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SYSTEMATIC REVIEWS AND META-ANALYSES

Impact of phytosterol supplementation on plasma lipoprotein(a) and free fatty acid (FFA) concentrations: A systematic review and meta-analysis of randomized controlled trials

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Abstract *Background and aim:* Although some earlier studies have indicated the effect of phytosterol (PS) supplementation on serum lipoprotein(a) (Lp(a)) and free fatty acid (FFA) concentration, findings are still conflicting. We aimed to assess the impact of PS supplementation on serum Lp(a) and FFA concentration through a systematic review and meta-analysis of available RCTs.

Methods and results: We performed a systematic search of all available RCTs conducted up to 21 February 2019 in the following databases: PubMed, Scopus, and Cochrane. The choice of fixed- or random-effect model for analysis was determined according to the I^2 statistic. Effect sizes were expressed as weighted mean difference (WMD) and 95% confidence interval (CI). Pooling of 12 effect sizes from seven articles revealed a significant reduction of Lp(a) levels following PS supplementation (MD: −0.025 mg/dl, 95% CI: −0.045, −0.004, $p = 0.017$) without significant heterogeneity among the studies ($I^2 = 0.0\%$, $p = 0.599$). Also, PS supplementation significantly lowered FFA (MD: −0.138 mg/dl, 95% CI: −0.195, −0.081, $p = 0.000$) without significant heterogeneity among the studies ($I^2 = 0.0\%$, $p = 0.911$). The results for meta-regression and sensitivity analysis were not significant.

Conclusion: The meta-analysis suggests that oral PS supplementation could cause a significant reduction in serum Lp(a) and FFA.

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Introduction

More than half of deaths worldwide is attributed to cardiovascular disease (CVD) [1], of which the incidence is declining in developed countries but is rising very rapidly in low- and middle-income countries [1,2]. There are many risk factors associated with CVD. The main risk factors include smoking, hypertension, advanced age, family history of CVD and dyslipidemia [3,4]. Recent reports have shown that lipoprotein(a) (Lp(a)) and plasma free fatty acid (FFA)are novel risk factors and biomarkers which can predict CVD [5,6]. Lp(a) is structurally very similar to low density lipoprotein (LDL) [7], so it possesses proatherogenic and prothrombotic properties which can lead to CVD [8,9]. Lp(a) raises cardiovascular risk by expressing adhesion molecules which facilitate the development of atherosclerotic lesions, mediating prothrombotic activities, and exerting pro-inflammatory effects [10–13].On the other hand, level and flux of plasma FFAs to the liver is known to increase following overproduction of LDL and very low density lipoprotein (VLDL) [14,15].

Several treatments of choice for patients with increased Lp(a) and FFA levels include niacin therapy, statins, eprotirome, a thyroid analogue, and lomitapide. Nevertheless, there has been a surge of interest to screen natural products (nutraceuticals/functional foods) for their effects on Lp(a) and FFA concentration.

One of the bioactive compounds found in functional foods such as nuts, seeds, vegetable oils, cereals and legumes is phytosterol (PS)which is structurally very similar to cholesterol [16–18].Numerous studies have indicated that PS is a cholesterol-lowering agent, which might be associated with reduction in Lp(a) and FFA levels. The role of PS supplementation in regulating the levels of LDL, HDL and triglycerides is well-ascertained, but studies investigating the effect of PS supplementation on other lipid parameters such as Lp(a) and FFA have reported contradictory findings [19–21].Therefore, the purpose of this study was to assess the effect of PS on Lp(a) and FFA concentrations through a systematic review of the literature and meta-analysis of randomized controlled trials(RCTs).

Methods

A systematic review and meta-analysis was performed to examine the effect of PS consumption on Lp(a) and FFA. The present systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [22].

