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Polymorphisms in the stearoyl-CoA desaturase gene modify blood glucose response to dietary oils varying in MUFA content in adults with obesity

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Abstract

Diets varying in SFA and MUFA content can impact glycaemic control; however, whether underlying differences in genetic make-up can influence blood glucose responses to these dietary fatty acids is unknown. We examined the impact of dietary oils varying in SFA/MUFA content on changes in blood glucose levels (primary outcome) and whether these changes were modified by variants in the stearoyl-CoA desaturase (*SCD*) gene (secondary outcome). Obese men and women participating in the randomised, crossover, isoenergetic, controlled-feeding Canola Oil Multicenter Intervention Trial II consumed three dietary oils for 6 weeks, with washout periods of ~6 weeks between each treatment. Diets studied included a high SFA/low MUFA Control oil (36·6 % SFA/28·2 % MUFA), a conventional canola oil (6·2 % SFA/63·1 % MUFA) and a high-oleic acid canola oil (5·8 % SFA/74·7 % MUFA). No differences in fasting blood glucose were observed following the consumption of the dietary oils. However, when stratified by *SCD* genotypes, significant SNP-by-treatment interactions on blood glucose response were found with additive models for rs1502593 ($P = 0·01$), rs3071 ($P = 0·02$) and rs522951 ($P = 0·03$). The interaction for rs3071 remained significant ($P = 0·005$) when analysed with a recessive model, where individuals carrying the CC genotype showed an increase (0·14 (SEM 0·09) mmol/l) in blood glucose levels with the Control oil diet, but reductions in blood glucose with both MUFA oil diets. Individuals carrying the AA and AC genotypes experienced reductions in blood glucose in response to all three oils. These findings identify a potential new target for personalised nutrition approaches aimed at improving glycaemic control.

Key words: **Fat quality: Stearoyl-CoA desaturase: Canola oil: High-oleic canola oil: Nutrigenetics: SFA: MUFA**

MUFA provide ~12 % energy to the diet[1] and are important molecules that serve as substrates for the production of neutral lipids (e.g., TAG cholesterol esters), influence the physical properties of cellular membranes and regulate numerous pathways such as insulin signalling and inflammation[2]. Increased MUFA intake in place of SFA has been reported to improve lipid profiles, glycated Hb (HbA1C) and insulin resistance in randomised control trials (reviewed in[3]). Further, the cardiometabolic benefits associated with the Mediterranean diet have been attributed, in part, to the high consumption of olive oil which is rich in the MUFA oleic acid.

Abbreviations: COMIT, Canola Oil Multi-Centre Intervention Trial; FA, fatty acid; HOCO, high-oleic acid canola oil; MetS, metabolic syndrome; RCO, regular canola oil; SCD, stearoyl-CoA desaturase; SNP, single nucleotide polymorphism.

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However, our body also synthesises MUFA from SFA through stearoyl-CoA desaturase (SCD)-mediated endogenous production. SCD is a desaturase located in the endoplasmic reticulum membrane that primarily converts palmitate and stearate (SFA) into palmitoleate and oleate (MUFA), respectively. A past study by Martín-Núñez *et al.* reported associations between SNPs in the *SCD* gene and estimated desaturase enzyme activity[4], implying that polymorphisms may influence endogenous MUFA production. This suggests that individuals carrying SNPs in the *SCD* gene that are associated with lower endogenous MUFA production may benefit from diets rich in MUFA. Furthermore, previous research has also revealed that SNPs in the *SCD* gene are associated with various cardiometabolic risk factors, including body weight[5], inflammation[6] and fasting glucose(7,8).

One of the first investigations of *SCD* gene variants identified an association between rs1502593 and the prevalence of the metabolic syndrome (MetS) in a population of Costa Rican adults[8], where individuals carrying the minor allele (CT or TT) had a greater prevalence of the MetS than those with the more common CC genotype. In this same study, a weak sex-specific association between rs1502593 and fasting blood glucose levels was also observed in women. Separately, Warensjö *et al.*[5] discovered that the rare allele of another *SCD* SNP (rs7849) was associated with a 23 % higher insulin sensitivity compared with the more common allele in elderly Swedish men. Finally, another SNP in *SCD* (rs508384) was reported by Rudkowska *et al.*[7] to modify blood glucose response in French Canadian adults supplemented with *n*-3 PUFA. This later study is of relevance and suggests that polymorphisms in the *SCD* gene could interact with dietary fats to modify markers of glycaemic control; however, this area remains poorly studied. To the best of our knowledge, no studies have yet examined if *SCD* polymorphisms can modify blood glucose response to dietary oils that vary in SFA/MUFA content.

