

REVIEW

Effects of phytosterols on cardiovascular risk factors: A systematic review and meta-analysis of randomized controlled trials

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Abstract

Cardiovascular diseases are the major cause of death globally. The primary risk factors are high blood lipid levels, hypertension, diabetes, and obesity. Phytosterols are naturally occurring plant bioactive substances. Short-term clinical trials have demonstrated phytosterols' cholesterol-lowering potential, but their effects on cardiovascular risk factors remain controversial, and relevant meta-analyses are limited and incomplete. We conducted a systematic and comprehensive search of PubMed, Web of Science, Embase and Cochrane Library up to December 22, 2023. A total of 109 randomized controlled trials (RCTs) of phytosterols (PS) intervention on cardiovascular risk factor outcomes were included in a preliminary screening of the retrieved literature by Endnote 20. We assessed the quality of all included randomized controlled trials using the Cochrane Collaboration's Risk of Bias tool. Cochrane data conversion tool was used for data conversion, and finally Stata was used for meta-analysis, egger test and sensitivity analysis of the included studies. The results indicated that dietary phytosterols intake could significantly decrease total cholesterol (TC) level (mean difference = -13.41 ; 95% confidence interval [CI]: -15.19 , -11.63 , $p < 0.001$), low density lipoprotein cholesterol (LDL-C) level (mean difference = -12.57 ; 95% CI: -13.87 , -11.26 , $p < 0.001$), triglycerides (TG) level (mean difference = -6.34 ; 95% CI: -9.43 , -3.25 , $p < 0.001$), C-reactive protein (CRP) level (mean difference = -0.05 ; 95% CI: -0.08 , -0.01 , $p = 0.671$), systolic blood pressure (SBP) level (mean difference = -2.10 ; 95% CI: -3.27 , -0.9 , $p < 0.001$), diastolic blood pressure (DBP) level (mean difference = -0.83 ; 95% CI: -0.58 , -0.07 , $p = 0.032$), increased high-density lipoprotein cholesterol (HDL-C) level (mean difference = 0.46 ; 95% CI: 0.13 , 0.78 , $p = 0.005$), but did not alter the levels of blood glucose (GLU) (mean difference = -0.44 ; 95% CI: -1.64 , 0.76 , $p = 0.471$), glycosylated hemoglobin, Type A1C (HbA1c) (mean difference = -0.28 ; 95% CI: -0.75 , 0.20 , $p = 0.251$), interleukin-6 (IL-6) (mean difference = 0.00 ; 95% CI: -0.02 , 0.02 , $p = 0.980$), tumor necrosis factor (TNF- α) (mean difference = 0.08 ; 95% CI: -0.08 , 0.24 , $p = 0.335$), oxidized low-density lipoprotein cholesterol (OXLDL-C) (standard mean difference = 0.16 ; 95% CI: -0.38 , 0.06 , $p = 0.154$), body mass index (BMI) (mean difference = 0.01 ; 95% CI: -0.07 , 0.09 , $p = 0.886$), waist

circumference (WC) (mean difference = -0.10 ; 95% CI: $-0.50, 0.30$, $p = 0.625$) and body weight (mean difference = 0.03 ; 95% CI: $-0.18, 0.24$, $p = 0.787$). Our results suggest that phytosterols may be beneficial in reducing the levels of TC, LDL-C, TG, CRP, SBP, and DBP, but have no significant effect on GLU, HbA1c, TNF- α , IL-6, OXLDL-C, BMI, WC, and Weight. However, there were a small number of RCTS included in this study and their small population size may have reduced the quality of the study. And most of the included studies were short-term intervention trials. Therefore, higher quality studies need to be designed in future studies to establish more accurate conclusions.

KEYWORDS

cardiovascular risk factors, meta-analysis, phytosterols, randomized controlled trials

1 | INTRODUCTION

Cardiovascular diseases (CVDs) are caused by heart and vascular disease, and the most common types of CVDs include coronary heart disease, cerebrovascular disease, and peripheral arterial disease. CVD is a leading cause of morbidity and mortality in many countries around the world (World Health Organization, 2011). The Global Burden of Disease 2021 shows that the prevalence of CVD has increased by 33.5% compared to 2010. The number of deaths increased from 18.6 million in 2019 to 19.4 million in 2021 (Global Burden of Disease 2021, 2024). Ischemic heart disease (IHD) is responsible for 8.99 million deaths worldwide, and ischemic stroke is responsible for 3.59 million deaths worldwide. CVD often occurs in conjunction with multiple comorbidities, such as obesity, diabetes, hypertension, or dyslipidemia. According to the latest data from GBD 2021, CVD is responsible for 428 million cases of diabetes in 2021 and is the leading secondary cause of disease burden. High blood pressure caused 10.9 million deaths worldwide, and high body mass index (BMI) caused 3.71 million deaths worldwide; high LDL cholesterol causes 87.7 million disabilities and 3.65 million deaths. According to the latest report from the World Health Organization (WHO) (World Health Statistics, 2024), the age-standardized prevalence of obesity among adults aged 18 and over increased from 6.6% to 15.8% globally in 2022 compared to 1990, with the number of obese adults dramatically increasing by nearly 700 million to 890 million. It can be seen that maintaining cardiovascular health is very important in our lives. It helps us prevent CVD and reduce the risk of heart disease, stroke and other diseases. Improve quality of life and prevent other diseases such as high blood pressure and diabetes.

There are many risk factors for CVD. Obesity, a sedentary lifestyle, high blood pressure, hyperlipidemia and glucose intolerance are traditional risk factors for CVD (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). Obesity, diabetes, high blood pressure and dyslipidemia are also four of the top 10 risk factors for global causes of death (Lacroix et al., 2017). According to the latest GBD 2021 projections, global life expectancy will increase by 4.6 years between 2022 and 2050, with declining

deaths from CVD being the main secondary cause of global life expectancy gains, along with high blood sugar, high body mass index, and other risks associated with obesity and metabolic syndrome. Therefore, managing cardiovascular risk factors is equally important. It helps us to reduce the risk of CVD and the risk of death due to CVD and prolong life; it also reduces the risk of complications such as diabetes, obesity and dyslipidemia and improves the quality of life. Phytosterols (PS) are naturally active substances in plants and are composed of more than 200 different compounds, mainly found in vegetable oils, nuts, fruits, cereals, and other plant products (Moreau et al., 2002). Phytosterols, structurally identical to cholesterol, can impede intestinal absorption of cholesterol, lowering LDL-C levels and the risk of CVD (Abumweis & Jones, 2008). Moreover, phytosterols have immunomodulatory effects (Nattagh-Eshtivani et al., 2022), anti-inflammatory (Morgan et al., 2021), antioxidant, and anticancer (Woyengo et al., 2009).

In recent years, an increasing number of studies have focused on the role of phytosterols in terms of cardiovascular risk factors, but the results remain controversial. Some related animal studies have found that dietary phytosterols supplementation can reduce serum cholesterol levels and atherosclerotic lesions (Moghadasian et al., 1999; Volger et al., 2001; Wilund et al., 2004). However, there are also studies showing negative vascular effects (Weingärtner et al., 2008). Mice fed a phytosterols-rich diet exhibited twice as many atherosclerotic lesions as ezetimibe treated mice. Furthermore, wild-type mice supplemented with a phytosterols-rich diet showed increased brain lesion size and impaired endothelium-dependent vasodilation after cerebral ischemia compared to mice on normal diet. Chen et al. (2010) reported elevated blood pressure in rats after consumption of phytosterol-rich foods. In a study by Nashed et al. (2005), serum IL-6 and TNF- α levels were found to be reduced in apolipoprotein (apo) E-deficient mice, and the anti-atherosclerotic effects of dietary phytosterols in apolipoprotein E knockout mice were associated with beneficial alterations in inflammatory pathways. However, Xu et al. (2008) discovered that altered hepatic gene expression regulating sterol metabolism in apolipoprotein E knockout (Apo E-KO) mice was not related to a direct effect of phytosterols on inflammatory

atherosclerosis. Conflicting results have likewise been found in human studies. A meta-analysis of the lipid-lowering effects of phytosterols showed that phytosterols were able to reduce LDL-C by 17%. However, there was a large interindividual variation. Some studies did not find any lipid-lowering effects of phytosterols (Denke, 1995; Jones et al., 2018; Weingärtner et al., 2017). In addition, a study has been proposed that consuming plant sterol-rich meals or supplements is an effective dietary treatment for lowering CVD risk (Trautwein et al., 2018). Therefore, we collected and summarized the published relevant literature and performed a meta-analysis to evaluate the effects of dietary phytosterols intake on indicators related to cardiovascular risk factors.

2 | MATERIALS AND METHODS

The 2020 Preferred Reporting Initiative for Systematic Evaluation and Meta-Analysis (PRISMA) Guidance Statement was followed when conducting this study. We have prospectively registered the study protocol at PROSPERO (<https://www.crd.york.ac.uk/prospero/>) as identifier CRD42024522181. The aim of this study protocol is to summarize the results of previous relevant studies, explore the effects of phytosterols on cardiovascular risk factors, and more comprehensively understand the role of phytosterols in human cardiovascular health, so as to provide references for the development and design of future studies.

