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Effects of mixed nuts as part of a Brazilian Cardioprotective diet on LDL-cholesterol in adult patients after myocardial infarction: a multicenter randomized controlled clinical trial

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Abstract

Background Nuts consumption is related to cardioprotective effects on primary cardiovascular prevention, but studies conducted in secondary prevention are small, scarce and controversial. The objective of this trial was to evaluate the effects of a regional and sustainable cardioprotective diet added or not with an affordable mixed nuts on cardiometabolic features in patients with previous myocardial infarction.

Methods DICA-NUTS study is a national, multi-center, and superiority-parallel randomized clinical trial. Males and females over 40 years old diagnosed with previous myocardial infarction in the last 2 to 6 months were included. Patients were allocated into two groups: the Brazilian Cardioprotective diet (DICA Br) supplemented with 30 g/day of mixed nuts (10 g of peanuts; 10 g of cashew; 10 g of Brazil nuts) (intervention group, $n = 193$); or only DICA Br prescription (control group, $n = 195$). The primary outcome was low-density lipoprotein cholesterol means (in mg/dL) after 16 weeks. Secondary outcomes were other lipid biomarkers, glycemic and anthropometric data and diet quality.

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Results After adjustment for baseline values, participating study site, time since myocardial infarction and statin treatment regimen (high potency, moderate and low potency/no statins), no significant difference was found between the groups in low-density lipoprotein cholesterol concentrations (intervention-control difference: 3.48 mg/dL [-3.45 to 10.41], $P=0.32$). Both groups improved their overall diet quality at the end of the study without differences between them after 16 weeks (intervention-control difference: 1.05 (-0.9 to 2.99); $P=0.29$). Other lipids, glycemic profile and anthropometrics were also not different between study groups at the end of the study.

Conclusion Adding 30 g/day of mixed nuts to the DICA Br for 16 weeks did not change lipid, glycemic and anthropometric features in the post-myocardial infarction setting.

Trial registration This study is registered on ClinicalTrials.gov website under number NCT03728127 and its World Health Organization Universal Trial Number (WHO-UTN) is U1111-1259–8105.

Keywords Myocardial Infarction, Diet, Healthy, Nuts, Cholesterol, LDL, Randomized Controlled Trial [Publication Type]

Introduction

Ischemic heart diseases (IHD), such as myocardial infarction (MI), are the leading cause of death worldwide [1]. Although IHD mortality rates have progressively decreased due to advances in treatment, the prevalence of cardiovascular risk factors (e.g., high cholesterol, high body mass index [BMI], type-2 diabetes mellitus [T2DM]) are increasing, suggesting a stagnating of recent progress [1]. Lifestyle changes are an integral component for the management of cardiovascular disease (CVD) risk factors, including in secondary prevention for patients with IHD [2, 3]. Higher diet quality is associated with lower CVD risk [4]. In this sense, diet quality is an essential lifestyle component to manage risk factors and to reduce the recurrence of cardiovascular events [5, 6].

Although most clinical trials have focused on primary cardiovascular prevention [7–10], it has been shown that the Mediterranean diet (MedDiet) improves cardiometabolic features and reduces major cardiovascular events among IHD patients [11, 12]. However, in a head-to-head comparison with other dietary patterns or minimal intervention, MedDiet showed no significant effect on cardiovascular risk factors in the secondary cardiovascular prevention setting [13]. Still, adherence to MedDiet is crucial to obtain such benefits, but not always feasible, affordable or culturally appropriate. The Brazilian Cardioprotective Diet (*DIeta CArdioprotetora Brasileira;* DICA Br) consists of a sustainable and culturally adapted dietary prescription combined with nutritional recommendations for IHD prevention [14]. On a large multicenter randomized clinical trial conducted among Brazilians with established IHD in the last ten years, the DICA Br improved adherence to a healthful diet but had no effect on lipids, body weight, and glycemic profile [15]. Thus, the DICA Br might be a feasible strategy to promote higher diet quality among individuals with IHD, but further investigation on its cardiometabolic effects is needed. In addition, the original DICA Br tool focuses on the prescription of food groups instead of specific foods that may be linked to cardiometabolic benefits.

Nuts are a key component of a heart-healthy dietary pattern and their consumption is recommended by guidelines for secondary cardiovascular prevention, despite most evidence were based on observational studies [16, 17]. Nuts are high in monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), L-arginine, dietary fiber, tocopherols, polyphenols, phytosterols and minerals, which synergize to positively influence metabolic and vascular pathways related to cardiovascular health [18]. However, randomized trials that evaluated the effects of different nuts on lipids [19, 20], glycemic control [21, 22] and anthropometric measures [21, 23] report mixed results and effects among individuals with established IHD are limited, mainly outside the MedDiet context.

The aim of this multicenter clinical trial was to evaluate the effects the DICA Br added with 30 g/day of mixed nuts on lipids, glycemic profile, and anthropometric indexes in comparison to the DICA Br without nuts supplementation. The primary outcome was the difference in low-density lipoprotein cholesterol (LDL-c), given its well-established role as a marker for the progression of IHD related to the destabilization of atherosclerotic plaques, exacerbation of cardiac remodeling post-MI [24], and the recurrence of MI and other cardiovascular events [25]; additionally, the management of individuals in secondary prevention for CVD is guided by LDL-c concentrations [16, 17]. Secondary outcomes were differences in the means of other lipids, glycemic features, anthropometric measures and diet quality at 16 weeks. We hypothesized that the DICA Br supplemented with mixed nuts would improve these

cardiometabolic outcomes among patients who suffered a MI within 2 to 6 months.

Materials and methods

Study design and ethical approval

The study protocol has been previously published in detail [26]. Briefly, it is a national, multi-center, and superiority-parallel (1:1 allocation rate) randomized clinical trial conducted in Brazil and led by Hcor Research Institute (IP-Hcor, São Paulo, Brazil). This study is registered on the ClinicalTrials.gov website under number NCT03728127 and its World Health Organization Universal Trial Number (WHO-UTN) is U1111-1259–8105. All procedures complied with the ethical human research principles. Hcor Institutional Review Board approved the study and at each participating site as well. All participants signed a consent form before inclusion in the trial, which was administered by a trained researcher.

Participants

Inclusion criteria were age ≥ 40 years and medical diagnosis of ST-Elevation MI (STEMI) or non-STEMI according to The Joint Task Force on Universal Definition for MI [27] within 2 to 6 months of the event. This window was chosen because biochemical markers may be altered up to 2 months after the MI and cardiac rehabilitation generally begins within 6 months of the event. Exclusion criteria were: coronary artery bypass graft (CABG) surgery scheduled during the intervention (in the upcoming 16 weeks); acquired immunodeficiency syndrome; chronic inflammatory diseases and chronic use of anti-inflammatory, immunosuppressive, and/or anticonvulsant medications; pregnancy or breastfeeding women; drug and alcohol abuse (alcoholism); physical disabilities that may impair anthropometric assessment; BMI ≥ 40 kg/m^2; history of allergy to nut intake; dietary use of nutritional supplements; participation in other clinical trials whose intervention may interfere with outcomes. Regular consumers of nuts/seed oils (> 3 times a week) were not included in the study.