Canola oil (derived from rapeseed) represents the third largest vegetable oil produced worldwide[9] and is characterised by low levels of SFA and high levels of MUFA, as well as being a rich source of PUFA, plant sterols and tocopherols. The consumption of canola oil is reported to improve blood lipid profiles, but its effect on glucose levels remains equivocal (reviewed in[10]). However, evidence supports a potential benefit of canola oil for improving glycaemic status[11,12], thus emphasising the need for continued investigation in the area. Therefore, the primary outcome of the present study was to determine if the 6-week consumption of regular canola oil (RCO) or high-oleic acid canola oil (HOCO) changes fasting blood glucose levels compared with a high SFA/low MUFA Control oil in participants recruited for the randomised crossover Canola Oil Multi-Centre Intervention Trial (COMIT) II[13]. As a secondary outcome, we conducted an exploratory nutrigenetics investigation to determine if SNPs in *SCD* could modify blood glucose responses to the various dietary oils.

Methods

Subjects and methods

Study design and population. The COMIT II trial was a randomised, controlled, double-blind, crossover study that investigated the effects of three dietary oils on body composition. The trial was conducted between 2014 and 2016 at three sites in Canada and one site in the USA: The Richardson Centre for Functional Foods and Nutraceuticals at the University of Manitoba (Winnipeg, Manitoba), The Canadian Centre for Agri-Food Research in Health and Medicine at the St. Boniface Hospital Albrechtsen Research Centre (Winnipeg, Manitoba), The Institute of Nutrition and Functional Foods at Laval University (Quebec City, Quebec) and The Departments of Nutritional Sciences and Biobehavioural Health at Pennsylvania State University (University Park, Pennsylvania). The protocol for the COMIT II trial was approved by all institutional research ethics boards, while the protocol for the exploratory nutrigenetics study was approved by the Universities of Manitoba and Guelph. The COMIT II trial was registered at clinicaltrials.gov (NCT02029833).

Male and female participants (aged 20–65 years) were eligible to participate if they had abdominal obesity according to the International Diabetes Federation cut-off point for waist circumference (94 cm in men, 80 cm in women) in addition to at least one additional component of the MetS: fasting glucose concentrations ≥ 5·6 mmol/l, TAG ≥ 1·7 mmol/l, HDL-cholesterol < 1 mmol/l (men) or 1·3 mmol/l (women), or blood pressure ≥ 130 mmHg (systolic) and/or ≥ 85 mmHg (diastolic)[14]. Exclusion criteria included thyroid disease, kidney disease, diabetes mellitus, liver disease, current smoker, high weekly alcohol intake and individuals unwilling to stop taking supplements at least 2 weeks prior to the study. Written consent was obtained from all participants. Participants were randomised to receive the different dietary oils in one of six sequences.

Study diets and treatment oils. Complete details regarding the study diets have been previously reported[13]. Briefly, the COMIT II trial involved participants consuming three treatment oils in a controlled isoenergetic, full-feeding diet with a fixed macronutrient composition (35 % total energy from fat, 50 % total energy from carbohydrate and 15 % total energy from protein). Menus for the three diet phases were identical except for the type of oil used. Participants consumed each of the diets for 6 weeks, with each separated by a washout period of approximately 6 weeks (range 4–8 weeks). Treatment oils comprised 20 % of daily total energy and were incorporated into a smoothie beverage that was equally divided and consumed at breakfast and supper. Treatment oils included RCO, HOCO and a Control oil. Whenever possible, smoothie consumption compliance was closely monitored in-person by the clinical coordinator at each feeding site. When a participant was unable to visit a feeding site, the participant completed a checklist detailing smoothie and menu compliance and submitted this to a clinical coordinator.

Fatty acid analysis and composition of treatment oils. Fatty acid (FA) content of treatment oils was analysed by KOH-catalysed methanolysis (transesterification)[15]. Methylated FA samples were analysed by GC using a FUSED SILICA Capillary Column (100 m × 0·25 mm; film thickness, 0·20 µm, SP™-2560; SUPELCO Analytical) on a Varian 430 gas chromatograph equipped with a flame ionisation detector. The injector and detector ports were set at 250 and 290°C, respectively. Oven temperature was set to 130°C for 2 min and then increased to 175°C (25°C/min), and held for 20 min. The temperature was then

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subsequently increased to 240°C (3°C/min), where it remained constant for 5 min, and the same temperature was maintained throughout, for a total runtime of 50·47 min. A split ratio of 20:1 and an injection volume of 1 µl were used. A known FA mixture was compared with samples to identify retention peaks using Galaxie software (Varian Inc.). The relative percentage of each FA was then calculated according to the corresponding peak area relative to that of all FA[16].

