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Original article

Association of rs670 variant of APOA-1 gene with cardiometabolic markers after consuming sesame, canola and sesame-canola oils in adults with and without type 2 diabetes mellitus

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SUMMARY

Background & aims: The inter-individual variations of the metabolic markers in response to dietary interventions may be mediated by genetic factors. We examined whether the type of dietary oils can modulate the effects of −75G/A polymorphism in *APOA-1* gene on cardiometabolic markers.
Methods: This study was a randomized, triple-blind, cross-over clinical trial. Participants with and without type 2 diabetes were randomly assigned to replace their regular oil with sesame oil, canola oil and sesame-canola oil for 9 weeks. Genotyping was conducted using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method.
Results: Ninety-five diabetes patients and 73 healthy individuals completed the study protocol. In patients with type 2 diabetes, the A allele carriers experienced greater decrease in systolic blood pressure compared with GG homozygotes following sesame-canola oil intake. Serum levels of HDL-C and TG: HDL ratio was increased and decreased following canola oil intake in patients carrying the A allele rather than non-A allele carriers, respectively. More reductions for risk of cardiovascular diseases and mortality, except risk of stroke were found in the A allele carriers compared with GG homozygotes after intakes of canola and sesame-canola oils, but not sesame oil. There was also a significant genotype effect as well as genotype-dietary oil interactions on cardiovascular risk scores. In healthy individuals, a considerable decrease in visceral fat was accompanied by a significant increase in HDL-C levels in the A allele carriers compared with non-A allele carriers after sesame oil intake.
Conclusion: Patients with diabetes carrying the A allele might benefit from canola and sesame-canola oils intakes, and healthy A allele carriers from sesame and sesame-canola oils intakes as well. Future clinical trials are recommended to warrant current findings.

1. Introduction

Cardiovascular disease (CVD) is the major cause of mortality, accounting for 30 percent of total deaths, globally [1]. The lifestyle modifications specifically dietary interventions are considered as effective options to reduce the burden of CVD [2]. The emerging

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evidence supports that the replacement of saturated fatty acids (SFAs) with unsaturated fatty acids, mono- (MUFAs) and poly-unsaturated fatty acids (PUFAs), could favorably affect cardiovascular risk factors [3,4].

Sesame oil (SO) which is widely used, especially in Asian countries, has considerable amounts of MUFAs (40%), PUFAs (43%) and lignans (sesamin, episesamin, and sesamolin) [5]. Canola oil (CO) is also another common plant-based oil which contains high amounts of MUFAs (64%), moderate amounts of PUFAs (28%), and low amounts of SFAs [6]. Although the health effects of dietary sesame and canola oils are adequately investigated in a wide range of clinical studies, the results are not convincing [7–9]. It has been shown that dietary fats cause different cardiometabolic responses and this might be mediated by genetic features [10,11].

APOA-1 gene is highly polymorphic and its common single nucleotide polymorphisms (SNPs) have been extensively investigated in relation to lipid profile markers [12]. A common G-to-A transition located at 75 bp upstream from transcription start site of *APOA-1* gene (rs670) has been reported by previous investigations [13]. While the presence of the A allele has been associated with higher apoA-1 and HDL-C concentrations in a number of the studies [14–16], other literature revealed null or negative associations between this polymorphism and serum lipid levels [17,18]. It has also shown that −75G/A SNP may cause considerably different serum low density lipoprotein cholesterol (LDL-C) as well as metabolic syndrome risk in response to the change in the dietary fat intake [19,20]. Indeed, it seems that cardiovascular risk factors can be influenced by genetic and dietary factors as well as their interactions [21].

Different cardiometabolic response to dietary oils varying in their MUFAs and PUFAs content may be explained by this −75G/A *APOA-1* SNP. Interactions between dietary oils and this SNP may contribute to changes in cardiovascular risk factors, rather than the individual effects of each dietary or genetic factor. Nevertheless, such hypothesis needs to be confirmed. To the best of our knowledge, no study has been conducted to assess the interaction effects of dietary sesame and canola oils with −75G/A polymorphism in *APOA-1* gene on cardiometabolic risk markers. Therefore, the aim of this study was to examine the effects of this polymorphism on some of cardiovascular risk factors such as obesity parameters, apolipoproteins and lipoproteins, glucose metabolism markers, and blood pressure as well as risk of different CVDs and mortality following the intake of sesame and canola oils and also a mixture of them in adults with and without type 2 diabetes mellitus (T2DM).

2. Methods

2.1. Study design

The current study is done in the context of a randomized triple-blind, cross-over, clinical trial which was designed to assess the effects of sesame, canola and sesame-canola oils (SCO) on cardiometabolic markers in participants with T2DM and their spouses. The complete methodology of the study has been published elsewhere [22]. Briefly, during a 4-week run-in period, sunflower oil was consumed, and then participants randomly received SO, CO and SCO in the intervention phases. Intervention phases lasted for 9 weeks and were separated by 4-week wash-out periods (sunflower oil was provided). The participants were clinically visited at the beginning, in the middle, and at the end of each intervention phase. The investigators received the oils, which were packaged in similar bottles and were labeled with three codes (S, B, and G). Moreover, during production of oils, the process of odor removal form oils was performed. Hence, neither the participants nor the personnel were aware of the intervention oils until the end of the study. To monitor the participants' compliance, any given and returned bottles of oil were weighted, and then the approximate amounts of consumed oils were measured. Three-day weighed food records were also completed to assess the amounts of consumed oils by the participants. The fatty acids content of three intervention oils including SO, CO, and a blended product of 40% sesame and 60% canola oils in addition to sunflower oil was assessed using gas chromatography with a flame ionizer detector (GC-FID) (results have been previously reported in the study protocol) [22].

The parent clinical trial was ethically approved by the ethics committee of Shahid Sadoughi University of Medical Sciences, Yazd, Iran (approval code: IR.SSU.REC.1395.25) and its protocol was registered in the Iranian Registry of Clinical Trials (IRCT) on 14th November 2016 (registration ID: IRCT2016091312571N6) [22]. The current study also received the ethical approval from the ethics committee (approval code: IR.SSU.SPH.REC.1397.139) separately. Written informed consents were obtained from all participants for all stages of the study including blood sampling and bio-banking of blood fractions as well as genetic analyses.

2.2. Study participants

In the parent clinical trial, 574 couples were screened through telephone calls and 162 couples were referred to an initial visit for further eligibility assessment. As it is provided in Fig. 1, from these 162 couples, 48 couples did not meet inclusion criteria and 12 couples did not intend to participate in the study. Therefore, in overall, 102 couples were included in the parent study and were randomized to receive the intervention oils [22].

