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Review

Apolipoprotein E Genetic Variant and Blood Lipid Responses to Plant Sterols: A Systematic Review and Pooled Analysis of Clinical Trials

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ABSTRACT: Plant sterols/stanols are effective cholesterol-lowering agents. However, it is unclear whether the apolipoprotein E (*ApoE*) genetic variants influence it. We investigated whether *ApoE* genetic variants modulate the responses of blood lipids to dietary intervention plant sterols/stanols in adults and if the intervention dose and duration, as well as the age and status of participants, influence this effect. Randomized clinical trials were identified by searching databases in the Cochrane Library. Random-effect models were used to estimate the pooled effect size of each outcome of interest total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein cholesterol, and triglycerides. Meta-regression and subgroup analysis were used to investigate the effects of potential modifiers on the outcomes of interest. Eleven articles were selected from 3,248 retrieved abstracts. Plant sterol/stanol intervention was associated with a more significant reduction in LDL levels in the E3 group [−0.251 mmol/L; 95% confidence interval (95% CI), −0.488 to −0.015] compared with both the E4 and E2 groups. In E4 carriers, the plant sterol/stanol intervention dose and duration resulted in a larger decrease in LDL levels (−0.088027 mmol/L; 95% CI, −0.154690 to −0.021364). In conclusion, *ApoE* genetic variants affected the response of blood LDL levels to supplementation with plant sterols/stanols, as individuals with E3 variant showed significantly decreased LDL levels compared with the other genotypes. However, future studies recruiting participants according to their *ApoE* genetic variants are needed to confirm our conclusion.

Keywords: apolipoprotein E, cholesterol, phytosterols

INTRODUCTION

Cardiovascular disease (CVD) is a leading cause of morbidity and mortality worldwide. It encompasses various diseases and conditions, typically presenting as heart attacks and strokes (Nitsa et al., 2018). According to the latest World Health Organization (WHO) estimates, CVD accounts for 32% of deaths worldwide (WHO, 2017). CVD is expected to surpass cancer as the leading cause of death worldwide by 2030 (Murray and Lopez, 1997; Lopez et al., 2006). CVDs require intensive treatment and follow-up procedures, significantly burdening patients' quality of life and national healthcare budgets (Leone, 2013).

As the prevalence of CVD continues to increase, it emphasizes the urgency for effective strategies in prevention and management. Dyslipidemia, characterized by abnormal elevations in total cholesterol (TC) and low-density lipoprotein (LDL) cholesterol, is a significant risk factor for CVD (Kopin and Lowenstein, 2017). Other key risk factors include hypertension, diabetes, smoking, abdominal obesity, apolipoprotein B/apolipoprotein A ratio, fruit/vegetable consumption, physical activity, and psychosocial factors (Yusuf et al., 2004). Addressing these individual risk factors should significantly improve cardiovascular health. Thus, there is an increasing interest in genetic and dietary factors that may influence risk factors for CVD, including lipid profile.

Numerous dietary interventions that influence blood lipid response have been identified, ultimately affecting the composition and levels of lipids in the body. These interventions are instrumental in maintaining a healthy lipid profile and mitigating the risk of CVDs. Dietary fat consumption is a critical factor in which both the type and quantity consumed significantly affect blood lipid levels (Arnett et al., 2019). Similarly, by incorporating soluble fiber from sources, including oats, barley, legumes, and

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certain fruits, individuals can effectively reduce LDL cholesterol levels as cholesterol binding is enabled in the digestive tract (Cicero et al., 2017). Plant sterols and stanols (also known as phytosterols) in some plant-based and functional foods can also obstruct cholesterol absorption, lowering LDL cholesterol levels (Cicero et al., 2017). Conversely, diets high in added sugars and refined carbohydrates have been associated with a higher risk of atherosclerotic CVD (Arnett et al., 2019). Importantly, individual responses to these dietary interventions may vary (Laddu and Hauser, 2019); necessitating consultation with healthcare professionals or registered dietitians who can provide personalized advice tailored to specific health conditions and goals. By understanding and implementing these nutritional interventions, individuals can make well-informed choices that improve cardiovascular health and decrease the likelihood of heart disease.

Apolipoprotein E (*ApoE*) plays a crucial role in eliminating circulating lipoproteins (Huang and Mahley, 2014). It is an integral component of these lipoproteins, aiding their clearance from the bloodstream (Marais, 2019). *ApoE* has three common isoforms: E2, E3, and E4. The wild-type allele is E3, and the variant alleles are E2 and E4 (Schwarzova et al., 2015). Carriers of the ApoE4 allele are at increased risk of CVD because of their higher plasma concentrations of LDL cholesterol and triglycerides (TG).

Many randomized clinical trials have evaluated the effects of *ApoE* genetic variants on blood lipid response to various dietary interventions such as plant sterols/stanols (Vanhanen et al., 1993; Miettinen and Vanhanen, 1994; Plat and Mensink, 2000; Geelen et al., 2002; Ishiwata et al., 2002; Lottenberg et al., 2002; Sanchez-Muniz et al., 2009; Bañuls et al., 2011; MacKay et al., 2015; Dong et al., 2016). Most of these studies have reported conflicting results; pooling these data allows for a rigorous analysis of these findings. This study aimed to use a pooled analysis or meta-analysis approach to examine whether *ApoE* genetic variants modulate the responses of blood lipids to dietary interventions with plant sterols/stanols and to determine whether the intervention dose and duration, as well as age and status of participants, influence the effect of the *ApoE* genotype on blood lipoprotein responsiveness to different nutritional interventions.

