.10	−0.55	(−0.84–0.26)	7.0 (good)
McPherson et al. 2005 study 1 (74)	12	13	46.5	26.0	44.0	Tablets	Stanols	Free	42	1.26	3.03	−0.32	(−0.55–0.08)	5.0 (low)
McPherson et al. 2005 study 2 (74)	13.5[7]	13.5	50.7	27.8	33.3	Capsules	Stanols	Free	42	1.01	3.50	−0.13	(−0.39 0.12)	5.0 (low)
Mensink et al. 2002 (15)	30	30	36.0	23.3	26.7	Yogurt	Stanols	Ester	28	3.00	2.92	−0.40	(−0.53–0.26)	5.5 (good)
Miettinen & Vanhanen 1994 stratum 1 (75)	8	9	45.0	25.2	—	Mayonnaise	Sterols	Free	63	1.00	4.09	−0.26	(−0.56 0.04)	6.5 (good)
Miettinen & Vanhanen 1994 stratum 2 (75)	8	7	45.0	25.2	—	Mayonnaise	Stanols	Free	63	1.04	3.73	−0.11	(−0.43 0.21)	6.5 (good)
Miettinen & Vanhanen 1994 stratum 3 (75)	8	7	45.0	25.2	—	Mayonnaise	Stanols	Ester	63	1.22	3.39	−0.28	(−0.55–0.01)	6.5 (good)
Miettinen et al. 1995 stratum 1 (76)	51	51	50.0	—	—	Margarine	Stanols	Ester	182	2.60	3.96	−0.44	(−0.62–0.26)	5.5 (good)
Miettinen et al. 1995 stratum 2 (76)	51	51	51.0	—	—	Margarine	Stanols	Ester	182	2.60	4.14	−0.52	(−0.70–0.34)	5.5 (good)
Neil et al. 2001 (27)	31	31	50.3	26.0	41.9	Margarine	Sterols	Ester	28	2.50	5.08	−0.72	(−1.21–0.23)	6.5 (good)
Niittynen et al. 2007 study 2 (77)	14	12	47.1	25.6	57.7	Low-fat yogurt drink	Sterols	Free	56	2.00	4.73	−0.28	(−0.88 0.29)	6.5 (good)
Plat et al. 2000b stratum 1 (78)	42	36	33.0	22.6	37.2	Margarine and shortening	Stanols	Ester	56	3.79	2.94	−0.37	(−0.51–0.22)	6.5 (good)
Plat et al. 2000b stratum 2 (78)	42	34	33.0	23.2	36.8	Margarine and shortening	Stanols	Ester	56	4.03	2.94	−0.34	(−0.51–0.18)	6.5 (good)
Quilez et al. 2003 (79)	29	28	30.9	23.3	43.9	Muffin and croissant	Sterols	Ester	56	3.20	2.50	−0.36	(−0.56–0.16)	5.0 (low)
Seki et al. 2003a (80)	28	32	39.1	24.2	100.0	Bread	Sterols	Ester	28	0.45	3.01	−0.07	(−0.21 0.07)	5.0 (low)
Seki et al. 2003b (81)	11	11	41.2	24.2	100.0	Bread	Sterols	Ester	28	1.34	2.58	−0.32	(−0.52–0.12)	5.0 (low)
Seppo et al. 2007 study 1 (16)	29	31	46.7	25.2	36.1	Yogurt	Stanols	Ester	35	2.00	3.40	−0.10	(−0.31 0.12)	5.0 (low)
Seppo et al. 2007 study 2 (16)	32	29	46.7	25.2	36.1	Low-fat yogurt drink	Stanols	Ester	35	2.00	3.40	−0.11	(−0.31 0.09)	5.0 (low)
Seppo et al. 2007 study 3 (16)	9	10	46.7	25.2	36.1	Low-fat yogurt drink	Stanols	Ester	35	2.00	3.40	−0.40	(−0.84 0.03)	7.0 (good)
Seppo et al. 2007 study 4 (16)	27	32	46.7	25.2	36.1	Low-fat milk	Stanols	Ester	35	2.00	3.40	−0.21	(−0.38–0.05)	5.0 (low)
Spilburg et al. 2003 (82)	13	11	50.6	26.1	33.3	Lemonade	Stanols	Free	28	1.90	3.83	−0.56	(−0.85–0.27)	4.0 (low)
Taichi et al. 2003 (83)	29	26	46.8	25.3	—	Mayonnaise	Sterols	Ester	28	0.88	3.81	−0.31	(−0.50–0.13)	2.0 (low)
Vanhanen et al. 1994a (84)	8	7	47.3	26.5	73.3	Mayonnaise	Stanols	Ester	63	0.80	3.39	−0.28	(−0.56 0.00)	4.5 (low)
Vanhanen 1994b (85)	7	7	55.0	25.5	35.7	Mayonnaise	Stanols	Ester	42	1.50	3.70	−0.07	(−0.44 0.30)	4.0 (low)
Varady et al. 2004 (86)	20	18	56.6	26.3	31.6	Margarine	Sterols	Ester	56	1.80	3.55	−0.39	(−0.56–0.22)	5.5 (good)
Woodgate et al. 2006 (87)	15	14	53.7	27.5	69.0	Capsules	Stanols	Ester	28	1.60	5.35	−0.39	(−0.78 0.00)	6.5 (good)

[1] Dose given as free equivalents in g/d.
[2] Net change was calculated by subtracting the mean change in the control group from the mean change in the treatment group (where mean change = LDL-C at the end of intervention − LDL-C at baseline).
[3] The maximum overall quality score was 7 for parallel trials. When a trial was given < 5.5 points, it was judged to be of low quality and a trial that was given ≥ 5.5 points was judged to be of high quality.
[4] Publications written in Portuguese or Japanese, so not all descriptive variables could be extracted.
[5] Multiple strata in 1 study corrected for the same single control group: indicated with stratum 1, stratum 2, stratum 3, etc.
[6] Multiple strata in 1 study, each corrected for a respective control group: indicated with study 1, study 2, study 3, etc.
[7] Number of subjects not reported in the publication. Therefore, it was assumed that the 27 subjects were distributed evenly across the groups.

with a pooled overall LDL-C concentration at baseline of 3.86 mmol/L (95% CI: 3.77–3.98). Most strata included both men and women (Supplemental Appendix 4).