2.1 | Literature search strategy

We systematically searched four databases for articles published up to December 22, 2023, including PubMed, Web of Science, Embase, and the Cochrane Library. We only included the relevant randomized controlled trials. Searches were conducted using subject words combined with free words method, and were not limited to the literature published in English to ensure comprehensiveness of the included literature. The following terms are used in electronic searches: ("Phytosterols"[MeSH Terms] OR "phytosterol"[Title/Abstract] OR "phytostanol"[Title/Abstract] OR "plant sterol"[Title/Abstract] OR "plant stanol"[Title/Abstract] OR "sterol plant"[Title/Abstract] OR "plant sterols"[Title/Abstract] OR "sterols plant"[Title/Abstract] OR "plant steroid"[Title/Abstract] OR "steroid plant"[Title/Abstract] OR "plant steroids"[Title/Abstract] OR "steroids plant"[Title/Abstract] OR "Phytosteroid"[Title/Abstract] OR "Phytosteroids"[Title/Abstract] OR "sitosterol"[Title/Abstract] OR "sitostanol"[Title/Abstract]) AND ("Heart Disease Risk Factors"[MeSH Terms] OR "Cardiovascular Risk Factor"[Title/Abstract] OR "CVD"[Title/Abstract] OR "cardiometa-bolic index"[Title/Abstract] OR "cholesterol"[Title/Abstract] OR "blood cholesterol"[Title/Abstract] OR "Low Density Lipoprotein Cholesterol"[Title/Abstract] OR "High Density Lipoprotein Cholesterol"[Title/Abstract] OR "LDL-C"[Title/Abstract] OR "HDL-C"[Title/Abstract] OR "total cholesterol"[Title/Abstract] OR "Triglycerides"[Title/Abstract] OR "Triglyceride"[Title/Abstract] OR "blood lipids"

TABLE 1 Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1. Subjects were over 18 years old;	1. The use of a co-intervention or the inability to discern the distinct effects of phytosterols;
2. The study was a single-blind or double-blind randomized controlled trial (parallel or cross-over);	2. Non-English language literature;
3. The intervention was a fortified food or supplement with intake of phytosterols as an active treatment;	3. Observational or animal studies, molecular experiments, book chapters, editorials, conference abstracts, letters, short surveys, and notes;
4. The study used cardiovascular risk factor indicators as one of the outcome variables.	4. Trials with incomplete or irrelevant data in the intervention or control groups.

[Title/Abstract] OR "serum lipids"[Title/Abstract] OR "TG"[Title/Abstract] OR "TC"[Title/Abstract] OR "lipid profile"[Title/Abstract] OR "blood glucose"[Title/Abstract] OR "Blood Sugar"[Title/Abstract] OR "Impaired Glucose Tolerance"[Title/Abstract] OR "HbA1c"[Title/Abstract] OR "Hemoglobin, Glycated"[Title/Abstract] OR "Glycated Hemoglobin A1c"[Title/Abstract] OR "Insulin Resistance"[Title/Abstract] OR "Blood Pressure"[Title/Abstract] OR "Diastolic Pressure"[Title/Abstract] OR "Systolic Pressure"[Title/Abstract] OR "Arterial Pressure"[Title/Abstract] OR "Hypertension"[Title/Abstract] OR "SBP"[Title/Abstract] OR "DBP"[Title/Abstract] OR "inflammation"[Title/Abstract] OR "Inflammation biomarkers"[Title/Abstract] OR "C-reactive protein"[Title/Abstract] OR "CRP"[Title/Abstract] OR "Oxidative Stresses"[Title/Abstract]). Furthermore, we checked the references of the retrieved publications for any relevant studies that may have been overlooked. Endnote 20 was used to manage the literature.

2.2 | Inclusion and exclusion criteria

The inclusion exclusion criteria for this study are shown in Table 1. We carefully screened the relevant literature by two researchers based on the title, abstract and full text, and any conflicts throughout the study selection process were resolved by a third researcher through discussion.

2.3 | Outcomes

Our current study includes 15 outcome indicators: (1) Serum total cholesterol (mmol/L), (2) Serum triglycerides (mmol/L), (3) Serum low density lipoprotein cholesterol (mmol/L), (4) Serum high-density lipoprotein cholesterol (mmol/L), (5) Serum C-reactive protein (mg/L), (6) Serum tumor necrosis factor- α (pg/mL), (7) Serum interleukin-6 (pg/mL), (8) Serum oxidized LDL cholesterol, (9) blood glucose (mg/dL), (10) Glycosylated hemoglobin (%), (11) Systolic blood pressure (mmHg), (12) Diastolic blood pressure (mmHg), (13) Body mass index (kg/m²), (14) waistline (cm), (15) weight (kg).

2.4 | Data extraction

Two separate researchers evaluated and collected data from articles that satisfied the inclusion criteria using a pre-designed data collection form. The data extracted included the first author's last name, the year of publication, the nation, the type of study, the total sample size, the male-to-female ratio, the age range, participant characteristics, the dose (g/d), the length of follow-up, esterification or not, and type of phytosterol. Additionally, indications associated with cardiovascular risk factors were retrieved from the literature, including the mean and standard deviation for each intervention and at the end of the study. When numerous measures were available and data were given, only the results after the intervention were included in the analysis; if data at the beginning or end of the intervention were not supplied, the before and after change values of the relevant indicator were extracted directly. In addition, we also unified the units for reliability of the results. To convert mg/dL to mmol/L, cholesterol was divided by 38.7 and TG by 88.6; to convert mmol/L to mg/dL, blood glucose needs to be multiplied by 18; mg/dL was converted to mg/l and CRP was multiplied by 10. Differences on data extraction and evaluation were resolved through discussions with a third person, and consensus was reached in all cases.

2.5 | Quality assessment

The Cochrane Collaboration risk of bias tool was used to assess the quality of all included RCTs (Higgins et al., 2011). Qualified studies are independently assessed for risk of bias by team members, and any discrepancies are determined by a third party. This involves randomized sequence generation, assignment concealment, subject and personnel blinding, outcome assessment blinding, insufficient outcome data, selective outcome reporting, and other biases. For the included literature, each project may be rated as "high risk," "low risk," or unclear. Detailed evaluation results can be found in Table S2.

2.6 | Data analysis

The extracted data was organized in Excel 2021 and imported into Stata SE 15.0 for analysis. All tests were two-sided, and the statistical significance threshold was set at 0.05.

We calculated the mean difference from baseline to post-intervention in serum indicators of relevant outcomes (TC, TG, LDL-C, HDL-C, GLU, HbA1c, CRP, TNF- α , IL-6, and OXLDL-C) and anthropometric indicators (SBP, DBP, BMI, WC, and body weight) between the supply group and the control group, and the standard deviation of the mean difference using the equation below (SD): $SD_{\text{change}} = (SD_{\text{baseline}}^2 + SD_{\text{endpoint}}^2 - 2 \times R \times SD_{\text{baseline}} \times SD_{\text{endpoint}})^{1/2}$, correlation coefficient $R = 0.5$ (Higgins et al., 2011). The combined weighted mean difference (WMD) and 95% confidence interval (CI) were used to investigate the impacts of serum cardiovascular risk factor-related (TC, TG, LDL-C, HDL-C, GLU, HbA1c, CRP, TNF- α , IL-6,

and OXLDL-C) and anthropometric indicators (SBP, DBP, BMI, WC, and body weight). The units could not be standardized due to the multiple methods used to measure serum oxidative markers (OXLDL-C), hence standardized mean difference (SMD) (Fu et al., 2011) was used for analysis.

The I^2 index was used to assess study heterogeneity. In general, a fixed-effects model is employed for the analysis, and when $I^2 > 50\%$, it shows considerable heterogeneity, at which time a random-effects model is used. To identify the source of heterogeneity, we also conducted subgroup analyses for country (Europe, America, Oceania, and Asia), population characteristics (Hypercholesterolemia, T2DM, NAFLD, GDM, Health, and Others), intervention dose (≤ 2 g/d and > 2 g/d), intervention period (≤ 12 W and > 12 W), esterification or not, and type of phytosterol (Sterol, Stanol, and Sterol/Stanol). Sensitivity analysis was used to evaluate the stability of the statistical results.

3 | RESULTS

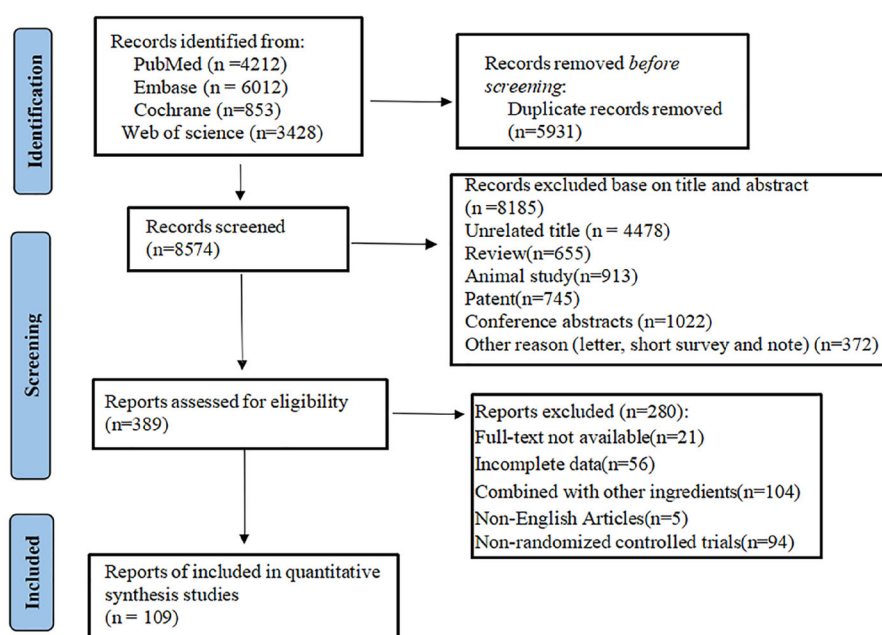
3.1 | Study selection process

After searching four databases, 14,505 relevant papers were retrieved, of which, 5931 duplicated literatures were excluded. Based on the titles and abstracts, 8185 irrelevant papers were excluded. A total of 389 literatures were reviewed for eligibility, of which 280 literatures were excluded due to the following reasons: (1) The full text cannot be obtained; (2) inadequate data; (3) the effect of phytosterols alone could not be examined; (4) non-English literature; and (5) non-randomized controlled trials. Finally, 109 articles were included in this analysis. It is worth noting that the data from seven of these articles were divided into two trials (one with a phytosterol intervention versus placebo and the other using a stanols intervention versus placebo), five articles were divided into two different dosage interventions, and one article included a different study population. Consequently, this meta-analysis included 109 articles (122 data sets). The detailed procedures of the literature search and screening are depicted in Figure 1.

