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Effects of a healthy diet enriched or not with pecan nuts or extra-virgin olive oil on the lipid profile of patients with stable coronary artery disease: a randomised clinical trial

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Keywords

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Abstract

Background: The present study aimed to assess the effect of a healthy diet, enriched or not with pecan nuts or extra-virgin olive oil, on the lipid profile of patients with stable coronary artery disease (CAD).

Methods: This was a randomised clinical trial conducted for 12 weeks with patients aged between 40 and 80 years with stable CAD for more than 60 days. Individuals were randomised into groups [control group (CG) with 67 patients, pecan nut group (PNG) with 68 patients and olive oil group (OOG) with 69 patients]. The CG was prescribed a healthy diet according to the nutritional guidelines; the PNG was prescribed the same healthy diet plus 30 g day⁻¹ of pecan nuts; and the OOG was prescribed a healthy diet plus 30 mL day⁻¹ of extra-virgin olive oil.

Results: In total, 204 subjects were submitted to an intention-to-treat analysis. After adjustment for baseline values and type of statin used, there was no difference regarding low-density lipoprotein (LDL)-cholesterol (primary outcome), high-density lipoprotein (HDL)-cholesterol, LDL-cholesterol/HDL-cholesterol ratio and HDL-cholesterol/triglycerides ratio according to groups. However, the PNG exhibited a significant reduction in non-HDL-c-cholesterol levels [PNG: 114.9 (31) mg dL⁻¹; CG: 127 (33.6) mg dL⁻¹; OOG: 126.6 (37.4) mg dL⁻¹; $P = 0.033$] and in the total cholesterol/HDL-c-cholesterol ratio [PNG: 3.7 (0.7); CG: 4.0 (0.8); OOG: 4.0 (0.8); $P = 0.044$] compared to the CG and OOG.

Conclusions: Supplementing a healthy diet with 30 g day⁻¹ of pecan nuts for 12 weeks did not improve LDL-cholesterol levels but may improve other lipid profile markers in patients with stable CAD.

Introduction

Atherosclerosis is an underlying mechanism of coronary artery disease (CAD) and stems from a multifactorial process that results in the thickening and reduced elasticity of the artery, and eventually in arterial stenosis⁽¹⁾. Because the atherosclerotic process is associated with abnormal serum levels of atherogenic lipids or lipoproteins,

dyslipidaemia contributes considerably to the increased risk of CAD⁽²⁾, which is considered as the leading cause of cardiovascular disease health lost globally^(3,4).

Among the modifiable risk factors that have an influence on the different aspects of the atherosclerotic process are an unhealthy diet, a sedentary lifestyle and excess body mass⁽⁵⁾. Adherence to a healthy diet is considered to be a crucial step in the promotion of cardiovascular

health, and the Mediterranean diet is one of the most prominent healthy diets, primarily as a result of two of its classic components: nuts and extra-virgin olive oil ⁽⁶⁾.

The biological activities related to the cardioprotective effect of consuming nuts and extra-virgin olive oil have been mainly attributed to the unsaturated fatty acid (UFA) composition and phytochemical compounds in these foods, especially polyphenols ^(7–9). UFAs and polyphenols are considered to be involved in the modulation of atherogenesis as a result of their anti-inflammatory, antioxidant ^(10,11) and transcriptomic effects ⁽¹²⁾.

The ingestion of nuts and olive oil has been associated with improvements in lipid and lipoprotein levels ^(7,13). However, these results have typically been derived from the context of the Mediterranean diet, which is not an easily available dietary pattern in all regions of the world. Furthermore, most of the studies that have evaluated the cardioprotective effect of nuts and olive oil are aimed at primary prevention ^(7,13–16). Few clinical studies have been conducted in patients with CAD ^(17–21), in different populations, and using different types and amounts of nuts and olive oil.

Thus, the present study aimed to assess the effect of a locally available healthy diet according to Brazilian guidelines, which was enriched or not with nuts or extra-virgin olive oil, on the lipid profile of patients with stable CAD. We decided to use pecan nuts because they are grown regionally and because their potentially cardioprotective effects ⁽²²⁾ have been rarely explored ^(23–25).

Materials and methods

Study design and ethical approvals

The present work comprises a subanalysis of the GENU-TRI study. The protocol of this study has been reported elsewhere ⁽²⁶⁾. Briefly, this was a pragmatic parallel single-centre randomised clinical trial with a 1:1:1 allocation ratio and a duration of 12 weeks, performed in a tertiary cardiology referral hospital (Porto Alegre, Brazil). Participants were recruited from the Hemodynamics Service of the institution and via a public notice.

All procedures of the present study were conducted in agreement with the ethical principles on human research established in the Declaration of Helsinki and in the Guidelines for Good Clinical Practice. Informed consent was obtained from each participant prior to inclusion in the study and after an explanation of all procedures that would be performed. The study protocol was approved by the Research Ethics Committee of the Institute of Cardiology/University Foundation of Cardiology (IC/FUC; protocol number UP 4861.13) and is registered in the ClinicalTrials.gov database under the identification

number NCT02202265. The study was conducted between August 2014 and June 2016.

Study population, randomisation and blinding

Subjects aged between 40 and 80 years old who had been diagnosed with stable CAD more than 60 days prior to the selection were included in the study. The exclusion criteria were: psychiatric diseases, extreme obesity [body mass index (BMI) ≥ 40 kg m⁻²], life expectancy less than 6 months, pregnancy or lactation, renal insufficiency on dialysis, being wheelchair-bound, uncontrolled hypo- or hyperthyroidism, congestive heart failure, the use of dietary supplements, long-term use of anti-inflammatory and immunosuppressive drugs, and participation in other clinical trials.