The mean phytosterol dose given to the study participants was 2.15 g/d (range 0.45–9.00 g/d), for a duration ranging from 21 to 182 d (Supplemental Appendix 4). Plant sterols were used in 74 strata and plant stanols in 53 strata; in 14 cases, a combination of plant sterols and stanols was used. Plant sterols and stanols were provided in their esterified form in most cases, except in 39 strata in which free plant sterols or stanols were directly dispersed or mixed in the food products. Phytosterols were incorporated in fat-based foods in ~65% of the strata (n = 91) and in foods with a lower fat content in ~35% of the strata (n = 50). In 26 strata, phytosterols were provided in dairy food

TABLE 3 Overview of the cross-over strata included in the meta-analysis

Author, publication year, and reference	Subject characteristics				Treatment characteristics					Blood lipid outcomes			Overall quality score[3]
										LDL cholesterol			
	Sample size	Mean age	Mean BMI	Male	Food format	Sterols or stanols	Ester or free	Duration	Dose free phytosterols[1]	Mean baseline	Net change[2]	95% CI	
	n	*y*	*kg/m²*	*%*				*d*	*g/d*	*mmol/L*			
AbuMweiss et al. 2006 stratum 1 (88)[4]	30	59.0	28.0	—	Margarine	Sterols	Free	29	1.72	3.80	−0.05	(−0.27 0.17)	7.0 (good)
AbuMweiss et al. 2006 stratum 2 (88)	30	59.0	28.0	—	Margarine	Sterols	Ester	29	1.72	3.80	−0.05	(−0.28 0.18)	7.0 (good)
Cater et al. 2005 study 1 stratum 1 (89)[5]	8	58.0	28.0	75.0	Margarine	Stanols	Ester	42	2.00	—	−0.52	(−0.79–0.25)	5.0 (low)
Cater et al. 2005 study 1 stratum 2 (89)	8	58.0	28.0	75.0	Margarine	Stanols	Ester	42	3.00	—	−0.54	(−0.77–0.32)	5.0 (low)
Cater et al. 2005 study 1 stratum 3 (89)	8	58.0	28.0	75.0	Margarine	Stanols	Ester	42	4.00	—	−0.57	(−0.79–0.35)	5.0 (low)
Cater et al. 2005 study 2 (89)	13	57.0	27.5	0.0	Margarine	Stanols	Ester	42	3.00	—	−0.54	(−0.67–0.42)	5.0 (low)
Cater et al. 2005 study 3 (89)	10	66.0	29.5	100.0	Margarine	Stanols	Ester	60	3.00	—	−0.44	(−0.62–0.26)	6.0 (low)
Chan et al. 2007 stratum 1 (90)	21	54.2	25.9	52.4	Vegetable oil	Sterols	Ester	28	1.70	3.91	−0.24	(−0.45–0.03)	6.0 (low)
Chan et al. 2007 stratum 2 (90)	21	54.2	25.9	52.4	Vegetable oil	Sterols	Ester	28	1.70	3.91	−0.35	(−0.58–0.12)	6.0 (low)
Cleghorn et al. 2003 (32)	50	46.7	26.0	38.0	Margarine	Sterols	Ester	28	2.10	3.98	−0.27	(−0.40–0.14)	7.5 (good)
Clifton et al. 2004 stratum 1 (10)	58/36[6]	54.0	26.2	39.7	Bread	Sterols	Ester	21	1.60	4.03	−0.42	(−0.57–0.27)	4.5 (low)
Clifton et al. 2004 stratum 2 (10)	58/40	54.0	26.2	39.7	Milk	Sterols	Ester	21	1.60	4.03	−0.72	(−0.85–0.58)	4.5 (low)
Clifton et al. 2004 stratum 3 (10)	58/58	54.0	26.2	39.7	Cereals	Sterols	Ester	21	1.60	4.03	−0.24	(−0.35–0.13)	4.5 (low)
Clifton et al. 2004 stratum 4 (10)	58/40	54.0	26.2	39.7	Yogurt	Sterols	Ester	21	1.60	4.03	−0.36	(−0.50–0.22)	4.5 (low)
Colgan et al. 2004 (91)	48	46.0	26.1	56.3	Margarine	Sterols	Ester	21	1.30	3.94	−0.11	(−0.29 0.07)	6.0 (low)
Geelen et al. 2002 study 1 (92)	31	26.0	23.0	51.6	Margarine	Sterols	Ester	21	3.00	—	−0.31	(−0.48–0.14)	7.5 (good)