Eligibility criteria

RCTs that compared intake of PS supplementation to a control group not consuming PS were included. Included RCTs reported $\geq$1 of the following outcome measures: Lp(a) concentration or FFA concentration. Trials were not excluded because of participants' characteristics, and no date restrictions were applied. Studies were excluded if they lacked a control group in which participants did not consume PS, or if they used a nonrandomized treatment allocation. In addition, RCTs that tested other dietary patterns or dietary components in addition to PS were excluded because the specific effect of PS could not be estimated in these studies. We also excluded retracted articles.

Search strategy and study selection

We conducted a systematic search using PubMed, Scopus and the Cochrane Collaboration Library databases through 21 February 2019. The search terms used were listed in the Supplemental Material. Two authors screened the title and abstract of each article identified in the search in duplicate. The full texts of articles identified as potentially eligible were also reviewed in duplicate. We resolved the disagreements by discussion with a third author.

Data extraction

Data was extracted from eligible studies in duplicate by two authors. The extracted data were then entered into standardized spreadsheets. The following data was extracted for each outcome measure: study design (parallel; crossover); PS supplementation studied and dose; status of the control groups; study population; number of participants included in the trials and follow-up duration; the mean (or median) variance; and number of subjects in the treatment and control groups. We extracted the *p* value from the paired analyses for crossover studies. In trials where more than 1 dose of PS was tested, the highest dose was selected. Data from the greatest time since baseline of trials were included if the subjects were followed-up more than once. We contacted the authors by email when necessary data for our meta-analysis was not reported in the papers.

Risk of bias

The Cochrane Risk of Bias Tool was used for assessment of risk of bias in the included studies [23]. This checklist has seven criteria for quality assessment, including: (i) random sequence, (ii) conceal allocation, (iii) blind participants, (iv) blind outcome assessors, (v) incomplete outcome data, (vi) outcome reporting, and (vii) other sources of bias. Then, we determined whether the included studies had low risk of bias, high risk of bias, or being unclear for each aforesaid criterion. Any disagreement was resolved by discussion with a third author (Supplementary Table 1).

Statistical analyses

Effect sizes for all outcomes of interest were mean difference between the intervention group and the control group at follow-up. Where this was not reported, the difference in change from the mean value at the baseline and end of the study was used. The mean and SD were

extracted from studies and where data were reported in a different format, the following method by Hozo et al. was used: SD = square root [(SD pre-treatment) 2 + (SD post-treatment) 2 − (2R × SD pre-treatment × SD post-treatment)] [24]. To enable a single pairwise comparison, if >1 control group is available, the groups were combined by applying a weighted average. When the results was presented only in the graphic form, the Plot digitizer software was used to decipher the data. Heterogeneity was calculated by the I^2 index [25]. An I^2 value of greater than 50% was considered as having substantial heterogeneity among the trials. We performed subgroup analysis to identify factors which contribute to the high heterogeneity. For each aforementioned quantitative parameter for subgroup analysis, the less or more than median was considered as the cut off values. To examine the impact of each study on the results, sensitivity analysis was done using the leave-one-out method [26]. The dose of PS supplementation was plotted against the mean difference for each outcome using meta-regression to determine whether a dose−response relation existed. Publication bias was identified using the funnel plot, either Begg's rank correlation or Egger's regression test. The statistical analyses were carried out using STATA version 11.0 (Stata Corp, College Station, TX) and p values < 0.05 were considered statistically significant.

Results

Study selection

In our primary search, 3965 articles were identified from PubMed, Scopus, and Cochrane Library databases after 381 duplicate articles were excluded. We further excluded 3586 articles based on the title and abstract screening approach. Lastly, we screened the remaining 379 articles by reading the full text and excluded 323 studies due to the following reasons: administered PS in combination with other components ($n = 5$), review articles ($n = 9$), duplicate dataset ($n = 4$), studies that did not report sufficient data for outcomes ($n = 303$) (Fig. 1).

