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Review Article

Effect of Low Protein Diet on Patients with Cardiovascular Disease: A Systematic Review and Meta-Analysis

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Abstract

Background: Low protein diet plays an important role in cardiovascular diseases. However, exact role is unclear so far. We aimed to find out the effect of low protein diet on patients with cardiovascular disease.

Methods: The PRISMA guidelines were followed throughout the research project until 10th Apr 2023. MeSH phrases and Boolean operators were used to search PubMed for suitable studies. The entire estimate was expressed as a 95% confidence interval around the mean difference. The model was picked because of the discrepancies found in the research. Choi's Q test and I^2 statistics were used to determine the degree of variation between experiments. The funnel plot was used to qualitatively examine the publishing bias.

Results: Low-protein diets have a greater impact on waist circumference [-8.82 (-9.51, -8.13), P<0000.1] and high-density lipoprotein (HDL) [-0.05 (-0.07, -0.03), *P*<0000.1] alteration than non-LPD diets, as measured by the standard mean difference (SMD). Further, significant changes were observed in weight loss [1.51 (1.25, 1.77), *P*<0.00001], BMI, [0.46 (0.25, 0.67), *P*<0.0001], change systolic [2.48 (1.20, 3.77), *P*=0.0002] and diastolic blood pressure [1.49 (0.72, 2.26), *P*=0.0002], low density lipoprotein [0.09 (0.06, 0.12), *P*<0.00001], triglyceride [0.52 (0.49, 0.55), *P*<0.00001], in non-LPD group as compared to LPD group.

Conclusion: The results indicated the role of low protein diet on patients with cardiovascular disease.

Keywords: Low protein diet; Cardiovascular diseases; Systematic review; Meta-analysis; Blood pressure; High-density lipoprotein (HDL)

Introduction

Diet has recently been recognized as a useful measure in avoiding the onset or progression of cardiovascular illnesses (1). In animals, dietary proteins are required for the formation of all amino acids, hence appropriate protein consumption is critical (2).The minimum recommended dietary allowance (RDA) for protein in the general population is 0.8 g/kg of body weight, regardless of age or gender (3). Patients with cardiovascular illnesses, on the other hand, may benefit from a higher protein intake since they have a higher protein need due to anabolic resistance and lower muscle perfusion. Nonetheless, due to physical impairments, socioeconomic constraints, and comorbidities, they frequently consume less protein. This disparity in demand and supply may

worsen the clinical outcomes of individuals suffering from cardiovascular illnesses (4-9).

The effects of a very low carbohydrate diet on body composition and cardiovascular risk factors were also studied in a randomised controlled trial. Results from a randomised controlled trials suggest that very low carbohydrate diets are more effective than low-fat diets for rapid weight loss (10). The mechanism of low protein diets on cardiovascular diseases is unclear so far. A low-protein diet raises energy intake and expenditure at the same time. Hyperphagia brought on by a low-protein diet may be mediated by elevated levels of ghrelin and fibroblast growth factor-21 (FGF21) in the bloodstream as well as hypothalamic neuropeptide Y (NPY) expression.

Abete et al. evaluated the impact of four low-calorie diets, each with a distinct dietary distribution or high protein content, on the metabolic alterations and mitochondrial oxidation that accompany weight reduction. The use of legumes or foods with a high protein content within a diet low in calories could activate mitochondrial oxidation, which could involve additional benefits in addition to those related with weight loss (11). According to the findings of the research, an increase in the consumption of whey protein did not result in a statistically significant change in the amount of weight lost or total fat reduction (12). People who suffer from cardiovascular disease do not yet have a clear picture of what the long-term repercussions of a diet low in protein will be.

Therefore, to investigate the effect of a low protein diet on cardiovascular illnesses, we did a comprehensive review and meta-analysis of randomised controlled trials (RCTs).

Methods

Search strategy

This study followed the PRISMA [Preferred Reporting Items for Systematic Review and Meta-analysis] guidelines. A thorough systematic search in PubMed was carried out utilising Medical Subject Headings (MeSH) and Boolean operators since from inception to 30th Apr 2023.

Study selection

The PICOS was considered as: Patients: Cardiovascular diseases; Intervention: low protein diet; Comparator: non-low protein diet, Outcomes: weight, body mass index (BMI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels, systolic blood pressure (SBP), and diastolic blood pressure (DBP). The food and anti-oxidants supplements and physical activity were considered as confounders. Following the exclusion of duplicate publications, two writers independently assessed study titles, abstracts, or full text to identify relevant articles. Finally, original papers were considered for inclusion in the current meta-analysis if they met the following criteria: 1) were randomized clinical trials studies; 2) administered diet as an intervention 3) enrolled adult participants (Age 18 yr and older); and 4) reported a variety of risk factors for cardiovascular disease, including weight, body mass index (BMI), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) levels, systolic blood pressure (SBP), and diastolic blood pressure (DBP). Studies that did not include a suitable comparator group were not included since they did not meet the requirements. Case reports, animal studies, review papers, and meta-analyses that had already been published were not considered.