For the current study, we included those with T2DM and also healthy spouses. Patients who had a minimum of 6 months or a maximum of 10 years history of T2DM with the following criteria were included in the current study: 1) aged older than 18 years, 2) took oral anti-glycemic agents not insulin, 3) did not change the dose of lipid lowering drugs at least for 3 months prior to starting the study, 4) had HbA1c values less than 8%. As we aimed to examine the associations in healthy participants, those spouses without history of diabetes (fasting blood glucose less than 126 mg/dL and/or HbA1c less than 6.5%) were also included in the current study. Participants with history of any other diseases like CVD (coronary artery disease, stroke, and congestive heart disease) and coronary artery bypass grafting, kidney or liver diseases, thyroid disease, and any types of cancer were not included. Moreover, dramatic changes of dietary habits and medications (underwent insulin therapy), pregnancy or chronic diseases like CVD or cancer experiences during study, and unwillingness to continue the study for any reason led to exclusion of the participants.

2.3. Anthropometric and blood pressure measurements

Body weight and composition as well as blood pressure were measured at the start, in the middle, and at the end of each treatment phase. Weight was measured without shoes and with light clothing to the nearest 0.1 kg with a calibrated scale (Omron, Japan, model: BF51). Height was measured in a standing position, without shoes, with a wall-fixed tape. Using a non-stretchable measuring tape, waist circumference was measured based on the standardized method to the nearest 1 cm. Body mass index (BMI) was computed by dividing weight (kg) by height squared (m^2). The percentage of muscle mass, total body and visceral fat were also assessed using a body composition analyzer (Omron, Japan model: BF51). Systolic and diastolic blood pressure (SBP and DBP, respectively) were measured by a well-trained investigator using a mercury sphygmomanometer (Riester, Germany, model: Diplomat-presameter) while participants were in a sitting position and after resting for

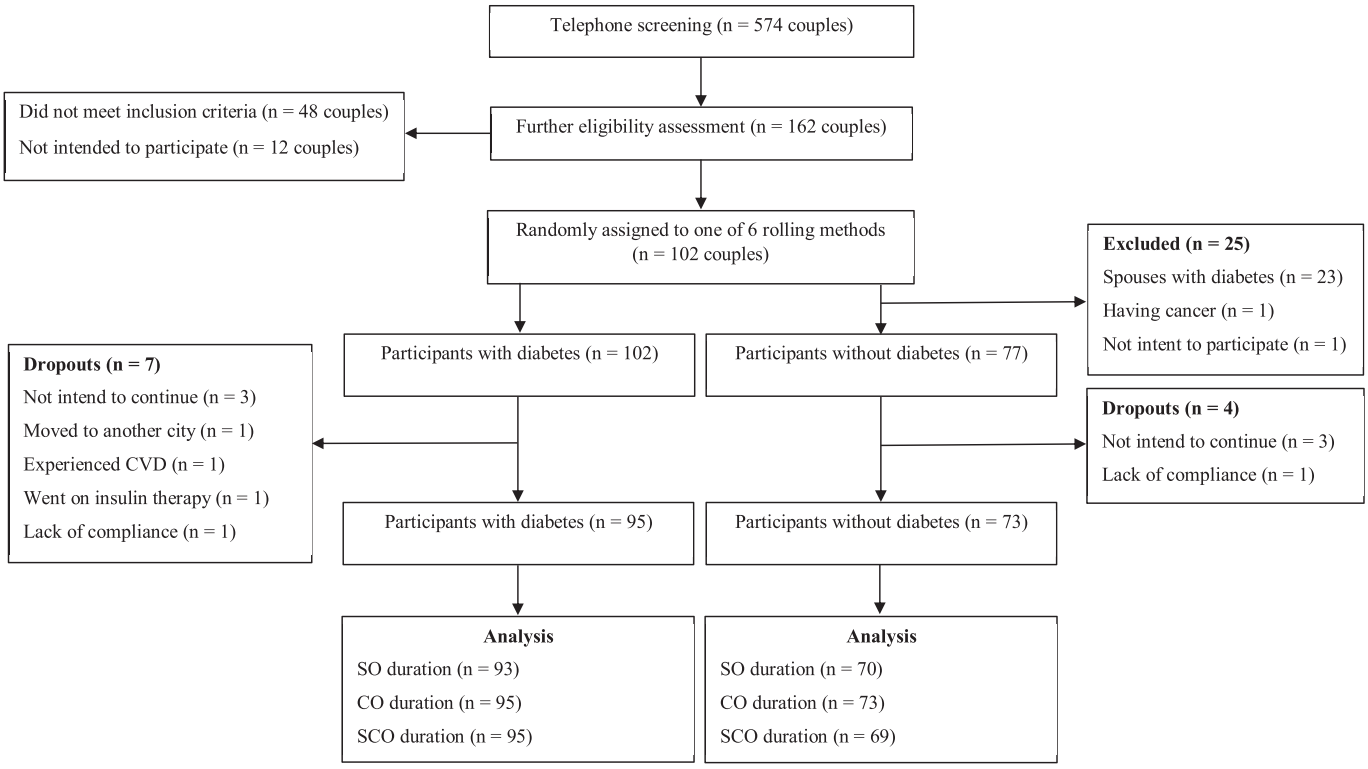

Fig. 1. Flowchart of study participation process. CVD, cardiovascular disease; CO, canola oil; SO, sesame oil; SCO, sesame-canola oil.

at least 5 min. All measurements were done three times and the mean values were recorded [22].

2.4. Blood markers' assessment

Venus blood samples were taken from participants after an overnight fast and then were aliquoted in DNase- and RNase-free microtubes and stored at −80 °C freezer until the biochemical analysis. Fasting blood sugar (FBS), serum total cholesterol (TC), triglyceride (TG), LDL-C, HDL-C, apoA-1, apoB, lipoprotein (a), and liver enzymes [alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyltransferase (GGT)] were measured using an auto-analyzer (model AT++, Alpha-classic, Iran) and commercial kits (Pars Azmun, Tehran, Iran). Fasting serum insulin levels were measured using enzyme-linked immunoassay (ELISA) kits (Mono-bind, USA). The assay sensitivity was 0.75 μIU/ml and the intra- and inter-assay CVs for serum insulin were 3.1% and 5.9%, respectively. Quantitative insulin sensitivity check index (QIUCKI) and hemostatic model assessment of insulin resistance (HOMA-IR) were calculated using suggested formulas [23,24]. The scores of cardiovascular risks [risk of coronary heart disease (CHD), risk of myocardial infarction (MI), risk of stroke, risk of CVD, risk of CHD death, and risk of CVD death] were estimated using age, gender, SBP, TC, and HDL-C suggested in the Framingham equations [25].