Geelen et al. 2002 study 2 (92)	57	25.0	23.0	40.4	Margarine	Sterols	Ester	21	3.00	—	−0.34	(−0.47–0.21)	7.5 (good)
Gylling & Miettinen 1994 (93)	11	57.8	—	100.0	Margarine	Stanols	Ester	42	3.00	—	−0.36	(−0.57–0.15)	4.5 (low)
Gylling & Miettinen 1999 (94)	21	52.7	25.7	0.0	Butter	Stanols	Ester	35	2.43	3.98	−0.45	(−0.66–0.24)	6.0 (low)
Gylling et al. 1997 (95)	22	51.0	26.0	0.0	Margarine	Stanols	Ester	49	3.00	3.85	−0.53	(−0.76–0.30)	5.0 (low)
Hallikainen et al. 2000 stratum 1 (50)	34	48.8	24.9	—	Margarine	Stanols	Ester	28	2.01	4.43	−0.53	(−0.71–0.35)	7.5 (good)
Hallikainen et al. 2000 stratum 2 (50)	34	48.8	24.9	—	Margarine	Sterols	Ester	28	2.04	4.43	−0.44	(−0.59–0.28)	7.5 (good)
Hayes et al. 2004 (96)	7	48.0		66.7	Tortilla chips	Sterols	Free	24	1.50	4.19	−0.62	(−1.10–0.14)	3.0 (low)
Hendriks et al. 1999 stratum 1 (97)	80	37.0	22.8	42.0	Margarine	Sterols	Ester	24	0.83	2.97	−0.20	(−0.31–0.10)	5.5 (low)
Hendriks et al. 1999 stratum 2 (97)	80	37.0	22.8	42.0	Margarine	Sterols	Ester	24	1.61	2.97	−0.26	(−0.36–0.15)	5.5 (low)
Hendriks et al. 1999 stratum 3 (97)	80	37.0	22.8	42.0	Margarine	Sterols	Ester	24	3.24	2.97	−0.30	(−0.41–0.20)	5.5 (Low)
Jakulj et al. 2005 (98)	39	55.5	25.9	87.5	Margarine	Sterols	Free	28	2.00	4.50	−0.35	(−0.58–0.13)	7.5 (good)
Jones et al. 2000 stratum 1 (30)	15	—	—	100.0	Margarine	Sterols	Ester	21	1.84	4.29	−0.56	(−0.77–0.35)	8.0 (good)
Jones et al. 2000 stratum 2 (30)	25	—	—	100.0	Margarine	Stanols	Ester	21	1.84	4.35	−0.27	(−0.50–0.04)	8.0 (good)
Jones et al. 2003 (99)	25	—	—	60.0	Non-fat beverage	Mix	Free	21	1.80	4.15	−0.08	(−0.41 0.25)	8.0 (good)
Judd et al. 2002 (100)	53	47.1	26.3	49.1	Salad dressing	Sterols	Ester	21	2.20	3.62	−0.34	(−0.38–0.29)	6.0 (low)
Kratz et al. 2007 stratum 1 (101)	17	32.0	22.0	—	Margarine	Sterols	Ester	42	2.03	2.77	−0.10	(−0.30 0.10)	7.5 (good)
Kratz et al. 2007 stratum 2 (101)	17	32.0	22.0	—	Margarine	Stanols	Ester	42	1.96	2.77	−0.23	(−0.38–0.08)	7.5 (good)
Lau et al. 2005 study 1 (102)	14	54.5	30.2	35.7	Margarine	Sterols	Free	21	1.80	3.24	−0.19	(−0.61–0.23)	8.0 (good)
Lau et al. 2005 study 2 (102)	15	55.1	26.9	40.0	Margarine	Sterols	Free	21	1.80	3.92	−0.30	(−0.57–0.03)	8.0 (good)
Lottenberg et al. 2003 (103)	60	55.8	26.4	16.7	Margarine	Sterols	Ester	28	1.68	5.00	−0.30	(−0.41–0.19)	6.0 (low)
Madsen et al. 2007 (104)	46	50.6	25.0	25.0	Margarine	Sterols	Ester	28	2.30	3.50	−0.29	(−0.45–0.14)	6.0 (low)
Mussner et al. 2002 (105)	62	42.0	24.0	38.7	Margarine	Sterols	Ester	21	1.82	3.93	−0.26	(−0.37–0.15)	5.5 (low)
Naumann et al. 2003 stratum 1 (106)	42	33.8	23.4	35.7	Margarine	Mix	Ester	21	1.96	—	−0.17	(−0.37–0.02)	4.0 (low)
Naumann et al. 2003 stratum 2 (106)	42	33.8	23.4	35.7	Margarine	Mix	Ester	21	1.99	—	−0.19	(−0.40–0.05)	4.0 (low)
Nestel et al. 2001 study 1 stratum 1 (107)	22	60.0	24.0	81.8	Bread, cereal, and margarine	Sterols	Ester	28	2.40	—	−0.45	(−0.76–0.14)	2.0 (low)
Nestel et al. 2001 study 1 stratum 2 (107)	22	60.0	24.0	81.8	Bread, cereal, and margarine	Stanols	Free	28	2.40	—	−0.30	(−0.60 0.00)	2.0 (low)
Nestel et al. 2001 study 2 (107)	15	43.7	—	—	Margarine	Sterols	Ester	28	2.40	—	−0.37	(−0.61–0.13)	4.0 (low)