Data extraction

MD assessed the data, and any differences were handled by LL. Researchers extracted data on the study's author, publication year, country, number of case and placebo groups, participants' gender, mean age (year), mean body mass index, diabetes type, diabetes duration, protein intake in the intervention and control groups, clinical trial design, and means and standard deviations (SD) of various cardiovascular disease factors.

Quality assessment

MD checked for the possibility of bias using the Cochrane Risk of Bias Tool for Randomised Controlled Trials. Random sequence generation adequacy, allocation concealment, blinding, identification of missing outcome data, selective outcome reporting, and other potential sources of bias were all taken into account by the quality assessment method. Each domain's risk of bias was rated as "Low," "High," or "Unclear" according to criteria laid out in the Cochrane Handbook. Any discrepancies in the data extraction or assessment of the possibility of bias were settled by a LL.

Statistical analysis

RevMan V.5.3 software was used for the statistical analysis. The overall estimate was computed as a mean difference with a 95% confidence range. The model was chosen based on differences across research. The Chochrane Q test and I^2 statistics were used to calculate study heterogeneity. The funnel plot was used to examine the publishing bias subjectively.

Results

A flowchart of the research selection procedure including exclusion criteria (Fig. 1).

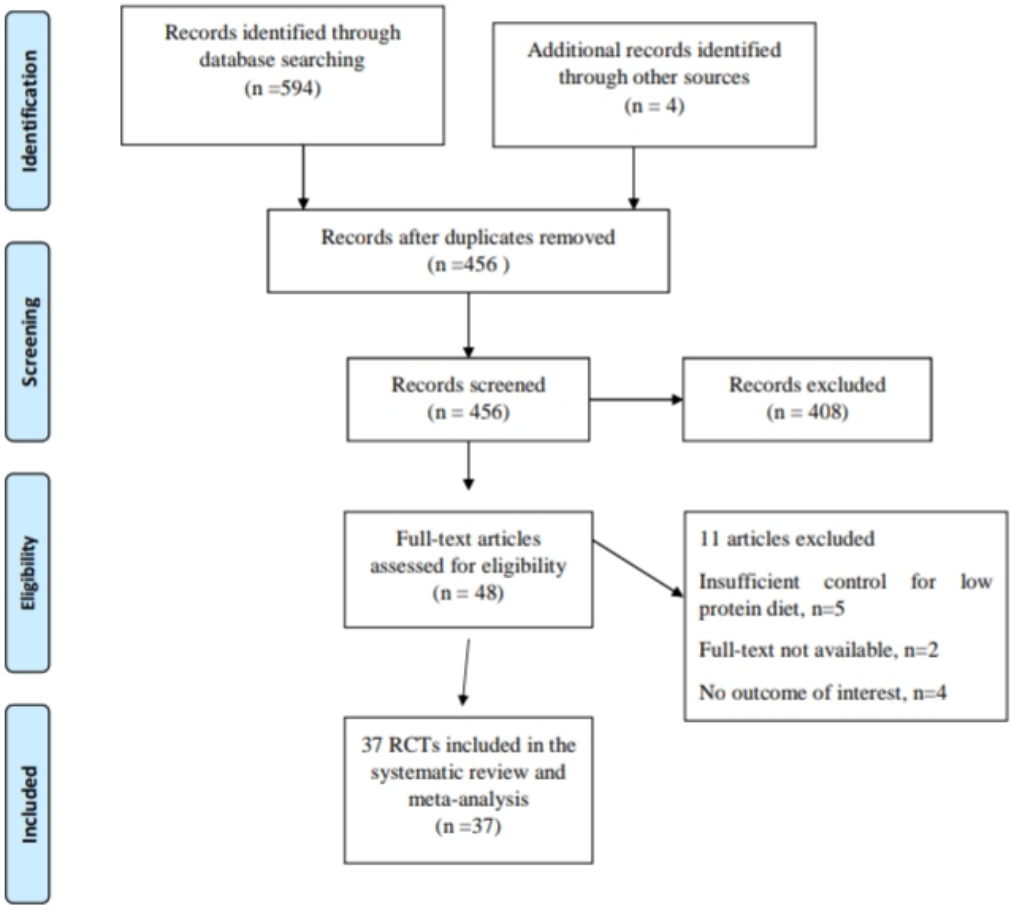


Fig. 1: Flowchart of the process of the study selection.

This figure contains 594 publications obtained from the aforementioned electronic databases. After removing duplicate studies, 456 papers remained. These publications were then reviewed by study title/abstract, with 408 articles being rejected because they did not fit the inclusion criteria. During the secondary screening, full-text retrieval yielded 48 publications. Eleven of those experiments were abandoned for various reasons. Overall, 36 research (12-47) investigating the effect of a low protein diet on patients with cardiovascular disease were judged to be relevant for the meta-analysis. Fig. 1 depicts the study selection as a PRISMA flow chart.