Participants identified in Hemodynamic Services, outpatient cardiology clinics, or during hospitalization were invited to participate in the study, provided all eligibility criteria were met. Outpatients who volunteered for the trial were also included [26].

Randomization and blinding

Randomization was centralized at the following website: http://dicanuts.hcor.novatela.com.br. The allocation sequence was 1:1, generated via validated software with random permuted blocks and stratification according to the study site. Investigators had to access the study website, fill in the electronic case report form (CRF) and confirm eligibility criteria to be granted access to randomization. Both participants and dietitians responsible for study visits were not blind to the interventions. Statisticians and staff involved with biochemical samples evaluation were blinded to the intervention groups [26].

Study interventions

Participants were allocated to one of two groups: 1) the DICA group (control) or 2) the DICA-NUTS group (intervention). Both groups received the DICA Br prescription, which was previously published in detail [14, 15, 26]. This nutrition strategy is based on nutritional recommendations feasible for the Brazilian population; DICA Br composition allows for the easy access and full use of foods, in addition to the prioritization of regional foods and receipts that are culturally accepted [26]. The prescribed calorie (Kcal) range was determined by BMI status and individual goal for weight maintenance (normal weight), weight loss (excess body weight) or weight gain (underweight). Following each caloric range, patients were advised to the number of foods they were allowed to consume for each food group (green, yellow and blue; these colors are those of the Brazilian flag). For example, the 1400 kcal range is composed by 9 portions from the green group, 6 portions from the yellow group and 2 portions from the blue group.

Briefly, foods in the green group are rich in vitamins, minerals, and dietary fibers and have a low energy density, saturated fatty acids (SFA), and dietary sodium content; the yellow group is mainly composed of foods rich in carbohydrates and vegetable fats; and the blue group is comprised of animal sources of proteins, with a higher content of dietary sodium, cholesterol, SFA, and high energy density. Consumption of ultra-processed foods (red group) was discouraged among all participants, who also received a handbook with information about the DICA Br, group composition and portions size. More details regarding the DICA Br approach and a list of foods included in each group (green, yellow, blue, and red) are provided in the Supplemental Material (Methods I), and an example of the DICA Br prescription was shown in the study protocol [26].

Since nuts originally belong to the yellow group and mixed nuts were being supplemented in our trial, the DICA-NUTS group was advised not to consider them when counting the yellow group. However, mixed nut supplementation was included in diet quality scoring. Participants in this group were provided with 30 g/day of an affordable mixed nuts (10 g of toasted cashews, 10 g of raw and peeled peanuts and 10 g of raw Brazil nuts – all unsalted) and were allowed to eat them at any time during the day; the size of the portion (30 g/day) was chosen based on previous guidelines for MI management [16].

Participants were also advised to not share mixed nuts received with family members or other people. At each visit, participants received a monthly supply of mixed nuts that were individually portioned for daily consumption. Participants also received guidance regarding nuts storage at monthly pickups. Empty bags were returned to study coordinators on the next visit to assess compliance. The DICA group was discouraged from consuming any type of nuts during the duration of the study. Energy content, centesimal composition, fatty acid profile, and mineral content of the mixed nuts provided in this trial were previously published [26]. The phenolic content of all nuts offered and the methods for its identification and quantification can be found in the Supplemental Material (Methods II).

Both groups were counseled about following DICA Br prescription at each study visit to improve adherence and advised to not change their physical activity levels. An example of dietary prescription for both DICA-NUTS and DICA groups including dietary composition and food servings according to DICA Br color groups was previously published as well [26]; diets were not isocaloric between intervention and control groups.

Data collection and follow-up

All variables and procedures collected/performed during DICA-NUTS trial and in each study visit were previously described in detail [26]. In short, participants attended a total of 5 visits (baseline, 4, 8, 12 and 16 weeks). At the baseline visit, participants provided data regarding demographic information, socioeconomic and educational status, smoking, alcohol consumption, physical activity, and medical history, including self-reported previous diagnoses. At each visit, participants were asked to inform study coordinators about medications in use and/or changes related to the previous visit – due to the higher likelihood of medication changes within the 60–180 days post-MI window, which could consequently influence study outcomes – and occurrence of adverse events. Body weight, waist and hip circumferences were also measured at each visit.

Diet assessments were performed using 24-h dietary recall and a quantitative food frequency questionnaire (FFQ) previously validated to the Brazilian population—already defined in the study protocol [26]. A FFQ was given at the initial and last visit whereas 24-h recalls were applied at each study visit. Dietary data were recorded in a specific software site (Sistema Vivanda de Alimentação®, São Paulo, Brazil). Diet quality was evaluated using the modified Alternative Healthy Eating Index (mAHEI) [28], which ranges from 0 to 70 points. Adherence to the dietary prescription was assessed using the BALANCE Dietary Index (BALANCE DI) [29], specifically validated for DICA Br evaluation, which ranges from 0 to 40 points. Both mAHEI and BALANCE DI were calculated from 24-h dietary recalls. Records with implausible energy intake according to the criteria < 500 and > 4000 kcal/day were excluded, and macro and micronutrients were adjusted for total energy intake according to the residual method [30].

Biochemical analyses

Blood samples were obtained after 12 h of overnight fast during the first and last visits. Biochemical assessment was carried out according to standardized techniques by the clinical analysis laboratories referenced for each center site. Total cholesterol (TC; mg/dL), high density lipoprotein-cholesterol (HDL-c; mg/dL), triglycerides (TG; mg/dL), fasting plasma glucose (FG; mg/dL), fasting insulin (FI; mU/L), glycated hemoglobin (HbA1c; %), and serum creatinine (Cr; mg/dL) were obtained directly from blood samples. LDL-c (mg/dL), very low-density lipoprotein-cholesterol (VLDL-c; mg/dL), non-HDL (NHDL-c; md/dL), ratios between lipids, estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2) and homeostatic model assessment for insulin resistance (HOMA-IR) were obtained by specific mathematical formulas [26].

Outcomes

The primary outcome was difference in mean LDL-c at 16 weeks between the DICA-NUTS and the DICA groups. Secondary outcomes were differences in the means of other lipid/lipoproteins, glycemic features, anthropometric measures and diet quality at 16 weeks.

Sample size

The sample size was estimated at 352 participants with a power of 80% to detect a minimum difference of 6 mg/dL in LDL-c between groups, with two-tailed alpha of 5%, based on the BALANCE study [15]. Adding 10% considering possible dropouts, the final sample size consisted of 388 individuals.

Statistical analysis

Continuous variables with a normal distribution were reported as means and standard deviation (SD). Variables with non-normal distributions were reported as medians and interquartile ranges (IQR). Categorical variables were summarized as frequencies. Comparisons between groups regarding baseline data were made using the Student's t-test (for variables with normal distribution), the Mann–Whitney test (for variables with non-normal distribution), or Fisher's exact test (for categorical variables). The main analysis followed the intention-to-treat

principle with the assumption that missed follow-up visits were missing at random.