MATERIALS AND METHODS

Literature search

Trials were identified by searching databases available in the Cochrane Library using the keywords "apolipoprotein E" and "ApoE" and filtered using "Clinical trial" and "Randomized controlled trial." For non-English language literature, if available, the abstract written in English was used to extract the required information; otherwise, the trial was included in the analysis.

Criteria for considering trials

Trials were selected for analysis if they met the following criteria: (1) they were randomized control trials of parallel or crossover design, (2) participants were adult humans with no restriction on health status, (3) they provided the dietary intervention compared with a control or placebo, and (4) they presented data using the common isoforms, E2, E3, and E4. The outcomes of interest were lipid profiles, including TC, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and TG. The first author conducted the trial search and screening.

Quality assessment of the trials

Randomized controlled studies were assessed for methodological quality using the Cochrane risk of bias (Higgins et al., 2011) tool. This involves examining random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential biases. The second and first authors conducted and checked the quality assessment, respectively.

Data abstraction

A pre-standardized form was used to extract data from studies that met the inclusion criteria. A measure of effects, including the mean values and standard deviations in mmol/L of TC, LDL cholesterol, HDL cholesterol, and TG, trial design (parallel or crossover), type of intervention (plant sterols or plant stanols), dose (g/d) and duration of therapy (in weeks), study population characteristics [age, sex, mean body mass index (BMI) health status], and *Apo E* genotype was performed. The *ApoE* genotype was categorized as genotype E2 (allele combination 2/2, 2/3, and 2/4), genotype E3 (allele combination 3/3), and genotype E4 (allele combination 3/4 and 4/4). Data were extracted if the study passed the third screening and were subsequently used for data analysis. Two authors independently extracted the data and then checked by the third author for any discrepancies.

Data analysis

Comprehensive Meta-Analysis V2 (Biostat) was used to calculate the effect size as the difference in means for outcomes and its standard error for every study to obtain pooled effect sizes for each outcome, which was presented using a forest plot. Comprehensive Meta-Analysis V2 was also used to test the heterogeneity between trial results using a standard chi-square test and I^2. I^2 was used to measure the percentage of variability in effect estimates attributed to heterogeneity rather than chance. We used a random-effects model whenever heterogeneity was present. The presence of publication bias was examined us-

ing a funnel plot. Meta-regression that allows for multiple potential modifier adjustment and subgroup analysis was used to explore the effects of potential modifiers on the outcomes of interest.

RESULTS

The initial search identified 3,248 abstracts, and 3,100 studies were assessed for the eligibility criteria. Studies were excluded from the analysis for the following reasons: (1) not analyzing *ApoE* genotype, (2) not measuring any outcome of interest, (3) not relevant, (4) conducted on children, no dietary intervention of interest, (5) not a randomized clinical trial, (6) not written in English, (7) results not yet posted or published, (8) full-text is unavailable or only published as an abstract, and (9) data is not presented using *ApoE* genotypes. Eligibility screening resulted in 291 studies ready for data extraction. Finally, 11 studies were used for the final analysis of plant sterols/stanols (Fig. 1).

Table 1 shows the characteristics of the eligible studies. The studies were randomized, double blind with parallel or crossover design. The study's duration varied from 4 to 24 weeks. The daily dosage of plant sterol/stanol ranged from 0.7 to 3.8 g/d. Most studies enrolled both male and female participants, ranging in age from 20 to 60 years, with normal or high baseline blood cholesterol concentrations at the time of recruitment. The weight status varied among studies.

Fig. 2~5 show the subgroup analysis according to *ApoE* groups. The reduced TC levels (Fig. 2) did not differ between the *ApoE* subgroups. However, the LDL levels were significantly reduced in the E3 group [−0.251 mmol/L; 95% confidence interval (95% CI), −0.488 to −0.015] (Fig. 3). Plant sterol/stanol intervention similarly affected HDL (Fig. 4) and TG (Fig. 5) levels across the different *ApoE* groups.

Meta-regression for multiple continuous covariates was conducted for studies on plant sterols/stanols because there are five or more studies for the E3 and E4 groups. In Model 1, the analysis included dosage and duration as covariates. Table 2 shows the results from the Model 1 meta-regressions. A high dose was associated with a less significant decrease in the TC levels in the E4 group (coefficient −0.412567; 95% CI, −1.285657 to −0.055069), whereas a more extended duration was associated with lower LDL levels in the E4 group (coefficient −0.088027; 95% CI, −0.154690 to −0.021364). Model 1 explained approximately 5% and 25% of the variance in the actual effects of plant sterols/stanols on TC and LDL levels, respectively, in the E4 group. Results (data not shown) from Model 2 meta-regressions, including status and age as covariates, demonstrate that this model could not explain any variations observed in blood lipid responses to plant sterols/stanols consumption regardless of the *ApoE* group.

Fig. 6 show summaries of each risk of bias item presented as percentages across all included studies. Fig. 7 depicts the authors' judgments about each risk of bias