2.5. DNA amplification and genotyping

DNA samples were isolated from whole blood samples using the DNJia Blood Kit (Roje Technologies, Iran), according to the manufacturer's protocol. The −75G/A SNP (major allele: G, minor allele: A) was genotyped by the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. The following primers were used for PCR: forward 5′-CACCTACCCGTCAGGAAGAGC-3′; reverse 5′-GACA-GAGCTGATCCTTGAACTCTTAAG -3′. PCR reactions were performed in a final volume of 20 μL, containing 1 μL extracted DNA, 0.5 μL (5 pmol) of each primers, 10 μL Master Mix (Ampliqon; Denmark), and 8 μL distilled water. DNA templates were denatured at 95 °C for 5 min; amplification consisted of 30 cycles at 95 °C for 30 s, annealing at 58 °C for 30 s, with a final extension at 72 °C for 5 min. Amplified DNA (5 μL) was digested with 5 U restriction enzyme MspI (Fermentase, Lithuania) at 37 °C, overnight. All products were visualized by electrophoresis in 3% agarose gel (SinaClon, Iran) at 100 V for 2.5 h. The accuracy of the genotyping was confirmed by direct gene sequencing of randomly selected samples.

2.6. Dietary and physical activity assessment

Three-day weighed food records (2 weekdays and 1 weekend day) were obtained from participants at the start, in the middle and at the end of the intervention periods to measure the energy and nutrients intake. All of the participants were taught to fill the food records by a trained nutritionist before their enrollment. The daily energy and nutrients were computed using Nutritionist IV software (version 3.5.2, Axxya Systems, Redmond, Washington, USA), modified for Iranian foods. Three-day records (2 weekdays and 1 weekend day) were used to assess participants' physical activity at the start, in the middle and at the end of each treatment phase. The participants were asked to keep their physical activity constant during the study period. The physical activity data were converted to metabolic equivalent-min per day, using the updated version of the compendium of physical activities [26].

2.7. Statistical analysis

The Kolmogorov–Smirnov test was used to determine the distribution of quantitative variables. All analyses were separately

conducted for participants with and without T2DM. The mean baseline values were compared between genotypes using one-way analysis of variance (ANOVA). Hardy–Weinberg equilibrium was assessed by a chi-square test. The effects of dietary oils, −75G/A SNP and their interaction on cardiometabolic factors were investigated by using linear mixed model. Potential confounders like age, gender, baseline BMI, calculated consumed oils per subject, changes in the energy intake as well as physical activity status were considered for adjusting models. Within-period comparisons were also performed using a mixed linear model with the same adjustments. The results are presented as means with corresponding standard error of the mean. Statistical analysis was carried out using IBM SPSS (version 24; IBM Corporation, USA). $P \leq 0.05$ was considered as statistically significant for all analyses.

3. Results

Ninety-five patients with T2DM and 73 healthy individuals completed the study protocol and were included in the current analysis. The study participation process is provided in Fig. 1. The genotype distributions were as follows: 69 (72.6%), 25 patients (26.3%), and 1 (1.05%) were GG, AG, and AA for patients with T2DM, respectively; and 55 (75.3%), 16 (21.9%), and 2 (2.7%) healthy individuals were GG, AG, and AA, respectively. The variant of *APOA-1* gene was in Hardy–Weinberg equilibrium in patients with T2DM ($P = 0.439$) and healthy participants ($P = 0.532$).

Baseline characteristics including anthropometric measurements, blood pressure and fasting biomarkers as well as risk of different CVDs and mortality for patients with T2DM and healthy individuals according to −75G/A *APOA-1* genotypes, are presented in Table 1. Gender distribution was 49 women and 46 men for patients with T2DM and 41 women and 32 men for non-diabetes individuals. Although the mean age was different between genotype groups for patients with T2DM ($P = 0.026$), it was not significantly different for non-diabetes individuals ($P = 0.972$). There was no evidence of a genotype-dependent difference in baseline anthropometric measurements, blood pressure, liver enzymes and glycemic indices for both populations. The analysis revealed that those with T2DM carrying GG genotype had significantly higher serum levels of TC, LDL-C and apoB rather than the A allele carriers (AG/AA). Serum levels of apoB and apoB: apoA-1 ratio were also higher in healthy individuals with GG genotype compared to the A allele carriers. Although the risks of MI, CVD and CHD death tended to be higher in diabetes patients carrying the A allele in comparison to those with GG genotype, inversely tended to be lower in non-diabetes individuals carrying the A allele.

In both included samples (diabetes and non-diabetes), no significant differences were observed between the intervention periods in terms of physical activity as well as total energy and the energy percent derived from protein, carbohydrate and fat intake. Nevertheless, dietary intake of MUFAs and PUFAs in diabetes patients and also SFAs in healthy individuals were considerably different between the intervention periods. The canola oil period provided the highest amount of MUFAs and lowest amount of PUFAs and SFAs compared to the other intervention periods (Supplemental Table 1).

3.1. The effect of dietary oils and genotype on cardiometabolic markers in patients with T2DM

3.1.1. Anthropometric measurements, blood pressure and liver enzymes

The multivariable adjusted change values for anthropometric measurements, blood pressure, and liver enzymes in T2DM patients across three treatment periods and -75G/A *APOA-1* genotypes are presented in Table 2. No significant differences between genotypes were observed for change values of body weight and composition (BMI, WC, visceral fat, body fat, muscle mass), blood pressure (SBP, DBP) and liver enzymes (ALP, GGT, AST, ALT) during the three dietary oil treatment periods, except a significant difference in two genotype groups for SBP changes following intake of SCO (GG vs. AG/AA, 0.05 ± 0.15 mmHg vs. -0.56 ± 0.25 mmHg, $P < 0.05$). No independent or interaction effects of dietary oils and genotypes were found for the mentioned outcomes (Table 2).

3.1.2. Blood lipid and glycemic control markers

Within-period analysis revealed no significant differences in change values of lipid profile (TC, TG, HDL-C, LDL-C and Lp (a)), apolipoproteins (apoA-1, apoB and apoB: apoA-1) and glycemic indices (FBS, insulin, HOMA-IR and QUICKI) between genotypes following SO and SCO treatments; nevertheless, the changes values for HDL-C and TG: HDL levels were significantly increased and decreased in patients carrying the A allele compared to those with GG genotype after CO intake (GG vs. AG/AA, 0.39 ± 0.92 mg/dL vs. 4.33 ± 1.52 mg/dL for serum HDL-C, and GG vs. AG/AA, 0.99 ± 1.12 mg/dL vs. -3.58 ± 1.85 mg/dL, for TG: HDL levels, Table 2). There was also a significant impact of genotype on LDL: HDL, TC: HDL and TG: HDL change values regardless of dietary oil interventions ($P = 0.010$, $P = 0.009$ and $P = 0.010$, respectively); indeed, these ratios significantly reduced in participants carrying the A allele compared with GG homozygotes. There were no independent or interaction effects of dietary oils and genotypes for other lipid and glycemic control markers (Table 2).