The missing values for the outcomes (lipid profile, glycemic profile, and anthropometric data) at the target visit were imputed with the multiple imputation technique by Gibbs sampling with the chain equation method considering 100 datasets [31]. The imputation process considered the intensity of statin treatment (high, moderate, or low intensity/no statin) at baseline and outcomes´ values observed at previous visits, as well as factors such as sex, age, and time since the diagnosis of MI. To evaluate differences between groups in outcomes related to lipid profile, ANCOVA models adjusted for baseline values of the assessed outcome, study site, time of MI diagnosis, and statin treatment intensity at baseline. Similar adjustments were applied to the glycemic profile outcomes, with the additional inclusion of the baseline variable representing the use of glucose-lowering drugs in the model. For anthropometric measurements, BALANCE DI, and mAHEI collected at baseline, 4, 8, 12, and 16 weeks, an analysis over time was conducted using generalized estimating equations (GEE) based on the data distribution adjusted for sex, age, and time since the diagnosis of MI. Sensitivity analysis including only participants with complete data at baseline and at 16 weeks were conducted.

Analyzes of pre-specified subgroups were also performed: sex (man vs. woman), age (≥ 60 years vs. < 60 years), type of MI (STEMI vs. non-STEMI), previous diagnosis of stroke, T2DM, hypertension and dyslipidemia (yes vs. no), previous angioplasty and previous revascularization surgery (yes vs. no) and statin treatment regimen (high potency vs. moderate potency vs. low potency/no statins).

For all analyses, statistical tests were conducted with a two-sided significance level of 5%, and the effects, along with their corresponding 95% confidence intervals (CI), were estimated. The analyses were performed utilizing R software, version 4.3.2 (R Foundation for Statistical Computing). Regarding secondary outcomes, it is imperative to acknowledge that the potential for type I error resulting from multiple comparisons was not adjusted for. Consequently, these outcomes should be interpreted in the context of exploration rather than definitive inference.

Changes in study protocol due to COVID-19 pandemic

Due to the timeframe related to the data collection, our study was impacted by the coronavirus 2019 (COVID-19) pandemic. We implemented changes to our protocol aimed at adhering to government recommendations for reducing and controlling infections related to COVID-19, and also those to mitigate risks to trial integrity [32]. As the initial and final consultations included biological samples, patients who were willing to collect it came in person to the laboratory or collected at home. However, patients were scheduled with greater space between appointments to reduce the circulation of people. Besides blood samples, researchers also performed anthropometric measures and patients received a video call to finish completing the questionnaires that did not require their physical presence (such as FFQ and 24-h recalls). Intermediate consultations (visits 2, 3 and 4) were carried out remotely via video call. Patients allocated to the DICA-NUTS group received the kit with mixed nuts at their homes through a delivery person hired for this purpose.

Results

Recruitment and participant characteristics

Between January 2019 and August 2021, 885 individuals were screened. Among them, 497 were excluded because they did not meet the inclusion criteria or had no interest in participating in the study (Fig. 1). In total, 388 males and females who were diagnosed with a previous MI were included in 9 centers distributed in four Brazilian regions (South, Southeast, Midwest and Northeast), 193 were randomized to the intervention group (DICA-NUTS) and 195 to the control group (DICA). Follow-up period ended in December 2021.

Table 1 presents baseline participants characteristics. Participants were predominantly male (72.2%) and white (65.5%). Additionally, 58.6% of participants were classified in lower socioeconomic strata based on self-reported household income, which was at or below 2 minimum wages. The mean age was 59.4 ± 9 years and the mean time since infarction diagnosis was 106.4 ± 36 days. In general, characteristics were balanced between the two groups; however, a greater proportion of individuals in higher economic strata were allocated to the DICA-NUTS group, and participants allocated to the control group were younger. Nevertheless, no statistical differences were found between study groups regarding baseline characteristics.

Table S1 (Supplementary Material) shows the drugs used by both groups at baseline and at the end of the study. In total, 96% of the participants were in some statin treatment regimen at the beginning of the trial, being 94% in use of moderate to high intensity schemes. Table S2 in the Supplementary Material describes the proportion of participants in both groups who achieved the therapeutic targets for lipid profile recommended by Brazilian guidelines for individuals at high cardiovascular risk [33]. The overall proportion of participants who were at target for LDL-c (< 50 mg/dL) remained consistent throughout the study (baseline: 8.3%; end of study: 8.2%).

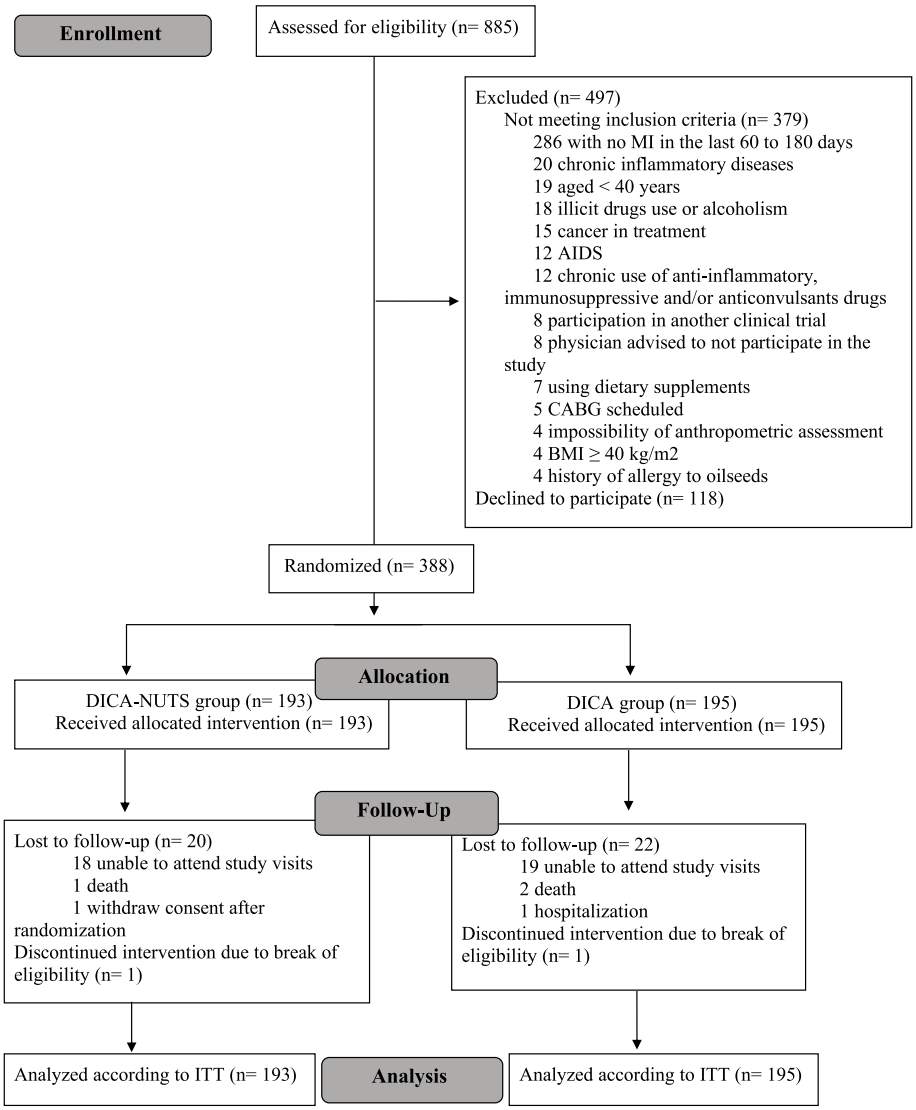

Fig. 1 DICA-NUTS study flowchart. MI: myocardial infarction; AIDS: acquired immunodeficiency syndrome; CABG: coronary artery bypass graft surgery; BMI: body mass index; ITT: intention-to-treat