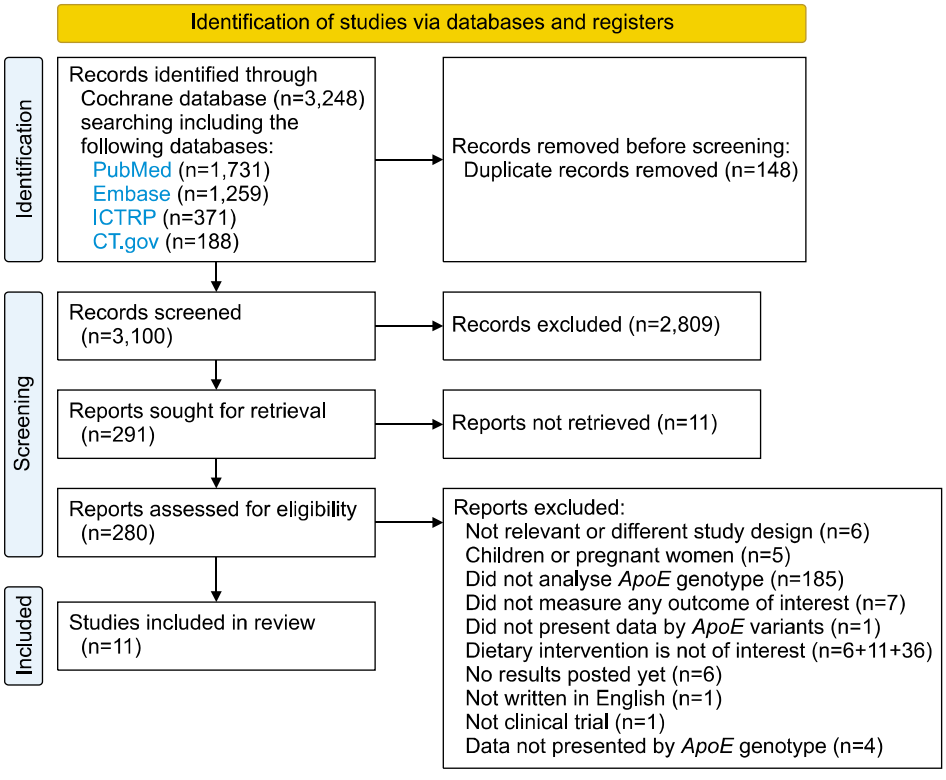


Fig. 1. Flow chart of the literature search. ICTRP, International Clinical Trials Registry Platform; CT.gov, ClinicalTrials.gov.

Table 1. Characteristics of studies identified as eligible

Reference	Design	Placebo-control	Blind	Who were blinded	Age (years)	BMI (kg/m^2)	Sex	Status	Dosage regime	Matrix	Background diet	Regimen of diet consumption	Control	Intervention	Dose (g)	Duration weeks
Geelen et al., 2002	C	No	Blind	NR	25.5±11.5	23±2.5	MF	N	Daily	Margarine	Free-living	No supervision	Control margarine	PS	3.2	6
Bañuls et al., 2011	P	No	NR	NR	49.9±12.0	28.2±5.0	MF	HC	Daily	500 mL of low fat milk, the PS-enriched milk was produced by Unilever and packed in white containers	Free-living	No supervision	Standard 500 mL/d low fat milk	PS	2	24
Dong et al., 2016	P	Yes	DB	I, S	61.7±4.5	25.63±3.6	M	HC	Daily	Soy milk powder after dispersing the powder in water, the drink was consumed	Free-living	No supervision	Soy milk without stanol ester	PS	2	12
Sanchez-Muniz et al., 2009	P	No	DB	S, I	58.0±10.7	27.2±3.7	MF	HC	Daily	Margarine	Free-living	No supervision	Control spread	PS	1.1	5
Lottenberg et al., 2002	C	Yes	DB	NR	NR	NR	MF	HC	Daily	Margarine	Free-living	No supervision	Placebo spread	PS	1.68	4
Lottenberg et al., 2003	C	Yes	DB	S, I	20~60	Ob	MF	HC	Daily	Margarine	Partially controlled	No supervision	Placebo margarine	PS	1.68	4
Miettinen and Vanhanen, 1994	P	No	DB	S, I	45±3	25.5±1.2	MF	HC	Daily	Mayonnaise	Free-living	No supervision	Mayonnaise	PS	0.7	9
Vanhanen et al., 1993	P	No	DB	S, I	45.5±2	25.59±0.7	MF	HC	Daily	Mayonnaise	Free-living	No supervision	Rapeseed oil without sitostanol	PS	3.4	6
Ishiwata et al., 2002	C	Yes	DB	S, I	47.3±13	23.7±3	MF	HC	Daily	Spread	Free-living	No supervision	Control spread without plant stanol	PS	3	4
Plat and Mensink, 2000	P	No	DB	I, S	33±15.3	22.9±3.5	MF	N	Daily	Margarine and shortening	Free-living	No supervision	Control rapeseed oil based margarine and shortening	PS	3.8	8
MacKay et al., 2015	C	Yes	SB	S	55.2±8.98	28.8±6.0	MF	HC	Daily	Margarine	Partially controlled	Consumed 1 meal/d under supervision for a minimum of 4~5 d/week and without supervision off-site for 2~3 d/week	Placebo	PS	2	4

Values are presented as mean±SD.
C, crossover; NR, not reported; MF, males and females; N, normal baseline low-density lipoprotein or total cholesterol; PS, plant sterols/stanols; P, parallel; HC, high baseline low-density lipoprotein cholesterol or total cholesterol; DB, double blind; I, investigators; S, subjects; M, males; Ob, obese; SB, single blind.