(Continued)

TABLE 3 *Continued*

Author, publication year, and reference	Subject characteristics: Sample size	Mean age	Mean BMI	Male	Treatment characteristics: Food format	Sterols or stanols	Ester or free	Duration	Dose free phyto-sterols[1]	Blood lipid outcomes: LDL cholesterol: Mean baseline	Net change[2]	95% CI	Overall quality score[3]
Niittynen et al. 2007 study 1 (77)	15	41.0	25.6	100.0	Low-fat yogurt drink	Sterols	Free	28	1.00	3.90	−0.19	(−0.41 0.03)	7.5 (good)
Noakes et al. 2002 study 1 stratum 1 (51)	46	56.7	26.2	43.5	Margarine	Sterols	Ester	21	2.30	4.38	−0.33	(−0.44–0.22)	7.5 (good)
Noakes et al. 2002 study 1 stratum 2 (51)	46	56.7	26.2	43.5	Margarine	Stanols	Ester	21	2.50	4.38	−0.41	(−0.51–0.31)	7.5 (good)
Noakes et al. 2002 study 2 (51)	35	57.3	26.0	57.1	Margarine	Sterols	Ester	21	2.00	4.20	−0.40	(−0.52–0.28)	7.5 (good)
Noakes et al. 2005 study 1 stratum 1 (11)	39	51.5	25.9	53.8	Margarine	Sterols	Ester	21	2.00	4.83	−0.49	(−0.66–0.32)	4.5 (low)
Noakes et al. 2005 study 1 stratum 2 (11)	39	51.5	25.9	53.8	Milk	Sterols	Ester	21	2.00	4.83	−0.38	(−0.50–0.26)	4.5 (low)
Noakes et al. 2005 study 1 stratum 3 (11)	39	51.5	25.9	53.8	Margarine and milk	Sterols	Ester	21	4.00	4.83	−0.55	(−0.69–0.41)	4.5 (low)
Noakes et al. 2005 study 2 stratum 1 (11)	40	60.4	26.5	42.5	Yogurt	Stanols	Ester	21	1.80	4.48	−0.23	(−0.33–0.13)	7.5 (good)
Noakes et al. 2005 study 2 stratum 2 (11)	40	60.4	26.5	42.5	Yogurt	Sterols	Ester	21	1.70	4.48	−0.27	(−0.37–0.17)	7.5 (good)
Ntanios et al. 2002 (108)	53	45.1	23.7	49.1	Margarine	Sterols	Free	21	1.80	—	−0.28	(−0.39–0.17)	5.5 (low)
Pelletier et al. 1995 (109)	12	22.7	22.3	100.0	Butter	Sterols	Free	28	0.74	—	−0.41	(−0.58–0.24)	5.0 (low)
Plat et al. 2000a stratum 1 (53)	39	31.0	22.7	28.2	Margarine	Stanols	Ester	28	2.47	—	−0.29	(−0.39–0.19)	7.5 (good)
Plat et al. 2000a stratum 2 (53)	39	31.0	22.7	28.2	Margarine and shortening	Stanols	Ester	28	2.46	—	−0.31	(−0.41–0.20)	7.5 (good)
Sierksma et al. 1999 (36)	75	44.0	24.4	51.3	Margarine	Sterols	Free	21	0.80	—	−0.19	(−0.23–0.15)	6.5 (good)
Temme et al. 2002 (110)	42	55.0	25.0	52.4	Margarine	Sterols	Ester	28	2.10	4.29	−0.47	(−0.62–0.31)	7.5 (GOOD)
Thomsen et al. 2004 stratum 1 (12)	69	60.0	25.9	26.1	Milk	Sterols	Free	28	1.17	4.37	−0.30	(−0.42–0.18)	4.0 (low)
Thomsen et al. 2004 stratum 2 (12)	69	60.0	25.9	26.1	Milk	Sterols	Free	28	1.60	4.37	−0.40	(−0.53–0.28)	4.0 (low)
Vanstone et al. 2002 stratum 1 (111)	15	47.8	30.8	60.0	Butter	Sterols	Free	21	1.80	4.00	−0.41	(−0.65–0.17)	8.0 (good)
Vanstone et al. 2002 stratum 2 (111)	15	47.8	30.8	60.0	Butter	Stanols	Free	21	1.80	4.11	−0.42	(−0.66–0.18)	8.0 (good)
Vanstone et al. 2002 stratum 3 (111)	15	47.8	30.8	60.0	Butter	Mix	Free	21	1.80	4.18	−0.46	(−0.70–0.22)	8.0 (good)
Volpe et al. 2001 (112)	30	—	—	70.0	Low-fat yogurt drink	Sterols	Free	28	1.08	4.67	−0.34	(−0.51–0.17)	6.5 (good)
Weststrate & Meijer 1998 stratum 1 (49)	76/76[7]	45.0	24.2	50.0	Margarine	Sterols	Ester	21	3.20	3.54	−0.44	(−0.48–0.40)	5.5 (low)
Weststrate & Meijer 1998 stratum 2 (49)	76/77	45.0	24.2	50.0	Margarine	Stanols	Ester	21	2.70	3.54	−0.40	(−0.44–0.36)	5.5 (low)
Yoshida et al. 2006 study 1 (113)	16	55.2	27.7	43.8	Cereal bar	Mix	Free	21	1.80	4.18	−0.24	(−0.48 0.00)	7.5 (good)
Yoshida et al. 2006 study 2 (113)	13	56.8	31.0	30.8	Cereal bar	Mix	Free	21	1.80	3.60	−0.09	(−0.33 0.15)	7.5 (good)

[1] Dose given as free equivalents in g/d.
[2] The net change in LDL-C was calculated as the mean LDL-C concentration at the end of the phytosterol treatment period minus the mean LDL-C concentrations at the end of the control period.
[3] The maximum overall quality score was 8 for cross-over trials. When a trial was given ≤ 6.0 points, it was judged to be of low quality and a trial that was given > 6.0 points was judged to be of high quality.
[4] Multiple strata in 1 study corrected for the same single control group: indicated with stratum 1, stratum 2, stratum 3, etc.
[5] Multiple strata in 1 study, each corrected for a respective control group: indicated with study 1, study 2, study 3, etc.
[6] Clifton et al. (2004) (10) used an incomplete cross-over design with 4 phytosterol treatments and 1 control treatment; all subjects followed a period with control treatment and only 3 periods with phytosterol treatment. Thus, the total number of subjects per treatment was not the same: 58 for the control treatment and 36, 40, 58, and 40 for the phytosterol treatments, respectively.
[7] Weststrate and Meijer (1998) (49) used an incomplete cross-over design with 5 phytosterol treatments (2 of which are included in this meta-analysis) and 1 control treatment; due to 4 drop-outs in the first period and 1 drop-out in the 3rd period, the total number of subjects per phytosterol treatment varied: 76 and 77 during the phytosterol treatments, respectively.

formats. Liquid food formats were used in 23 strata. In most strata, phytosterols were consumed in multiple daily intakes ($n = 87$), at all 3 meals ($n = 37$), or at various combinations of 2 meals ($n = 20$). When consumed once a day ($n = 14$ strata), phytosterols were ingested at breakfast ($n = 7$ strata), lunch ($n = 5$ strata), or dinner ($n = 2$ strata). Subjects were allowed to