3.2 | Study characteristics

Table 2 shows the essential characteristics of the papers included in this meta-analysis. The studies were published between 1994 and 2023. A total of 7048 subjects were enrolled, including 4140 males and 2908 females, from Asia, Europe, America, and Oceania. The population characteristics included hyperlipidemia, non-alcoholic fatty liver disease, type 2 diabetes mellitus, gestational diabetes mellitus, healthy people, and others. Most of them were hyperlipidemia, gestational diabetes mellitus and non-alcoholic fatty liver disease were the least, and only two studies were included. The age range was 18–84 years. The duration of phytosterols supply ranged from 11 days to 85 weeks, with doses ranging from 0.5 to 8.8 g/d.

FIGURE 1 PRISMA flow chart of selected articles.



3.3 | Risk of bias assessment

We also conducted a risk of bias assessment for the included literature. Most studies were rated as having a low risk of bias. In addition, in most of the included trials, the risk generated by the randomized sequence was unknown, so there was not enough information to generate a risk rating. A detailed risk assessment table is provided in Table S2.

3.4 | Results of meta-analysis

3.4.1 | Effects of phytosterols on indices related to glucose and lipid metabolism

As shown in Table 3 (for detailed forest maps, see Figure S1). We used both random and fixed effects models for analysis. For serum total cholesterol, a total of 6988 participants were included in 98 studies (109 effect sizes) ($n = 3541$ [intervention], $n = 3447$ [control]). Pooled results from a random-effects model using serum TC as the outcome measure showed that total cholesterol levels were lower in the intervention group than in the control group (mean difference = -13.41 ; 95% CI: -15.19 , -11.63 , $p < 0.001$). There was a moderate to high degree of heterogeneity among studies ($I^2 = 72.8\%$, $p < 0.001$).

For low-density lipoprotein cholesterol (LDL-C), pooled random-effects models from 100 studies (112 effect sizes) showed that phytosterols reduced serum LDL-C levels (mean difference = -12.57 ; 95% CI: -13.87 , -11.26 , $p < 0.001$), and there was moderate heterogeneity between studies ($I^2 = 53.5\%$, $p < 0.001$).

A total of 100 studies with 111 effect sizes were included in the serum HDL-C level analysis. Random-effects model results showed

that phytosterols as an intervention increased HDL-C levels (mean difference = 0.46 ; 95% CI: 0.13 , 0.78 , $p = 0.005$). There was moderate heterogeneity between studies ($I^2 = 49.2\%$, $p < 0.001$).

For triglycerides, pooled results from 95 studies (106 effect sizes) using a random-effects model showed that phytosterols intervention reduced serum TG levels (mean difference = -6.34 ; 95% CI: -9.43 , -3.25 , $p < 0.001$) showed moderate heterogeneity ($I^2 = 63.1\%$, $p < 0.001$).

A total of 6 studies were included in the analysis of HbA1c level. Compared with placebo, the phytosterols intervention had no significant effect on HbA1c level (mean difference = -0.28 ; 95% CI: -0.75 , 0.20 , $p = 0.251$, $I^2 = 87.5\%$).

For blood glucose, the pooled results of 16 studies (17 effect sizes) using fixed effects model showed that the phytosterols intervention had no significant effect on GLU level (mean difference = -0.44 ; 95% CI: -1.64 , 0.76 , $p = 0.471$) between studies ($I^2 = 9.8\%$, $p = 0.340$).

3.4.2 | Effects of phytosterols on markers related to inflammation and oxidative stress

In total, 15 publications with 16 effect sizes were included in the analysis of serum CRP level. The intervention of phytosterols exerted a statistically significant effect on the level of CRP (mean difference = -0.05 ; 95% CI: -0.08 , -0.01 , $p = 0.671$). There was no heterogeneity across studies ($I^2 = 0.0\%$, $p = 0.671$).

Among the six studies for the serum TNF- α levels analysis. The results of the fixed-effects model showed no significant effect of phytosterols on TNF- α levels (mean difference = 0.08 ; 95% CI: -0.08 , 0.24 , $p = 0.335$), and no significant between-study heterogeneity was observed ($I^2 = 0.0\%$, $p = 0.496$).

TABLE 2 Baseline characteristics of the studies included.

Literature	Year	Study region	Study design	No. of patients	Female (%)	Age range	Participant	Dose (g/d)	Period	Type	Easter
Gylling et al. (2010)	2010	Finland	Parallel	49	32 (65%)	18–75	Hypercholesterolemia	8.8	10 W	Stanol	Yes
Lye et al. (2019)	2019	Singapore	Crossover	15	0	21–33	23.5 kg/m ² ≤ BMI ≤ 35 kg/m ²	2	11 D	Sterol	No
Párraga-Martínez et al. (2015)	2015	Spain	Parallel	182	99 (54%)	>18	Hypercholesterolemia	2	12 M	Stanol	No
Lee et al. (2003)	2003	Germany	Parallel	81	45 (56%)	NA	T2DM	1.6	12 W	Sterol	No
Wang et al. (2019)	2019	China	Parallel	58	29 (50%)	51–65	Impaired glucose regulation	1.7	12 W	Sterol	No
Earnest et al. (2007)	2007	America	Parallel	54	25 (46%)	20–70	Hypercholesterolemia	2.6	12 W	Sterol	Yes
Patch et al. (2005)	2005	Australia	Parallel	25	NA	30–75	Hypercholesterolemia	2	12 W	Sterol/ Stanol	No
Hallikainen-M et al. (2008)	2008	Finland	Parallel	19	11 (58%)	29–53	Type 1 diabetes	2	12 W	Stanol	No
Song et al. (2020)	2020	China	Parallel	37	32 (86%)	30–67	NAFLD	3.3	12 W	Sterol	Yes
Ras et al. (2016)	2016	Netherlands	Parallel	222	NA	40–65	Hypercholesterolemia	3	12 W	Sterol	No
Simonen, Lommi, et al. (2015)	2015	Finland	Parallel	36	21 (58%)	58–84	Severe aortic stenosis	2 g	14 W	Sterol/ Stanol	No
De Jong, Plat, Bast, et al. (2008)	2008	Netherlands	Parallel	41	21 (51%)	18–65	Statin treatment	2.5/2.5	16 W	Sterol/ Stanol	No
Athyros et al. (2011)	2011	Greece	Parallel	100	52 (52%)	NA	Hypercholesterolemia	2	16 W	Stanol	Yes
Li and Xing (2016)	2016	China	Parallel	206	NA	25–34	GDM	2	16 W	Sterol	No
Nigon et al. (2001)	2001	France	Crossover	53	31 (58%)	22–76	Hypercholesterolemia	1.6	2 M	Sterol	No
Sialvera et al. (2012)	2012	Greece	parallel	108	48 (44%)	NA	Metabolic syndrome	4	2 M	Sterol	No
Söderholm et al. (2012)	2012	Finland	Parallel	63	47 (75%)	NA	Healthy	2	2 W	Sterol	No
Bañuls et al. (2010)	2009	Spain	Parallel	40	NA	24–69	Hypercholesterolemia	2	3 M	Sterol	No
Bañuls et al. (2014)	2011	Spain	Parallel	75	NA	18–76	Hypercholesterolemia	2	3 M	Sterol	No
Jones et al. (1999)	1999	Canada	Parallel	32	NA	25–60	Hypercholesterolemia	1.7	30 D	Sterol	No
Ishizaki et al. (2003)	2003	Japan	Parallel	55	NA	30–60	Hypercholesterolemia	0.884	3 M	Sterol	Yes
Hernández-Mijares et al. (2010)	2010	Spain	Parallel	55	40 (73%)	18–76	Hypercholesterolemia	2	3 M	Sterol	No
Hernández-Mijares et al. (2011)	2011	Spain	Parallel	48	30 (63%)	18–76	Hypercholesterolemia	2	3 M	Sterol	No
Timar et al. (2014)	2014	Romania	Parallel	94	NA	NA	T2DM	2	3 M	Sterol	No
San Mauro-Martin et al. (2016)	2016	Spain	Crossover	54	30 (56%)	18–50	BMI ≤ 30 kg/m ²	2.24	3 W	Sterol	No
Cheung et al. (2017)	2017	China	Parallel	221	180 (81%)	24–79	Healthy	1.5	3 W	Sterol	No
Clifton et al. (2004)	2004	Australia	Crossover	58	35 (60%)	20–75	Hypercholesterolemia	1.6	3 W	Sterol	No
Colgan et al. (2004)	2004	Ireland	Crossover	48	21 (43%)	NA	Hypercholesterolemia	1.6	3 W	Sterol	Yes