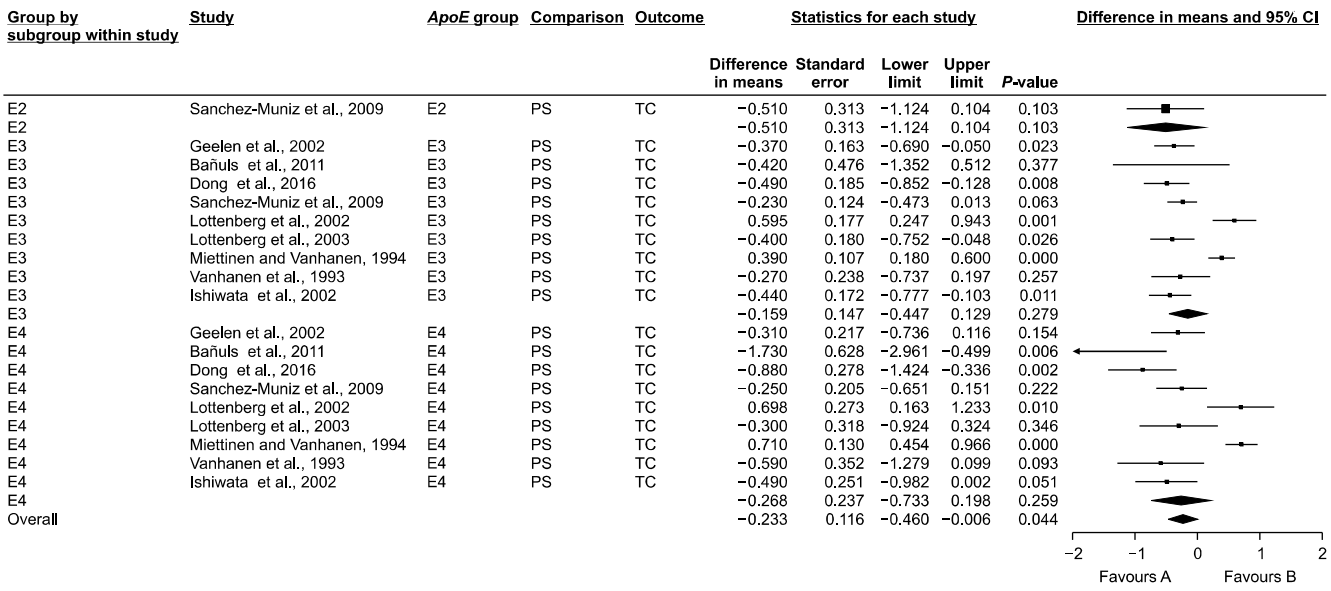


Fig. 2. Mean difference (mmol/L) and 95% confidence interval (95% CI) in total cholesterol concentrations associated with the consumption of plant sterols/stanols using the apolipoprotein E subgroups. The square represents the individual studies' mean differences for that outcome. The size of the square reflects the weight of the study in the overall analysis. The black lines across the square represent the CIs of a study. The diamond represents the overall mean difference, and its CI is represented by its outer edges. PS, plant sterols/stanols; TC, total cholesterol.

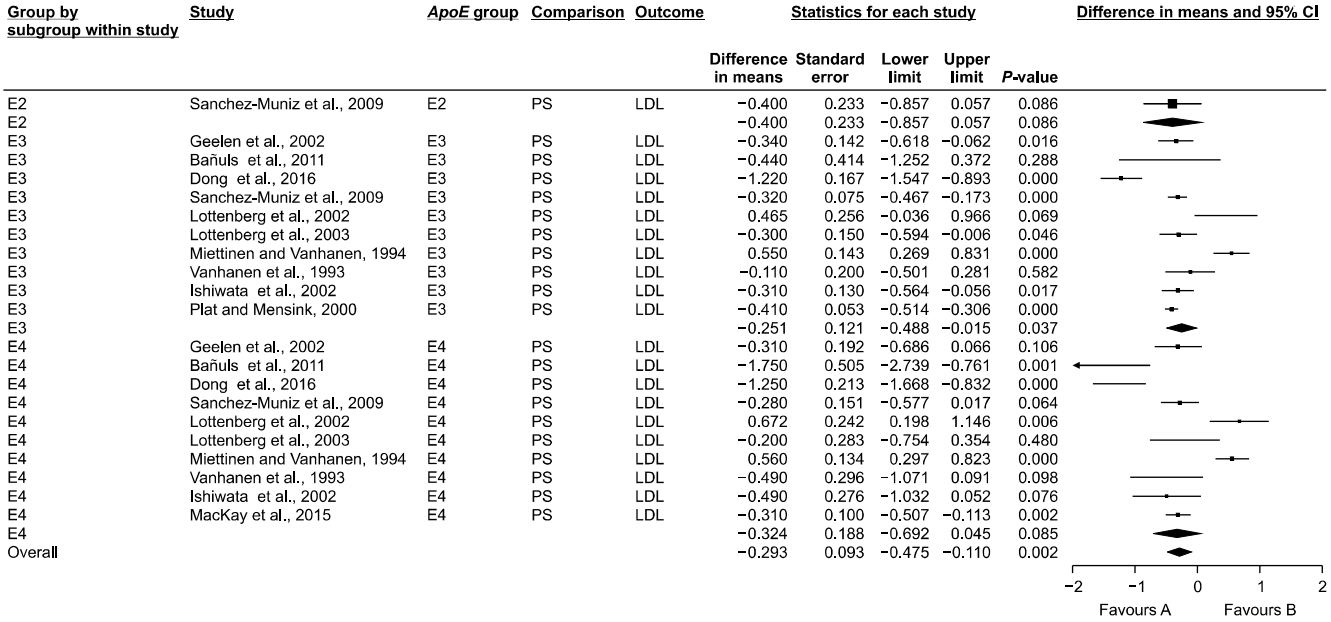
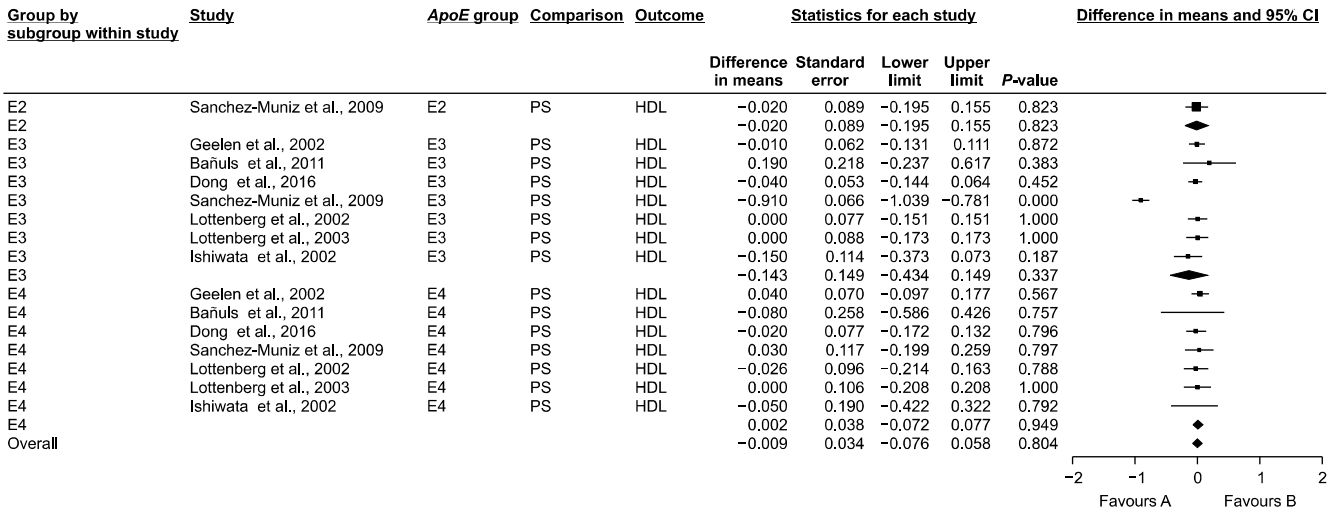