A randomisation plan with blocks of six individuals was generated with an online tool (www.randomization.com). Sequences were generated by a computer and then placed into sealed opaque envelopes that were serially numbered. After a cardiologist confirmed the eligibility criteria and the participants signed the informed consent form, independent researchers randomly allocated them into one of the three study groups according to the following randomisation plan: group 1, control diet (CG, control group); group 2, diet supplemented with 30 g day⁻¹ of pecan nuts (PNG, pecan nut group); and group 3, diet supplemented with 30 mL day⁻¹ of extra-virgin olive oil (OOG, olive oil group). Only one researcher, who was not involved in data collection, had access to the randomisation plan. The group each participant was allocated to was known to the participants and the researchers responsible for the consultations, assessments and the attribution of interventions. The team that performed the biochemical and statistical analyses was blinded to the allocation groups.

The procedures of randomisation, allocation, data collection and follow-up took place in the nutrition outpatient unit of the hospital.

Study interventions

All participants received an individualised dietary prescription according to their specific energy requirements, irrespectively of the treatment group that they were in. The distribution of macronutrients (carbohydrates, proteins, total fats, and fatty acids) in the CG diet was determined according to the Brazilian nutritional guidelines in effect at the beginning of the study ⁽²⁶⁾. Table 1 shows the nutritional composition of the diets prescribed to the study groups with the example of a total energy value (TEV) of 2000 kcal day⁻¹. The number of calories was not the same among the study groups. All participants

Table 1 Example of the nutritional composition of a diet prescribed to the study groups

	CG	PNG	OOG
Total energy (kcal)	2000	2198	2238
Carbohydrate (% TE)	53.91	50.20	48.18
Protein (% TE)	20.73	19.27	18.52
Total fat (% TE)	25.36	30.54	33.30
Saturated fatty acids (% TE)	7.03	7.56	8.44
Monounsaturated fatty acids (% TE)	12.63	17.51	18.68
Polyunsaturated fatty acids (% TE)	5.54	5.57	6.01
Dietary cholesterol (mg)	183	183	183
Dietary fibre (g)	32.3	34.4	32.3

% TE, percentage of total energy; CG, control group; OOG, olive oil group; PNG, pecan nut group.

received the same dietary pattern as the CG; however, those of the PNG and OOG added pecan nuts or olive oil, respectively, to their daily diet, with the instruction to not use these supplements as a substitute for other foods.

In addition to the dietary prescription, the PNG received 1 kg of vacuum-packed pecan nuts for 30 days of treatment (approximately 900 g, considering a daily consumption of 30 g) with instructions on product storage and preservation. To ensure the correct dosage of 30 g day⁻¹, a measuring cup was enclosed. Participants were advised to consume pecan nuts raw (*in natura*). Similarly, in addition to the dietary prescription, participants of the OOG were given a sufficient amount of extra-virgin olive oil (Arbequina variety), properly conditioned, for 30 days of treatment [1000 mL, considering a daily consumption of 30 mL (two full tablespoons)], plus educational material on product storage and preservation⁽²⁶⁾. It was recommended that the olive oil should be preferentially consumed raw in salads, although it could be also cooked during the meal to improve adhesion. The participants of both groups were advised not to ingest any oleaginous food, nuts or olive oil during follow-up other than those given to them by the research group. Furthermore, all participants received, in addition to the dietary prescription, a table listing foods to be avoided, eaten in moderation or on a daily basis, and a folder with general advice on a healthy diet.

The foods provided to the participants were purchased directly from local producers in the south of Brazil (Cachoeira do Sul) in the same region where the study took place (Rio Grande do Sul). Table 2 shows the fat and total polyphenol content of pecan nuts and olive oil. Compared to olive oil, pecan nuts exhibit a 17-fold higher amount of total polyphenols, whereas olive oil exhibits more than double the concentration of saturated fatty acids (SFAs) compared to the nuts. The nutritional content in both of these foods exhibited similarities with

Table 2 Nutritional composition of pecan nuts and extra-virgin olive oil

	Pecan nuts	Extra-virgin olive oil
Unsaturated fatty acids (%)	53.69	72.40
<i>n</i> -3 PUFA (%)	0.38	0.64
<i>n</i> -6 PUFA (%)	3.95	9.37
<i>n</i> -9 MUFA (%)	48.95	60.21
Saturated fatty acids (%)	7.43	17.85
Trans fatty acids (%)	0	0
Total polyphenols (mg GAE kg ⁻¹)	2935	172

GAE kg⁻¹, gallic acid equivalent per kg; MUFA, monounsaturated fatty acids; *n*-3, omega-3; *n*-6, omega-6; *n*-9, omega-9; PUFA, polyunsaturated fatty acids.

previously published data^(27–29). The analytical methods used for the bromatological, fatty acid profile and antioxidant compound analyses of the foods are presented in the Supporting information (Tables S1 to S3).

Data collection and follow-up

In the first evaluation after inclusion in the study, a blood sample of each participant was drawn, followed by a consultation with the research team (physicians and nutritionists), during which a standardised questionnaire was administered to collect demographic data (age, sex, school education and self-reported skin color), clinical data (current and previous clinical/surgical history, use of medications) and information regarding lifestyle. The physical activity level was assessed by means of the International Physical Activity Questionnaire, short form. Hypertension (HTN), type 2 diabetes mellitus (T2DM) and dyslipidaemia were determined according to the guidelines in effect at the beginning of the study⁽²⁶⁾.