TABLE 2 (Continued)

Literature	Year	Study region	Study design	No. of patients	Female (%)	Age range	Participant	Dose (g/d)	Period	Type	Easter
Jones et al. (2000)	2000	Canada	Crossover	15	0	37–61	Hypercholesterolemia	1.84/1.84	3 W	Sterol/ Stanol	Yes
Vanstone et al. (2002)	2002	Canada	Crossover	15	6 (40%)	35–58	Hypercholesterolemia	1.8	3 W	Sterol/ Stanol	No
Charest et al. (2004)	2004	Canada	Crossover	14	(8/6)	35–58	Hypercholesterolemia	1.8	3 W	Sterol	No
Lau et al. (2005)	2005	Canada	Crossover	14	9 (64%)	40–84	Others	1.8	3 W	Sterol	No
Yoshida et al. (2006)	2006	Canada	Crossover	34	22 (65%)	35–75	Non-diabetic/T2DM	1.8	3 W	Sterol	No
Cicero et al. (2023)	2023	Italian	Crossover	53	34 (64%)	20–65	Hypercholesterolemia	2.5	3 W	Sterol	No
Lagstrom et al. (2006)	2006	Finland	Parallel	42	NA	35–55	Hypercholesterolemia	2	3 W	Stanol	No
Chau et al. (2020)	2020	China	Parallel	159	74 (47%)	>18	Healthy	2	3 W	Sterol	No
Alhassan et al. (2006)	2006	America	Parallel	26	NA	40–65	Male and postmenopausal female		4 W	sterol	Yes
Sarkkinen et al. (2018)	2018	Finland	Parallel	70	44 (63%)	18–70	Hypercholesterolemia	1.6	4 W	Stanol	Yes
Saito et al. (2006)	2006	Japan	Parallel	34	0	NA	Hypercholesterolemia	0.5	4 W	Sterol	Yes
Thomsen et al. (2004)	2004	Switzerland	Crossover	69	51 (74%)	45–65	Hypercholesterolemia	1.2/1.6	4 W	Sterol	No
Ruiu et al. (2009)	2009	Italy	Crossover	15	5 (33%)	NA	Healthy	1.6	4 W	Sterol	No
Rudkowska et al. (2008)	2008	Canda	Crossover	26	NA	40–80	Hypercholesterolemia	1.6	4 W	Sterol	No
Ferro et al. (2020)	2020	Italy	Parallel	48	27 (56%)	>20	Hypercholesterolemia	1.6	4 W	Sterol	No
De Graaf et al. (2002)	2002	Netherlands	Parallel	62	32 (52%)	21–75	Hypercholesterolemia	1.8	4 W	Sterol	No
Buyuktuncer et al. (2013)	2013	Turkey	Parallel	70	41 (59%)	20–70	Hypercholesterolemia	1.9	4 W	Stanol	Yes
Volpe et al. (2001)	2001	Italy	Crossover	30	9 (30%)	33–69	Hypercholesterolemia	1	4 W	Sterol	No
Theuwissen et al. (2009)	2009	Netherlands	Parallel	28	12 (43%)	18–70	Hypercholesterolemia	2.5	4 W	Stanol	Yes
Matvienko et al. (2002)	2002	America	Parallel	34	0	20–29	Hypercholesterolemia	2.7	4 W	Sterol	No
Woodgate et al. (2006)	2006	Canada	Crossover	30	9 (30%)	33–70	Hypercholesterolemia	2.7	4 W	Stanol	Yes
Hallikainen-M et al. (2013)	2013	Sweden	Parallel	56	45 (80%)	25–65	Hypercholesterolemia	2.7	4 W	Stanol	Yes
Gonçalves et al. (2006)	2006	Portuguese	Parallel	37	NA	30–45	Hypercholesterolemia	2	4 W	Sterol	No
Khandelwal et al. (2009)	2009	Indian	Parallel	93	14 (15%)	35–55	Hypercholesterolemia	2	4 W	Sterol	No
Vasquez-Trespalcacios and Romero-Palacio (2014)	2014	Columbia	Crossover	40	30 (75%)	20–50	Hypercholesterolemia	2	4 W	Stanol	Yes
Stelmach-Mardas et al. (2014)	2014	Poland	Parallel	77	77 (100%)	NA	Obese Women	2	4 W	Stanol	Yes
Salo and Kuusisto (2016)	2016	Finland	Parallel	60	42 (70%)	25–65	Hypercholesterolemia	2	4 W	Stanol	Yes
Ho et al. (2016)	2016	Singapore	Crossover	18	12 (67%)	>21	Healthy	2	4 W	Sterol	Yes
Nigon et al. (2017)	2017	Canada	Parallel	66	17 (26%)	25–60	Hypercholesterolemia	2	4 W	Sterol	No

(Continues)

TABLE 2 (Continued)

Literature	Year	Study region	Study design	No. of patients	Female (%)	Age range	Participant	Dose (g/d)	Period	Type	Easter
Laitinen et al. (2017)	2017	Finland	Parallel	103	77 (75%)	21–84	Hypercholesterolemia	2	4 W	Stanol	Yes
Ferguson et al. (2018)	2018	Australia	Parallel	35	20 (57%)	18–70	Hypercholesterolemia	2	4 W	Sterol	No
Lestiani et al. (2018)	2018	Indonesian	Parallel	88	50 (57%)	24–68	Hypercholesterolemia	2	4 W	Stanol	No
Doornbos et al. (2006)	2006	Netherlands	Parallel	109	NA	NA	Hypercholesterolemia	3.2/2.8	4 W	Sterol	No
Yae et al. (2005)	2005	Finland	Parallel	51	25 (49%)	20–39	Healthy	3.3	4 W	Stanol	Yes
Kriengsinyos et al. (2015)	2015	Thailand	Parallel	119	90 (76%)	25–60	Hypercholesterolemia	3.4	4 W	Stanol	Yes
Homma et al. (2003)	2003	Japan	Parallel	105	67 (64%)	>20	Healthy	3.4/5.1	4 W	Stanol	Yes
Mensink et al. (2002)	2002	Netherlands	Parallel	60	NA	18–65	Non-hypercholesterolemic	3	4 W	Stanol	Yes
Carr et al. (2009)	2009	America	Parallel	32	NA	19–70	Normo-and hypercholesterolemic	3	4 W	Sterol	Yes
Mensink et al. (2010)	2010	Netherlands	Parallel	46	21 (46%)	NA	Healthy	3	4 W	Stanol	Yes
Hallikainen et al. (2011)	2011	Finland	Parallel	24	12 (50%)	18–70	Type 1 diabetes	3	4 W	Stanol	Yes
Gao et al. (2017)	2016	China	Parallel	244	NA	26–35	GDM	4	4 W	Sterol	No
Hendriks et al. (2003)	2003	Netherlands	Parallel	185	95 (51%)	35–64	Healthy	1.6	52 W	Sterol	Yes
Gagliardi et al. (2010)	2010	America	Parallel	37	23 (62%)	NA	Metabolic syndrome	2.4	5 W	Sterol	No
Jauhiainen et al. (2006)	2006	Finland	Parallel	67	43 (64%)	25–65	Hypercholesterolemia	2	5 W	Stanol	Yes
Alvarez-Sala et al. (2018)	2018	Spain	Crossover	38	38 (100%)	45–65	Hypercholesterolemia	2	6 W	Sterol	No
Christiansen et al. (2001)	2001	Finland	Parallel	135	NA	25–64	Hypercholesterolemia	1.5/3	6 M	Sterol	No
Miettinen et al. (1995)	1995	Finland	Parallel	153	NA	NA	Hypercholesterolemia	2.6	6 M	Stanol	Yes
Dong et al. (2016)	2016	China	Parallel	137	NA	55–65	Hypercholesterolemia	2	6 M	Sterol	Yes
Gylling et al. (2013)	2013	Finland	Parallel	92	57 (62%)	25–66	Hypercholesterolemia	3	6 M	Stanol	No
Simonen, Stenman, and Gylling (2015)	2015	Finland	Parallel	92	57 (62%)	NA	Hypercholesterolemia	3	6 M	Stanol	No
Ruuth et al. (2020)	2020	Finland	Parallel	90	56 (62%)	24–66	Healthy	3	6 M	Stanol	Yes
Sukmaniah et al. (2008)	2008	Indonesia	Parallel	31	20 (65%)	25–55	Hypercholesterolemia	1.2	6 W	Sterol	No
McPherson et al. (2005)	2005	America	Crossover	25	14 (56%)	NA	Healthy	1.26	6 W	Stanol	No
Hansel et al. (2007)	2007	France	Parallel	194	64 (33%)	18–75	Hypercholesterolemia	1.6	6 W	Sterol	No
Plana et al. (2008)	2008	Spain	Parallel	84	NA	18–75	Hypercholesterolemia	1.6	6 W	Sterol	No
Mannarino et al. (2009)	2009	Italy	Parallel	116	65 (56%)	NA	Hypercholesterolemia	1.6	6 W	Sterol	No
Maki et al. (2012)	2012	America	Crossover	32	19 (59%)	21–79	BMI ≤ 35 kg/m ²	1.8	6 W	Sterol	Yes
Goldberg et al. (2006)	2006	America	Parallel	26	17 (65%)	40–78	Long-term statin therapy	1.8	6 W	Stanol	No
Bertolami et al. (2014)	2014	Brazil	Crossover	37	19 (51%)	NA	T2DM	2.1	6 W	Stanol	Yes
Trautwein et al. (2018)	2018	Australia	Parallel	138	59 (43%)	51–75	T2DM	2.26	6 W	Sterol	No