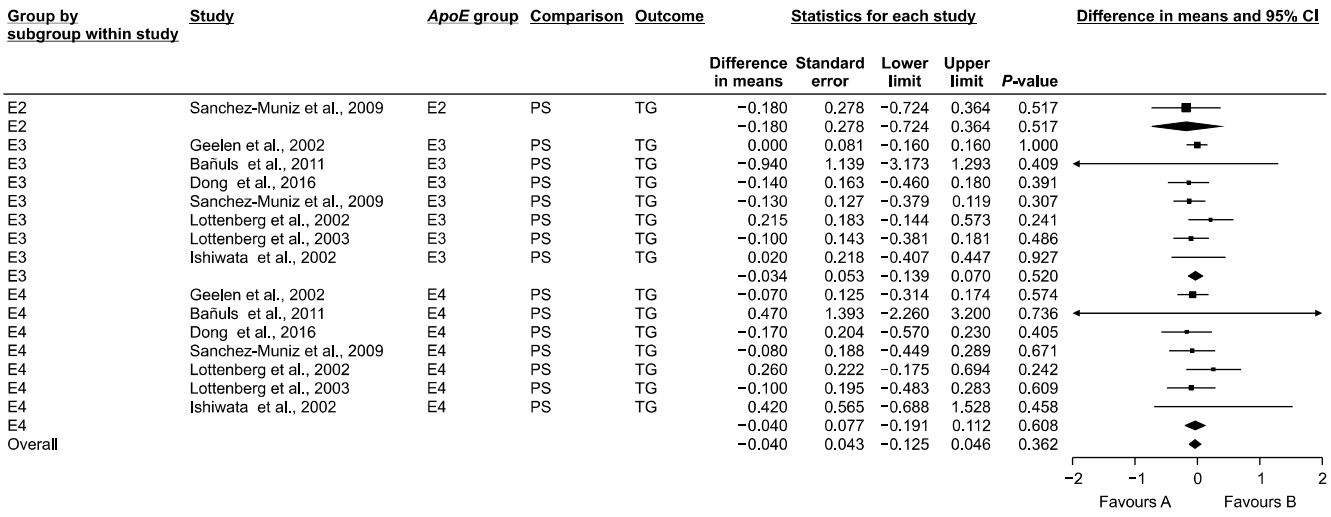
Fig. 3. Mean difference (mmol/L) and 95% confidence interval (95% CI) in low-density lipoprotein cholesterol concentrations associated with the consumption of plant sterols/stanols using apolipoprotein E subgroups. The square represents the individual studies' mean differences for that outcome. The size of the square reflects the weight of the study in the overall analysis. The black lines across the square represent the CIs of a study. The diamond represents the overall mean difference, and its CI is represented by its outer edges. PS, plant sterols/stanols; LDL, low-density lipoprotein.

item for individual studies. The random sequence generation method was performed in only one study (approximately 10%). In contrast, two studies (18%) were at high risk of bias, and an unclear risk of bias was judged for the remaining studies as they provided no detail about random generation. Furthermore, 10% of the trials employed and described allocation concealment clearly, whereas 18% of the trials were at high risk of bias. Approximately 70% of the studies were regarded as unclear risk of detection bias because they provided insufficient information regarding blinding of outcome assessors, whereas the remaining trials were at low risk of detection bias. Approximately 50% of the trials did not report whether or how the participants and study personnel were blinded. However, the other 50% of the trials were at low risk as they provided adequate details about the participants and