Bodyweight, height and waist circumference were assessed according to a published protocol⁽²⁶⁾. The BMI was calculated by dividing weight (kg) by the height squared (m²). Systolic and diastolic blood pressures (SBP/DBP) were also assessed according to the protocol⁽²⁶⁾.

Daily food intake was assessed by means of the 24-h dietary recall form (R24h). Interviews were conducted by trained nutritionists and/or academic nutritionists, and the nutritional value was calculated with food chemical composition tables and databases with home recipes by means of Avanutri Revolution software (Avanutri, Rio de Janeiro, Brazil).

Serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c) and triglyceride (TG) levels were assessed by an enzymatic colorimetric method, and high-density lipoprotein cholesterol (HDL-c) was assessed by immunoprecipitation (Modular P Química Analyzer;

Roche, Basel, Switzerland). Non-HDL cholesterol (NHDL-c) was calculated by the difference between TC and HDL-c. TC/HDL-c ratio (Castelli index I) was determined by dividing the TC by the HDL-c and the LDL-c/HDL-c ratio (Castelli index II) was determined by dividing the LDL-c by the HDL-c. The TG/HDL-c ratio was determined by dividing the TG levels by the HDL-c levels. The atherogenic index (AI) was determined by the ratio of NHDL-c to HDL-c. The participants fasted for 12 h prior to the blood tests.

Patients were followed-up for three months (12 weeks). Follow-up consultations were performed at days 30, 60 and 90 (last consultation) during which blood was drawn for laboratory analysis. Patients were reminded and notified about the consultations by telephone.

Outcomes

The primary outcome was a change in LDL-c level between baseline and after 12 weeks of follow-up. Secondary outcomes were changes in the values of TC, HDL-c, NHDL-c, TG, TC/HDL-c ratio, LDL-c/HDL-c ratio, TG/HDL-c ratio and the AI after 12 weeks of follow-up. Bodyweight, BMI, waist circumference and blood pressure were also considered secondary outcomes.

Sample size

To obtain a significance level of 5% and a statistical power of 80%, with a difference of 13 mg dL^{-1} in the primary outcome (LDL-c), the calculated minimum sample size was 171 participants. By adding 20% as a result of losses during follow-up, the total sample size was determined to be 204 patients (68 for each group) ⁽²⁶⁾.

Statistical analysis

The statistical analysis was conducted with SPSS, version 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were described as the mean (SD); categorical variables were described as absolute numbers and proportions. Comparisons between means (for symmetric variables) were performed by analysis of variance and comparisons between medians (for asymmetric variables) were performed by the Kruskal–Wallis test. Proportion comparisons were performed by Pearson's chi-squared test (between-group analysis) and McNemar's test (intra-group analysis). Repeated measures regarding the intake of nutrients, anthropometry, blood pressure and lipid profile markers were assessed according to treatment group and time by the generalised estimating equation, with a normal probability distribution for symmetric variables and a gamma probability distribution for

asymmetric variables, followed by Bonferroni's test. Dietary variables (R24h) were adjusted for TEV according to the residual method ⁽³⁰⁾. Means of lipid profile markers were adjusted for baseline values and type of statin used. All analyses were based on intention-to-treat. Missing data were dealt with by the baseline carried forward method, and sensitivity analyses including only individuals who completed the protocol were made to confirm the results. The level of significance $P < 0.05$ (two-tailed) was considered statistically significant. No interim analyses were planned.

Results

In total, 370 individuals were recruited between August 2014 and January 2016. Of these, 166 did not meet the inclusion criteria or had no interest in participating (Figure 1). Finally, 204 men and women with stable CAD were included in the study, of whom 67 were randomised to the CG, 68 to the PNG and 69 to the OOG. The CG exhibited 21 withdrawals (plus one withdrawal for change in address and one death); the PNG exhibited 11 withdrawals, and the OOG had 10 withdrawals, of which two were a result of adverse effects (nausea and gastric discomfort) related to the ingestion of olive oil. All participants were included in the final analysis by intention-to-treat. Thus, an adherence rate (assessed by the presence in consultations) of 66% was found in the CG, whereas the adherence rates for PNG and OOG were 84% and 86%, respectively. Figure 1 shows the flowchart of the study.

Table 3 shows patient characteristics at baseline. HTN was less prevalent in the OOG with respect to the other groups, and there was no significant difference between the remaining variables according to group. There was no difference in the basal characteristics between participants who completed the study with respect to those who withdrew from the study. Similarly, among patients who did not complete the study, there was no significant difference between basal characteristics according to group (see Supporting information, Tables S4 and S5).

At baseline, 7.7% of the participants used no statins; among those who used these drugs ($n = 184$), there was no difference in LDL-c levels between the beginning and end of the study according to the type of statin ($P \geq 0.07$). In the intragroup analysis, basal LDL-c levels did not differ according to the type of statin used ($P \geq 0.08$). However, in the CG, participants using simvastatin exhibited higher LDL-c levels at the end of the study compared to those using atorvastatin or rosuvastatin ($P = 0.03$). In the PNG and OOG, no differences were found regarding final LDL-c levels according to the type of statin used ($P \geq 0.52$) (see Supporting information, Tables S6 and S7).