TABLE 2 (Continued)

Literature	Year	Study region	Study design	No. of patients	Female (%)	Age range	Participant	Dose (g/d)	Period	Type	Easter
Gomes et al. (2017)	2017	Brazilian	Parallel	21	7 (33%)	NA	Statin therapy	2	6 W	Sterol	No
Cuevas-Tena et al. (2019)	2018	Spain	Crossover	36	36 (100%)	50–65	Postmenopausal women	2	6 W	Sterol	No
Ferguson et al. (2020)	2020	Australia	Parallel	36	22 (61%)	18–70	Hypercholesterolemia	2	6 W	Sterol	No
Polagruto et al. (2006)	2006	America	Parallel	67	47 (70%)	NA	Hypercholesterolemia	3	6 W	Sterol	No
Javanmardi et al. (2019)	2018	Iran	Parallel	38	21 (56%)	NA	NAFLD	1.6	8 W	Sterol	No
De Jong, Plat, Lütjohann, et al. (2008)	2008	Netherlands	Parallel	54	22 (41%)	18–65	BMI < 32 kg/m ²	2.5/2.5	85 W	Sterol/ Stanol	No
Kelly et al. (2011)	2011	Netherlands	Parallel	30	13 (43%)	18–65	BMI < 32 kg/m ²	2.5/2.5	85 W	Sterol/ Stanol	No
Shin et al. (2003)	2003	Korea	Crossover	45	30 (67%)	31–75	Hypercholesterolemia	1.6	8 W	Sterol	No
Ribas et al. (2017)	2017	Brazil	Crossover	28	NA	6–19	Dyslipidemias outpatients	1.2	8 W	Sterol	No
Amundsen et al. (2002)	2002	Norway	Crossover	38	19 (50%)	NA	Healthy	1.7	8 W	Sterol	Yes
Varady et al. (2004)	2004	Canada	Parallel	38	26 (68%)	40–70	Hypercholesterolemia	1.8	8 W	Sterol	No
Collins et al. (2007)	2007	Canada	Parallel	38	NA	40–70	Hypercholesterolemia	1.8	8 W	Sterol	No
Hongu et al. (2014)	2014	America	Parallel	24	19 (79%)	21–50	Overweight and obese	1.8	8 W	Sterol	No
Hallikainen and Uusitupa (1999)	1999	Finland	Parallel	55	35 (64%)	20–60	Hypercholesterolemia	2.31/2.16	8 W	Stanol	Yes
Weidner et al. (2008)	2008	France	Parallel	50	31 (62%)	19–65	Hypercholesterolemia	2.6	8 W	Sterol	Yes
Devaraj et al. (2004)	2004	America	Parallel	72	41 (57%)	20–73	Hypercholesterolemia	2	8 W	Sterol	No
Devaraj et al. (2006)	2006	America	Parallel	72	41 (57%)	19–74	Healthy	2	8 W	Sterol	No
Niittynen et al. (2008)	2008	Finland	Crossover	26	15/11	25–59	Hypercholesterolemia	2	8 W	Sterol	No
Brüll et al. (2016)	2016	Netherlands	Parallel	58	42 (72%)	18–70	Allergic asthma	4	8 W	Stanol	No
Vanhanen et al. (1994)	1994	Finland	Parallel	15	4 (27%)	37–55	Hypercholesterolemia	0.8	9 W	Sterol	No
Plat et al. (2009)	2009	Netherlands	Parallel	18	6 (33%)	55–70	Metabolic Syndrome	2	9 W	Stanol	No

Abbreviations: D, days; GDM, gestational diabetes mellitus; M, months; NA, not available; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus; W, weeks.

TABLE 3 Results of meta-analysis of each index.

Indicator	Studies, <i>n</i>	MD (95% CI)	<i>p</i> Value	Heterogeneity	
				<i>I</i> ² (%)	<i>p</i>
TC (mmol/L)	98 (109 effect sizes)	−13.41 (−15.19, −11.63)	<0.001	72.8	<0.001
LDL-C (mmol/L)	100 (112 effect sizes)	−12.57 (−13.87, −11.26)	<0.001	53.5	<0.001
HDL-C (mmol/L)	100 (111 effect sizes)	0.46 (0.13, 0.78)	0.005	49.2	<0.001
TG (mmol/L)	95 (106 effect sizes)	−6.34 (−9.43, −3.25)	<0.001	63.1	<0.001
GLU (mg/dL)	16 (17 effect sizes)	−0.44 (−1.64, 0.76)	0.471	9.8	0.340
HbA1c (%)	6	−0.28 (−0.75, 0.20)	0.251	87.5	<0.001
CRP (mg/L)	15 (16 effect sizes)	−0.05 (−0.08, −0.01)	0.671	0.0	0.671
TNF-α (pg/mL)	6	0.08 (−0.08, 0.24)	0.335	0.0	0.496
IL-6 (pg/mL)	5	0.00 (−0.02, 0.02)	0.980	41.1	0.147
OXLDL-C	3 (4 effect sizes)	0.16 (−0.38, 0.06)	0.154	0.0	0.612
SBP (mmHg)	18	−2.10 (−3.27, −0.9)	<0.001	15.4	0.269
DBP (mmHg)	18	−0.83 (−1.58, −0.07)	0.032	0.0	0.697
BMI (kg/m ²)	22	0.01 (−0.07, 0.09)	0.886	0.0	0.999
WC (cm)	8	−0.10 (−0.50, 0.30)	0.625	0.0	0.541
Weigh (kg)	14	0.03 (−0.18, 0.24)	0.787	0.0	1.0

Note: The summarized results for OXLDL-C are expressed as standard mean difference (SMD).

The five studies used to analyze serum IL-6 levels, indicated that phytosterols supplementation has no significant effect on IL-6 (mean difference = 0.00, 95% CI: −0.02, 0.02, *p* = 0.980), and the inter-study heterogeneity was low (*I*² = 41.1%, *p* = 0.147).

The results of serum OXLDL-C were calculated in four comparisons from three studies. The applied random-effects model showed that the phytosterols intervention had no significant effect on OXLDL-C levels (standard mean difference = 0.16; 95% CI: −0.38, 0.06, *p* = 0.154). There was no heterogeneity between studies (*I*² = 0.0%, *p* = 0.612).

3.4.3 | Effects of phytosterols on blood pressure, BMI, body weight, and waist circumference

For SBP, the pooled results of 18 studies using fixed effects models showed that phytosterols supplementation was able to significantly reduce SBP levels (mean difference = −2.10; 95% CI: −3.27, −0.9, *p* < 0.001), and the inter-study heterogeneity was low (*I*² = 15.4%, *p* = 0.269).

A total of 18 studies were included in the analysis of DBP level. Phytosterols could significantly reduce DBP levels (mean difference = −0.83; 95% CI: −1.58, −0.07, *p* = 0.032), and no significant between-study heterogeneity was observed (*I*² = 0.0%, *p* = 0.697).

For BMI, the results of fixed effect model of 22 studies showed that phytosterols intervention had no significant effect on BMI level (mean difference = 0.01; 95% CI: −0.07, 0.09, *p* = 0.886), and there was no heterogeneity among the studies (*I*² = 0.0%, *p* = 0.999).

A total of eight studies were included in the WC level analysis. Phytosterols had no significant effect on WC level. (Mean difference = −0.10; 95% CI: −0.50, 0.30, *p* = 0.625). There was no heterogeneity between studies (*I*² = 0.0%, *p* = 0.541).

Fourteen studies were used to analyze Weight levels. The results of fixed effects model showed that phytosterols intervention had no significant effect on Weight level (mean difference = 0.03; 95% CI: −0.18, 0.24, *p* = 0.787, *I*² = 0.0%).

3.5 | Subgroup analysis

Based on the collected data, subgroup analyses were performed by region, population characteristics, dose, intervention time, esterified or not, and type of phytosterols. The results of subgroup analyses of TC, TG, LDL-C, HDL-C, CRP, GLU in serum and anthropometric indicators (SBP, DBP, BMI, WC, and Weight) are specified in Table S3. Subgroup analyses of HbA1c, OXLDL-C, TNF-α, and IL-6 in serum were not performed because subgroups were selected based on the minimum number of studies required, with at least 6–10 studies for continuous variables, according to the criteria specified by Fu et al. (2011).

Subgroup analysis from different regions showed different effects of phytosterols on serum HDL-C level (HDL-C: *p* < 0.001). In particular, the effect of phytosterols on raising HDL-C levels was more pronounced in Asia compared to the Americas, but heterogeneity was higher. In addition, the effects of phytosterols on lowering serum TC and serum LDL-C were not significant across regions (TC: *p* = 0.281, LDL-C: *p* = 0.741). Subgroup analysis showed that phytosterols reduced serum TC, TG, and LDL-C levels in different populations, and the differences were significant (TC: *p* < 0.001, TG: *p* < 0.001, LDL-C: *p* < 0.001). Phytosterols have a significant lipid-lowering effect on patients with hyperlipidemia, and also have a certain preventive effect on healthy people. Among them, for women with gestational diabetes, the results were unreliable because only two studies were included.