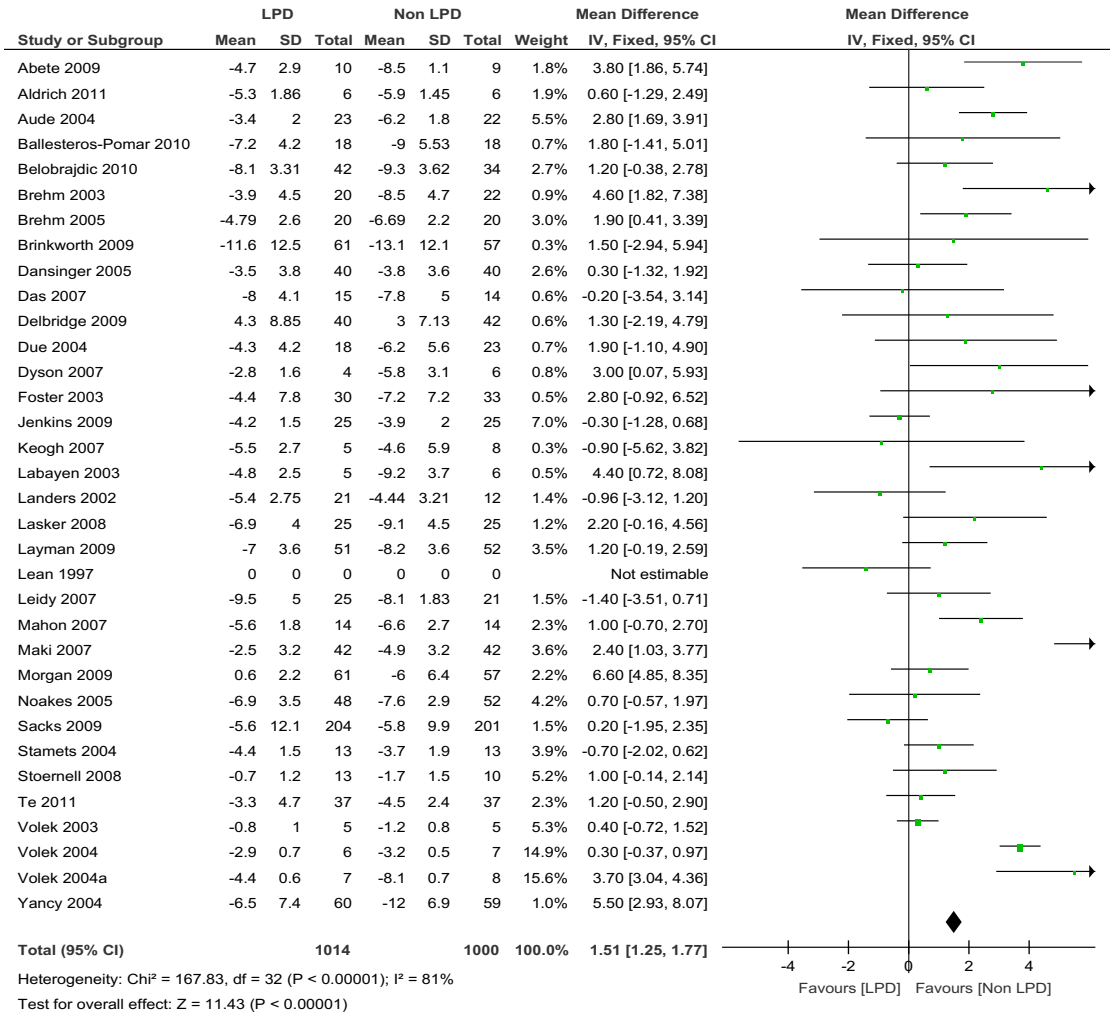
Study characteristics

The characteristics of included studies were compiled in Table 1 (Supplementary material).

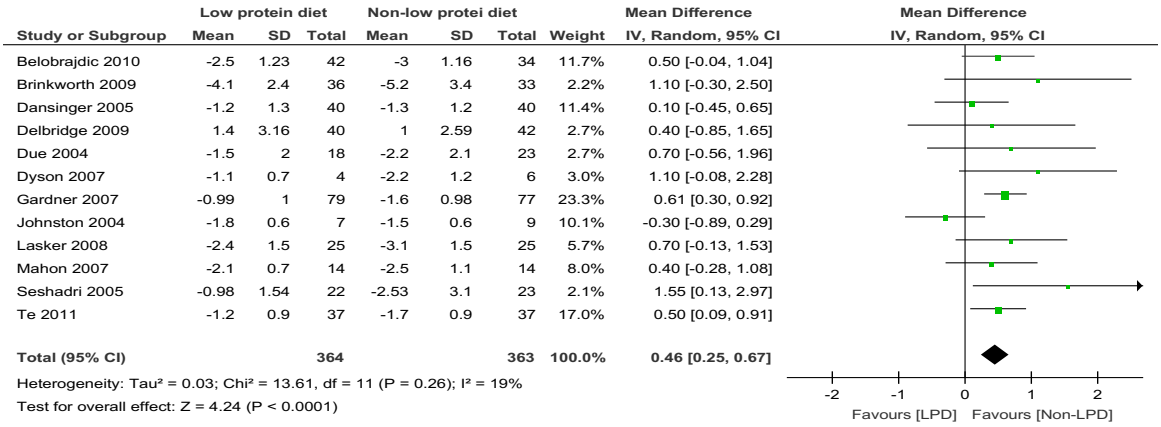
Meta-analysis

Effect of low protein diet on Weight loss

The overall estimate measure in terms of standard mean difference was found to be 1.51 [1.25, 1.77] which indicate significant effect of non-low protein diet on the weight loss as compared to low protein diet as shown in Fig. 2a. The heterogeneity among studies was found to be 81% as indicated by I^2 statistics. The symmetrical shape of funnel plot indicated a less involvement of publication bias (Fig. S1).