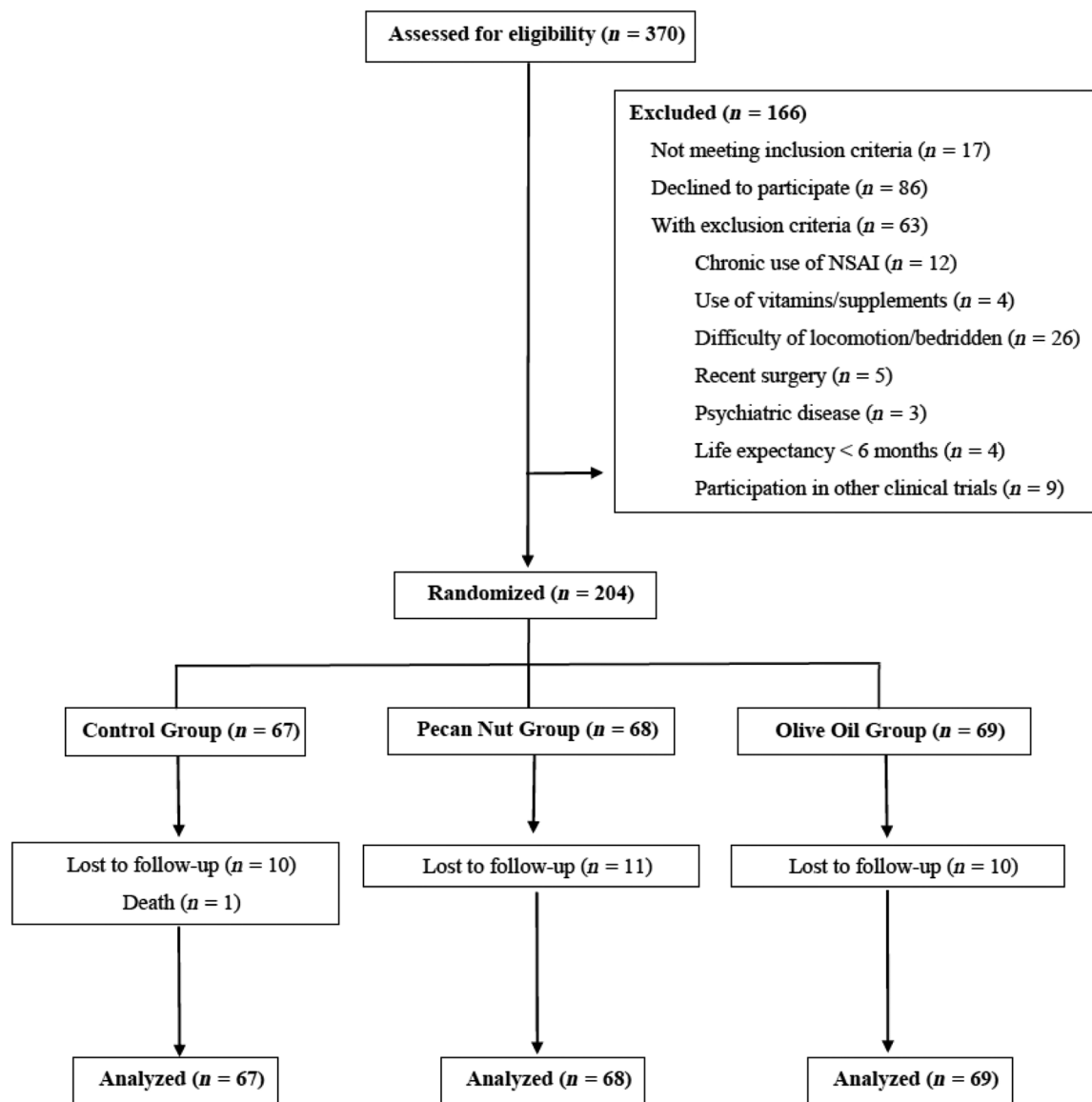


Figure 1 Flowchart of the study. NSAID, nonsteroidal anti-inflammatory drugs.

At the end of the study, there was no difference among the groups regarding the number of patients who changed the dose or type of statin ($P = 0.38$) or other drugs (antiplatelet agents, insulin, anti-diabetic and antihypertensive drugs; $P = 0.13$). Similarly, there was no difference with respect to the physical activity level among the participants allocated to the same group at the end of follow-up ($P \geq 0.20$) (see Supporting information, Tables S8 to S10).

All groups exhibited a reduction in anthropometric indicators compared to the beginning of the study ($P \leq 0.01$): bodyweight [CG: -0.75 kg (-1.27 to -0.22); PNG: -1.63 kg (-2.27 to -1.00); OOG: -0.97 kg (-1.49 to -0.46); BMI [CG: -0.27 kg m^{-2} (-0.46 to

-0.08); PNG: -0.57 kg m^{-2} (-0.80 to -0.35); OOG: -0.35 kg m^{-2} (-0.54 to -0.16)]; and waist circumference [CG: -1.27 cm (-1.97 to -0.58); PNG: -1.21 cm (-1.97 to -0.50); OOG: -1.27 cm (-2.20 to -0.35)]. However, there was no significant difference between groups after 12 weeks of intervention regarding changes of these variables (all $P > 0.10$). Sensitivity analyses also showed no difference between groups regarding bodyweight ($P = 0.20$), waist circumference ($P = 0.82$) and BMI ($P = 0.23$) (data not shown).