3.1.3. Risk of cardiovascular diseases and mortality

Within-period analysis shed light on a considerable difference in all of CVDs risk and their corresponding risk of mortality (risk of CHD, risk of MI, risk of CVD, risk of CHD death and risk of CVD death), except risk of stroke after SCO and CO intake, but not SO intake; greater risk reductions were found in the A allele carriers compared with GG homozygotes. While no detectable effects of dietary oils were observed for the mentioned variables, there was a significant genotype effect as well as genotype-dietary oil interactions on all of CVDs risk and their corresponding mortality risk, except for the risk of stroke ($P > 0.05$, Table 2). Indeed, cardiovascular risk scores have been reduced in the A carriers compared with GG homozygotes and specifically tended to be decreased following SCO and CO, but not SO intake.

3.2. The effect of dietary oils and genotype on cardiometabolic markers in healthy individuals

3.2.1. Anthropometric measurements, blood pressure and liver enzymes

Table 3 details the change values for the outcome measurements in non-diabetes individuals across treatment periods and -75G/A *APOA-1* genotypes. Although no significant within-period changes were observed for the measured variables after CO treatment, a considerable decrease was seen for visceral fat in the A allele carriers rather than GG homozygotes (GG vs. AG/AA, 0.10 ± 0.21% vs. -0.84 ± 0.37%, $P < 0.05$) after SO intake. Serum GGT concentrations were also decreased in the A allele carriers in comparison to GG homozygotes (GG vs. AG/AA, 0.30 ± 0.90 U/L vs. -3.37 ± 1.57 U/L, $P < 0.05$) in the SCO period. No significant genotype or genotype * intervention effects were found for any of the anthropometric, blood pressure and liver enzymes variables (Table 3). However, a detectable effect of dietary oil interventions on serum GGT and ALT was observed regardless of genotype effects ($P = 0.031$, $P = 0.018$, respectively), such that significantly reduced after SCO intake compared with CO.

Table 1
Baseline characteristics of individuals with and without type 2 diabetes based on -75G/A *APOA-1* genotypes [a]

	Type 2 diabetes		P-value	Non-type 2 diabetes		P-value
	GG	AG/AA		GG	AG/AA	
Number, Females	69, 35	26, 14	0.786	55, 32	18, 9	0.544
Age, y	50.13 (0.80)	46.63 (1.31)	**0.026**	47.45 (1.10)	47.38 (1.93)	0.972
Weight, kg	77.11 (1.39)	75.80 (2.30)	0.631	76.30 (1.61)	71.77 (2.83)	0.169
BMI, kg/m^2	29.05 (0.44)	28.61 (0.74)	0.611	28.47 (0.62)	27.44 (1.08)	0.414
WC, cm	101.38 (1.08)	100.06 (1.78)	0.533	100.12 (1.41)	95.84 (2.47)	0.139
Visceral fat, %	10.82 (0.36)	10.31 (0.59)	0.472	9.43 (0.41)	8.79 (0.73)	0.452
Body fat, %	33.77 (0.68)	33.52 (1.12)	0.857	33.95 (0.77)	33.20 (1.38)	0.638
Muscle mass, %	29.73 (0.30)	29.74 (0.49)	0.988	29.28 (0.33)	29.91 (0.60)	0.363
SBP, mmHg	10.16 (0.16)	10.83 (0.26)	0.034	11.09 (0.66)	9.65 (1.16)	0.286
DBP, mmHg	7.26 (0.13)	7.60 (0.22)	0.207	7.35 (0.14)	6.97 (0.25)	0.193
FBS, mg/dL	117.48 (3.37)	110.42 (5.56)	0.285	87.72 (1.62)	86.60 (2.84)	0.734
Insulin, mIU/mL	29.00 (2.52)	27.03 (4.22)	0.693	24.70 (1.73)	21.91 (3.06)	0.432
HOMA-IR	3.70 (0.29)	3.44 (0.50)	0.666	3.04 (0.20)	2.69 (0.35)	0.398
QUICKI	0.29 (0.003)	0.30 (0.005)	0.134	0.30 (0.003)	0.31 (0.005)	0.161
TC, mg/dl	166.32 (3.62)	147.79 (5.97)	**0.010**	185.28 (4.52)	169.29 (7.91)	0.084
HDL-C, mg/dL	39.14 (1.24)	35.53 (2.05)	0.141	41.41 (1.38)	44.15 (2.42)	0.330
LDL-C, mg/dL	83.68 (2.14)	72.82 (3.53)	**0.011**	96.00 (2.92)	84.60 (5.11)	0.058
TG, mg/dL	154.13 (9.19)	160.04 (15.17)	0.742	143.11 (7.81)	121.41 (13.67)	0.173
Lp (a), mg/dL	24.36 (2.91)	18.19 (4.91)	0.287	27.55 (2.87)	18.58 (4.94)	0.122
LDL: HDL	2.34 (0.17)	2.64 (0.28)	0.368	2.66 (0.22)	1.97 (0.38)	0.124
TC: HDL	4.65 (0.35)	5.41 (0.57)	0.271	5.18 (0.48)	3.94 (0.84)	0.206
TG: HDL	4.68 (0.74)	7.27 (1.23)	0.079	4.92 (1.10)	2.99 (1.92)	0.389
ApoB, mg/dL	100.08 (4.00)	80.68 (6.61)	**0.015**	108.84 (4.41)	87.32 (7.72)	**0.018**
ApoA-1, mg/dL	154.75 (3.01)	145.07 (4.97)	0.103	160.06 (3.53)	159.75 (6.18)	0.966
ApoB: ApoA-1	0.66 (0.03)	0.57 (0.05)	0.138	0.69 (0.03)	0.55 (0.05)	**0.033**
Risk of CHD, %	6.80 (0.64)	8.87 (1.06)	0.102	6.15 (0.70)	2.97 (1.22)	**0.027**
Risk of MI, %	2.90 (0.41)	4.47 (0.69)	0.057	2.71 (0.47)	0.80 (0.82)	**0.050**
Risk of Stroke, %	0.94 (0.06)	1.06 (0.10)	0.302	2.23 (1.37)	0.27 (2.39)	0.481
Risk of CVD, %	9.17 (0.65)	11.40 (1.07)	0.084	7.39 (1.03)	3.51 (1.79)	0.065
Risk of CHD death, %	0.72 (0.14)	1.27 (0.24)	0.059	1.31 (0.28)	0.24 (0.49)	0.068
Risk of CVD death, %	0.88 (0.11)	1.23 (0.19)	0.123	1.66 (0.41)	0.38 (0.71)	0.123
ALP, U/L	185.67 (5.73)	185.72 (9.46)	0.997	183.57 (5.75)	181.92 (10.07)	0.887
GGT, U/L	28.87 (1.72)	29.65 (2.84)	0.817	24.13 (1.76)	22.55 (3.08)	0.658
AST, U/L	22.88 (1.45)	25.96 (2.40)	0.281	23.83 (1.35)	21.27 (2.36)	0.351
ALT, U/L	25.19 (1.96)	29.11 (3.23)	0.308	21.34 (1.81)	19.12 (3.17)	0.546