Group by subgroup within study	Study	*ApoE* group	Comparison	Outcome	Difference in means	Standard error	Lower limit	Upper limit	*P*-value
E2	Sanchez-Muniz et al., 2009	E2	PS	HDL	−0.020	0.089	−0.195	0.155	0.823
E2					−0.020	0.089	−0.195	0.155	0.823
E3	Geelen et al., 2002	E3	PS	HDL	−0.010	0.062	−0.131	0.111	0.872
E3	Bañuls et al., 2011	E3	PS	HDL	0.190	0.218	−0.237	0.617	0.383
E3	Dong et al., 2016	E3	PS	HDL	−0.040	0.053	−0.144	0.064	0.452
E3	Sanchez-Muniz et al., 2009	E3	PS	HDL	−0.910	0.066	−1.039	−0.781	0.000
E3	Lottenberg et al., 2002	E3	PS	HDL	0.000	0.077	−0.151	0.151	1.000
E3	Lottenberg et al., 2003	E3	PS	HDL	0.000	0.088	−0.173	0.173	1.000
E3	Ishiwata et al., 2002	E3	PS	HDL	−0.150	0.114	−0.373	0.073	0.187
E3					−0.143	0.149	−0.434	0.149	0.337
E4	Geelen et al., 2002	E4	PS	HDL	0.040	0.070	−0.097	0.177	0.567
E4	Bañuls et al., 2011	E4	PS	HDL	−0.080	0.258	−0.586	0.426	0.757
E4	Dong et al., 2016	E4	PS	HDL	−0.020	0.077	−0.172	0.132	0.796
E4	Sanchez-Muniz et al., 2009	E4	PS	HDL	0.030	0.117	−0.199	0.259	0.797
E4	Lottenberg et al., 2002	E4	PS	HDL	−0.026	0.096	−0.214	0.163	0.788
E4	Lottenberg et al., 2003	E4	PS	HDL	0.000	0.106	−0.208	0.208	1.000
E4	Ishiwata et al., 2002	E4	PS	HDL	−0.050	0.190	−0.422	0.322	0.792
E4					0.002	0.038	−0.072	0.077	0.949
Overall					−0.009	0.034	−0.076	0.058	0.804

Fig. 4. Mean difference (mmol/L) and 95% confidence interval (95% CI) in high-density lipoprotein cholesterol concentrations associated with the consumption of plant sterols/stanols using apolipoprotein E subgroups. The square represents the individual studies' mean differences for that outcome. The size of the square reflects the weight of the study in the overall analysis. The black lines across the square represent the CIs of a study. The diamond represents the overall mean difference, and its CI is represented by its outer edges. PS, plant sterols/stanols; HDL, high-density lipoprotein.



Group by subgroup within study	Study	*ApoE* group	Comparison	Outcome	Difference in means	Standard error	Lower limit	Upper limit	*P*-value
E2	Sanchez-Muniz et al., 2009	E2	PS	TG	−0.180	0.278	−0.724	0.364	0.517
E2					−0.180	0.278	−0.724	0.364	0.517
E3	Geelen et al., 2002	E3	PS	TG	0.000	0.081	−0.160	0.160	1.000
E3	Bañuls et al., 2011	E3	PS	TG	−0.940	1.139	−3.173	1.293	0.409
E3	Dong et al., 2016	E3	PS	TG	−0.140	0.163	−0.460	0.180	0.391
E3	Sanchez-Muniz et al., 2009	E3	PS	TG	−0.130	0.127	−0.379	0.119	0.307
E3	Lottenberg et al., 2002	E3	PS	TG	0.215	0.183	−0.144	0.573	0.241
E3	Lottenberg et al., 2003	E3	PS	TG	−0.100	0.143	−0.381	0.181	0.486
E3	Ishiwata et al., 2002	E3	PS	TG	0.020	0.218	−0.407	0.447	0.927
E3					−0.034	0.053	−0.139	0.070	0.520
E4	Geelen et al., 2002	E4	PS	TG	−0.070	0.125	−0.314	0.174	0.574
E4	Bañuls et al., 2011	E4	PS	TG	0.470	1.393	−2.260	3.200	0.736
E4	Dong et al., 2016	E4	PS	TG	−0.170	0.204	−0.570	0.230	0.405
E4	Sanchez-Muniz et al., 2009	E4	PS	TG	−0.080	0.188	−0.449	0.289	0.671
E4	Lottenberg et al., 2002	E4	PS	TG	0.260	0.222	−0.175	0.694	0.242
E4	Lottenberg et al., 2003	E4	PS	TG	−0.100	0.195	−0.483	0.283	0.609
E4	Ishiwata et al., 2002	E4	PS	TG	0.420	0.565	−0.688	1.528	0.458
E4					−0.040	0.077	−0.191	0.112	0.608
Overall					−0.040	0.043	−0.125	0.046	0.362

Fig. 5. Mean difference (mmol/L) and 95% confidence interval (95% CI) in triglyceride concentrations associated with the consumption of plant sterols/stanols using apolipoprotein E subgroups. The square represents the individual studies' mean difference for that outcome. The size of the square reflects the weight of the study in the overall analysis. The black lines across the square represent the CIs of a study. The diamond represents the overall mean difference, and its CI is represented by its outer edges. PS, plant sterols/stanols; TG, triglycerides.

study personnel blinding. In contrast, 45% of the trials provided insufficient information on withdrawals or loss of follow-up to permit an evaluation of attrition bias. Reporting bias was judged as an unclear risk of bias in most trials (9 of 11 trials) because of insufficient information.

Funnel plots representing the relationship between a study difference in mean and standard error are shown in Fig. 8 and 9 for TC and LDL cholesterol levels, respectively. An examination of the funnel plots shows a symmetrical appearance and, thus, the absence of publication bias.

DISCUSSION

To the best of our knowledge, this analysis is the first to pool data on *ApoE* genetic variants and blood lipid responses to plant sterols. This pooled analysis confirmed a statistically significant association between *ApoE* genetic variants and LDL responses to plant sterols/stanols.