After adjustment for basal values and previous diagnosis of HTN, there was no difference regarding final means of SBP [CG: 127.9 (19.7) mmHg; PNG: 126.3 (21.3) mmHg; OOG: 121.7 (18.6) mmHg; $P = 0.58$] and

Table 3 Baseline characteristics of participants according to study group

	CG (<i>n</i> = 67)	PNG (<i>n</i> = 68)	OOG (<i>n</i> = 69)
Age (years), mean (SD)	60.40 (8.54)	59.59 (8.40)	57.51 (11.72)
Male sex, <i>n</i> (%)	49 (73.1)	55 (80.9)	51 (73.9)
School education (years), mean (SD)	9.19 (3.07)	9.90 (3.18)	9.49 (2.86)
White ethnicity, <i>n</i> (%)	62 (92.5)	64 (94.1)	65 (94.2)
Current or previous smoking, <i>n</i> (%)	46 (68.7)	38 (55.9)	46 (66.7)
Alcohol abuse, <i>n</i> (%)	3 (4.5)	6 (8.8)	2 (2.9)
Physical activity level			
Active, <i>n</i> (%)	19 (28.3)	11 (16.1)	19 (27.5)
Irregularly active, <i>n</i> (%)	31 (46.3)	35 (51.5)	30 (43.5)
Sedentary, <i>n</i> (%)	17 (25.4)	22 (32.4)	20 (29.0)
Body mass (kg), mean (SD)	79.43 (15.91)	84.08 (16.90)	80.78 (16.42)
BMI (kg m ⁻²), mean (SD)	29.06 (3.98)	29.78 (5.60)	29.12 (4.36)
Waist circumference (cm), mean (SD)	98.59 (11.66)	100.15 (12.55)	98.93 (11.44)
Dyslipidaemia, <i>n</i> (%)	40 (59.7)	38 (55.9)	38 (55.1)
Diabetes mellitus, <i>n</i> (%)	24 (35.8)	23 (33.8)	19 (27.5)
HTN, <i>n</i> (%)	47 (70.1)	50 (73.5)	35 (50.7)
Systolic blood pressure (mmHg), mean (SD)	133.28 (21.41)	133.87 (20.61)	127.25 (19.70)
Diastolic blood pressure (mmHg), mean (SD)	74 (13.10)	76.53 (10.60)	73.36 (10.30)
Premature CAD FH, <i>n</i> (%)	26 (38.8)	29 (42.6)	31 (44.9)
Previous AMI, <i>n</i> (%)	60 (89.6)	62 (91.2)	62 (89.9)
Previous PCI, <i>n</i> (%)	53 (79.1)	58 (85.3)	61 (88.4)
Previous SMR, <i>n</i> (%)	8 (11.9)	9 (13.2)	7 (10.1)
Statins (<i>n</i> = 184)			
Simvastatin, <i>n</i> (%)	50 (80.7)	37 (62.7)	49 (77.8)
Rosuvastatin, <i>n</i> (%)	7 (11.3)	11 (18.6)	8 (12.7)
Atorvastatin, <i>n</i> (%)	5 (8.1)	11 (18.6)	6 (9.5)

AMI, acute myocardial infarction; BMI, body mass index; CAD FH, family history of coronary artery disease; CG, control group; HTN, hypertension; OOG, olive oil group; PCI, percutaneous coronary intervention; PNG, pecan nut group; SMR, surgical myocardial revascularisation.

DBP [CG: 71.6 (12) mmHg; PNG: 73.3 (10.7) mmHg; OOG: 70.1 (10.2) mmHg; $P = 0.68$] between groups at the end of the study. Sensitivity analyses confirmed results regarding SBP ($P = 0.89$) and DBP ($P = 0.93$) (data not shown).

The participants' dietary profiles after 12 weeks of follow-up are provided in Table 4, according to group. At the end of the study, there was no difference between groups with respect to energy, dietary fibre and cholesterol, as well as percent carbohydrates, total fats, SFAs and polyunsaturated fatty acids (PUFAs). In the intra-group analysis, PNG and OOG exhibited a significant increase in the ingestion of monounsaturated fatty acids (MUFAs; %) compared to baseline ($P < 0.001$); however, there was no difference with respect to the CG at the end of follow-up ($P = 0.41$).

Table 5 shows the mean values of lipid profile markers before and after the interventions (crude and after adjustments). After adjustment for baseline values and type of statin, there was no difference regarding LDL-c ($P = 0.19$), TC ($P = 0.059$), HDL-c ($P = 0.80$), TG ($P = 0.09$), LDL-c/HDL-c ratio ($P = 0.15$), TG/HDL-c ratio ($P = 0.21$) and AI ($P = 0.078$) according to groups.

However, compared to the CG and the OOG, PNG had significantly reduced NHDL-c ($P = 0.033$) and TC/HDL-c ratio values ($P = 0.044$). Sensitivity analyses (see Supporting information, Table S11) including only individuals who completed the protocol showed the same results. Lipid profile was not adjusted for energy intake because it was not different between groups.

During follow-up, one participant of the CG with a previous diagnosis of T2DM had a new acute myocardial infarction, followed by a percutaneous coronary intervention. Two participants of the PNG reported gastric discomfort (nausea and constipation) related to the ingestion of nuts.

Discussion

In the present study, a healthy diet enriched with 30 g day⁻¹ of pecan nuts for 12 weeks did not reduce LDL-c levels compared to a healthy diet alone or one enriched with extra-virgin olive oil; however, it may improve other markers of the lipid profile, including atherogenic particles such as NHDL-c. We also found a reduced body-weight, BMI and waist circumference in all groups.