a)



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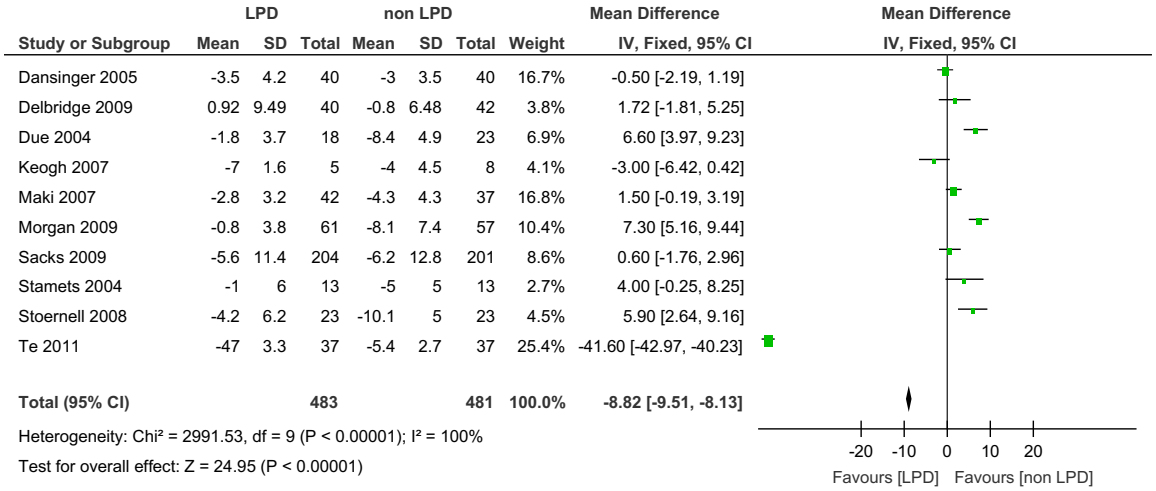


c)

Fig. 2: Forest plot showing effects of low protein diet (LPD) as compared to non-low protein diet on a) weight loss b) BMI c) Waist circumference

Effect of low protein diet on Body Mass Index (BMI)

The overall standard mean difference (SMD) was found to be 0.46 [0.25, 0.67] which indicates significant effect of non-LPD on BMI as compared to the LPD group (Fig. 2b). The heterogeneity among studies was found to be 19%. There is a involvement of publication bias as indicated by funnel plot (Fig. S2).

Waist circumference

The overall estimate measure in terms of standard mean difference was found to be -8.82 [-9.51, -8.13] which indicate significant effect of low protein diet on the waist circumference as compared to non-LPD (Fig. 2c). However, the heterogeneity among studies was found to be very high as indicated by I^2 statistics. Fig. S3 indicated a involvement of publication bias.

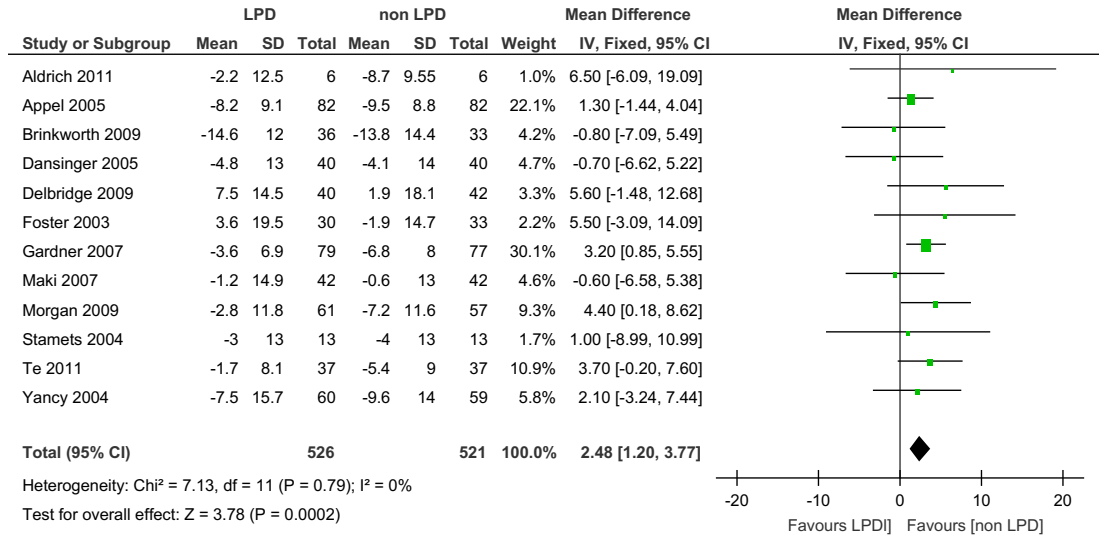
Change in systolic blood pressure

The effect of low protein diet on change in blood pressure was also checked. The overall estimate was found to be 2.48 [1.20, 3.77] which indicates significant change in systolic blood pressure in non-LPD group as compared to LPD group as