FA composition of the treatment oils is reported in Table 1. The FA composition of RCO (Canola Harvest Canola Oil, Richardson International) was comprised of 6·2 % SFA, 63·1 % MUFA, 22·4 % *n*-6 PUFA and 8·3 % *n*-3 PUFA. The FA composition of HOCO (Canola Harvest Canola Oil, Richardson International) was comprised of 5·8 % SFA, 74·7 % MUFA, 17·3 % *n*-6 PUFA and 2·2 % *n*-3 PUFA. The Control oil consisted of a blend of ghee (49 %, Verka), safflower oil (29 %, eSutras), coconut oil (8 %, eSutras) and flaxseed oil (14 %, Shape Foods), resulting in a FA composition comprised of 36·6 % SFA, 28·2 % MUFA, 26·5 % *n*-6 PUFA and 8·7 % *n*-3 PUFA.

Blood measurements. Participants underwent anthropometric measurements on two consecutive days before and after each diet phase, with mean values calculated for weight, height and waist circumference. Blood was collected following a 12 h fast, including abstinence from alcohol for 48 h prior to collection. Serum was isolated from blood samples and stored at −80°C until analysis. Frozen serum sample aliquots were shipped on dry ice to the central laboratory at St. Michael's Hospital (Toronto, Ontario) for the analysis of glucose, insulin, fructosamine and blood lipids. All measurements were made using an enzymatic, colorimetric method on the Roche/Hitachi Cobas c 501 analyser (Roche Diagnostics). Frozen serum sample aliquots were also shipped to Laval University for the analysis of adiponectin by ELISA (#K1001–1, B-Bridge International).

DNA extraction and genotyping

Fasted blood samples were collected at the beginning of the trial and stored at −80°C until shipped to the Richardson Centre. Genomic DNA was extracted from buffy coat samples using the Qiagen DNeasy Blood and Tissue Kit, as per manufacturer's instructions (Qiagen Sciences, Inc.). DNA quality and quantity were measured with a Thermo Scientific NanoDrop 2000 (Thermo-Fisher Scientific, Inc.). Polymorphisms were assayed with specific TaqMan SNP Genotyping Assays and TaqPath™ ProAmp Master Mix (Thermo-Fisher Scientific, Inc.) using the StepOne Plus (Thermo-Fisher Scientific, Inc.). Data were analysed using StepOne 2.1 software.

SNPs in the *SCD* gene were selected with the LD TAG SNP Selection tool in SNPInfo[17], using a minor allele frequency ≥ 5 % and pairwise tagging ($r^2 \geq 0·8$). The following SNPs were previously reported in the literature to be associated with various blood markers and were therefore included into the tag SNP selection: rs1502593[8], rs7849[5], rs508384[7], rs10883463[4] and rs11190480[18]. Since rs7849 and rs508384 are in high linkage disequilibrium ($r^2 > 0·99$), only rs7849 was selected for analysis in the present study. The following seven tag SNPs in *SCD* were analysed: rs11190480, rs7849, rs3071, rs522951, rs3829160, rs1502593 and rs10883463. All samples were run in duplicate for each SNP to ensure genotyping accuracy.