Retention and adherence

All participants received the interventions according to the allocation group. The DICA-NUTS group had 20 losses to follow-up (18 absences from final consultations and loss of contact, 1 withdrawal of post-randomization consent form and 1 death) and one discontinuation of the intervention due to lack of eligibility (protocol deviation). The DICA group had 22 losses to follow-up (19 absences from final consultations and loss of contact, 1 hospitalization and 2 deaths) and one discontinuation of the intervention due to lack of eligibility. Thus, 173 (89.6%) patients in the intervention group and 173 (88.7%) patients in the control group completed the follow-up. All participants were included in the final intention-to-treat outcome analysis. Figure 1 presents the study flowchart.

The proportion of participants with low levels of physical activity was lower among study completers in comparison to those who did not complete the study (Supplementary Table S3). There were no differences in baseline characteristics according to the study groups among participants who did not complete the study (Supplementary Material Table S4).

Overall visit attendance rates (in-person or online) were 91% at visit 2, 87.4% at visit 3, 85.3% at visit 4, and 89.2% at visit 5 (final), with no differences between groups (P values > 0.18). Among participants in the DICA-NUTS group, 79.8% consumed all of the daily portions of nuts

Table 1 Baseline characteristics of study participants

	DICA-NUTS group	DICA group
Male sex—no./total no. (%)	143/193 (74.1)	137/195 (70.3)
Age, in years, mean (SD)	60.3 (9.7) (*n* = 193)	58.4 (9.1) (*n* = 195)
Race—no./total no. (%)		
White	134/193 (69.4)	120/195 (61.5)
Black	21/193 (10.9)	23/195 (11.8)
Multiracial	35/193 (18.1)	45/195 (23.1)
Other race	3/193 (1.6)	7/195 (3.6)
Family status—no./total no. (%)		
Married	114/193 (59.1)	109/195 (55.9)
Other	79/193 (40.9)	86/195 (44.1)
Scholarity (in years of study)—no./total no. (%)		
< 5 years	34/191 (17.8)	38/193 (19.7)
5 to < 8 years	34/191 (17.8)	41/193 (21.2)
8 to < 11 years	25/191 (13.1)	30/193 (15.5)
11 to < 15 years	58/191 (30.4)	52/193 (26.9)
≥ 15 years	40/191 (20.9)	32/193 (16.6)
Number of minimum wages—no./total no. (%)[a]		
> 2	91/191 (47.7)	68/193 (35.2)
≤ 2	100/191 (52.4)	125/193 (64.8)
Current smokers—no./total no. (%)	14/191 (7.3)	23/193 (11.9)
Alcohol consumption, in g/day, median (IQR)	0 (0—1)	0 (0—0)
Physical activity—no./total no. (%)		
Sedentarism/low levels	68/191 (35.6)	59/193 (30.6)
Moderate/high levels	123/191 (64.4)	134/193 (69.4)
Time of diagnosis of MI, in days, mean (SD)	104.2 (34.9) (*n* = 193)	108.7 (36.1) (*n* = 195)
ST-Elevation MI—no./total no. (%)[b]	105/187 (56.2)	116/187 (62)
non-ST-Elevation MI—no./total no. (%)[b]	82/187 (43.9)	71/187 (38)
Treatment post-event—no./total no. (%)		
Clinical treatment	17/193 (8.8)	25/195 (12.8)
Angioplasty	19/193 (9.8)	18/195 (9.2)
Angioplasty with stent	151/193 (78.2)	148/195 (75.9)
Surgery (bypass)	6/193 (3.1%)	4/195 (2.1%)
Statin treatment regimen—no./total no. (%)		
No statin/low intensity	9/191 (4.7%)	16/193 (8.3%)
Moderate intensity	109/191 (57.1%)	101/193 (52.3%)
High intensity	73/191 (38.2%)	76/193 (39.4%)
Other drugs in use—no./total no. (%)		
Antihypertensive	184/191 (96.3%)	187/193 (96.9%)
Antiplatelet	185/191 (96.9%)	186/193 (96.4%)
Glucose-lowering drugs	57/191 (29.8%)	40/193 (20.7%)
Insulin	20/191 (10.5%)	17/193 (8.8%)
Previous medical diagnosis—no./total no. (%)[c]		
Dyslipidaemia	72/191 (37.7)	84/194 (43.3)
Hypertension	123/191 (64.4)	116/194 (59.8)
Type 2 diabetes mellitus	62/191 (32.5)	49/194 (25.7)
Stroke	10/191 (5.2)	12/194 (6.2)
Glomerular filtration rate, in mL/min/1.73m^2, median (IQR)	75.3 (64—88.7) (*n* = 188)	77.8 (66.1—92.9) (*n* = 190)

MI Myocardial infarction, *SD* Standard deviation, *IQR* Interquartile range

[a] One Brazilian minimum wage represents US$ 285.00. Classification was based on self-reported household income

[b] Obtained from medical records

[c] Self-reported

offered for the period according to the count of empty individual packages at visit 2; for visits 3, 4 and 5, these proportions were, respectively: 81.6%, 76.6% and 78%. In the control group, the contamination rates (number of participants who consumed nuts during the period) for visits 2, 3, 4 and 5 were 24%, 15.2%, 13.5% and 14.2%, respectively. The median number of days nuts were consumed during the control group ranged from 1.5 days per month (IQR 1 – 4, visit 5) to 2 days per month (IQR 1 – 6, visit 2).

Both groups showed an increase in the BALANCE DI, indicating improved adherence to DICA Br at the end of the study (Table S5, Supplementary Material); however, there was no difference between groups (intervention-control difference: 0.11 [-1.65 to 1.86], $P=0.91$). The DICA-NUTS group had a higher score in the yellow category than the control group after 16 weeks of intervention (intervention-control difference: 0.86 [0.13 to 1.58], $P=0.02$). In Table S6 of the Supplementary Material, macro and micronutrients intake according to the groups at the beginning and end of the study are described.

Primary outcome

Table 2 shows the primary outcome after 16 weeks of follow-up according to the DICA-NUTS and DICA groups. After adjustment for baseline values, participating study site, time since MI and statin treatment regimen (high potency, moderate and low potency/no statins) at baseline, no significant difference was found between the groups in LDL-c concentrations (intervention-control difference: 3.48 mg/dL [-3.45 to 10.41], $P=0.32$).

Secondary outcomes

There was no difference between the groups in other lipids/lipoproteins, glycemic features and anthropometrics after follow-up (Table 2).