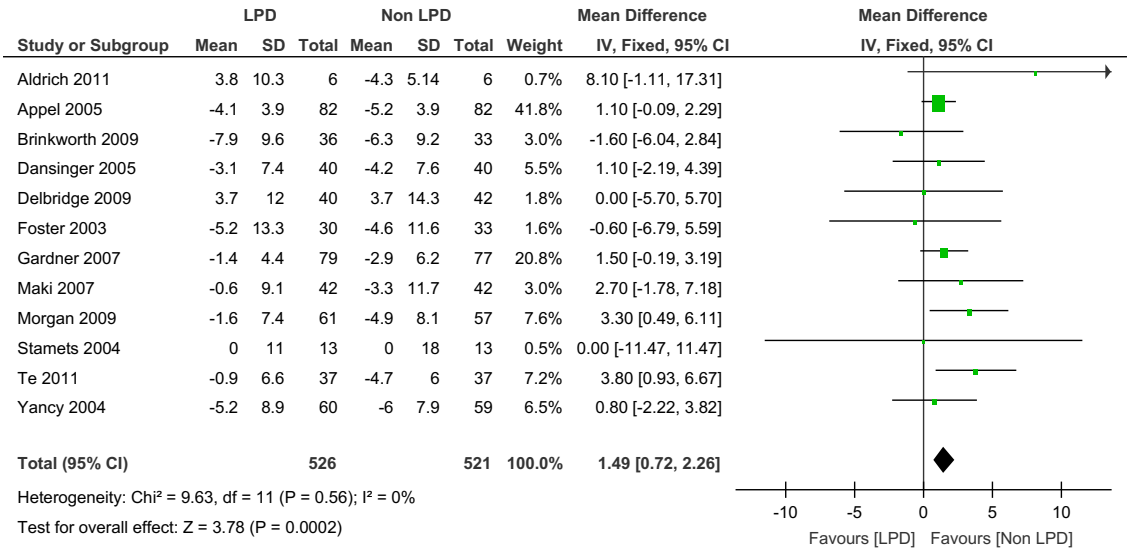
shown in Fig. 3a. There is a involvement of publication bias (Fig. S4).

Change in diastolic blood pressure

The overall estimate measure in terms of standard mean difference was found to be 1.49[0.72, 2.26] which indicate significant effect of non-LPD as compared to LPD on change in diastolic blood pressure. Further, no heterogeneity among studies was found (Fig. 3b) and less involvement of publication bias (Fig. S5).



a)



b)

Fig. 3: Forest plot showing effects of low protein diet (LPD) as compared to non-low protein diet on a) change in systolic blood pressure b) Change in diastolic blood pressure

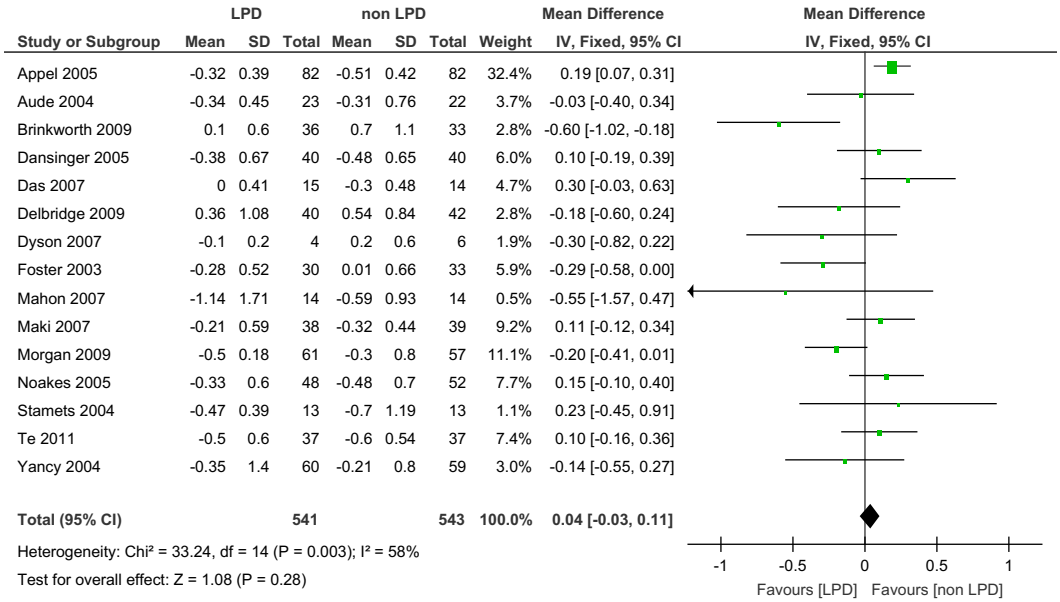
Change in total cholesterol

The overall estimate measure in terms of standard mean difference was found to be 0.04 [-0.03, 0.11] which indicate non-significant effect of low protein diet on change in total cholesterol. The heterogeneity among studies was found to be