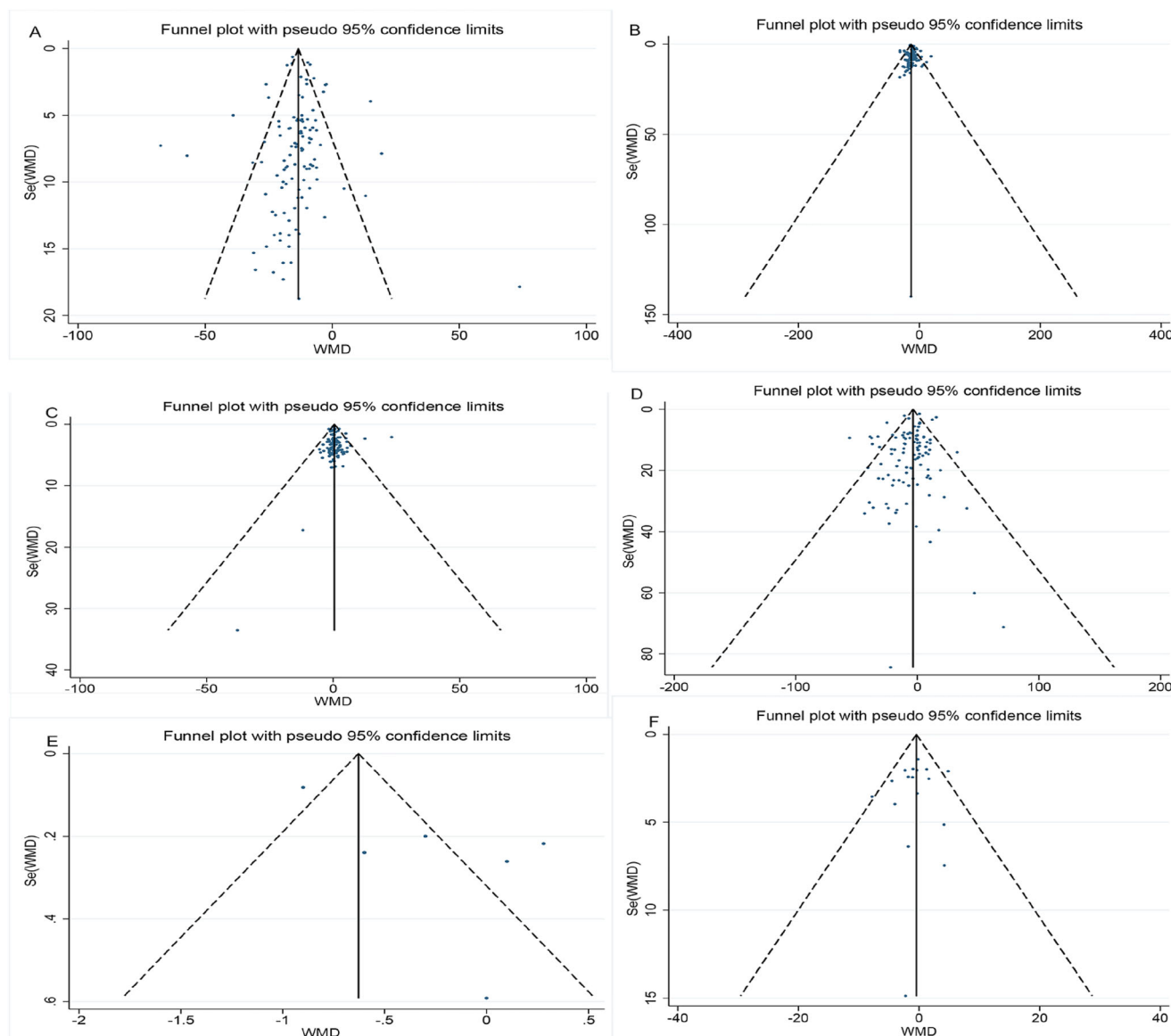


FIGURE 2 Funnel plot and Egger's test for assessing publication bias. (a) TC Egger's test ($p = 0.967$), (b) LDL-C Egger's test ($p = 0.138$), (c) HDL-C Egger's test ($p = 0.210$), (d) TG Egger's test ($p = 0.086$), (e) HbA1c Egger's test ($p = 0.062$), (f) GLU Egger's test ($p = 0.623$). GLU, blood glucose; HbA1c, glycosylated hemoglobin, Type A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

We used 2 g/d as the cut-off point for subgroup analysis, and found that both high and low doses reduced the levels of serum TC, LDL-C, HDL-C, TG, and SBP, but the differences were not significant (TC: $p = 0.14$, LDL-C: $p = 0.083$, HDL-C: $p = 0.565$, TG: $p = 0.755$, SBP: $p = 0.123$). The intervention period was divided into short-term intervention (≤ 12 weeks) and long-term intervention (> 12 weeks). The long-term intervention was better than other interventions (TC: $p = 0.003$, CRP: $p = 0.018$). However, there was heterogeneity in the TC group, and the heterogeneity was higher ($I^2 = 72.8\%$, $p < 0.001$). The heterogeneity in the CRP group was very low ($I^2 = 0.0\%$, $p = 0.847$). In addition, both long-term and short-term intervention could reduce the levels of serum LDL-C and TG, but the difference was not significant (LDL-C: $p = 0.382$, TG: $p = 0.065$). Both esterified phytosterols and unesterified phytosterols could reduce TC and

LDL-C, but the difference was not significant (TC: $p = 0.615$, LDL-C: $p = 0.491$). Both phytosterols and stanols could reduce serum TC and LDL-C, but the difference was not significant (TC: $p = 0.904$, LDL-C: $p = 0.596$). Because only one study was included, the mixed effect of the two could not be explored.

3.6 | Publication bias and sensitivity analysis

Funnel plots and the Egger test were used to evaluate whether there was any publication bias in the studies. The points in the funnel plot indicate the included studies. As shown in Figures 2–4, the results of the funnel plot and Egger test indicated that there was no publication bias (TC Egger's test: $p = 0.967$, LDL-C Egger's test: $p = 0.138$,

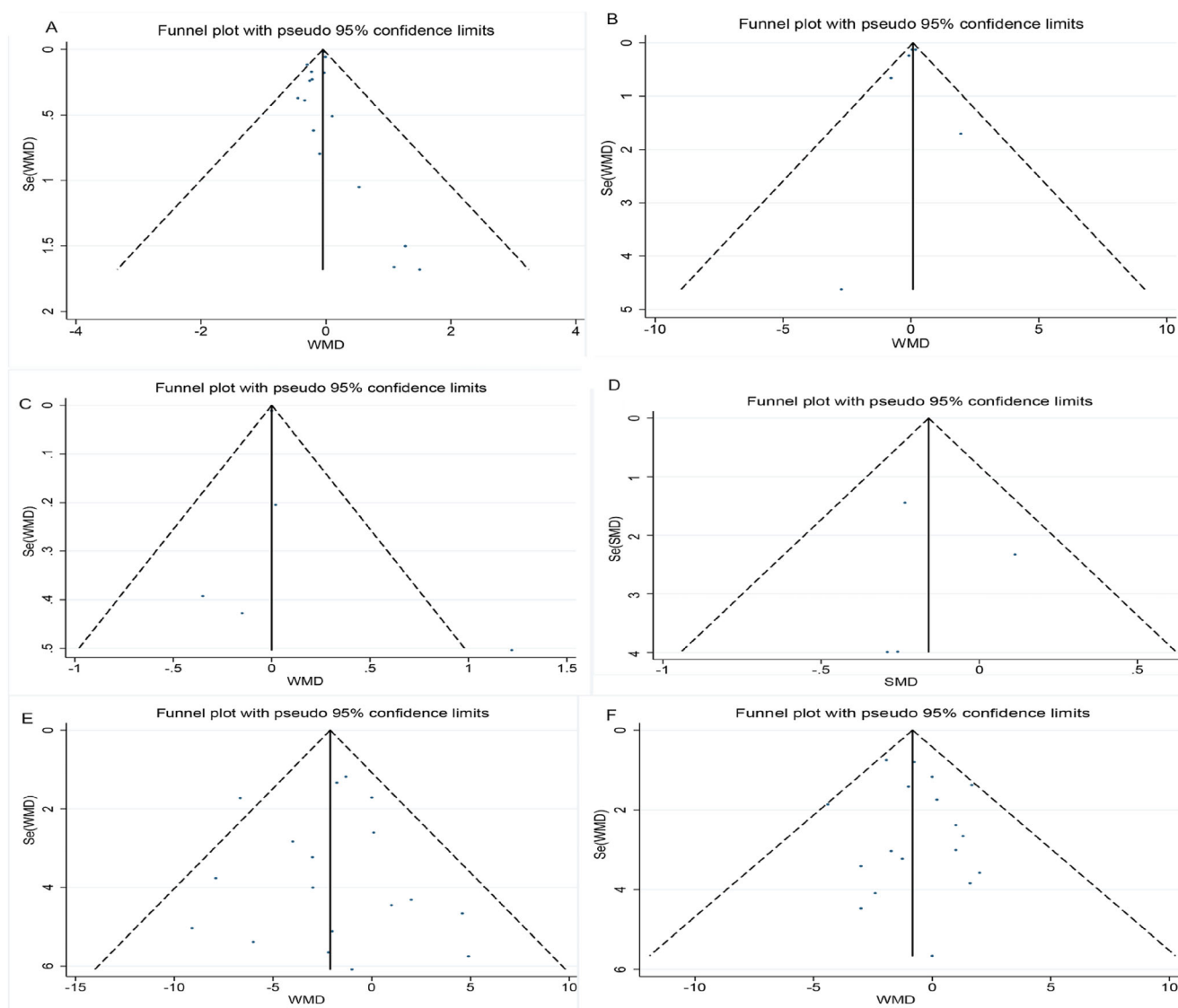


FIGURE 3 Funnel plot and Egger's test for assessing publication bias. (a) CRP Egger's test ($p = 0.441$), (b) TNF- α Egger's test ($p = 0.592$), (c) IL-6 Egger's test ($p = 0.687$), (d) OXLDL-C Egger's test ($p = 0.926$), (e) SBP Egger's test ($p = 0.994$), (f) DBP Egger's test ($p = 0.488$). CRP, C-reactive protein; DBP, diastolic blood pressure; IL-6, Interleukin-6; OXLDL-C, oxidized low-density lipoprotein cholesterol; SBP, systolic blood pressure; TNF- α , tumor necrosis factor.