Table 4 Dietary profile of the participants according to follow-up time and study group [mean (SD)]

	CG (n = 67)				PNG (n = 68)				OOG (n = 69)			
	Baseline	4 weeks	8 weeks	12 weeks	Baseline	4 weeks	8 weeks	12 weeks	Baseline	4 weeks	8 weeks	12 weeks
TEV (kcal)	1719 (638)	1421 (522)	1424 (528)	1570 (752)	1721 (740)	1608 (680)	1622 (467)	1672 (637)	1767 (681)	1600 (522)	1701 (611)	1656 (552)
Carbohydrates (% TE)	56.3 (27.6)	55.0 (15.1)	62.9 (23.3)	64.2 (32.1)	59.3 (31.2)	50.2 (13.3)	52.8 (22.2)	52.4 (21.3)	59.2 (30.7)	49.0 (12.8)	51.6 (27.1)	53.8 (30.5)
Proteins (% TE)	23.6 (10.6)	25.6 (11.8)	23.7 (9.9)	24.4 (11.4)	22.3 (11.5)	21.1 (10.6)	19.4 (80.5)	19.2 (7.58)	20.1 (12.7)	18.9 (7.1)	19.1 (9.2)	18.8 (7.7)
Total fats (% TE)	36.6 (17.3)	32.5 (9.9)	41.8 (22.3)	39.0 (21.5)	40.7 (23.7)	36.0 (13.5)	37.5 (18.3)	38.8 (14.8)	37.0 (19.7)	35.4 (9.8)	39.0 (19.3)	40.7 (16.6)
SFA (% TE)	10.7 (5.9)	11.1 (6.2)	11.7 (7.1)	11.6 (6.6)	10.9 (7)	10.8 (87.5)	9.3 (5.17)	10 (5.5)	10.1 (6.6)	9.7 (4.3)	9.8 (5.4)	10.4 (5)
MUFA (% TE)	4.9 (3.1)	4.9 (3.1)	6.0 (4.2)	5.1 (3.3)	4.9 (4)	4.8 (3.9)	4.2 (3.03)	4.6 (3.4)	4.7 (3.3)	4.7 (3.1)	4.5 (3.3)	5.17 (2.9)
PUFA (% TE)	9.9 (6.6)	9.9 (6.5)	11.3 (8.1)	10.4 (7)	10.6 (7.3) ^a	14.6 (9.4) ^b	14.1 (7.7) ^b	14.3 (7) ^b	10.4 (7.7) ^a	12.4 (6.4) ^b	14 (7.9) ^b	14 (6.9) ^b
Cholesterol (mg)	233 (134)	181 (197.1)	185 (83.4)	237 (194)	203 (119)	186 (114)	184 (133)	177 (106)	179 (118)	171 (108)	184 (123)	190 (124)
Dietary fibre (g)	13.1 (5.7)	12.7 (5.9)	12.5 (7.0)	11.6 (6.6)	13.7 (7.3)	15.0 (9.1)	14.4 (6.1)	12.8 (5.9)	15.2 (10.4)	13.7 (6.71)	13.0 (6.8)	14.1 (13.1)

Different superscript letters indicate intragroup differences in the course of the study ($P < 0.001$). Generalised estimating equation with normal probability distribution (symmetric variables) and gamma probability distribution (asymmetric variables), followed by a Bonferroni test and adjusted for total energy value using the residual method.

P -values regarding differences between groups at the end of the study: TEV: $P = 0.81$; carbohydrates: $P = 0.37$; proteins: $P = 0.76$; total fats: $P = 0.68$; SFA: $P = 0.76$; PUFA: $P = 0.58$; MUFA: $P = 0.41$; cholesterol: $P = 0.38$; dietary fibre: $P = 0.75$.

% TE, percentage of total energy; CG, control group; MUFA, monounsaturated fatty acids; OOG, olive oil group; PNG, pecan nut group; PUFA, polyunsaturated fatty acids; SFA, saturated fatty acids; TEV, total energy value.

A systematic review with a meta-analysis of 24 clinical trials and 1020 participants in primary prevention showed that supplementation with 15–108 g day⁻¹ of walnuts significantly reduced LDL-c [-5.51 mg dL⁻¹ (95% CI = -7.72 to -3.29 mg dL⁻¹)] and TC levels [-6.99 mg dL⁻¹ (95% CI = -9.39 to -4.58 mg dL⁻¹)] compared to control diets, exhibiting reductions of 3.73% and 3.25% in LDL-c and TC levels, respectively. A more pronounced effect was found in the comparison of a nut-enriched diet with a typical American or standard Western diet⁽¹³⁾. In the present study, we chose to compare supplementation with nuts or olive oil to that based on a diet considered healthy and appropriate for CAD according to the Brazilian nutritional guidelines because the participants already exhibited an established cardiovascular disease. In another systematic review with a meta-analysis of 61 clinical trials that evaluated the effects of tree nuts (including pecan nuts) on blood lipids and apolipoproteins, the major determinant of cholesterol-lowering was suggested to be nut dose (≥ 60 g nuts day⁻¹) rather than nut type⁽³¹⁾.

Regarding secondary prevention, the results from supplementation with nuts are inconclusive. In Americans with CAD, supplementation with 85 g day⁻¹ of nuts had no effect on the lipid profile compared to a healthy diet⁽¹⁷⁾. In turn, the ingestion of 10 g day⁻¹ of almonds (compared to a healthy diet) significantly reduced the values of TC, LDL-c, TG, the TC/HDL-c ratio and the AI among Pakistanis with CAD⁽¹⁸⁾. However, in contrast to the study of Jamshed *et al.*⁽¹⁸⁾, we found no increase in HDL-c levels after the ingestion of pecan nuts. In addition to the type of nut and the offered amount, the differences among the results of the secondary prevention parameters could be explained by the profile of the assessed participants (including the time of diagnosis), the length of follow-up, the design of the studies and the medical conduct in the treatment of CAD. The schedule of nut intake might also be an important factor because a greater beneficial effect is expected if these are taken as a snack on an empty stomach for increasing satiety, improving the glycaemic response and suppressing a second-meal plasma non-esterified free fatty acids response⁽³²⁾; an instruction that was not given in the present study in an attempt to enhance adherence to the food instructions.