Study characteristics

The general characteristics of the eligible RCTs are outlined in Table 1. Sample sizes varied from 11 to 105 participants. The studies were published between 2000 and 2013 and conducted in Japan [20,27−29], Netherlands [21,30], Turkey [19], and France [31]. Mean ages of participants ranged from 33 to 60 years. One trial was performed exclusively in women [28] and others included both genders. The dosage of PS supplements ranged from 500 [20] to 4000 mg/day [28], and the duration of PS administration ranged from 4 [19,28] to 16 weeks [27]. The majority of trials employed a parallel design [19,21,27,30], while four trials were of a crossover design [20,28,31].Studies included patients with hypercholesterolemia [19,20,27−29], hyperlipidemia [31], and metabolic syndrome [30].

Lipoprotein(a)

Seven studies with a total of 363 participants (case = 178, and control = 85) reported lipoprotein(a) as an outcome measure. Combined results using the random-effects model showed a significant reduction in lipoprotein(a) following PS consumption (MD: −0.025 mg/dl, 95% CI: −0.045, −0.004, $p = 0.017$) without significant heterogeneity among the studies ($I^2 = 0.0\%$, $p = 0.599$) (Fig. 2). Sensitivity analysis indicated that no single study had a significant impact on the overall effect sizes. Assessment of publication bias by visual inspection of funnel plot did not indicate the presence of publication bias in the meta-analysis of PS consumption on lipoprotein(a) ($p = 0.848$) (Fig. 1). Following dose−response evaluation, lipoprotein(a) did not change in non-linear fashion based on PS dosage (mg/day) (P-nonlinearity = 0.374) and treatment duration (weeks) (P-nonlinearity = 0.145) (Fig. 4).

Free fatty acid (FFA)

Five studies with a total of 302 participants (case = 151, and control = 151) reported FFA as an outcome measure. Combined results using the random-effects model showed a significant decrease in FFA following PS consumption (MD: −0.138 mg/dl, 95% CI: −0.195, −0.081, $p = 0.000$) without significant heterogeneity among the studies ($I^2 = 0.0\%$, $p = 0.911$) (Fig. 3). Sensitivity analysis indicated that no single study had a significant impact on the overall effect sizes. Assessment of publication bias by visual inspection of funnel plot did not indicate the presence of publication bias in the meta-analysis of PS consumption on FFA ($p = 0.401$) (Supplementary Fig. 1). Following dose−response evaluation, FFA did not change in non-linear fashion based on PS dosage (mg/day) (P-nonlinearity = 0.037) and treatment duration (weeks) (P-nonlinearity = 0.973) (Fig. 4).

Discussion

To our knowledge, this is the first systematic review and meta-analysis of RCTs to analyze the effect of PS supplementation on plasma Lp(a) and FFA concentrations. Albeit with small numbers of subjects, the analysis suggests a significant reduction of Lp(a) and FFA levels following oral supplementation with PS. Therefore, consumption of PS may have important clinical implications such as reducing the incidence of atherogenesis and thus, cardiovascular risk. The studies included in the meta-analysis were heterogenous as indicated by an I^2 value of 0% for both Lp(a) and FFA. Possible bias was further minimized by not limiting the search to English language publications.

The results of this meta-analysis corroborate those of an earlier systematic review which reported the beneficial effects of PS on lipid profile. In the study by Quı'lez et al. [32], pooling of data from 19 RCTs revealed that consumption of 1.5−3.0 g of PS per day could lead to a 8−15% reduction in LDL-C concentration in normocholesterolemic subjects. Besides, in a recent meta-analysis of 11 RCTs,