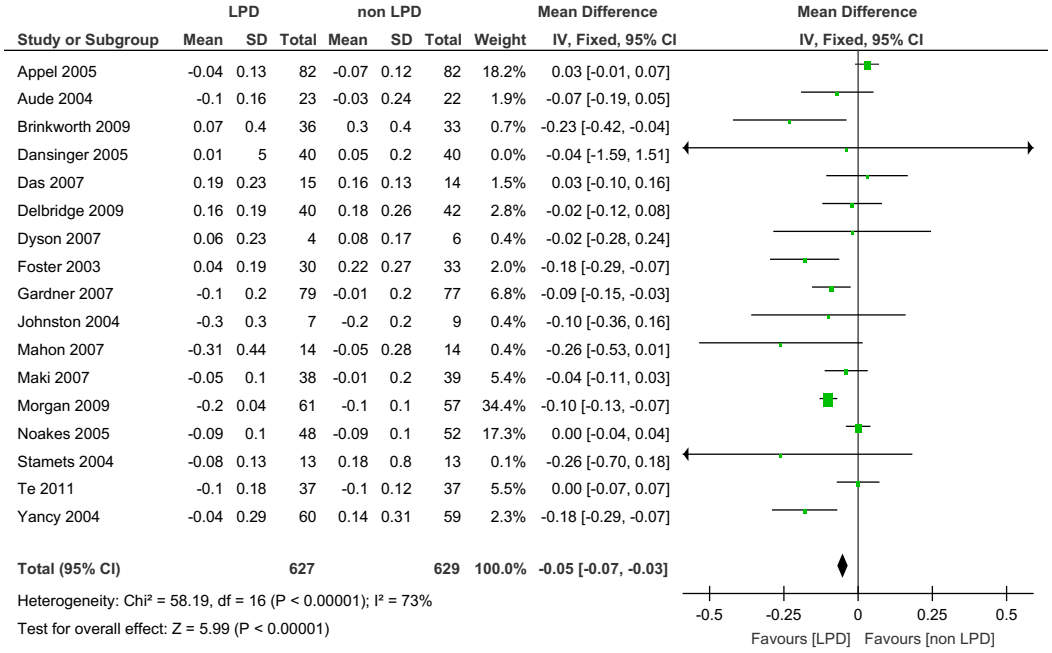
58% as indicated by I^2 statistics (Fig. 4a). Fig. S6 represents somewhat symmetrical shape of funnel plot which indicated less involvement of publication bias.

Change in high density lipoprotein

The overall estimate measure in terms of standard mean difference was found to be -0.05[-0.07, -0.03] which indicate significant effect of low protein diet on change in high density lipoprotein. The heterogeneity among studies was found to be 73% as indicated by I^2 statistics (Fig. 4b). The funnel plot has indicated high involvement of publication bias (Fig. S7).



a)

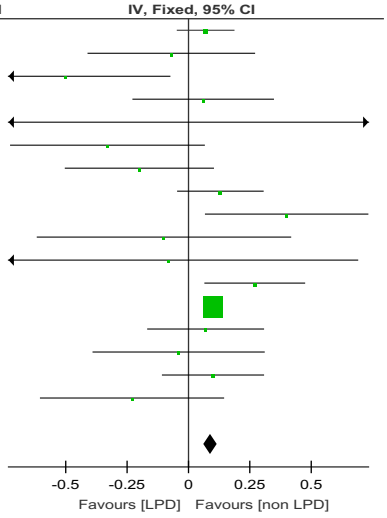


b)

Study or Subgroup	LPD Mean	LPD SD	LPD Total	non LPD Mean	non LPD SD	non LPD Total	Weight	Mean Difference IV, Fixed, 95% CI
Appel 2005	-0.3	0.36	82	-0.37	0.39	82	6.4%	0.07 [-0.04, 0.18]
Aude 2004	-0.17	0.4	23	-0.1	0.71	22	0.7%	-0.07 [-0.41, 0.27]
Brinkworth 2009	0.1	0.6	36	0.6	1.1	33	0.5%	-0.50 [-0.92, -0.08]
Dansinger 2005	0.31	0.6	40	0.25	0.7	40	1.0%	0.06 [-0.23, 0.35]
Delbridge 2009	-1.4	9.49	40	0.33	0.58	42	0.0%	-1.73 [-4.68, 1.22]
Dyson 2007	-0.17	0.21	4	0.16	0.42	6	0.5%	-0.33 [-0.72, 0.06]
Foster 2003	-0.18	0.5	30	0.02	0.71	33	0.9%	-0.20 [-0.50, 0.10]
Gardner 2007	0.19	0.5	79	0.06	0.6	77	2.8%	0.13 [-0.04, 0.30]
Jenkins 2009	-0.5	0.57	25	-0.9	0.62	25	0.8%	0.40 [0.07, 0.73]
Johnston 2004	-0.4	0.6	7	-0.3	0.4	9	0.3%	-0.10 [-0.62, 0.42]
Mahon 2007	-0.52	1.29	14	-0.44	0.7	14	0.1%	-0.08 [-0.85, 0.69]
Maki 2007	0.09	0.5	38	-0.18	0.4	39	2.1%	0.27 [0.07, 0.47]
Morgan 2009	-0.1	0.08	61	-0.2	0.1	57	78.8%	0.10 [0.07, 0.13]
Noakes 2005	-0.19	0.6	48	-0.26	0.6	52	1.5%	0.07 [-0.17, 0.31]
Stamets 2004	0.3	0.4	13	0.34	0.5	13	0.7%	-0.04 [-0.39, 0.31]
Te 2011	-0.3	0.48	37	-0.4	0.42	37	2.0%	0.10 [-0.11, 0.31]
Yancy 2004	-0.19	1.1	60	0.04	0.97	59	0.6%	-0.23 [-0.60, 0.14]
Total (95% CI)			**637**			**640**	**100.0%**	**0.09 [0.06, 0.12]**