Other studies also did not find an improvement in the lipid profile among Spanish participants with CAD after ingesting 50 mL day⁻¹ of olive oil in a nutritional composition similar to that of the present study^(19,20). However, they found a significant reduction in oxidised (ox)-LDL levels⁽²⁰⁾, a marker that we did not assess. The amount of olive oil that we supplemented (30 mL day⁻¹) was below the amount used in other studies (50 mL day⁻¹) that found benefits in the consumption of olive

Table 5 Initial and final means (crude and adjusted) of lipid profile markers after 12 weeks of follow-up according to study group

	CG (n = 67)			PNG (n = 68)			OOG (n = 69)		
	Baseline	12 weeks*	Adjusted 12 weeks [†]	Baseline	12 weeks*	Adjusted 12 weeks [†]	Baseline	12 weeks*	Adjusted 12 weeks [†]
TC (mg dL ⁻¹)	170.1 (39.4)	173.6 (46.2)	172.6 (32.9)	162.5 (33.7)	154.9 (37)	161 (31.5)	174.9 (44.8)	177.7 (54.6)	172.2 (36.8)
LDL-c (mg dL ⁻¹)	94.2 (34.8)	96.2 (40.4)	96.1 (29.1)	86.1 (24.8)	80.5 (27.7)	87.0 (28.9)	100.3 (39.7)	102.0 (50.9)	96.2 (34.1)
HDL-c (mg dL ⁻¹)	47.7 (13.9)	47.6 (14.5)	45.6 (7.3)	45.2 (12.1)	45.4 (14.0)	46.0 (6.5)	44.5 (9.9)	44.0 (9.7)	45.2 (6.7)
TG (mg dL ⁻¹)	146.1 (87.5)	149.7 (83.5)	141.5 (48.3)	156.2 (84.4)	139.9 (78)	129.0 (52)	158.3 (95.1)	161.6 (109.3)	144.1 (56.5)
NHDL-c (mg dL ⁻¹) [‡]	122.3 (40.2)	125.8 (47.1)	127 (33.6) ^a	117.3 (31.3)	109.3 (36.8)	114.9 (31) ^b	130.1 (45.9)	133.4 (56.4)	126.6 (37.4) ^a
Castelli index [#]	3.8 (1.2)	3.86 (1.4)	4.0 (0.8) ^a	3.8 (1) ^{ss}	3.6 (1.2)	3.7 (0.7) ^b	4.1 (1.4)	4.2 (1.6)	4.0 (0.8) ^a
Castelli index II	2.1 (0.9)	2.2 (1.1)	2.3 (0.7)	2.0 (0.67)	1.2 (0.8)	2.1 (0.7)	2.3 (1.0)	2.4 (1.2)	2.2 (0.8)
HDL-c:TC ratio	3.5 (2.6)	3.5 (2.4)	3.2 (1.6)	3.9 (2.8)	3.5 (2.5)	3.0 (1.7)	4.1 (3.2)	4.1 (3.5)	3.4 (1.7)
AI	2.8 (1.2)	2.9 (1.4)	3.0 (0.8)	2.8 (1)	2.6 (1.2)	2.7 (0.7)	3.1 (1.4)	3.2 (0.6)	3.0 (0.8)

Different superscript letters indicate a difference between groups after 12 weeks (time × group interaction: [‡]P = 0.033; [#]P = 0.044). Generalised estimating equation with normal probability distribution (symmetric variables) and gamma probability distribution (asymmetric variables), followed by Bonferroni test.

For TC, HDL-c and LDL-c conversion (mg dL⁻¹ to mmol L⁻¹), divide by 38.67. For TG conversion (mg dL⁻¹ to mmol L⁻¹), divide by 88.57. For NHDL-c conversion (mg dL⁻¹ to mmol L⁻¹), divide by 38.58.

AI, atherogenic index; CG, control group; HDL-c, HDL-cholesterol; LDL-c, LDL-cholesterol; NHDL-c, non-HDL cholesterol; OOG, olive oil group; PNG, pecan nut group; TC, total cholesterol; TG, fasting triglycerides.

^aCrude means after 12 weeks of intervention.

[†]Means after 12 weeks adjusted for baseline data and type of statin in use.

oil with respect to the lipid profile in primary prevention⁽³³⁾. Furthermore, the nutritional composition and the polyphenols amount of the olive oil that we used might have differed significantly; it is known that nutrigenomic, chemoprotective, anti-inflammatory and anti-atherosclerotic activities of virgin olive oil phenolics differ according to content and population evaluated^(34–36). However, we chose to use olive oil produced in our region and to supplement with a smaller amount because the Brazilian population is not adapted to its ingestion. A study conducted in Brazil found that the healthy and low-fat eating habits recommended by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATPIII) significantly reduced LDL-c and TC levels in patients with CAD compared to those on a Mediterranean diet enriched with 15 mL day⁻¹ of extra-virgin olive oil and 10 g day⁻¹ of mixed nuts⁽²¹⁾. Notably, in that study, the NCEP-ATPIII group patients were instructed to supplement their diet with 2 g day⁻¹ of phytosterols, which is far above what can be obtained via natural sources⁽³⁷⁾.