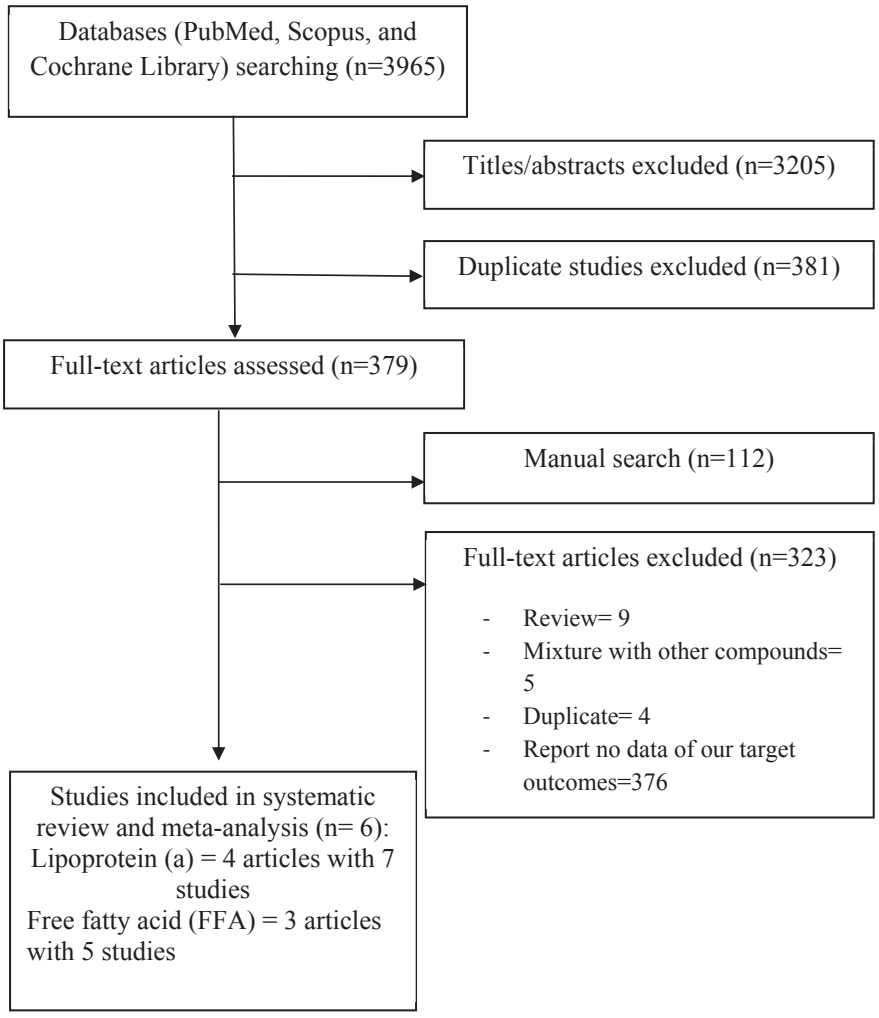

Figure 1 Flowchart of study identification and inclusion. This figure shows the process of selecting studies which fulfilled our inclusion criteria.

consumption of 1.6–2.8 g of PS per day was found to lead to a 0.64 mmol/L reduction in LDL-C in subjects with familial hypercholesterolemia [33].Our findings were also similar to those of Thomsen et al. [34], which indicated that nonesterified, nonhydrogenated PS reduced the serum Lp(a) concentration in mildly hypercholesterolemia patients. However, data on the effects of PS on plasma FFA concentrations in humans is still limited, with only a few small scale studies available. For example, a Japanese study found no change in plasma FFA concentration in response to PS supplementation in normocholesterolemic and mildly hypercholesterolemic subjects. On the contrary, Plat et al. [30] reported that PS supplementation may reduce serum FFA concentration in patients with metabolic syndrome. FFAs are known to elevate the formation and release of triglycerides by the liver and promote the overproduction of very low density lipoprotein (VLDL) [35,36].However, the exact molecular mechanism by which PS reduces FFA levels is not entirely known. Hence, further studies are required to clarify this matter.

The findings of our meta-analysis that PS could reduce Lp(a) concentration were contradictory to those of Plat and Mensink [21]. In the latter study, PS consumption (2.6 g sitostanol plus 1.2 g campestanol) for 12 weeks did not affect the Lp(a) concentration among non-hypercholesterolemia men and women, although adjustment for potential confounders was not performed in the study. Furthermore, according to Nigon et al. [31], there was no significant association between 1.6 g/day PS supplementation and high density lipoprotein-cholesterol (HDL-C) and lipoprotein(a) concentrations following a2-month cross-over trial with a 2-month washout period. Nevertheless, the study demonstrated that supplementation with PS decreased plasma cholesterol and LDL-C levels by 8.5–14.6% [31]. It is plausible that the difference in ethnic background and dose of PS in different studies might cause discrepancy in study findings. Also, it has been suggested that the baseline LDL-cholesterol level could be a confounding variable in response to PS [19]. In this regard, Moruisi et al. [33] showed that cholesterol reduction followingPS/stanol treatment was equally effective in patients with familial hypercholesterolemia as in non-familial hypercholesterolemia subjects.