Heterogeneity: Chi² = 28.96, df = 16 (P = 0.02); I² = 45%

Test for overall effect: Z = 6.09 (P < 0.00001)



c)

Fig. 4: Forest plot showing effects of low protein diet (LPD) as compared to non-low protein diet on a) Change in total cholesterol. b) high density lipoprotein c) change in low density lipoprotein

Change in low density lipoprotein

The overall estimate measure in terms of standard mean difference was found to be 0.09 [0.06, 0.12] which indicate significant effect of non-low protein diet on change in low density lipoprotein. The heterogeneity among studies was found to be 45% as indicated by I^2 statistics (Fig. 4c). The funnel plot has indicated high involvement of publication bias (Fig. S8).

Change in C-reactive protein

The overall estimate measure in terms of standard mean difference was found to be 0.20 [-0.25, 0.64] non-which indicate significant effect of low protein diet on change in CRP. The heterogeneity among studies was found to be 1% as indicated by I^2 statistics (Fig. 5a). Publication bias was not assessed due to availability of limited number of studies.

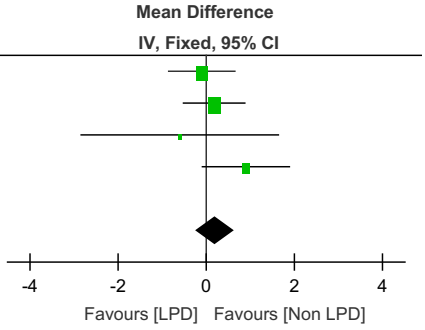
Changes in Triglyceride

The significant change in triglyceride was found in non-LPD as compared to LPD group as indicated by overall mean difference i.e. 0.52 [0.49, 0.55] (Fig. 5a). However, very high heterogeneity among studies was observed (Fig. 5b). Fig. S9 represents asymmetrical shape of funnel plot which indicated involvement of publication bias.

Study or Subgroup	LPD Mean	LPD SD	LPD Total	Non LPD Mean	Non LPD SD	Non LPD Total	Weight	Mean Difference IV, Fixed, 95% CI
Brinkworth 2009	-1.4	1.8	30	-1.3	1.1	31	35.0%	-0.10 [-0.85, 0.65]
Dansinger 2005	-0.04	1.2	40	-0.22	1.9	40	40.8%	0.18 [-0.52, 0.88]
Mahon 2007	-0.6	4	14	0	1.5	14	3.9%	-0.60 [-2.84, 1.64]
Noakes 2005	-0.8	2.1	48	-1.7	2.9	52	20.3%	0.90 [-0.09, 1.89]
Total (95% CI)			**132**			**137**	**100.0%**	**0.20 [-0.25, 0.64]**

Heterogeneity: Chi² = 3.04, df = 3 (P = 0.39); I² = 1%

Test for overall effect: Z = 0.87 (P = 0.38)

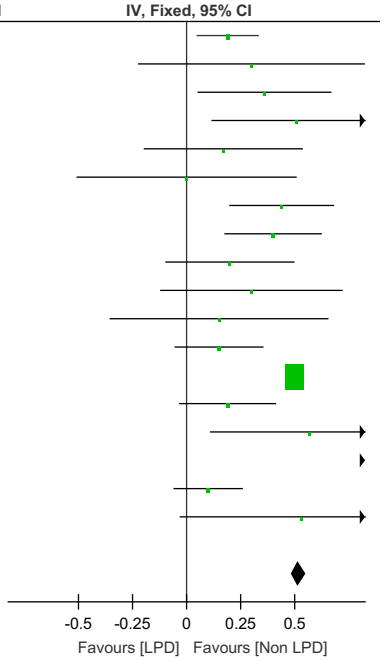


a)