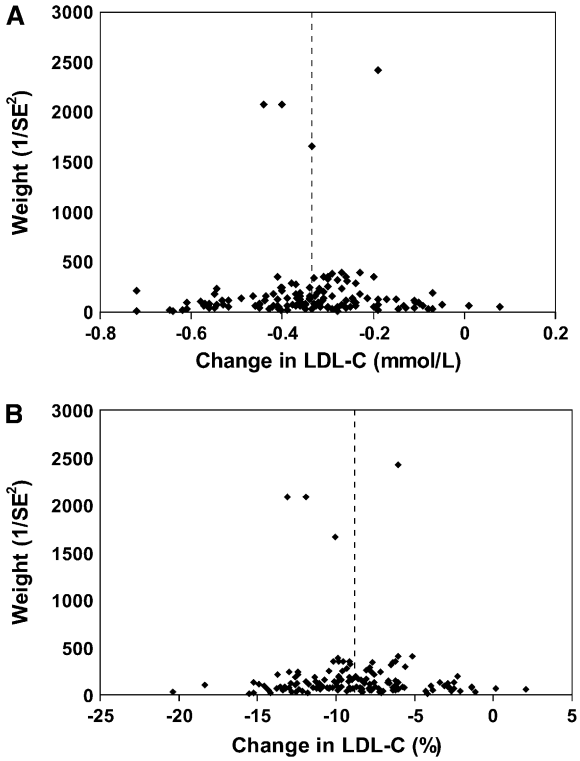

FIGURE 2 Funnel plots of the weights ($1/SE^2$) against the absolute changes in LDL-C (*A*) and the relative changes in LDL-C (*B*) in 141 strata from 81 randomized controlled trials investigating the cholesterol-lowering effect of phytosterols. The LDL-C changes are scattered around the pooled overall estimate of −0.34 mmol/l (*A*) and −8.83% (*B*).

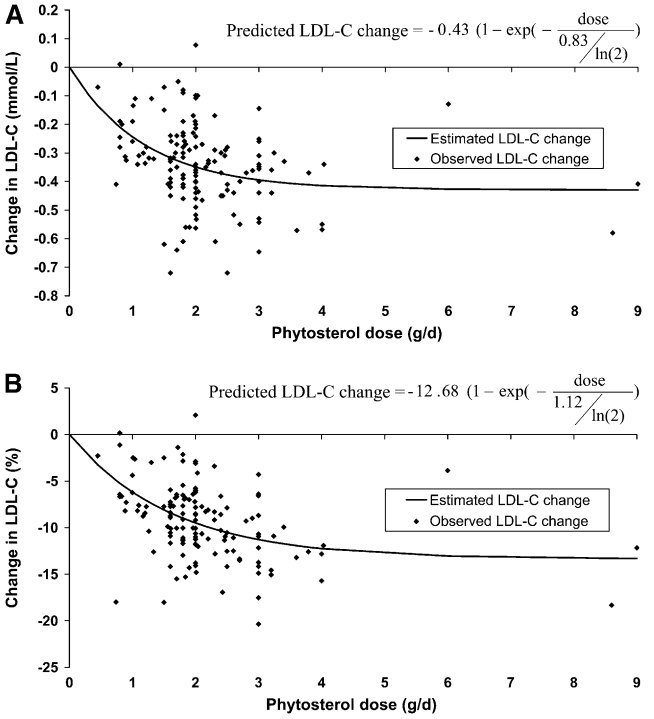

FIGURE 3 Dose-response relationship for the absolute (*A*) and relative (*B*) LDL-C–lowering effect of phytosterols.

maintain their usual dietary pattern in the majority ($n = 98$) of strata. Overall study quality was good for 68 of 141 strata and low for the remaining 73 strata (Supplemental Appendix 4).

Between-trial heterogeneity as assessed by the Q-statistic was significant (351.1, $P < 0.001$ and 242583.1, $P < 0.001$ for the absolute and relative changes in LDL-C, respectively). Visual inspection of the funnel plots (**Fig. 2**) as well as the probability plot of the ranked changes in LDL-C (not shown) suggested the absence of publication bias.

Effect of phytosterol intake on LDL-C and TC:HDL-C. On average, phytosterols lowered LDL-C by 0.34 mmol/L (95% CI: −0.36, −0.31), which corresponds to a relative decrease of 8.8% (95% CI: −9.4, −8.3). There was an absolute reduction in LDL-C concentrations in 139 of 141 strata (Tables 2 and 3) and the reduction was significant in 109 strata. In only 2 strata (18,45), LDL-C concentrations were not decreased at 4 wk (time point used for the meta-analysis). Data reported for these strata after 8 or 12 wk showed a significant reduction in LDL-C.

The dose-response curve for the relationship between phytosterol dose and LDL-C–lowering was described in Eq. 2, where the best parameters to fit the observed data were: a = −0.43 mmol/L (95% CI: −0.51 to −0.35) and b = 0.83 g/d (95% CI: 0.42–1.23) for the predicted absolute LDL-C change (mmol/L) ($P < 0.001$) and a = −12.68% (95% CI: −15.38 to −9.99) and b = 1.12 g/d (95% CI: 0.62–1.63) for the relative (%) LDL-C change ($P < 0.001$), respectively (**Fig. 3**). According to the dose-response relationship, the predicted LDL-C–lowering effect of the recommended daily dose of phytosterols (2 g) would be −0.35 mmol/L or −9%.

Eq. 2 was also used to describe the relationship between phytosterol dose and absolute changes in TC:HDL-C ratios. The values of parameters a and b obtained for the equation describing the absolute changes in TC:HDL-C were −0.42 mmol/L (95% CI: −0.57 to −0.27) and 1.06 g/d (95% CI: 0.23–1.90), respectively ($P < 0.001$). For the recommended dose of 2 g/d phytosterols, the equation predicts a 0.3% decrease in the TC:HDL-C ratio. To verify whether this estimate was reliable, the deviations between the mean ratio calculated from individual ratios available from 8 of our previous studies and the ratios calculated from the mean TC and HDL-C concentrations (as was done in the present meta-analysis) were determined. The mean deviation, weighed by the number of subjects, was −6.45% (range: −3.99% to −8.78%), suggesting that TC:HDL-C ratios calculated from the reported means were underestimated.