Although the present meta-analysis showed that PS supplementation could reduce Lp(a) levels, it is unknown whether the finding is clinically significant in comparison

Table 1 Characteristics of eligible studies.

Placebo Group	Intervention Group	Outcome	Period (weeks)	Dose (mg)	Sample Size Case/Placebo	Sex	Mean Age	Population	Clinical Trial Design	Country	Author (year)
Placebo juice	Vegetable And Fruit Juice Mix, Enriched With Free Plant Sterol	Free fatty acid	16	800	50/51	Both	42.9	Hypercholesterolemia Patients	Parallel	Japan	Hironaka et al. (2006)
Placebo Juice	Vegetable And Fruit Juice Mix, Enriched With Free Plant Sterol	Free fatty acid	16	1600	54/51	Both	43.2	Hypercholesterolemia Patients	Parallel	Japan	Hironaka et al. (2006)
Placebo Dressing	Dressing Containing Plant Sterol	Free fatty acid	12	800	30/30	Both	46	Hypercholesterolemic Patients	Parallel	Japan	Kurokowa et al.(2008)
Rapeseed Oil Based Margarine Without Stanol	Pine Wood Based Stanol Ester Added Mixture	Lipoprotein (a)	8	3800	36/42	Both	33	Non-Hypercholesterolemia	Parallel	Netherlands	Plat et al. (2000)
Rapeseed Oil Based Margarine Without Stanol	Vegetable Oil Stanol Ester Added Mixture	Lipoprotein (a)	8	3700	34/42	Both	33	Non-Hypercholesterolemia	Parallel	Netherlands	Plat et al. (2000)
Placebo	placebo + stanol drink	Free fatty acid	9	2000	9/9	Both	60	Metabolic syndrome	Parallel	Netherlands	Plat et al. (2009)
simvastatin	simvastatin + stanol drink	Free fatty acid	9	2000	8/10	Both	60	Metabolic syndrome	Parallel	Netherlands	Plat et al. (2009)
placebo yoghurt	low-fat yoghurt with 1.9 g/d plant stanols as esters	Lipoprotein (a)	4	1900	35/35	Both	45.5	mild to moderate hypercholesterolemia	Parallel	Turkey	Buyuktuncer et al. (2013)
non-enriched control spread	Spread enriched with plant sterols	Lipoprotein (a)	8	1600	53/53	Both	55	Hyperlipidemic	Cross-over	France	Nigon et al. (2001)
diacylglycerol (DAG)	Plant sterols (PS), dissolved in diacylglycerol (DAG) oil	Lipoprotein (a)	12	500	7/6	Both	58	Hypercholesterolemic(HC: baseline serum campesterol levels _16.47 mmol/L))	Cross-over	Japan	Takeshita et al.(2008)
diacylglycerol (DAG)	Plant sterols (PS), dissolved in diacylglycerol (DAG) oil	Lipoprotein (a)	12	500	7/9	Both	58	Hypercholesterolemic(LC: serum compesterol levels <16.47 mmol/L)	Cross-over	Japan	Takeshita et al. (2008)
diacylglycerol (DAG)	plant sterols (PS) in a diacylglycerol (DAG)-rich oil	Lipoprotein (a)	4	4000	40/40	women	52	postmenopausal women hypercholesterolemia	Cross-over	Japan	Takeshita et al.(2007)