Diet quality scores for the mAHEI are described in Table 3. Both groups improved their overall mAHEI score at the end of the study; however, there was no difference between groups after 16 weeks (intervention-control difference: 1.05 (-0.9 to 2.99); $P=0.29$). As expected, the DICA-NUTS group had higher scores in the "nuts and soy protein" component compared to the DICA group (intervention-control difference: 1.64 [0.77 to 2.52], $P<0.00$).

Adverse events

Table S7 (Supplementary Material) describes the main adverse events identified during the study, for each group. Approximately 22% of participants experienced at least one adverse event. The most frequent intervention-related adverse event was diarrhea, reported by 11 participants (2.8%). Regarding the occurrence of serious adverse events unrelated to the intervention, 14 participants in the DICA-NUTS group (7.3%) and 18 in the DICA group (9.2%) had some cardiovascular event (new MI, angina, hospitalization) during the study period. No statistical difference between groups was detected regarding occurrence of adverse events.

Subgroup and sensitivity analyses

Sensitivity analyses including only participants with complete data from both groups (Table S8, Supplementary Materials) did not alter the findings for lipids/lipoproteins, glycemic profile, or anthropometrics. Analysis of pre-specified subgroups also did not indicate differences on LDL-c (primary outcome) according to sex (man vs. woman), age (≥ 60 years vs. <60 years), type of MI (STEMI vs. non-STEMI), previous diagnosis of stroke, T2DM, hypertension and dyslipidemia (yes vs. no), previous angioplasty and previous myocardial revascularization (yes vs. no), and statin treatment regimen (high potency vs. moderate potency vs. low potency/no statins) (Fig. 2).

Discussion

This multicenter randomized clinical trial was aimed at evaluating the effects of the DICA Br prescription and 30 g/daily of mixed nuts on LDL-c concentrations among MI patients after 16 weeks. In this trial, there was no significant difference in LDL-c concentrations between the DICA-NUTS and the DICA groups. Other lipids, glycemic profile, anthropometrics and diet quality were also similar between groups. Overall, the addition of nuts to a healthful dietary pattern had similar effects on cardiometabolic markers and diet quality among individuals that have suffered an MI within the previous 2–6 months.

While nut consumption has been shown to improve cardiometabolic factors [34–36] in primary cardiovascular prevention [37, 38] similar effects among populations in secondary prevention for CVD are conflicting. In Brazilians with IHD who consumed one Brazil nut per day (approximately 5 g) for three months, there were no differences in fasting blood glucose [22] or lipid profile [39] at the end of the follow-up compared to the group that did not consume nuts. In another population of Brazilians with stable IHD, consumption of 30 g/day of pecan nuts for three months decreased body mass (-0.9 kg) compared to the control group (healthy diet without nuts) [21]. Among Iranians with stable IHD who consumed between 39 and 60 g/day of a mix of nuts (roasted unsalted pistachios, almonds, and peanuts) added to an isoenergetic hypocaloric diet, there was no difference in BMI and waist circumference in relation to the control group (only low-calorie diet) after 8 weeks [23]. The consumption of pecan nuts for 90 days also did not change LDL-c concentrations in Brazilians [19], as did the consumption of 85 g/day of

Table 2 Primary and secondary biochemical outcomes at baseline and after 16 weeks of follow-up according to study groups

	DICA-NUTS ($n=193$)			DICA ($n=195$)			Between-group mean difference (95% CI)[a]
	Baseline	Final	Final adjusted	Baseline	Final	Final adjusted	
Primary outcome							
LDL-c, mg/dL	87.9 (32.3)	92.7 (35.3)	93.98 (89.21; 98.75)[b]	92.3 (33.7)	91.4 (36.3)	90.21 (85.57; 94.86)[b]	3.77 (-2.9; 10.43)
Secondary outcomes							
Total cholesterol, mg/dL	153.4 (40.4)	159.5 (42.6)	160.85 (155.54; 166.15)[b]	158 (40)	157.9 (41.5)	156.56 (151.34; 161.77)[b]	4.29 (-3.18; 11.76)
HDL-c, mg/dL	41.1 (9.5)	41.9 (10.3)	41.88 (40.72; 43.05)[b]	40.9 (10)	41.7 (10.3)	41.69 (40.52; 42.87)[b]	0.19 (-1.51; 1.89)
VLDL-c, mg/dL	29.5 (15.9)	29.9 (16.7)	30.12 (27.72; 32.51)[b]	29.8 (14.5)	30.1 (19.6)	29.8 (27.24; 32.37)[b]	0.31 (-3.19; 3.82)
Non-HDL-c, mg/dL	112.4 (39.1)	117.6 (41.7)	118.97 (113.69; 124.25)[b]	117.1 (38.1)	116.3 (40.59)	114.86 (109.69; 120.02)[b]	4.11 (-3.31; 11.53)
TC/HDL-c ratio	3.9 (1.2)	4 (1.3)	4.01 (3.85; 4.17)[b]	4 (1.2)	4 (1.3)	3.92 (3.76; 4.08)[b]	0.09 (-0.14; 0.32)
LDL-c/HDL-c ratio	2.2 (0.9)	2.3 (1)	2.37 (2.23; 2.5)[b]	2.4 (1)	2.3 (1.1)	2.28 (2.15; 2.42)[b]	0.08 (-0.11; 0.28)
Triglycerides, mg/dL	147.3 (79.3)	149.3 (83.5)	150.58 (138.58; 162.57)[b]	149.1 (72.5)	150.3 (98.2)	149.02 (136.18; 161.86)[b]	1.56 (-15.97; 19.08)
Triglycerides/HDL-c ratio	3.9 (2.5)	3.9 (2.6)	3.92 (3.55; 4.28)[b]	3.9 (2.3)	3.9 (3.1)	3.89 (3.51; 4.28)[b]	0.03 (-0.5; 0.56)
Glycated hemoglobin, %	6.4 (1.4)	6.4 (1.6)	6.32 (6.17; 6.47)[c]	6.3 (1.3)	6.3 (1.6)	6.4 (6.24; 6.55)[c]	-0.08 (-0.29; 0.14)
Fasting glucose, mg/dL	115.6 (42.8)	117.6 (52.1)	116.06 (110.79; 121.32)[c]	112.9 (39.7)	113.9 (46.8)	115.41 (110; 120.83)[c]	0.64 (-6.88; 8.17)
Fasting insulin, mU/L	15.6 (22.5)	14.6 (21.5)	13.89 (11.37; 16.41)[c]	13.6 (12.7)	15.3 (17.7)	15.98 (13.4; 18.55)[c]	-2.08 (-5.72; 1.55)
HOMA-IR	4.8 (8.5)	4.5 (8.4)	4.17 (3.25; 5.1)[c]	3.9 (4.3)	4.4 (6)	4.7 (3.73; 5.66)[c]	-0.52 (-1.87; 0.82)
Body weight, kg	78 (14.7)	77.9 (14.4)	78.05 (76.05; 80.06)[d]	77.9 (15.6)	77.4 (15.4)	77.24 (75.02; 79.45)[d]	0.82 (-2.19; 3.82)
Body mass index, kg/m^2	28.5 (4.3)	28.5 (4.2)	28.51 (27.89; 29.13)[d]	28.3 (4.5)	28.2 (4.6)	28.17 (27.51; 28.82)[d]	0.35 (-0.56; 1.25)
Waist circumference, cm	98.6 (11.3)	97.8 (10.9)	97.86 (96.22; 99.50)[d]	97.3 (11.5)	96.3 (11.2)	96.26 (94.58; 97.94)[d]	1.6 (-0.77; 3.97)
Waist-to-hip ratio	0.98 (0.08)	0.97 (0.09)	0.968 (0.954; 0.982)[d]	0.97 (0.08)	0.96 (0.08)	0.957 (0.943; 0.971)[d]	0.011 (-0.01; 0.03)
Waist-to-height ratio	0.60 (0.07)	0.59 (0.07)	0.593 (0.583; 0.604)[d]	0.59 (0.07)	0.58 (0.07)	0.582 (0.573; 0.592)[d]	0.011 (-0.003; 0.03)