HDL-C Egger's test: $p = 0.210$, TG Egger's test: $p = 0.086$, CRP Egger's test: $p = 0.441$, TNF- α Egger's test: $p = 0.592$, IL-6 Egger's test: $p = 0.687$, OXLDL-C Egger's test: $p = 0.926$, SBP Egger's test: $p = 0.994$, DBP Egger's test: $p = 0.488$, BMI Egger's test: $p = 0.753$, WC Egger's test: $p = 0.708$, Weigh Egger's test: $p = 0.696$, GLU Egger's test: $p = 0.623$, HbA1c Egger's test: $p = 0.062$, Cr Egger's test: $p = 0.834$). Specific values are detailed in Table S4.

4 | DISCUSSION

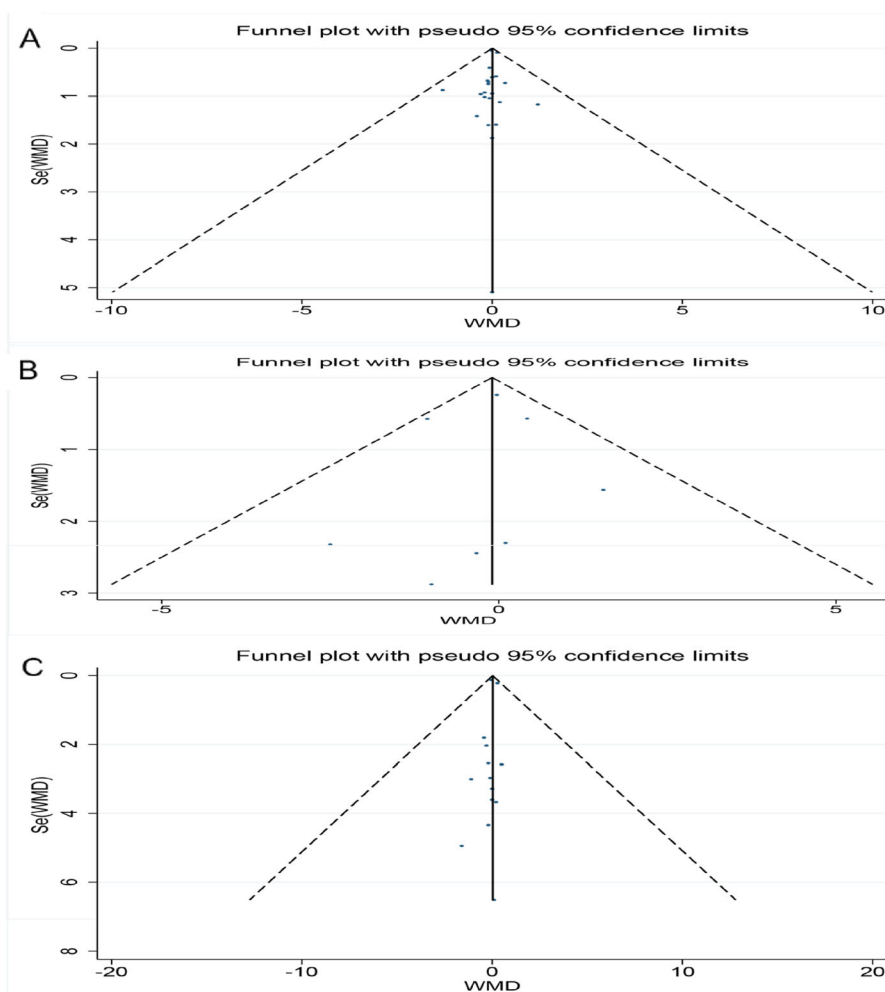
4.1 | Main findings and corresponding discussion

To the best of our knowledge, our current study is a relatively comprehensive analysis of the effects of dietary phytosterols intake on

cardiovascular risk factors. In this meta-analysis, we found that the intervention with phytosterols helped to reduce the serum levels of TC, TG, LDL-C, CRP and the levels of SBP and DBP. Furthermore, phytosterols intervention was found to increase serum HDL-C level. However, no significant effects of phytosterols on serum TNF- α , serum IL-6, serum OXLDL-C, GLU, HbA1c, BMI, WC, and Weight were observed.

Previous studies have found that phytosterols supplementation can significantly reduce TC and LDL-C contents, but not HDL-C and TG contents (Katan et al., 2003). However, in this meta-analysis, it was found that phytosterols could reduce serum TC, TG, and LDL-C, and increase HDL-C levels in humans. This may be related to factors such as articles excluding inclusion criteria, subject characteristics, and inconsistent dose and time of phytosterols intake. Subgroup analysis showed that intake of phytosterols for more than 12 weeks had a

FIGURE 4 Funnel plot and Egger's test for assessing publication bias. (a) BMI Egger's test ($p = 0.753$), (b) WC Egger's test ($p = 0.708$), and (c) Weight Egger's test ($p = 0.696$). BMI, body mass index; WC, waist circumference.



more significant effect on TC reduction. At present, the population intervention trials of phytosterols are mainly short-term, and long-term (more than 1 year) intervention trials are rare. A 1-year intervention study showed that a daily intake of 1.6 g phytosterols could reduce blood cholesterol levels without any adverse effects (Hendriks et al., 2003).

The effects of phytosterols on cardiovascular risk factors other than hyperlipidemia have not been well demonstrated (Cabral & Klein, 2017). Therefore, the antihypertensive effects of phytosterols were also investigated in this study. The mechanism by which phytosterols lower blood pressure remains unclear due to the lack of appropriately designed mechanistic studies. It has been expressed that the swelling properties of phytosterols are a direct result of the ability of phytosterols to promote the release of prostaglandins from vascular smooth muscle cells (Awad et al., 2001; Lin et al., 2015). Prostaglandins are potent vasodilators that reduce peripheral vascular resistance and arterial stiffness, thereby lowering blood pressure (Fetalvero et al., 2007). Another plausible mechanism to explain the blood pressure-lowering effects of phytosterols is their total cholesterol and LDL-C lowering properties, which have been well documented in several meta-analyses (Abumweis et al., 2008; Demonty et al., 2009; Ras et al., 2014). Current conclusions regarding the antihypertensive

effects of phytosterols are controversial; some studies have found positive effects of phytosterols on blood pressure, but others have shown that dietary intake of phytosterols increases blood pressure in patients (Cheung et al., 2017; Medina-Remón et al., 2015; Yue et al., 2015). The pooled results of a previous meta-analysis showed that phytosterols had antihypertensive effects, which was consistent with the results of this study. Therefore, based on the results of the current study, phytosterols supplementation may be a beneficial adjunct to the treatment of hypertensive patients as well as an individual option for supplemental prevention of prehypertension and normotension, which needs to be further investigated in future studies.

Inflammation plays an important role in the development of atherosclerosis and CVDs. In this process, in addition to inflammatory cells, some inflammatory mediators can stimulate the liver to secrete acute phase response proteins (C-reactive proteins) (Fain et al., 2004), such as IL-6. CRP is a low-grade systemic inflammatory marker that is positively associated with the risk of future cardiovascular events (Calder et al., 2009; Lemieux & Després, 2020). A related study found that CRP levels were significantly elevated in patients with heart attacks (Othman & Moghadasian, 2011). Some studies have shown that IL-6 is associated with cardiovascular risk and subclinical

atherosclerosis (Kaptoge et al., 2014; Ridker, 2016). One of the related inflammatory mechanisms: helper Th1 cells secrete cytokines such as TNF- α , which promote inflammation through macrophages or vascular cells, thereby accelerating atherosclerosis (Moriya, 2019). The results of current studies on the effects of phytosterols on inflammatory markers are still controversial (Devaraj et al., 2004, 2006; Kris-Etherton & Hilpert, 2003). A previous meta-analysis of the effect of dietary supplementation with phytosterols on CRP levels indicated that the results did not significantly alter CRP levels (Rocha et al., 2016). However, as we gather and synthesize the latest evidence, we find that phytosterols supplements have a significant effect on reducing CRP levels, and subgroup analysis showed that the effect of long-term intervention was more significant. This may be because most of the CRP in this inclusion of literature was measured by high sensitivity (hs-CRP). hs-CRP can be used to improve cardiovascular risk assessment (Ridker et al., 2007). In addition, different inclusion criteria for the literature may have had some impact on the results. Studies on the effects of phytosterols on TNF- α and IL-6 levels are limited. In a study of long-term phytosterols supplementation in apolipoprotein E-knockout (Apo E-KO) mice (Groux et al., 1997), reduced TNF- α and IL-6 production was observed. However, no effect of phytosterols supplementation on TNF- α and IL-6 levels was found in the population results we summarized. The anti-inflammatory effects of phytosterols have been demonstrated in a large number of in vitro studies and animal experiments, but not all of the effective effects seen at various experimental levels are equally effective in the clinical setting. It has been reported that phytosterols circulating levels are <1 mg/dL due to its low bioavailability (Chan et al., 2006). This may be one of the reasons why we did not observe a significant effect of phytosterols on TNF- α and IL-6 in the population results. Second, there are currently few population trials evaluating the effects of phytosterols on TNF- α and IL-6, with small sample sizes. In addition, several studies included in the analysis were short-term interventions, which may cause some bias in the results. Therefore, the results should be interpreted with caution, future trials may need to pay more attention to hs-CRP as a biomarker for predicting cardiovascular risk and to be carefully designed.