We found a similar amount of MUFAs in both foods offered in the present study. However, much higher polyphenol levels were found in the pecan nuts, which might explain the benefits found only in the PNG. Among the most prominent antioxidant and anti-inflammatory mechanisms attributed to polyphenols are blockage of the free-radical chain reactions and regulation of the signaling pathway related with oxidative stress⁽³⁸⁾, inhibition of LDL-c oxidation⁽³⁹⁾, inhibition of cholesterol synthesis⁽⁴⁰⁾, chelation of metal ions and suppression of nitric oxide production⁽⁴¹⁾, and an increase in the HDL-c efflux capacity⁽⁴²⁾. In addition to being an excellent source of MUFAs and phytochemicals (total phenols, flavonoids, hydrolysable tannins, proanthocyanidins), pecan nuts are rich in PUFAs, dietary fibre and bioactive compounds, such as phytosterols⁽²⁷⁾, all of which are considered cardioprotective and can act synergistically to modulate the lipid profile⁽⁴³⁾.

Compared to olive oil, nuts are stronger in reducing the levels of small and dense LDL-c and in changing lipoprotein subfractions into a less atherogenic pattern⁽⁴⁴⁾. However, both extra-virgin olive and nuts are foods with potential 'nutraceutical' properties, which may represent useful compounds that can improve the lipid profile by acting parallel to statins or as adjuvants, reducing 7 α -hydroxylase, increasing faecal excretion of cholesterol and decreasing 3-hydroxy-3-methylglutaryl-CoA reductase mRNA levels⁽⁴⁵⁾.

The beneficial effects of pecan nuts have been poorly studied. In animal models, pecan nuts regulate the liver mRNA expression of the LDL receptor and apolipoprotein B receptor in high-fat diets⁽⁴⁶⁾. In humans,

supplementation with approximately 68 g day⁻¹ of pecan nuts significantly reduced LDL-c levels in healthy adults (-5.81 mg dL⁻¹)⁽²³⁾ and substituting approximately 20% of the daily TEV for pecan nuts improved the antioxidant status the plasma⁽²⁴⁾ and lipid profile, with an emphasis on the LDL-c and TC levels⁽²⁵⁾. In overweight adults, a diet enriched with approximately 40 g day⁻¹ of pecan nuts reduced LDL-c levels in a more pronounced way in individuals with dysglycaemia and reduced TC levels among the participants with the lowest LDL-c levels at the beginning of the study⁽²²⁾. To our knowledge, the present study is the first to assess the effects of pecan nuts on individuals with established heart disease and with ≥ 12 weeks of follow-up.

The study has certain limitations. We did not use rigorous strategies to improve adherence to consultations by sending specific phone messages or e-mails. We did not ask participants to return the empty food packages, and food intake was assessed by means of the R24h, which might not provide a reliable estimate of the patient's food intake as a result of daily variations, as well as by depending on the patient's memory (multiple R24h recalls were not used at each time point to assess usual intake). The duration of follow-up and the sample size might not have been sufficient to optimally identify differences among groups. We did not assess important markers of atherosclerosis, such as apolipoproteins and ox-LDL, nor oxidative stress indices. Additionally, the supplements could have been depleted between the consultations if the consultation had to be rescheduled. We did not evaluate the bioactive profile, specific polyphenols content and other chemical analyses in both food matrices. Some polyphenols in olive oil, if cooked, were missing. The doses used for both the olive oil and nuts might have been insufficient for inducing a pronounced effect. Losses to follow-up might have influenced the results (the CG might have lost motivation, thus contributing to a higher withdrawal rate in this group). Finally, missing data values were dealt with carried forward method, and this strategy is not unanimous among researchers⁽⁴⁷⁾. Among the strengths of the present study is the intention-to-treat analysis; the proximity to 'real life' for being a pragmatic study and instructing participants not to substitute foods for the supplements offered in the study, which appears to have happened naturally, considering that there were no differences in the TEV values between the groups at the end of the study.

In conclusion, supplementing a healthy diet according to the nutritional guidelines with 30 g day⁻¹ of pecan nuts for 12 weeks did not reduce LDL-c levels compared to supplementation with extra-virgin olive oil or a healthy diet alone, although it may improve other markers of the lipid profile, such as NHDL-c, TC/HDL-c ratio, TC, AI and TG independently of the statin used. Furthermore,

daily supplementation with nuts and olive oil did not increase adiposity and contributes to significant increase in MUFA intake. This suggests that the above intervention may be considered with respect to reducing atherogenicity and improving health among individuals with CAD. However, further clinical trials are necessary.

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Conflict of interests, source of funding and authorship

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Transparency declaration

The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported. The reporting of this work is compliant with CONSORT. The lead author affirms that no important aspects of the study have been omitted and that any discrepancies from the study as planned (clinicaltrials.gov Identifier: NCT02202265) have been explained.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Analytical methods used for the bromatological analysis of the pecan nuts and olive oil used in the present study.

Table S2. Identification of the acidity index and of total antioxidant compounds in the pecan nuts and olive oil used in the present study.

Table S3. Fatty acid profile [% (g 100 g⁻¹)] of the pecan nuts and olive oil used in the present study.

Table S4. Comparison of baseline characteristics among participants who completed and those who withdrew from the study [mean (SD), *n* (%)].

Table S5. Baseline characteristics of participants who withdrew from the study according to group allocation [mean (SD), *n* (%)].

Table S6. Comparison between initial and final means (after 12 weeks) of LDL-c (mg dL⁻¹) according to type of statin.

Table S7. Comparison between initial and final means (after 12 weeks) of LDL-c (mg dL⁻¹) according to type of statin and study group.

Table S8. Participants who changed the dose or type of statin in the course of the study [*n* (%)] according to group.

Table S9. Participants who changed the dose or type of other medication in the course of the study [*n* (%)] according to group.

Table S10. Participants who changed the level of physical activity in the course of the study [*n* (%)] according to group.

Table S11. Sensibility analysis including only individuals who completed the protocol (initial and final means of lipid profile markers after 12 weeks of follow-up according to study group).