[a] All data are presented as mean (standard error), age and gender adjusted values. The comparison was done using one-way analysis of variance (ANOVA). Bold values are statistically significant P-values. ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase, BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; FBS, fasting blood sugar; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein a; MI, myocardial infarction; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

3.2.2. Blood lipids and glycemic control markers

In all treatment periods and genotype groups, there were no differences in change values either in lipid profile and apolipoprotein levels or in glycemic control indices, except a significant difference in HDL-C changes between two genotype groups after SO intake (GG vs. AG/AA, 0.41 ± 1.19 mg/dL vs. 5.34 ± 2.09 mg/dL, $P < 0.05$). However, the results revealed an independent effect of dietary oils for changes in HDL-C ($P = 0.035$). No other independent or interaction effects were observed.

3.2.3. Risk of cardiovascular diseases and mortality

Within-treatment analysis did not reveal any significant differences for risk of cardiovascular diseases and their mortality in terms of *APOA-1* genotypes. There were also no independent effects of dietary oils and genotypes as well as their interactions on the above-mentioned the risk of CVD and mortality.

4. Discussion

To the best of our knowledge, the current study is the first clinical trial which investigated the interaction effects of -75G/A *APOA-1* polymorphism and sesame, canola and sesame-canola oils on cardiometabolic markers as well as risk of CVDs and mortality.

In patients with T2DM, after SCO treatment, carriers of the A allele had a greater decrease in SBP compared to those with GG genotype. Serum HDL-C and TG: HDL levels were improved in the A allele carriers rather than GG homozygotes following CO intake. Regardless of dietary oil effects, the significant genotype effects, which were greater reductions for LDL: HDL, TC: HDL and TG: HDL ratios in diabetes patients with the A allele rather than GG homozygotes, were reported. A considerable interaction effects between dietary oils and genotypes were also detected for risk of CVDs and mortality, except risk of stroke in patients with T2DM, but not healthy individuals. Indeed, the highest CVDs and mortality risk reductions were observed in the A allele carriers compared with GG homozygotes after SCO intervention, followed by CO. It can be said that the observed changes in cardiovascular risk scores are related to factors involved in the Framingham equations including HDL and TC levels and SBP. Taken together, SCO and CO resulted in favorable changes in cardiometabolic risk factors and subsequently the risk of CVDs and mortality in the A allele carrier patients with T2DM. In healthy individuals, a considerable decrease in visceral fat was accompanied by a significant increase in HDL-C levels in the A allele carriers compared to non-A allele carriers after SO intake. In addition, SCO intake resulted in a greater reduction of serum GGT levels in carriers of the A allele compared with GG homozygotes.

Research has demonstrated that G-to-A transition in *APOA-1* gene has been related with increased promoter activity, resulting in higher apoA-1 and HDL-C levels [27]. The observational studies that investigated the interaction effects of -75G/A SNP and dietary

Table 2
Change values in anthropometric measurements, blood pressure, lipid profile, lipoproteins, glycemic indices and risk of cardiovascular diseases and mortality in patients with type 2 diabetes mellitus across treatment periods and -75G/A *APOA-1* genotypes.[a]