Circulating oxidized LDL is a useful marker capable of identifying patients at high risk of coronary heart disease (Ehara et al., 2001; Holvoet et al., 2001) and initiating and accelerating atherosclerosis formation (Steinberg, 1997). The fundamental mechanism: modified or oxidized LDL activates TOII-like receptors expressed on macrophages, which in turn triggers the innate immune response and exacerbates plaque inflammation. No OXLDL-C lowering effect of phytosterol intake was found in our study. To our knowledge, we are the first meta-analysis to investigate the effects of plant sterols on OXLDL-C. At present, there are few populations randomized controlled trials studying antioxidant effects, and the sample size is limited, which will affect the results to a certain extent. Second, several of the studies included in the analysis looked at patients receiving statins, which may interfere with the antioxidant effects of phytosterols (De Jong, Plat, Bast, et al., 2008). Therefore, we should interpret the

results with caution and design the study for different populations as much as possible in future studies.

The mechanisms underlying the effects of dietary phytosterols on blood glucose are still unclear. Reports have speculated a possible association with the expression and translocation of glucose transporter 4 in skeletal muscle, liver, and white adipose tissue, which β -sitosterol enhances by stimulating AMPK phosphorylation (Hwang et al., 2008; Kurth-Kraczek et al., 1999; Subash-Babu et al., 2015). The effects of phytosterols on blood glucose have yielded conflicting results in several trials (Becker et al., 2013; Cheung et al., 2017; Li & Xing, 2016). Previous meta-analysis (Salehi-Sahlabadi et al., 2020) also investigated the effect of phytosterols on blood glucose and HbA1c and found no significant effect, which is consistent with the results obtained by us. Possible reasons are as follows: (1) The intervention cycles of the included studies were basically consistent, and almost all were short-term interventions. It has been reported that a medium dose applied for a longer period of time can lead to higher levels and better effects of phytosterols (Calpe-Berdiel et al., 2009; Patel & Thompson, 2006). (2) The characteristics of the population included in the study were mostly hypercholesterolemia, not diabetes, which may affect the hypoglycemic effect of phytosterols to a certain extent. Although this study did not find the hypoglycemic effect of plant sterols, it can provide reference value for future research. For example, conducting long-term intervention studies and conducting trials for specific populations.

In this meta-analysis, no effect of dietary intake of phytosterols was found on BMI, WC, and Weight, which are closely related to diseases such as hyperlipidemia, obesity, and metabolic syndrome. Related in vitro studies have mentioned that plant sterols can stimulate the AMPK pathway, and AMPK activators are effective candidates for the treatment of these diseases (Drynan et al., 1996; Hardie & Hawley, 2001; Merrill et al., 1997). There is currently no literature proposing the exact mechanism of the effects of phytosterols on anthropometric indices, and there are contradictions regarding the effects of phytosterols on anthropometric indices. Our results are contradicted by a previous meta-analysis that suggested that phytosterols have a BMI lowering effect (Ghaedi et al., 2019). May have something to do with the differences between the studies we included. For example, the population we covered included both healthy and unhealthy people, whereas previous meta-analyses targeted overweight, obese subjects. The use of different forms of phytosterols in combination with other foods during the experiment, as well as the size of the sample, will have different degrees of influence on the results. In our conclusion, phytosterols supplements also did not affect body weight and WC. We found that the number of current studies evaluating these effects was small, the sample size was small, and the studies were very similar in terms of intervention duration and intervention dose (mostly less than 12 weeks or less than 2 g), which we suspect may be related to these factors. In the future, the relevant study design needs to be further refined, such as setting different doses and different intervention times, in order to better explore the effects of phytosterols on body weight and WC.

4.2 | Potential sources of bias and strategies to reduce bias

Potential sources of bias in this study are as follows: (1) We only included relevant published studies and only included English literature. (2) The sample size of some included studies was small. (3) Some studies did not report non-significant data. In response to any possible bias, we have taken the following steps to improve the reliability and interpretability of our results: (1) We have developed a rigorous search strategy with comprehensive searches across multiple databases. We also manually searched and screened reference lists from reviews and meta-analyses to ensure the comprehensiveness and rigor of the literature we included. (2) We have prospectively registered a research protocol with PROSPERO, which specifies the purpose and methods of this study to reduce reporting bias. (3) The process of literature screening and data extraction was carried out by two independent researchers. When disagreements arise, they are resolved through discussion by a third researcher, which can reduce selection bias and measurement bias in the analysis. (4) We also conducted sensitivity analyses to ensure the robustness of the study results. (5) We used the Cochrane Collaboration Bias Risk tool to assess the quality of included randomized controlled trials.

4.3 | Strengths and limitations of the study

Systematic reviews and meta-analyses represent the highest rung in the hierarchy of clinical evidence (Izzo et al., 2016). It is worth mentioning that our research has significant advantages. First, we present the most comprehensive synthesis of evidence to date on the effects of phytosterols supplementation on cardiovascular risk factors and include recent studies on the effects of phytosterols on cardiovascular risk factors. Second, the included studies included healthy and non-healthy participants, which enhances the applicability and relevance of our findings and enhances the generality of our findings. Finally, the study design was conducted in accordance with Cochrane correlation and PRISMA, which ensured the normativity of the study. Still, some limitations of the study must be acknowledged. First, some of the included studies had small sample sizes and low-quality evidence, which may affect reliability, and further high-quality studies are needed to firmly determine the clinical efficacy of phytosterols. Second, confounding factors between different studies cannot be controlled. For example, the study included populations that were not entirely consistent in terms of age, sex, genetics, and ethnicity, which may have influenced the results to some extent. Finally, most of the interventions included in the studies were short duration, which may limit the assessment of the long-term effects of phytosterols intake on cardiovascular risk factors.

4.4 | Implications of study and expectation

Over the past 30 years, the rising incidence of CVD has become a public health priority. There is a lack of studies exploring endpoints such as CVD events and mortality to obtain direct evidence of the effect of

phytosterols on CVD. However, its effect on cardiovascular risk factors has aroused public health and clinical practice concerns. This is despite strong evidence that a large number of foods, nutrients, bioactive compounds and dietary antioxidants may have potential health benefits on cardiovascular risk factors or directly on the development of CVD. However, the effect of phytosterols on cardiovascular risk factors remains controversial. It is worth mentioning that in the joint ESC/EAS guidelines, individuals with high cholesterol levels at moderate and low cardiovascular risk are recommended; Supplementation of 2 g phytosterols in patients who do not qualify for drug therapy, in high and very high-risk patients who fail to meet LDL-C targets on the basis of drug therapy or are unable to receive statins, and in individuals with familial hypercholesterolemia. Phytosterols may also be valuable from a clinical perspective, which could provide a non-drug treatment option for clinical practice. But due to the lack of strict regulation, the need for nutraceutical manufacturers to demonstrate the efficacy, safety and quality of marketed products has not been strongly enforced in the pharmaceutical sector. Many available products may not work (Williamson et al., 2020). Therefore, clinicians should be cautious when using phytosterols supplements to manage cardiovascular-related diseases. Based on the results of this study, plant sterols can effectively reduce the levels of TC, LDL-C, TG, CRP, SBP, and DBP in serum, and public health institutions can consider including phytosterols in dietary recommendations, especially for people with high cholesterol. In addition, in future population trials, researchers should conduct more long-term intervention trials to comprehensively evaluate the long-term effects of phytosterols on cardiovascular risk factors. Secondly, increasing the sample size can improve the research quality and reduce the bias to a certain extent. Finally, future studies should consider the effects of phytosterols on cardiovascular risk factors as fully as possible, focusing on inflammation, oxidative stress, and anthropometric indicators.

5 | CONCLUSION

In conclusion, phytosterol supplements were shown to reduce serum TC, serum TG, serum LDL-C, serum CRP, SBP, and DBP levels, but had no effect on serum TNF- α , serum IL-6, serum OXLDL-C, GLU, HbA1c, BMI, WC, and Weight. This suggests that phytosterols can promote lipid health, ameliorate inflammation, regulate blood pressure, and provide insights into the prevention of CVD. Future studies may consider exploring the mechanisms of action of phytosterols to improve relevant indicators in patients with CVD.

AUTHOR CONTRIBUTIONS

Yanhong Yang: Data curation; formal analysis; visualization; writing – original draft; writing – review and editing. **Jiayue Xia:** Conceptualization; methodology; writing – review and editing. **Tingqing Yu:** Data curation; validation. **Shiyun Wan:** Data curation. **Yajie Zhou:** Supervision. **Guiju Sun:** Funding acquisition; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

Data Availability Statement

All data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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