Data presented as means (SD) and means (95% confidence interval)

TC Total cholesterol, *LDL-c* Low-density lipoprotein cholesterol, *HDL-c* High-density lipoprotein cholesterol, *VLDL* Very low-density lipoprotein cholesterol, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance

[a] DICA-NUTS – DICA group mean difference at 16 weeks

[b] Analysis of covariance adjusted by baseline values, study site, time of myocardial infarction diagnosis, and statin treatment intensity at baseline (high, moderate, or low intensity/no statin)

[c] Analysis of covariance adjusted by baseline values, study site, time of acute myocardial infarction diagnosis, using lowering-glucose drugs (yes or no) and statin treatment intensity at baseline (high, moderate, or low intensity/no statin)

[d] Generalized estimating equations adjusted by baseline values, study site, time of myocardial infarction diagnosis, statin treatment intensity at baseline (high, moderate, or low intensity/no statin) and considering data from visits 2, 3 and 4

almonds among Americans [40]. Consumption of 10 g/day of almonds for 12 weeks reduced LDL-c concentrations (-~40%) from baseline to a greater extent than the control group (-~10%) in Pakistanis with a history of IHD [20]. A series of methodological differences likely explain the conflicting results, such as the small number of participants included in the trials; the lack of standardization of control groups; the different quantities and type of nuts offered, different follow-up times; different study designs (parallel vs. crossover clinical trials); and the reporting of outcomes that were not considered primary. This trial did not show differences in cardiometabolic markers when providing nuts and guidance on a healthful dietary pattern versus guidance alone among individuals 2–6 months following an MI. The degree of IHD in our participants may partly explain the differences in effect, as IHD presents with various clinical manifestations [41]. Unlike other trials that evaluated nut consumption in a secondary prevention setting, we specifically chose the rehabilitation phase following MI to test our intervention. Further research is needed to understand at what stage of IHD the addition of nuts may affect cardiometabolic markers or if more aggressive nutritional interventions are needed to support patient care.

Table 3 mAHEI component scores and total mAHEI scores at baseline and after 16 weeks of follow-up according to the study groups

	DICA-NUTS	DICA	Between-group mean difference (95% CI)[a]
Ratio of fish/(meat + eggs)			
Baseline	0.6 (2.3) (*n* = 190)	0.7 (2.3) (*n* = 193)	
Final	0.5 (1.9) (*n* = 171)	0.5 (2) (*n* = 170)	
Final (adjusted)[b]	0.41 (0.11; 0.71)	0.48 (0.17; 0.78)	-0.06 (-0.48; 0.36)
Vegetables			
Baseline	2.8 (3) (*n* = 190)	2.7 (2.8) (*n* = 193)	
Final	3.1 (3) (*n* = 171)	3.5 (3.1) (*n* = 170)	
Final (adjusted)[b]	3.02 (2.54; 3.5)	3.36 (2.86; 3.87)	-0.34 (-0.94; 0.27)
Fried foods			
Baseline	8.2 (3.45) (*n* = 190)	8.2 (3.4) (*n* = 193)	
Final	8.5 (3.12) (*n* = 171)	8.4 (3.28) (*n* = 170)	
Final (adjusted)[b]	8.37 (7.84; 8.9)	8.15 (7.6; 8.7)	0.22 (-0.44; 0.89)
Fruits			
Baseline	4.1 (3.67) (*n* = 190)	4.3 (3.81) (*n* = 193)	
Final	5 (3.58) (*n* = 171)	5.2 (3.57) (*n* = 170)	
Final (adjusted)[b]	5.32 (4.68; 5.96)	5.51 (4.88; 6.14)	-0.19 (-0.91; 0.54)
Whole grains			
Baseline	3 (3.95) (*n* = 190)	3 (4.04) (*n* = 193)	
Final	3.2 (3.89) (*n* = 171)	3.4 (3.99) (*n* = 170)	
Final (adjusted)[b]	3.22 (2.53; 3.91)	3.38 (2.73; 4.03)	-0.16 (-1; 0.69)
Nuts and soy protein			
Baseline	5.4 (4.68) (*n* = 190)	6.8 (4.29) (*n* = 193)	
Final	8 (3.85) (*n* = 171)	6.3 (4.53) (*n* = 170)	
Final (adjusted)[b]	7.93 (7.24; 8.63)	6.29 (5.55; 7.03)	1.64 (0.77; 2.52)[1]
Alcohol intake			
Baseline	0.12 (0.95) (*n* = 190)	0.12 (0.98) (*n* = 193)	
Final	0.12 (0.98) (*n* = 171)	0.25 (1.33) (*n* = 170)	
Final (adjusted)[b]	0.09 (-0.05; 0.23)	0.22 (0.02; 0.41)	-0.13 (-0.38; 0.12)
Total mAHEI score			
Baseline	24.4 (9.2) (*n* = 190)	25.8 (9.1) (*n* = 193)	
Final	28.3 (9.1) (*n* = 171)	27.5 (9.7) (*n* = 170)	
Final (adjusted)[b]	28.37 (26.86; 29.88)	27.32 (25.82; 28.83)	1.05 (-0.9; 2.99)

Data expressed as means (SD)

mAHEI Modified Alternative Healthy Eating Index, which ranges from 0 to 70 points. mAHEi was calculated from 24 h dietary recalls

[a] DICA-NUTS – DICA group mean difference at 16 weeks. [1] *P*-value < 0.001

[b] Generalized estimating equations adjusted by baseline values, study site, time of myocardial infarction diagnosis, statin treatment intensity at baseline (high, moderate, or low intensity/no statin) and considering observations from visits 2, 3 and 4

Individuals with IHD are often taking multiple drugs, many of which directly interfere with effects of nuts on cardiometabolic parameters (lipids, glycemic and anthropometric features) measured in this trial. Statins, the basis of drug treatment for MI, are known to modify glycemic indicators. Although the mechanisms are not yet fully established, statins may decrease insulin secretion by increasing the expression of the LDL receptor in the pancreas with consequent accumulation of cellular LDL-c, resulting in lipotoxicity in pancreatic β-cells [42]. Furthermore, statins contribute to insulin resistance by activating AMPKα and blocking AKT in skeletal muscles [43] reducing glucose uptake by adipocytes [44] upregulation of genes involved in hepatic gluconeogenesis, and generation of short-chain acyl carnitines by modifying the metabolism of branched-chain amino acids [42]. Statins are also related to an increase in body mass (which in itself impairs lipid and glycemic parameters), probably by decreasing the expression of leptin in adipocytes [45]—with a consequent increase in food