	Sesame oil (n = 93)		Sesame-Canola oil (n = 95)		Canola oil (n = 95)		P^1	P^2	P^3
	GG	AG/AA	GG	AG/AA	GG	AG/AA			
Weight, kg	0.26 (0.18)	0.46 (0.30)	0.09 (0.18)	−0.34 (0.29)	0.43 (0.19)	0.07 (0.32)	0.153	0.198	0.463
BMI, kg/m^2	0.10 (0.06)	0.17 (0.11)	0.03 (0.07)	−0.12 (0.11)	0.15 (0.07)	0.02 (0.11)	0.165	0.260	0.481
WC, cm	−0.66 (0.22)	−0.66 (0.37)	−0.55 (0.30)	−1.22 (0.51)	−0.55 (0.29)	−0.75 (0.49)	0.818	0.268	0.700
Visceral fat, %	0.09 (0.07)	0.20 (0.11)	−0.05 (0.14)	−0.16 (0.24)	0.16 (0.06)	0.08 (0.11)	0.274	0.817	0.598
Body fat, %	0.29 (0.25)	0.11 (0.41)	0.24 (0.22)	−0.25 (0.36)	0.29 (0.16)	0.38 (0.27)	0.455	0.397	0.564
Muscle mass, %	−0.06 (0.10)	0.001 (0.16)	−0.08 (0.10)	0.13 (0.17)	−0.16 (0.10)	−0.26 (0.16)	0.269	0.557	0.572
SBP, mmHg[b]	0.06 (0.16)	0.27 (0.26)	0.05 (0.15)	−0.56 (0.25)*	0.10 (0.14)	−0.14 (0.23)	0.160	0.161	0.179
DBP, mmHg	0.19 (0.14)	0.54 (0.23)	−0.02 (0.14)	0.16 (0.24)	0.28 (0.13)	0.09 (0.22)	0.349	0.358	0.385
FBS, mg/dL	1.81 (2.44)	0.63 (4.08)	−3.88 (3.78)	0.93 (6.27)	6.62 (3.60)	10.97 (5.97)	0.083	0.516	0.691
Insulin, mIU/mL	−5.63 (2.09)	−5.99 (3.40)	−4.73 (1.81)	−5.79 (3.01)	−3.79 (1.74)	0.37 (2.95)	0.219	0.663	0.524
HOMA-IR	−0.68 (0.25)	−0.71 (0.41)	−0.62 (0.21)	−0.64 (0.36)	−0.39 (0.22)	0.08 (0.38)	0.185	0.586	0.666
QUICKI	0.010 (0.003)	0.005 (0.005)	0.009 (0.003)	0.010 (0.005)	0.004 (0.003)	−0.003 (0.005)	0.101	0.278	0.483
TC, mg/dL	2.20 (3.35)	1.82 (5.60)	−1.99 (3.67)	2.95 (6.09)	1.43 (3.15)	5.08 (5.23)	0.819	0.493	0.850
HDL-C, mg/dL[b]	−0.09 (1.06)	−0.10 (1.81)	−0.10 (0.92)	2.11 (1.52)	0.39 (0.92)	4.33 (1.52)*	0.219	0.060	0.368
LDL-C, mg/dL	1.21 (1.90)	−1.82 (3.17)	−1.72 (2.20)	1.29 (3.65)	−0.50 (1.89)	4.87 (3.14)	0.502	0.465	0.202
TG, mg/dL	3.73 (9.55)	22.82 (15.93)	−0.24 (8.55)	−1.85 (14.19)	6.31 (8.34)	−25.18 (13.83)	0.195	0.591	0.099
Lp (a), mg/dL	−0.53 (1.60)	−0.22 (2.71)	1.42 (1.11)	0.49 (1.90)	−2.39 (1.80)	2.17 (3.17)	0.719	0.476	0.447
LDL: HDL	0.04 (0.08)	−0.08 (0.15)	−0.002 (0.26)	−0.98 (0.43)	0.18 (0.23)	−0.58 (0.38)	0.230	**0.010**	0.223
TC: HDL	0.10 (0.18)	−0.13 (0.31)	0.03 (0.58)	−2.12 (0.97)	0.43 (0.49)	−1.39 (0.81)	0.225	**0.009**	0.172
TG: HDL[b]	0.24 (0.43)	−0.22 (0.73)	0.12 (1.47)	−5.05 (2.45)	0.99 (1.12)	−3.58 (1.85)*	0.238	**0.010**	0.158
ApoB, mg/dL	−0.99 (2.51)	0.41 (4.19)	−5.37 (3.30)	2.25 (5.47)	−0.64 (2.69)	3.70 (4.46)	0.740	0.133	0.769
ApoA-1, mg/dL	−0.25 (2.32)	−3.21 (3.87)	−2.77 (2.38)	4.06 (3.94)	5.43 (2.75)	3.79 (4.56)	0.213	0.792	0.224
ApoB: ApoA-1	−0.004 (0.01)	0.02 (0.03)	−0.03 (0.02)	−0.009 (0.03)	−0.02 (0.01)	0.01 (0.02)	0.606	0.127	0.883
Risk of CHD, %[b]	0.12 (0.41)	0.44 (0.69)	0.47 (0.68)	−3.19 (1.14)**	0.59 (0.62)	−2.43 (1.03)*	0.104	**0.003**	**0.029**
Risk of MI, %[b]	0.05 (0.25)	0.33 (0.42)	0.38 (0.48)	−2.33 (0.79)**	0.43 (0.42)	−1.64 (0.70)*	0.084	**0.002**	**0.014**
Risk of Stroke, %	0.005 (0.06)	0.13 (0.10)	0.01 (0.06)	−0.16 (0.10)	0.02 (0.05)	−0.02 (0.09)	0.203	0.634	0.174
Risk of CVD, %[b]	0.05 (0.49)	0.91 (0.83)	0.45 (0.65)	−3.31 (1.08)**	0.56 (0.57)	−2.07 (0.94)*	0.068	**0.007**	**0.017**
Risk of CHD death, %[b]	−0.008 (0.08)	0.07 (0.14)	0.17 (0.27)	−1.20 (0.46)*	0.16 (0.16)	−0.57 (0.26)*	0.116	**0.004**	**0.011**
Risk of CVD death, %[b]	0.00 (0.07)	0.12 (0.12)	0.12 (0.19)	−0.85 (0.31)**	0.10 (0.11)	−0.38 (0.18)*	0.071	**0.007**	**0.010**
ALP, U/L	1.16 (3.02)	−7.13 (5.05)	−2.34 (3.93)	−4.87 (6.53)	1.32 (2.54)	7.33 (4.22)	0.100	0.643	0.193
GGT, U/L	−0.61 (1.38)	−1.04 (2.30)	1.65 (1.52)	−1.22 (2.53)	1.30 (0.97)	2.75 (1.61)	0.120	0.582	0.423
AST, U/L	0.77 (0.90)	0.09 (1.50)	−1.99 (1.02)	0.06 (1.69)	0.09 (1.08)	−2.82 (1.80)	0.320	0.665	0.241
ALT, U/L	0.15 (1.24)	0.52 (2.07)	−2.09 (1.18)	−1.13 (1.97)	1.24 (1.60)	−3.53 (2.65)	0.424	0.463	0.322

Bold values are statistically significant P-values. P^1, comparisons of change values between the treatment oils using linear mixed effects model, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake.
P^2, comparisons of change values between the genotypes using linear mixed effects model, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake.
P^3, interaction between -75G/A SNP and treatment oils on the outcomes of interest, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake.

[a] All data are presented as mean (standard error). ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; FBS, fasting blood sugar; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein a; MI, myocardial infarction; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.

[b] Within treatment period comparisons of change values between genotypes using linear mixed effects model, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake ($^*P < 0.05$, $^{**}P < 0.01$).

intakes on the risk of chronic diseases are limited. It has been shown that the A allele may have a protective role against metabolic syndrome risk in patients with high sugar intakes [28]. Moreover, Philips et al. reported that the risk of metabolic syndrome was exacerbated among the G allele homozygotes who were high-fat consumers [20]. The findings of the current clinical study revealed that participants with the A allele may have better cardiometabolic responses following dietary oil treatments compared with GG homozygotes. On the other hand, the results of different clinical trials assessing the interaction effects of *APOA-1* gene polymorphism and various dietary interventions shed light on the favorable metabolic responses in the A allele carriers as well. For instance, in a study by de Luis et al., the effect of -75G/A SNP among 82 obese subjects who were on hypocaloric diets was assessed; after 12 weeks of intervention, body weight, waist circumference, fat mass, and SBP decreased in both genotype groups; however, these reductions were greater in the in the A allele carriers than non-A allele carriers. The serum levels of TC, LDL-C, insulin and HOMA-IR were also decreased only in the A allele carriers [29]. In another study by the same group, the interaction effects of low calorie/high fat diet vs. low-calorie/low fat diet for 12 weeks and this polymorphism were assessed among 282 obese individuals. The body weight and composition measurements, SBP and leptin levels were decreased following both diets regardless of genotype effects; however, insulin levels and HOMA-IR favorably changed only in the A allele carriers. In addition, low fat diet resulted in a statistically significant improvement in HDL-C among the A allele carriers rather than non-A allele carriers [30].