Controversy exists among trials assessing the cholesterol-lowering action of plant sterols/stanols in adults with different *ApoE* genetic variants. A randomized clinical trial that supplemented 3.2 g of plant sterols in margarine for three weeks found that *ApoE* genetic variants do not affect the serum cholesterol response to plant ster-

Table 2. Meta-regression of plant sterols/stanols supplementation dose and duration on lipid profile using the apolipoprotein E groups

Apolipoprotein E group	Outcome	Covariate	No. of studies	Coefficient	95% confidence interval	*P*-value
E3	TC	Dose	9	−0.412567	−0.854252 to 0.029118	0.0671
		Duration		−0.005806	−0.068577 to 0.056964	0.8561
E4	TC	Dose	9	−0.670363	−1.285657 to −0.055069	0.0327
		Duration		−0.056443	0.045245 to 0.032234	0.2122
E3	LDL	Dose	10	−0.160048	−0.432956 to 0.112861	0.2504
		Duration		−0.031707	−0.089536 to 0.026121	0.2825
E4	LDL	Dose	10	−0.339041	−0.722386 to 0.044303	0.0830
		Duration		−0.088027	−0.154690 to −0.021364	0.0097
E3	HDL	Dose	7	0.231371	−0.173639 to 0.636380	0.2629
		Duration		0.020791	−0.024081 to 0.065664	0.3638
E4	HDL	Dose	7	0.018633	−0.082982 to 0.120249	0.7193
		Duration		−0.003348	−0.022022 to 0.015325	0.7253
E3	TG	Dose	7	0.050605	−0.072949 to 0.174160	0.4221
		Duration		−0.021778	−0.065191 to 0.021635	0.3255
E4	TG	Dose	7	−0.004206	−0.189003 to 0.180591	0.9644
		Duration		−0.019614	−0.075335 to 0.036107	0.4903

TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides.

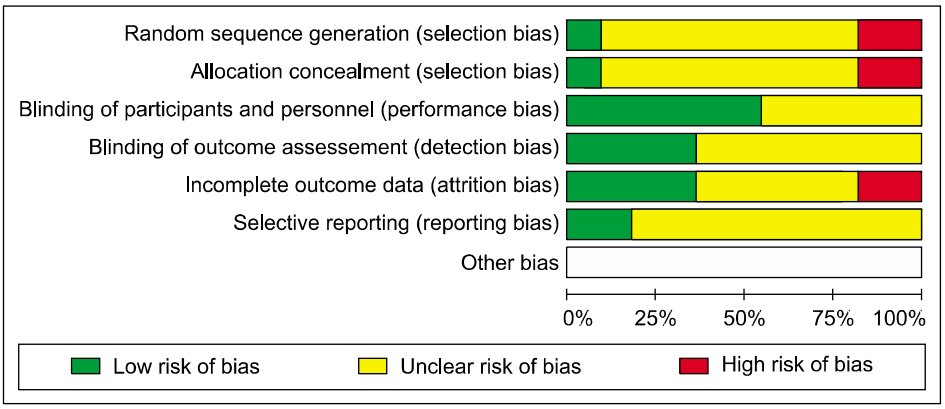


Fig. 6. Risk of bias graph. Risk of bias for each item, including randomization, blinding, allocation concealment, incomplete outcome data, and selective outcome reporting, presented as percentages across all included studies using the Cochrane's Risk of Bias for randomized clinical trials. Red, high risk of bias; Yellow, unknown risk of bias; Green, low risk of bias.

ols in healthy subjects who were on a low-cholesterol diet (Geelen et al., 2002). In another randomized clinical trial on 75 participants with hypercholesteremia, the *ApoE* genotype did not influence lipid responses to 2 g of plant sterols administered for 12 weeks (Bañuls et al., 2011). In contrast, 1.1∼2.2 g/d for five weeks of sterol intake reduced TC and LDL cholesterol levels in only E2 and E3 participants and decreased TG levels in only E2 participants (Sanchez-Muniz et al., 2009). The presented analysis showed that the E3 genotype (allele combination 3/3) significantly reduced LDL levels after plant sterol/stanol consumption, whereas the dose and duration of plant sterol/stanol consumption influenced the LDL level reduction in E4 isoform carriers. Compared with previous meta-analysis investigating the efficacy of plant sterols/stanols as cholesterol-lowering agents, the reduced LDL blood levels observed in participants with the E3 isoform are within the range of those reported in the general population. For instance, Amir Shaghaghi et al. (2013) reported a reduction of 0.31 mmol/L (95% CI, −0.35 to −0.27) with the intake of foods enriched with plant sterols/stanols. Furthermore, a previous meta-analysis demonstrated that plant sterols/stanols are dose-dependently effective (Demonty et al., 2009). In our analysis, individuals carrying the E4 isoform are most likely to benefit from a higher dose of plant sterols/stanols.

This analysis confirmed that *ApoE* genetic variants influence individual responses to plant sterols/stanols intervention as cholesterol-lowering agents. However, the influence of the less common E2 isoform was inadequately addressed because of limited data. Nevertheless, the E2 isoform, in contrast to the E4 isoform, may not increase the risk of coronary heart disease. For instance, a meta-analysis of 11,804 patients with coronary heart disease and 17,713 controls from 30 studies showed that E4 carriers had a 46% increased risk of coronary heart disease compared with E3 carriers. In contrast, carriers of *ApoE2* showed no significant decrease in the risk of coronary heart disease (Xu et al., 2016). The reported associations between *ApoE* isoforms and the risk of CVD are heterogeneous, as shown in individual studies and the recent analysis by Xu et al. (2016), and it could be