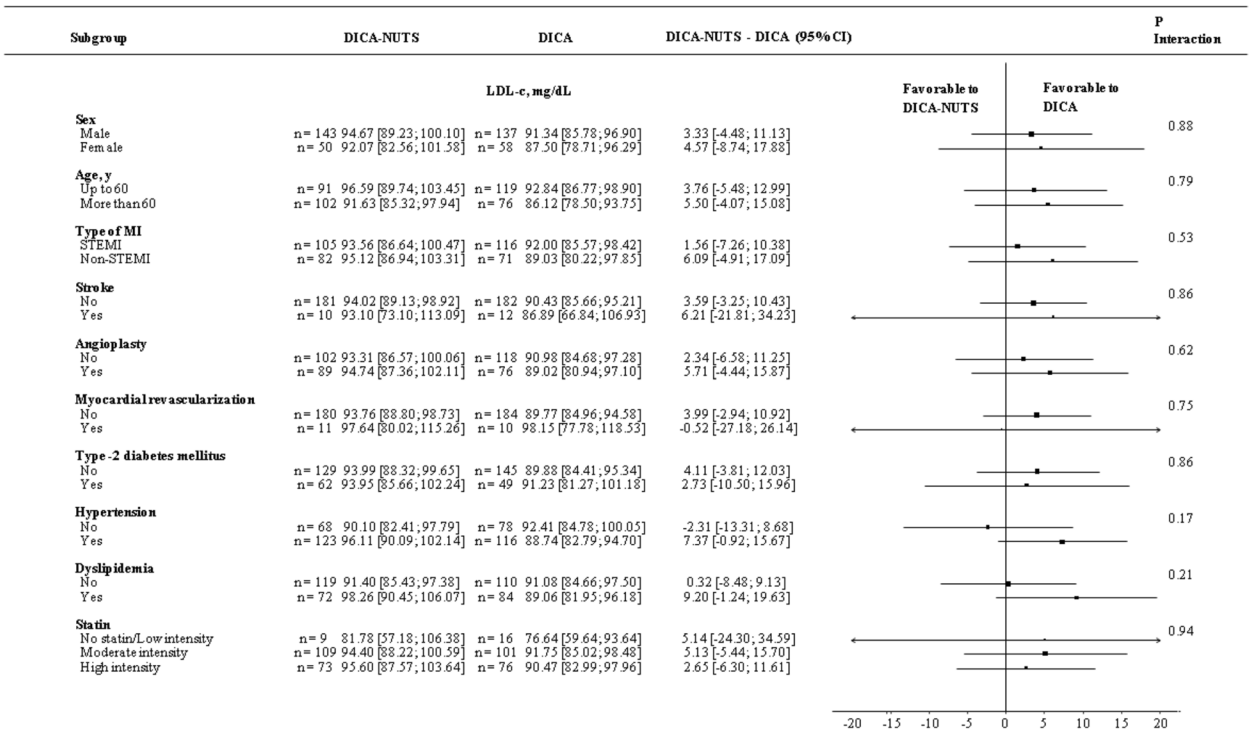

Fig. 2 Subgroup analyses on DICA-NUTS trial regarding low-density lipoprotein cholesterol levels (LDL-c, primary outcome) after 16 weeks of follow up. MI: myocardial infarction; STEMI: ST-Elevation MI. Type of MI was obtained from medical records; previous medical diagnosis (stroke, type-2 diabetes mellitus, hypertension, and dyslipidemia) were self-reported

consumption and a decrease in energy expenditure—and by the false sensation of improvement of the lipid profile mediated only by the medication – leading to less dietary control [46]. On the other hand, some classes of antihypertensive medications (such as first-generation beta-blockers and potassium-losing diuretics) can negatively modify the lipid profile [47]. Most participants included in the DICA-NUTS trial were under statins (94.2% at the end of the study) and other drugs, being subject to their potential effects on the cardiometabolic parameters evaluated in the study. Even though the use of medications was considered in our adjusted analyses, we did not rule out a probable residual effect related to the synergy of these drugs on the outcomes evaluated. In this sense, even with already well-established beneficial effects [18], the quantity of nuts offered in our study as well as the intervention time may have been insufficient to observe a more robust result, considering the impact of the medications used by the participants on the outcomes evaluated—which likely masked the effects of the diet. Noteworthy is the fact that 92.3% of the participants who completed DICA-NUTS trial were in use of moderate to high intensity statin schemes.

The type of nut offered may also have contributed to our results, as in general walnuts, pistachios and almonds, foods not typical of the Brazilian diet, tend to have a greater impact on the lipid profile [48–50]. However, we chose to offer locally accessible and lower-cost nuts with the aim of respecting the local culture and the possibility of implementation in clinical practice after completion of the study. Also noteworthy is the fact that nuts (especially heat-treated and roasted ones), due to their high lipid and protein content, are dietary sources of glyoxal and methylglyoxal, reactive α-dicarbonyl compounds precursors of dietary advanced glycation end products (dAGEs) [51]– which are related to worsening of cardiometabolic markers [52]. Although the participants were instructed to consume the nut mix preferably fresh, we do not rule out the hypothesis that some may have used it as a culinary ingredient in recipes in which there was heat treatment; this may have improved adherence to the intervention, but it might also have negatively contributed to our results.

Among approximately 4,100 male and female who survived an MI in the US, those who adhered to a high-quality diet (identified by the Alternative Healthy Eating Index 2010 [AHEI-2010]) had a 24% lower risk (HR 0.76, 95% CI 0.60 to 0.96) for total mortality compared to those with low quality diets; however, in this study, there was no association between diet quality and cardiovascular mortality [6].

Diet quality improved from baseline to 16 weeks of follow-up in both groups of the DICA-NUTS trial. Component scores for nuts and soy were higher following the DICA Br and nuts group versus control reflecting compliance to the intervention. However, the control group still scored higher than expected in the nuts and soy category despite advice to avoid nuts during the trial. Although diet recalls were only performed in the prior 24 h, higher-than-expected consumption of nuts and soy in the control group may be a contributing factor to the lack of difference between groups in cardiometabolic features. Also, total mAHEI scores remained low (~40%) in our population despite an increase from baseline; in this regard, we believe that the small improvement in the overall diet quality, combined with the short study follow-up period, may have been insufficient to positively impact the primary study outcomes. Total mAHEI scores may be biased towards lower values since consumption of no alcohol results in a 0 for that category. Most participants in our trial are likely to avoid alcohol following an MI. Other component scores revealed a dietary pattern that suggests participants knew well what foods to avoid (e.g., fried foods) but had inadequate intakes of healthful foods (e.g., fruits, vegetables, fish, whole grains). This may reflect the dietary guidance received by participants from the time of hospital discharge, considering that in Brazilian public institutions (the main setting where the DICA-NUTS study was conducted), the encouragement to consume cardioprotective foods such as fruits, vegetables, and legumes appears to be lower, with recommendations focusing more on restricting fats, fried foods, and sodium [53]. Future trials involving dietary interventions for secondary prevention may prioritize consumption of healthful foods to influence cardiometabolic outcomes rather than foods that should be avoided.