Impact of subject baseline characteristics on the LDL-C–lowering effect of phytosterols. Residuals (differences between the absolute LDL-C changes predicted with the dose-response curve and the observed LDL-C changes) were most strongly correlated with baseline LDL-C concentrations ($r = −0.4$; $P < 0.0001$), with 16% of the variation in residuals explained by this variable. Age was also correlated with the residuals ($r = −0.17$; $P = 0.045$) but explained only 3% of the variation. BMI was not significantly correlated with gender ($r = −0.17$; $P = 0.051$) or residuals ($r = −0.18$; $P = 0.052$). When all 4 covariates were simultaneously included in the model, the effect of age on the residuals was no longer significant ($P = 0.45$), whereas the impact of baseline LDL-C concentrations remained significant ($P = 0.001$), suggesting colinearity between age and baseline LDL-C concentrations. Given the substantial impact of baseline LDL-C concentrations on the absolute LDL-C reductions due to phytosterol intake, with the larger reductions in populations with higher baseline LDL-C concentrations, comparisons between

TABLE 4 Impact of categorical covariates related to the type of phytosterols, food format, study quality and study design on the absolute and relative dose-response curve

Treatment or study characteristic	Categories compared, *strata* (*n*)	Difference in parameter a,[1,2] *mmol/L or %*	95% CI	Difference in parameter b[1,2] *g/d*	95% CI
Absolute curve[3]					
Type of phytosterols	Plant stanols ($n = 53$) vs. plant sterols ($n = 74$)	−0.13	(−0.38, 0.12)	0.65	(−0.63, 1.93)
Food format	Non fat-based ($n = 50$) vs. fat-based ($n = 88$)	0.05	(−0.12, 0.21)	−0.24	(−1.08, 0.60)
	Non-dairy ($n = 114$) vs. dairy ($n = 26$)	−0.02	(−0.18, 0.14)	0.36	(−0.45, 1.16)
	Solid ($n = 116$) vs. liquid ($n = 24$)	−0.11	(−0.24, 0.02)	0.51	(−0.27, 1.29)
Quality	High ($n = 85$) vs. low ($n = 52$) compliance	−0.01	(−0.17, 0.16)	−0.09	(−0.95, 0.76)
	Well ($n = 110$) vs. poorly ($n = 27$) randomized	−0.04	(−0.20, 0.11)	0.15	(−0.46, 1.14)
	High ($n = 68$) vs. low ($n = 69$) quality	−0.04	(−0.25, 0.17)	0.29	(−0.76, 1.33)
Design	Cross-over ($n = 68$) vs. parallel ($n = 73$)	1.96	(−5.90, 9.81)	−0.38	(−1.79, 1.03)
Relative curve[3]					
Type of phytosterols	Plant stanols ($n = 53$) vs. plant sterols ($n = 74$)	−6.66	(−18.33, 5.02)	1.13	(−0.98, 3.23)
Food format	Non fat-based ($n = 50$) vs. fat-based ($n = 88$)	1.45	(−4.83, 7.72)	−0.17	(−1.31, 0.97)
	Non-dairy ($n = 114$) vs. dairy ($n = 26$)	—	—	—	—
	Solid ($n = 116$) vs. liquid ($n = 24$)	−5.23	(−8.63, -1.83)*	0.86	(0.02, 1.71)*
Quality	High ($n = 85$) vs. low ($n = 52$) compliance	−0.93	(−7.07, 5.20)	0.09	(−1.05, 1.23)
	well ($n = 110$) vs. poorly ($n = 27$) randomized	−3.36	(−7.73, 1.02)	0.75	(−0.11, 1.61)
	high ($n = 68$) vs. low ($n = 69$) quality	−8.66	(−27.49, 10.17)	1.66	(−1.59, 4.90)
Design	Cross-over ($n = 68$) vs. parallel ($n = 73$)	0.12	(−0.16, 0.39)	−0.60	(−1.89, 0.69)

[1] The differences in parameters a and b of the curves obtained for subcategories of a covariable were calculated by re-parameterizing the equation with terms for differences between categories.
[2] Parameter a is the maximal LDL-C– lowering effect and parameter b is the dose step needed to achieve an additional effect, which is one-half the size of the previous dose effect.
[3] For the absolute curve, the change in parameter a is expressed in mmol/L, and for the relative curve, it is expressed in % from baseline/control.
[4] *$P < 0.05$.

subgroups of categorical covariates were made by comparing not only the absolute but also the relative curves. Indeed, the use of the relative (%) changes resulted in less variation in residuals (only 0.05% of the variation was due to baseline LDL-C) than the use of the absolute values and the relative curve was more precise ($F = 477.1$) than the absolute curve ($F = 425.9$).

Impact of food format and other treatment characteristics on the LDL-C–lowering effect of phytosterols. The impact of the categorical covariates was evaluated by comparing the dose-response curves obtained for the respective subgroups (**Table 4**). The fat content of the food format (fat-based vs. non fat-based) and the type of phytosterols (plant sterols vs. stanols) did not significantly affect the absolute and relative dose-response curves (Table 4 ; **Fig. 4**). The dairy or non-dairy nature of the foods also did not significantly affect the absolute dose-response curve (not shown). A relative curve for the dairy food formats could not be calculated due to the small number of strata and the narrow distribution of the net changes in LDL-C. Therefore, the mean relative LDL-C changes were calculated separately for strata in which dairy and non-dairy foods were used and for a narrow range (1.6–2.0 g/d) of doses. The mean LDL-C–lowering effect of dairy and non-dairy food formats was −8.53% (95% CI: −9.71, −7.34) for a mean phytosterol intake of 1.85 g/d and −7.97% (95% CI: −8.79, −7.15) for a mean dose of 1.81 g/d, respectively, indicating no significant difference between dairy and non-dairy food formats. The only significant effect was the effect of solid compared to liquid food format on the relative curve. At high doses, the maximal estimated LDL-C–lowering effect of solid foods was 5.2% larger than that of liquid foods (parameter a), and at low doses, the curve was steeper for liquid than for solid foods (parameter b) (Table 4). However, the curves obtained for