Study or Subgroup	LPD Mean	LPD SD	LPD Total	Non LPD Mean	Non LPD SD	Non LPD Total	Weight	Mean Difference IV, Fixed, 95% CI
Appel 2005	0	0.45	82	-0.19	0.47	82	5.0%	0.19 [0.05, 0.33]
Aude 2004	-0.17	0.52	23	-0.47	1.14	22	0.4%	0.30 [-0.22, 0.82]
Brinkworth 2009	-0.22	0.7	36	-0.58	0.6	33	1.1%	0.36 [0.05, 0.67]
Dansinger 2005	-0.1	0.4	40	-0.61	1.2	40	0.6%	0.51 [0.12, 0.90]
Delbridge 2009	0.3	0.7	40	0.13	0.97	42	0.7%	0.17 [-0.19, 0.53]
Dyson 2007	-0.1	0.4	4	-0.1	0.4	6	0.4%	0.00 [-0.51, 0.51]
Foster 2003	0.02	0.58	30	-0.42	0.35	33	1.7%	0.44 [0.20, 0.68]
Gardner 2007	-0.19	0.6	79	-0.59	0.8	77	2.0%	0.40 [0.18, 0.62]
Jenkins 2009	-0.4	0.47	25	-0.6	0.59	25	1.1%	0.20 [-0.10, 0.50]
Johnston 2004	0.1	0.5	7	-0.2	0.3	9	0.6%	0.30 [-0.12, 0.72]
Mahon 2007	-0.11	0.78	14	-0.26	0.56	14	0.4%	0.15 [-0.35, 0.65]
Maki 2007	-0.13	0.5	38	-0.28	0.4	39	2.4%	0.15 [-0.05, 0.35]
Morgan 2009	-0.1	0.1	61	-0.6	0.1	57	76.4%	0.50 [0.46, 0.54]
Noakes 2005	-0.11	0.4	48	-0.3	0.7	52	2.0%	0.19 [-0.03, 0.41]
Seshadri 2005	0.05	0.5	22	-0.52	1	23	0.5%	0.57 [0.11, 1.03]
Stamets 2004	-0.23	0.6	13	-33	1	13	0.2%	32.77 [32.14, 33.40]
Te 2011	-0.2	0.33	37	-0.3	0.36	37	4.0%	0.10 [-0.06, 0.26]
Yancy 2004	-0.31	1.1	60	-0.84	1.9	59	0.3%	0.53 [-0.03, 1.09]
Total (95% CI)			**659**			**663**	**100.0%**	**0.52 [0.49, 0.55]**

Heterogeneity: Chi² = 10031.31, df = 17 (P < 0.00001); I² = 100%

Test for overall effect: Z = 32.20 (P < 0.00001)



b)

Fig. 5: Forest plot showing effects of low protein diet (LPD) as compared to non-low protein diet on a) Change in CRP b) change in triglyceride

Discussion

Heart disease is the leading killer worldwide. In 2019, CVDs were responsible for an estimated 32.5% of all deaths worldwide, or 17.9 million people. It is anticipated that cardiovascular diseases claimed the lives of 17.9 million people worldwide in 2019, making up 32% of all deaths (48). The majority of these deaths (85%) were caused by cardiovascular events such heart attacks and strokes. The vast majority of cardiovascular diseases can be avoided by addressing behavioural risk factors such as smoking, eating a bad diet, being overweight, not being physically active enough, and drinking too much alcohol. In the present investigation, we conducted a thorough literature search and meta-analysis to investigate whether or not a low-protein diet is associated with an increased risk of cardiovascular disease. Sohouli et al. have conducted a systematic review and meta-analysis of randomized-controlled trials evaluating the influence of low protein and high protein diets on cardiovascular risk factors and kidney function in diabetic nephropathy. These researchers looked at the trials to determine which diet was more beneficial. Urine urea and HbA1c levels both dropped noticeably when participants switched to a diet that contained much less protein (49). Zhu et al. carried out an exhaustive analysis of randomised controlled trials in order to assess whether or not a low-protein diet is effective in the treatment of diabetic nephropathy. A diet reduced in protein does not appear to be associated with an improvement in renal function in individuals who have type 1 or type 2 diabetic nephropathy (50). A systematic review and meta-analysis of controlled trials using GRADE to investigate the effect of the Portfolio dietary pattern on the primary therapeutic lipid target for the prevention of cardiovascular disease, low-density lipoprotein cholesterol (LDL-C), as well as other well-

established cardiometabolic risk factors. According to the findings of the study, following the portfolio dietary pattern can lead to clinically significant changes in LDL-C levels, in addition to other well-established cardiometabolic risk factors and an estimated 10-year increase in the risk of developing CHD (51). Schwingshackl et al. have carried out a network meta-analysis in addition to a systematic review in order to examine the impact of various dietary approaches on blood pressure in individuals who are hypertensive or are at risk of developing hypertension. The Dietary Approaches to Stop Hypertension (DASH) may be the most effective dietary approach for lowering blood pressure in hypertensive and pre-hypertensive patients based on data of a high quality (52).

The term "heterogeneity" describes the variations in study findings among investigations. Being heterogeneous just means that your data is variable, which is nothing to be afraid about (53-56). The findings of this research have also demonstrated the existence of heterogeneity among studies. A funnel plot is typically utilised in order to conduct a qualitative analysis of publication bias (57), which is yet another essential factor to investigate. The findings of the most recent inquiry have pointed to the possible role of publication bias.

The studies published in English language are only considered. Further, the only one database i.e. PubMed was searched for relevant studies. The heterogeneity among studies was found to be a little bit high.

Conclusion

The results of the current study have indicated the beneficial effects of low protein diet on cardiovascular disorders. It is advised that further research be conducted in order to throw light on these findings.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Conflict of interest

The authors declare that there is no conflict of interests.

Data availability

All supplementary data not published here will be sent to the respected readers for reasonable application. Please contact the corresponding author.

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