Previous studies have shown that polymorphisms in *APOA-1* gene can account for up to 33% of inter-individual variations following high-fat diets intake [31,32]. It is speculated that dietary fat composition can modulate the effects of SNP along with the direct effects of SNP itself on the metabolic pathways [21]. For instance, findings of a case–control study showed that the metabolic syndrome risk was greater in non-A allele carriers who had high fat intakes [20]. Besides, a clinical study concluded that a PUFA-rich diet resulted in a greater LDL-C decrease in carriers of the A allele than non-A allele carriers, especially among women,

Table 3
Change values in anthropometric measurements, blood pressure, lipid profile, lipoproteins, glycemic indices and risk of cardiovascular diseases and mortality in healthy individuals across treatment periods and -75G/A *APOA-1* genotypes. [a]

	Sesame oil (n = 70)		Sesame-Canola oil (n = 73)		Canola oil (n = 69)		P^1	P^2	P^3
	GG	AG/AA	GG	AG/AA	GG	AG/AA			
Weight, kg	0.15 (0.20)	−0.19 (0.35)	−0.59 (0.55)	0.28 (0.97)	0.05 (0.17)	0.32 (0.32)	0.580	0.523	0.206
BMI, kg/m^2	0.05 (0.07)	−0.06 (0.13)	−0.25 (0.22)	0.09 (0.39)	0.02 (0.06)	0.12 (0.12)	0.542	0.516	0.219
WC, cm	−0.73 (0.28)	−1.25 (0.50)	−0.73 (0.31)	−1.08 (0.55)	−0.62 (0.33)	−0.03 (0.61)	0.289	0.778	0.427
Visceral fat, %[b]	0.10 (0.21)	−0.84 (0.37)*	0.05 (0.08)	0.06 (0.15)	−0.05 (0.06)	0.06 (0.12)	0.186	0.098	0.070
Body fat, %	0.29 (0.18)	−0.39 (0.32)	0.25 (0.20)	0.11 (0.37)	0.35 (0.16)	0.38 (0.29)	0.353	0.147	0.457
Muscle mass, %	−0.15 (0.11)	0.28 (0.19)	−0.15 (0.12)	−0.15 (0.23)	−0.44 (0.20)	−0.24 (0.37)	0.239	0.208	0.484
SBP, mmHg	−0.63 (0.67)	0.25 (1.20)	−0.26 (0.17)	0.11 (0.31)	−0.01 (0.17)	0.23 (0.32)	0.737	0.300	0.906
DBP, mmHg	−0.06 (0.16)	0.18 (0.28)	−0.01 (0.15)	0.17 (0.26)	0.00 (0.14)	0.33 (0.26)	0.894	0.111	0.955
FBS, mg/dL	2.64 (2.03)	−3.25 (3.55)	1.34 (1.34)	1.58 (2.32)	3.79 (1.70)	4.46 (3.11)	0.255	0.432	0.425
Insulin, mIU/mL	−4.51 (1.66)	−3.53 (3.05)	−1.49 (1.85)	0.95 (3.17)	−3.80 (2.30)	−7.83 (4.16)	0.210	0.993	0.765
HOMA-IR	−0.52 (0.19)	−0.42 (0.36)	−0.17 (0.20)	0.04 (0.35)	−0.42 (0.25)	−0.90 (0.46)	0.250	0.891	0.787
QUICKI	0.008 (0.003)	0.011 (0.006)	0.004 (0.004)	0.003 (0.006)	0.006 (0.004)	0.014 (0.007)	0.448	0.473	0.791
TC, mg/dl	2.42 (3.40)	2.56 (5.96)	−0.41 (3.85)	−1.82 (6.66)	−1.30 (3.18)	2.13 (5.81)	0.805	0.881	0.862
HDL-C, mg/dL[b]	0.41 (1.19)	5.34 (2.09)*	−0.53 (1.07)	−2.17 (1.85)	0.25 (1.34)	1.53 (2.45)	**0.035**	0.278	0.145
LDL-C, mg/dL	0.88 (2.16)	1.15 (3.78)	−0.83 (2.41)	−1.14 (4.18)	−1.24 (1.95)	1.13 (3.57)	0.817	0.794	0.892
TG, mg/dL	−4.35 (9.02)	−26.37 (15.79)	6.70 (6.95)	6.47 (12.05)	5.84 (9.39)	5.73 (17.14)	0.209	0.432	0.672
Lp (a), mg/dL	1.29 (1.74)	3.59 (3.06)	1.48 (1.98)	0.03 (3.33)	−0.08 (1.75)	−0.24 (3.10)	0.594	0.930	0.700
LDL: HDL	−0.20 (0.24)	−0.15 (0.43)	−0.02 (0.10)	0.09 (0.17)	−0.10 (0.11)	−0.01 (0.20)	0.667	0.633	0.965
TC: HDL	−0.44 (0.54)	−0.31 (0.94)	−0.03 (0.19)	0.18 (0.34)	−0.21 (0.19)	−0.04 (0.36)	0.641	0.633	0.967
TG: HDL	−1.07 (1.26)	−0.84 (2.21)	−0.07 (0.43)	0.25 (0.74)	−0.10 (0.40)	0.12 (0.72)	0.694	0.702	0.937
ApoB, mg/dL	−1.35 (3.52)	2.40 (6.16)	−0.87 (3.46)	0.44 (5.99)	−1.69 (3.04)	3.40 (5.55)	0.972	0.395	0.922
ApoA-1, mg/dL	−3.65 (3.12)	5.00 (5.46)	−0.73 (3.44)	−4.58 (5.97)	3.16 (3.34)	7.86 (6.10)	0.125	0.454	0.352
ApoB: ApoA-1	0.01 (0.02)	−0.004 (0.04)	0.02 (0.03)	0.02 (0.06)	−0.02 (0.02)	0.001 (0.04)	0.690	0.830	0.830
Risk of CHD, %	−0.49 (0.79)	−0.38 (1.37)	−0.03 (0.37)	0.18 (0.64)	−0.37 (0.43)	0.31 (0.79)	0.820	0.608	0.874
Risk of MI, %	−0.42 (0.54)	−0.20 (0.95)	0.04 (0.22)	0.01 (0.39)	−0.22 (0.25)	0.23 (0.45)	0.821	0.623	0.787
Risk of Stroke, %	−1.64 (1.48)	−0.01 (2.63)	−0.004 (0.04)	−0.01 (0.07)	−0.05 (0.05)	0.11 (0.09)	0.780	0.560	0.444
Risk of CVD, %	−0.96 (1.12)	−0.41 (1.94)	−0.04 (0.39)	0.08 (0.67)	−0.41 (0.46)	0.59 (0.83)	0.794	0.534	0.827
Risk of CHD death, %	−0.18 (0.33)	−0.11 (0.57)	0.10 (0.13)	−0.04 (0.22)	−0.09 (0.13)	0.14 (0.23)	0.863	0.839	0.643
Risk of CVD death, %	−0.24 (0.45)	−0.14 (0.79)	0.09 (0.11)	−0.08 (0.20)	−0.11 (0.13)	0.19 (0.23)	0.881	0.828	0.515
ALP, U/L	0.26 (3.53)	−4.68 (6.18)	0.90 (3.36)	−1.47 (5.82)	3.80 (2.93)	0.26 (5.36)	0.709	0.309	0.969
GGT, U/L[b]	−2.70 (1.93)	−2.13 (3.38)	0.30 (0.90)	−3.37 (1.57)*	2.69 (1.34)	3.92 (2.46)	**0.031**	0.548	0.160
AST, U/L	−0.30 (0.96)	1.68 (1.69)	−1.25 (1.33)	−3.18 (2.31)	−0.78 (0.84)	0.26 (1.54)	0.251	0.778	0.521
ALT, U/L	−1.75 (1.27)	−0.59 (2.22)	−1.57 (1.67)	−5.94 (2.89)	1.83 (1.50)	3.93 (2.74)	**0.018**	0.825	0.308