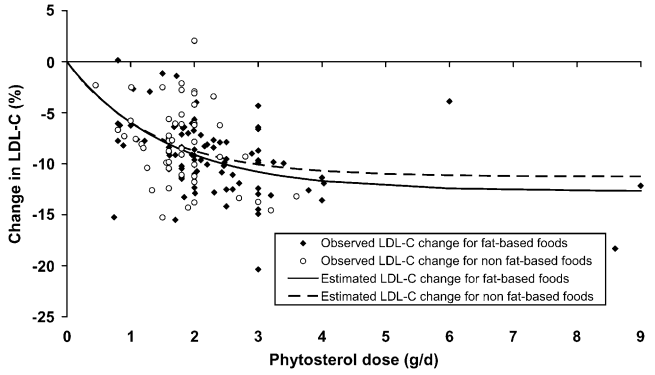

FIGURE 4 Relative dose-response curves of the LDL-C–lowering effect of phytosterols incorporated in fat-based compared to non fat-based food formats.

solid vs. liquid foods crossed at phytosterol intakes of ~1.5 g/d, and at ~2 g/d, the difference between the 2 curves was small (data not shown).

Post hoc analyses were performed to evaluate the impact of phytosterol esterification and frequency of intake on the dose-response curve. Free phytosterols and phytosterol esters did not differ in the maximal LDL-C reduction or in the incremental dose-step (Table 4). Due to the small number of strata ($n = 14$) in the single daily intake subgroup and the narrow distribution of net LDL-C changes in this subgroup, a dose-response curve could not be established for the once-a-day intakes. Therefore, to evaluate the effect of frequency of intake, the mean relative LDL-C change for a narrow range of doses (1.6–2.0 g/d) was calculated for strata in which phytosterols were consumed once per day compared to ≥2 times/ d. The relative LDL-C– lowering effect was more pronounced when phytosterols were consumed in multiple daily intakes (−8.91%; 95% CI: −9.75, −8.07 for a mean phytosterol dose of 1.81 g/d) than in single daily intakes (−6.14%; 95% CI: −8.19, −4.10 for a mean dose of 1.76 g/d). Because the mean dose was slightly higher for the multiple daily intakes, regression analyses were performed to determine the respective impact of dose and frequency of consumption. When included separately in the model, the dose contributed to 14% of the variation in LDL-C changes ($P < 0.0001$) and the frequency of intake contributed to 5% of the variation ($P = 0.0054$). An increase in the number of daily intakes was associated with a larger decrease in LDL-C concentrations. However, when dose and frequency of intake were simultaneously included in the model ($r^2 = 0.26$), the effect of dose on LDL-C changes remained significant ($P < 0.0001$), whereas frequency of intake only tended ($P = 0.054$) to affect the relative decreases in LDL-C concentrations. These data suggest that the effect of frequency of intake was partly confounded by the influence of dose.

Impact of study quality and study design on the LDL-C–lowering effect of phytosterols. The overall quality of the trials, the compliance, and the randomization method did not significantly affect either the absolute or the relative dose-response curve. We performed a post hoc analysis to evaluate the effect of study design (cross-over vs. parallel) on the dose-response curves. Study design did not have an impact on the curves (Table 4).

Discussion

The key outcome of this review and meta-analysis is the generation of a physiologically relevant, continuous dose-response relationship for the LDL-C–lowering effect of phytosterols. By including not only fat-based foods consumed multiple times per day but also low-fat or fat-free foods and food formats intended for once-a-day use, this approach provides an updated estimation of the LDL-C–lowering efficacy of phytosterols in the variety of available food formats. The dose-response equation predicts an LDL-C– lowering effect of −9% for the recommended 2 g/d dose of phytosterols, which is consistent with our pooled estimate showing an 8.8% decrease in LDL-C for a mean dose of 2.15 g/d and with the mean 8.9% reduction reported by Katan et al. (3) for phytosterol doses of 2.0–2.4 g/d provided mainly in fat-based food formats.

We attempted to estimate as well the dose-response relationship for the effect of phytosterols on the TC:HDL-C ratio, but firm conclusions could not be drawn because the ratio calculated from the reported means of TC and HDL-C was underestimated. Results from a recent meta-analysis of individual subject data (46) provide more insights into this question. Phytosterols (in this case, plant stanols) were shown to significantly lower TC:HDL-C ratios and decreases were more pronounced in subjects with higher baseline values. In subjects with low baseline HDL-C concentrations, HDL-C was slightly increased, while in subjects with high baseline concentrations, it was marginally lowered (46). According to the authors, this slight reduction in HDL-C in subjects with high baseline values would not increase cardiovascular risk, because at the same time, LDL-C would be decreased substantially.

The LDL-C–lowering dose-response curve obtained from the present meta-analysis had a plateau at phytosterol intakes of ~3 g/d, corresponding to an LDL-C–lowering effect of −10.7%, which is consistent with the estimation by Katan et al. (3), according to which doses > 2.5 g/d provided only little additional benefit. The present meta-analysis indicated that most phytosterol treatment characteristics (fat-based vs. non fat-based formats, dairy vs. non-dairy formats, free phytosterols vs. phytosterol esters, and plant sterols vs. stanols) had no noticeable impact on the LDL-C–lowering efficacy. The LDL-C–lowering effect of free phytosterols and phytosterol esters has so far not been directly compared in single trials, but cholesterol absorption inhibition was shown to be similar (47) or even larger (48) with free plant sterols than with the esters. In short (3–4 wk) (30,49–51) and longer term (up to 85 wk) (52) trials where stanols and sterols were compared side by side, no difference was observed between sterols and stanols, which is consistent with the present results.