Although we made changes to our protocol to minimize the damage caused by the COVID-19 pandemic and guarantee the integrity of the study, the DICA-NUTS trial was impacted by the restrictions imposed at the time – mainly in relation to the collection of the primary outcome, as well as other clinical studies conducted around the world [54]. Elderly Americans with multiple comorbidities, for example, were asked about their interest in participating in clinical studies between May and September 2020, and 32% reported that they were not interested in studies that required blood collection and 27% for those whose intervention was related to changing lifestyle [55]. Furthermore, there was a worsening of food security and diet quality [56], as well as access to health services during periods of isolation, especially in low-income/developing countries. These factors need to be considered when interpreting our results; however, we believe that the possibility of conducting visits online, the option for home blood collection, and the delivery of the nuts (for the intervention group) to participants' homes, along with the support provided by the researchers, contributed to participant retention in this study. The fact that participants did not experience impairment in their diet quality and body weight during pandemics might be a positive result to be considered.

Brazil is a large country with cultural differences between states, so one of the main strengths of our study was being multicenter. Our results can be considered nationally representative, since we included participants from different regions of Brazil. Another strength of our study is the fact that we limited the time since the MI from 2 to 6 months. In general, studies investigating dietary interventions on this timeframe are scarce [57, 58], but they are particularly relevant to better guide dietary recommendations and further contribute to intensive lifestyle changes that are being implemented during the rehabilitation period. We also analyzed the nutrient composition of the mixed nuts to more accurately quantify the actual doses provided to participants. Among the study limitations, participants randomized during the restrictions imposed by the COVID 19 pandemic had intermediate consultations (visits 2, 3 and 4) performed via phone or video call, which made it challenging to provide nutritional education regarding the DICA Br and evaluating adherence to nuts supplementation, in addition to the impaired evaluation of most outcomes. Also, due to the characteristics of the intervention, participants and dietitians performing the visits were not blinded. However, statisticians and staff were blinded to the intervention groups. Another limitation is regarding recall bias related to both 24-h recall and FFQ, which may not demonstrate the participant's real food intake [59]. Secondary outcomes may have an inflated risk of type I error since p values were not adjusted for multiple comparisons [60]; in this sense, significance among secondary outcomes should be considered hypothesis-generating. And finally, more than 90% of the participants were using statins and basal LDL-c concentrations were low – despite most were not at the therapeutical lipid targets suggested for this population; therefore, the difficulty of further reducing lipids biomarkers in these patients is greater [13].

Conclusion

In this multicenter randomized controlled clinical trial, there was no significant effect of including affordable mixed nuts to the DICA Br on LDL-c in individuals after MI. However, improvements on diet quality were observed among participants following the DICA Br. Further studies are needed to better define lipid modulation of patients with recent MI in response to culturally adapted and sustainable dietary interventions.

Abbreviations

AHEI-2010	Alternative Healthy Eating Index 2010
AIDS	Acquired Immunodeficiency Syndrome
BALANCE DI	BALANCE Dietary Index
BMI	Body mass index
CABG	Coronary artery bypass graft
CI	Confidence intervals
Cr	Serum creatinine
CRF	Case report form
CVD	Cardiovascular disease
dAGEs	Dietary advanced glycation end products
DICA Br	Brazilian Cardioprotective Diet (*Dleta CArdioprotetora Brasileira)*
eGFR	Estimated glomerular filtration rate
FFQ	Food frequency questionnaire
FG	Fasting plasma glucose
FI	Fasting insulin
GEE	Generalized estimating equations
HbA1c	Glycated hemoglobin
HDL-c	High-density lipoprotein cholesterol
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
IHD	Ischemic heart diseases
IQR	Interquartile ranges
ITT	Intention-to-treat
LDL-c	Low-density lipoprotein cholesterol
mAHEI	Modified Alternative Healthy Eating Index
MedDiet	Mediterranean Diet
MI	Myocardial infarction
MUFA	Monounsaturated fatty acids
NHDL-c	Non-HDL cholesterol
PUFA	Polyunsaturated fatty acids
SD	Standard deviation
SFA	Saturated fatty acids
STEMI	ST-Elevation MI
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
VLDL-c	Very low-density lipoprotein cholesterol

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-024-01020-5.

Additional file 1: Appendix I: Consolidated Standards of Reporting Trials (CONSORT) checklist. Supplementary Methods I: the DICA Br approach and examples of foods included in groups green, yellow, blue, and red. Supplementary Methods II: Content of phenolic compounds in peanuts, Brazil nuts, and cashew offered in the DICA-NUTS trial (in micrograms [ug]). Table S1. Drugs in use at baseline and after 16 weeks according to study groups. Table S2. Participants who achieved therapeutic targets for lipid profile according to study groups at baseline and after 16 weeks. Table S3. Comparison of baseline characteristics of study completers versus the participants who did not complete the study. Table S4. Comparison of baseline characteristics among individuals who did not complete the study according to study groups. Table S5. Adherence to BALANCE Dietary Index at baseline and after 16 weeks of follow-up according to groups. Table S6. Energy and nutrients intake at baseline and after 16 weeks of follow-up according to groups. Table S7. Adverse events reported according to study groups. Table S8. Sensitivity analysis for primary and secondary outcomes, including only participants with complete data according to study groups.

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Authors' contributions

Conceptualization, A.M. and A.C.B-F.; Methodology, A.M.; A.C.B-F.; A.S.Q.; R.H.N.S. and A.B.C; Formal Analysis, R.H.N.S. and G.R.S.; Investigation, C.W.; J.L.S; L.R.S.; G.C.S.; S.M.P.; A.P.T.F.; D.S.B.; A.P.P.F.C.; M.M.A.M.; S.M.V.; M.V.R.S.; J.A.F.N.; L.P.P.D.; F.E.Z.N.; C.C.P.A.; A.S.B.M. and R.D.O.; Data Curation, R.H.V.M.; D.H.K.M. and E.R.R.S.; Writing – Original Draft Preparation, A.C.B-F.; C.W.; T.M.R and A.M.; Writing – Review & Editing, all authors; Supervision, A.M.; E.O.A-S; M.M.R.; E.A.F.S.T. and A.B.C.; Project Administration, A.M; R.H.V.M. and L.N.L.; Funding Acquisition, A.M.; B.W. and A.B.C. All authors read and approved the final manuscript.

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Availability of data and materials

Data and materials are available upon reasonable request for the corresponding author, after filling a specific form provided by IP-Hcor and considering the institutional data sharing politics.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Ethics Committee (REC) of Hcor (CAAE 95382518.6.0000.0060 and number 2.826.317: first version of the protocol in 08/16/2018; first amendment in 10/05/2018; second amendment in 11/14/2018; third amendment in 02/11/2019; and fourth amendment in 05/15/2019). The study was also approved in all study sites´ REC. Informed consent was obtained from all participants involved in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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