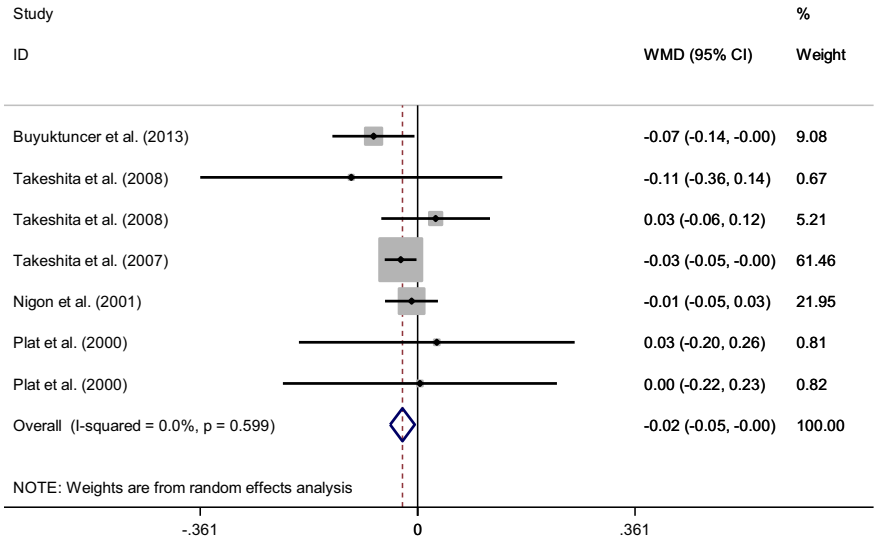

Figure 2 Forest plot of the effects of PS supplementation on Lp(a) levels.

to other studies [28]. However, multiple lines of evidence have shown that the lipid-lowering effect of PS supplementation may improve vascular function and reduce cardiovascular events [37,38].A few studies have been undertaken to investigate the mechanism by which PS supplementation influences Lp(a) concentration. The main mechanism by which PS contributes to a low cholesterol level is by preventing the absorption of dietary cholesterol through creation of bio-unavailable crystals which compete with dietary and biliary cholesterol in the intestines and subsequently reduces the level of exogenous cholesterol [39]. Furthermore, recent evidence suggests that PS may regulate proteins implicated in cholesterol metabolism in both enterocytes and hepatocytes, including by increasing the activity of ATP-binding cassette transporter A1 (ABCA1) and ABCG5/G8 heterodimer [40]. ABCA1 functions as an effector of basolateral systemic cholesterol absorption [41]. During the influx of dietary cholesterol, its expression is increased by the 27-hydroxycholesterol (27OH-C) generated, whereas apical ABCG5/G8 expression remains unchanged. PS may reduce 27OH-C formation and subsequently, prevent the self-priming component of systemic cholesterol absorption, hence leading to a low cholesterol level [42].Due to the PS cholesterol-lowering efficacy and good safety profile, it seems that the specific categories of patients (e.g., those with statin intolerance or diabetic patients) could benefit from its use those with statin intolerance or diabetic patients [43].

Multiple studies have confirmed that an elevated serum Lp(a) level is associated with increased risks of cardiovascular events [44,45].Therefore, natural products such as PS may represent a potential therapeutic agent for lowering Lp(a) levels. A recent review has reported the beneficial effects of other natural products, including xuezhikang, coenzyme Q_{10}, pectin, *Ginkgo biloba*, flaxseed, red wine, resveratrol and curcuminoidsin improving Lp(a)