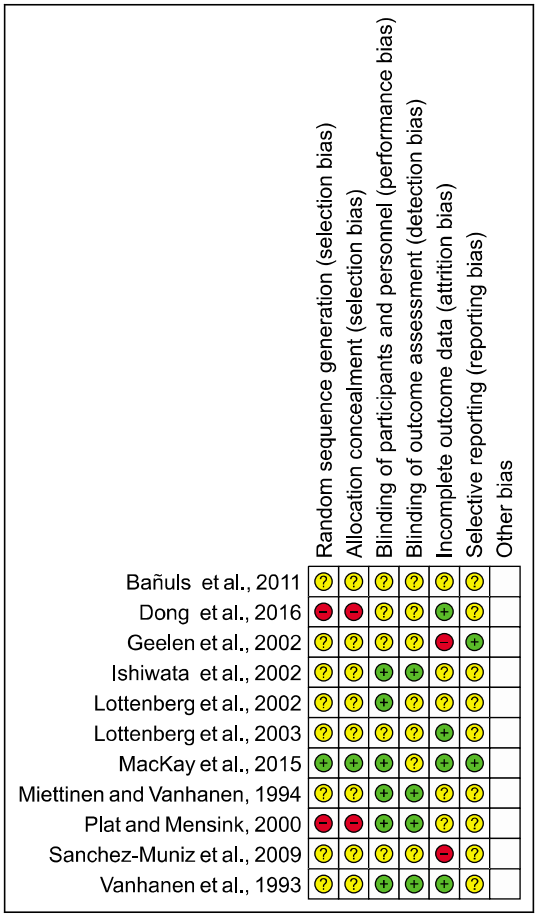


Fig. 7. Risk of bias summary. Risk of bias for each bias item, including randomization, blinding, allocation concealment, incomplete outcome data, and selective outcome reporting, of each included study using the Cochrane's Risk of Bias for randomized clinical trials. Red (–), high risk of bias; Yellow (?), unknown risk of bias; Green (+), low risk of bias.

related to environmental factors, including dietary ones (Minihane et al., 2007).

There are several strengths to this study. This analysis is the first to pool data on *ApoE* genetic variants and blood lipid responses to dietary interventions. Study data were pooled, effectively reducing potential sources of variance between studies and enhancing study power. The inclusion of many participants and events enhanced generalizability and allowed us to investigate several potential effect modifiers. A possible limitation of the current analysis is that the influence of plant sterol matrix, blood baseline concentrations of lipids, and diet background was not analyzed. This is primarily because of the small number of available studies. Future studies are needed to investigate the effect of the aforementioned covariates on blood lipid responses in each *ApoE* genetic variant. Another limitation inherited from some studies is that recruiting was not performed according to *ApoE* genetic variants, and the randomization and allocation to treatment in most studies were unclear, which increased the risk of selection bias.

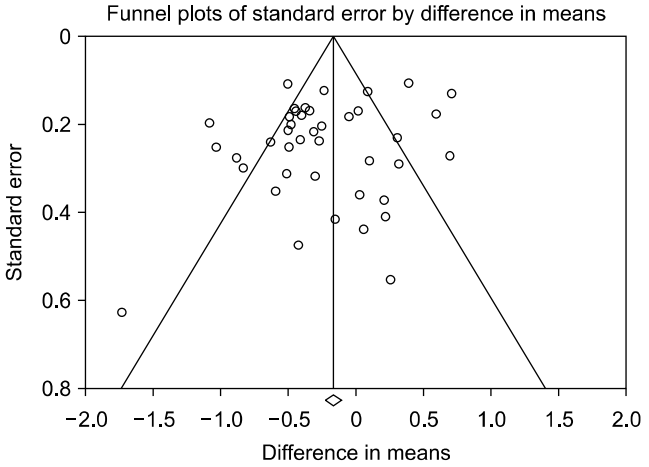


Fig. 8. Funnel plots of standard error (study precision) vs. mean difference (effect size) for total cholesterol concentrations for evaluating publication bias. A symmetrical inverted funnel indicates the absence of publication bias.

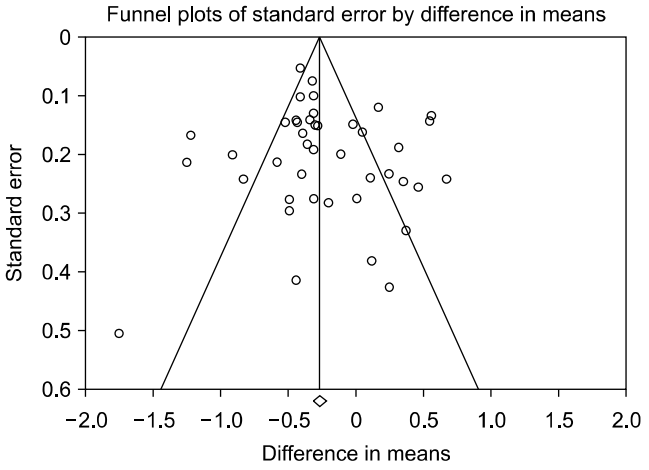


Fig. 9. Funnel plots of standard error (study precision) vs. mean difference (effect size) for low-density-lipoprotein cholesterol concentrations for evaluating publication bias. A symmetrical inverted funnel indicates the absence of publication bias.

In conclusion, in this analysis, the *ApoE* genotype affected the response of blood LDL levels to supplementation with plant sterols/stanols, as individuals with the *ApoE3* genotype showed a more significant decrease in LDL levels compared with the other genotypes. However, future studies recruiting participants according to their *ApoE* genetic variants are needed to confirm our conclusion.

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None.

AUTHOR DISCLOSURE STATEMENT

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept and design: Suhad A. Analysis and interpretation: Suhad A, LA. Data collection: Suhad A, LA, Sarah A. Writing the article: Suhad A, LA. Critical revision of the article: Suhad A, LA. Final approval of the article: all authors. Statistical analysis: Suhad A. Overall responsibility: Suhad A.

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