Results from the present meta-analysis suggest that solid food formats may result in a larger LDL-C–lowering effect than liquid foods when the phytosterol dose is high (>2 g/d). In a previous study, a yogurt drink enriched with ~3 g/d plant sterols had a greater efficacy when consumed with a lunch meal than after an overnight fast (20). These data could provide support to the hypothesis of a beneficial impact of the simultaneous presence of a solid meal on the cholesterol-lowering efficacy of liquid food formats, perhaps by a longer transit time in the gastrointestinal tract. However, in most studies included in this meta-analysis, the phytosterol-enriched liquid foods were consumed at meal time. Proper side-by-side comparisons in the same trial and using the same daily dose would be needed to confirm a difference in efficacy between solid and liquid food formats. One previous study comparing the efficacy of plant sterol-enriched (1.6 g/d) milk, yogurt, cereal, and bread consumed at meal time showed the greatest efficacy with the milk format (10). In addition, the greater efficacy of solid food formats was observed in this meta-analysis only at high intakes, for which few strata were available, suggesting that this finding may have little practical relevance for phytosterol doses close to the recommended intake of 2 g/d.

Another factor that may affect the LDL-C–lowering efficacy of phytosterols is the number of portions consumed over the day. So far, only one trial has directly compared the effects of once per day compared to a 3 times/d intake of phytosterols provided in a fat-based spread consumed at meal time and showed no significant difference between the 2 frequencies of intakes (53). Other studies in which once-per-day intake of phytosterols was assessed had significant reductions in LDL-C (13,16,21–24). Nevertheless, the tendency towards a larger effect of multiple daily intakes than single intakes in the present meta-analysis may suggest that a modest effect of frequency of intake may exist but was not detected previously due to a lack of statistical power. Based on the main mechanism of action of phytosterols, which is considered to be the competition with cholesterol for micellar incorporation (8), it could be hypothesized that multiple daily intakes, by favoring the simultaneous presence in the gut of phytosterols, cholesterol, and bile acids in repeated occasions during the day, would lead to a greater efficacy than a single intake. In fact, the mechanisms by which once-a-day intake of phytosterols would substantially lower LDL-C are not fully understood and warrant further investigations.

The present meta-analysis shows a clear impact of baseline LDL-C concentrations on the magnitude of the absolute decreases in LDL-C concentrations resulting from phytosterol consumption. The previous meta-analyses by Law et al. (2) and Katan et al. (3) had shown larger reductions in older subjects and it was hypothesized that this effect was due mainly to the higher baseline LDL-C concentrations with increasing age. The regression analysis performed in the present work, with no significant effect of age when baseline LDL-C concentrations were included in the model, confirmed this hypothesis. A recent meta-analysis of individual subject data (46) also showed larger absolute LDL-C reductions with plant stanol consumption when baseline concentrations were higher. The relative dose-response curves obtained from the present meta-analysis therefore present an advantage over the absolute curves by taking into account the baseline LDL-C levels.

The equations describing the continuous dose-response relationship offer a novel approach to predict the LDL-C–lowering effect of a given dose of phytosterols in populations, which could not be derived from previous data (3). However, due to the large variability between studies in which the same dose of phytosterols was tested, the predicted effect should be used as an indication only. It could be argued that with such variability around the dose-response curve, a linear fit would have performed as well as the nonlinear relationship. To verify this hypothesis, the sum of the residuals between the observed LDL-C changes and the predicted changes obtained with the curve or with a linear fit crossing the y axis at zero (without a maximal reduction estimate) were compared. The sum of the residuals was considerably lower with the curve (370%) than with the linear relationship (475%), indicating that the nonlinear, physiologically relevant model is more appropriate.

The dose-response curves reported here were established by deliberately including studies in which phytosterol intakes could be as high as 10 g/d, because data obtained with such intakes could provide useful information regarding the expected plateau while still being realistically achievable through the consumption of phytosterol-enriched foods or supplements. A post hoc analysis showed that the dose-response curve was not significantly influenced by the inclusion of studies with doses of 5–10 g/d. Indeed, the maximal LDL-C reduction (parameter a) and the incremental dose step (parameter b) were −13.26 (95% CI: −17.04 to −9.48) and 1.22 (95% CI: 0.54–1.90) for the curve including doses of <5 g/d compared to −12.68 (95% CI: −15.38 to −9.99) and 1.12 (95% CI: 0.62–1.63) for the curve including doses of up to 10 g/d.

Although various background diets were used in the studies included in the present meta-analysis, comprising usual diets as well as low-fat, low-cholesterol diets consumed both in free-living or more controlled conditions, we did not investigate the potential impact of the background diet on the cholesterol lowering efficacy of phytosterols. Results from one recent trial suggest that the cholesterol content of the background diet may have no significant effect on plant sterol efficacy (54). Subject ethnicity is another factor that could potentially affect phytosterol efficacy beyond baseline LDL-C concentrations. Additional investigations to further study this factor, together with the effect of genetic polymorphisms, are warranted.

In summary, the present meta-analysis confirmed the significant LDL-C– lowering effect of phytosterols. Equations based on the underlying mechanism of action of plant sterols and stanols were determined to describe the dose-response relationship and could potentially be used to predict the LDL-C– lowering effect of a given phytosterol dose. However, the use of the curve as a prediction tool should be done cautiously due to the large inter-trial variability at fixed doses. For the recommended intake of 2 g/d, the expected LDL-C–lowering effect of phytosterols is −9%. A reduction in LDL-C of ~10% would reduce the incidence of CHD by ~10–20% (2,4). Although no direct evidence is available yet for the ability of phytosterols to lower CHD incidence, the well-documented cholesterol-lowering effect of phytosterols is the basis for recommendations to include phytosterols into strategies to lower LDL-C concentrations. The present meta-analysis did not show significant differences in efficacy of various food formats providing phytosterol doses around the recommended intake. However, at high phytosterol doses, solid food formats may have a more pronounced LDL-C–lowering effect than liquid food formats. Although not significant ($P = 0.054$), the possibility of an impact of frequency of intake over the day could not be excluded. Further investigations are warranted to gain more insights into the effect of these factors on the efficacy of phytosterols to lower LDL-C concentrations.

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