Bold values are statistically significant P values. P^1, comparisons of change values between the treatment oils using linear mixed effects model, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake.
P^2, comparisons of change values between the genotypes using linear mixed effects model, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake.
P^3, interaction between -75G/A SNP and treatment oils on the outcomes of interest, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake.
[a] All data are presented as mean (standard error). ApoA-1, apolipoprotein A-1; ApoB, apolipoprotein B; ALP, alkaline phosphatase; AST, aspartate aminotransferase; ALT, alanine aminotransferase; BMI, body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; FBS, fasting blood sugar; GGT, gamma-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; LDL-C, low-density lipoprotein cholesterol; Lp (a), lipoprotein a; MI, myocardial infarction; QUICKI, quantitative insulin sensitivity check index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride; WC, waist circumference.
[b] Within treatment period comparisons of change values between genotypes using linear mixed effects model, adjusted for age, gender, baseline BMI, amount of consumed oils, change levels of physical activity and change in energy intake ($^*P < 0.05$).

compared with a SFA-rich diet [33]. A significant interaction was also detected between *APOA-1* genotypes and PUFAs intake on HDL-C concentrations; when PUFAs intake was less than 4% of total energy, GG subjects had approximately 14% higher HDL-C concentrations than did carriers of the A allele. In contrast, PUFAs intake greater than 8% of the total energy was associated with higher HDL-C levels (approximately 13%) in carriers of the A allele than those with GG genotype [34].

The current study was a randomized, triple blind, cross-over clinical trial with a relatively large sample size in which the participants served as their controls. The influence of genetic polymorphisms which contributes to inter-individual variations as well as differences in diet responsiveness minimized by using a cross-over design. Moreover, the results of the current study may be generalizable to two different population characteristics (adults with and without T2DM) since we included both groups independently. We tried to design a practical study which is close to the real life by substitution of household dietary oils with the intervention oils since we did not use specific amounts of edible oils or in restricted manners, like most of the clinical studies. Thus, our findings may be of greater importance to be implemented in the real life.

Our study limitations were as follows: Firstly, we combined the AG and AA genotypes, and compared them with GG homozygotes due to the small sample size of the A allele carriers. In addition, we also could not perform a sex-stratified analysis because of the mentioned issue. Secondly, we could not able to determine the exact amount of consumed oils by each participant due to the nature of our study design which was replacing the regular oil consumption with the treatment oils, but we tried to calculate the consumed oils by using dietary records and the weighing the oil bottles. Thirdly, focusing on a single gene may not give us a firm conclusion since it is well understood that metabolic parameters are influenced by multiple genetic factors. Therefore, a contribution of gene–gene interactions may provide us a more concise and clear insight toward chronic conditions. Moreover, although Dual-energy X-ray absorptiometry (DEXA) is a highly accurate and precise method for measuring body composition [35], we did not have

access to this method and we alternatively used the body composition analyzer. Therefore, we must be more cautious about our finding regarding the significant reducing effect of SO on visceral fat in A allele carriers compared to non-A allele carriers.

In conclusion, the A allele mutation in the promoter region of *APOA-1* gene may not only modify the metabolic responses to dietary oils, differing in MUFAs and PUFAs content, but also it may favorably change the risk of CVDs and their corresponding mortality in patients with T2DM. Altogether, there were most favorable metabolic effects following SCO and CO in T2DM patients carrying the A allele. On the other hand, some beneficial health effects were seen in healthy individuals carrying the A allele after SCO and SO intakes. Further investigations should be focused to assess the interaction effects of different polymorphisms and other edible oils which can help to improve therapeutic efficacy of dietary oil recommendations with a personalized nutrition approach, wherein the genetic profile may determine the best choices of dietary oils for each person.

Authors' contribution

ASA, NRJ, EFY and AM conceived and designed the study. MA and FM recruited the participants and followed them. MA, HRD, FM and AZ performed the data collection and the data entry. HRD performed the biochemical analysis. NRJ, SA and EFY conducted the genetic analysis. NRJ and ASA conducted the statistical analyses. EFY, AM, HMK and SAYA provided counseling for interpreting the results. NRJ drafted the manuscript. ASA critically reviewed the manuscript. All authors approved the final draft of the manuscript and agreed to be accountable for all aspects of the work, ensuring its integrity and accuracy.

Declaration of Competing Interest

The study was jointly funded by Shahid Sadoughi University of Medical Sciences (http://www.ssu.ac.ir) and Datis Corporation (http://www.neshatavar.com/?l=EN). Datis Corporation provided all of the intervention dietary oils consumed during the study. The investigators state that they did not have a direct financial relationship with Datis Corporation. Shahid Sadoughi University of Medical Sciences received the funds and delivered it to the investigators. Datis Corporation had no role in design and conduction of the study, data collection, data management, analysis and interpretation of the data, and also preparation of this manuscript. Datis Corporation did not have any other relationship with the investigators. The authors declare that they have no other potential personal or financial conflicts of interest. The principal investigator (ASA) declares that he has full access to the data provided by this project.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.05.016.

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