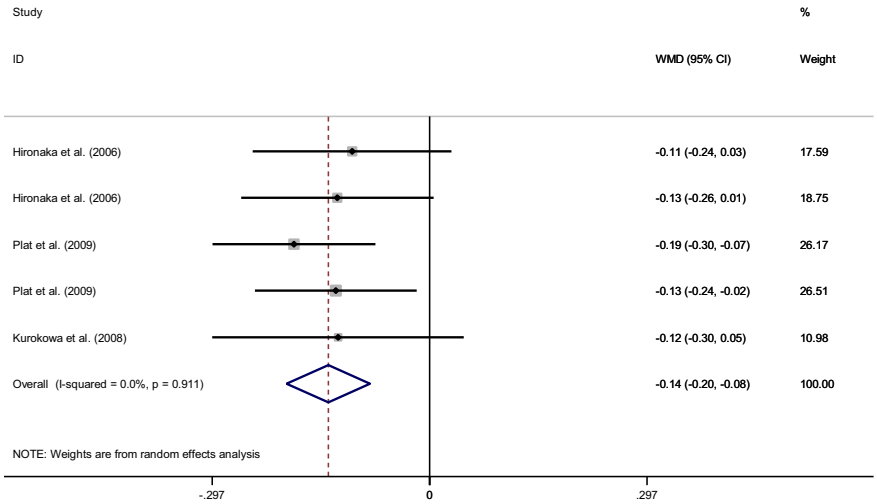

Figure 3 Forest plot of the effects of PS supplementation on FFA levels.

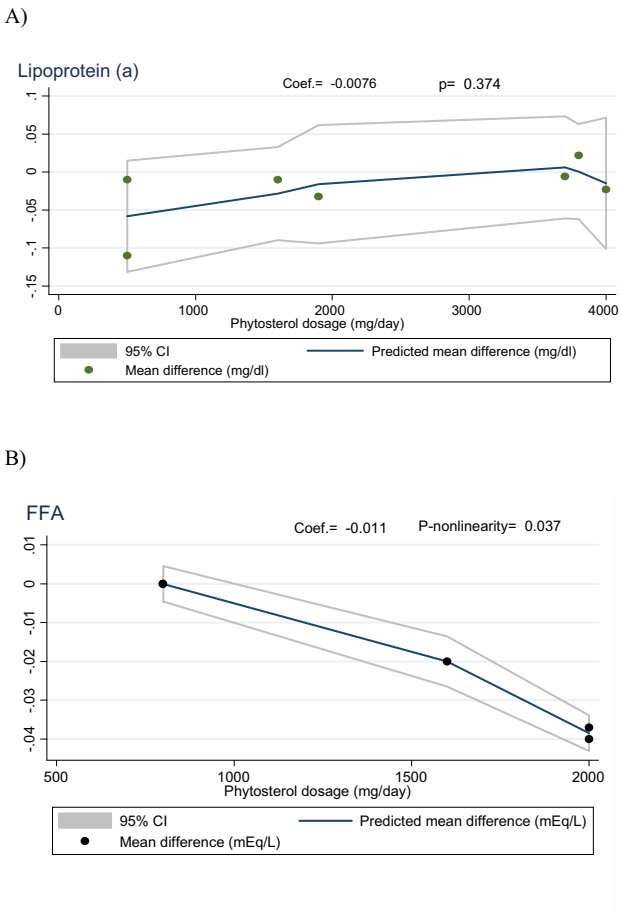

Figure 4 Non-linear dose-responses between PS supplementation and unstandardized mean difference in Lp(a) (A) and FFA (B). The 95% CI is depicted in the shaded regions.

levels [46]. Hence, the findings of the current meta-analysis can be helpful for nutritionists and researchers in developing a dietary plan for individuals with high Lp(a) levels.

The present meta-analysis had several limitations. First, the overall sample size was limited as the number of participants in some of the included studies was small. Second, the diversity of plant sterol types in the included studies was low, and this may limit the generalizability of the findings to other plant sterol types.

Despite these limitations, the meta-analysis has notable strengths. First, it is the first systematic review and meta-analysis of RCTs to analyze the effect of PS supplementation on plasma Lp(a) and FFA concentrations. Second, the analysis was performed using the random-effects model, which allows for accurate estimation of effect sizes even when heterogeneity was present among trials. Finally, no evidence of bias was noted through both sensitivity analyses and funnel plot tests, which suggests that the results were robust.

Conclusion

The results of this meta-analysis, being the first of its kind, indicated that PS supplementation could significantly reduce plasma Lp(a) and FFA concentrations. Further investigations are required to clarify if this effect of PS accounts, at least in part, for any cardiovascular benefit.

Conflicts of interest

All the authors declared that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.07.011.

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