Table 1. Fatty acid composition of treatment oils*

Fatty acid	Control oil	Regular canola oil	High-oleic acid canola oil
C8:0	1·05	ND	ND
C10:0	1·06	ND	ND
C12:0	4·92	0·02	0·02
C14:0	4·07	0·02	0·02
C14:1	ND	0·06	0·07
C15:0	0·60	0·03	0·03
C16:0	15·44	4·19	3·82
C16:1*n*-7	1·42	0·17	0·22
C17:0	0·52	0·04	0·07
C17:1	0·24	0·10	0·16
C18:0	8·90	1·84	1·82
C18:1*n*-9	26·40	62·26	73·72
C18:2*n*-6	26·13	20·94	15·75
C18:3*n*-6	0·23	1·32	1·38
C18:3*n*-3	8·56	8·32	2·15
C20:0	0·06	0·06	0·05
C20:1*n*-9	0·12	0·30	0·35
C20:2*n*-6	0·02	0·01	ND
C20:3*n*-6	0·01	0·02	0·04
C20:4*n*-6	0·02	ND	ND
C20:3*n*-3	0·06	0·01	0·02
C22:0	ND	0·01	0·01
C22:1*n*-9	0·05	0·16	0·17
C20:5*n*-3	ND	ND	ND
C22:2*n*-6	0·03	0·10	0·15
C22:4*n*-6	0·02	ND	ND
C22:5*n*-3	0·03	ND	ND
C22:6*n*-3	0·05	ND	ND
C24:0	ND	ND	ND
C24:1*n*-9	ND	ND	ND
Total SFA	36·6	6·2	5·8
Total MUFA	28·2	63·1	74·7
Total PUFA	35·2	30·7	19·5
Total *n*-6 PUFA	26·5	22·4	17·3
Total *n*-3 PUFA	8·7	8·3	2·2

ND, not detected.
* The values are percentage abundance of each fatty acid in relation to total fatty acids.

Statistical analysis

Sample size for the COMIT II trial was calculated according to the primary aim to evaluate the effect of MUFA consumption on body composition, as described previously[19]. For the current analysis, only the 108 participants who provided consent for genetic analyses were considered. Hardy Weinberg equilibrium was tested by χ^2 analysis. Distribution of alleles in the COMIT II trial was compared by Fisher exact test with that reported in the 1000 Genomes European population.

Statistical analyses were conducted using JMP software V14.3 and GraphPad Prism V8. Variables were checked for normal distribution with a Shapiro–Wilk test. Outlier values (*n* 4) for fasting glucose were identified by ROUT analysis and these individuals were excluded from the analysis. Data are reported as mean values with their standard error of mean. Change in fasting blood glucose (Δglucose) was the primary outcome of interest and corresponded to the difference between endpoint and baseline for each diet phase (e.g., final value for Control oil diet – baseline value for Control oil diet). Repeated measures mixed models

Table 2. Participant characteristics at the start of the trial*

Characteristics	Total (*n* 101)	SEM	Female (*n* 59)	SEM	Male (*n* 42)	SEM
Age (year)	43·2	1·3	45·5	1·7	40·0	2·0**
Ethnicity (*n*)						
Caucasian	78		47		31	
African	4		3		1	
Asian	8		4		4	
Hispanic	3		1		2	
Other	8		4		4	
BMI (kg/m^2)	31·1	0·5	31·0	0·7	31·3	0·8
Waist circumference (cm)	103·5	1·3	100·7	1·5	107·6	1·9**
Total cholesterol (mmol/l)	5·22	0·09	5·27	0·10	5·16	0·15
HDL-cholesterol (mmol/l)	1·36	0·04	1·47	0·05	1·21	0·05**
TAG (mmol/l)	1·52	0·08	1·43	0·09	1·64	0·13
Glucose (mmol/l)	5·23	0·05	5·19	0·07	5·30	0·07
Insulin (pmol/l)	95·7	6·1	91·7	7·4	101·4	10·5
HOMA-IR	3·7	0·3	3·6	0·3	4·0	0·5
Fructosamine (µmol/l)	225·9	1·6	223·3	2·1	229·6	2·5**
Adiponectin (ng/ml)	9·63	0·48	11·07	0·66	7·62	0·58**

* Differences between females and males were determined using a Mann–Whitney *U* test (GraphPad V8).
** Indicates a significant sex difference, $P < 0·05$.

were used to assess the effect of the three dietary oils on Δglucose. Treatment, sex, age, ethnicity, BMI and baseline fasting glucose were included as fixed effects, and treatment sequence, clinical site and participants were included as random effects. Participant was a repeated factor. Individual SNPs were first analysed using an additive model with the aforementioned mixed model, without correction for multiple testing. Dominant (defined as two copies of the major allele compared with at least one copy of the minor allele) and recessive (defined as at least one copy of the major allele compared with two copies of the minor allele) models were only investigated if a significant gene-by-treatment interaction (P_{int}) effect was detected with the additive model. For SNPs having a significant P_{int}, we also ran similar analyses for fasting insulin, Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), adiponectin and fructosamine (also analysed as Δ values) using the same statistical approach. HOMA-IR was calculated using the formula developed by Matthews *et al.*[20]: (fasting plasma glucose (mmol/l) × fasting serum insulin (mU/l))/22·5. A *P* value ≤ 0·05 was used as the threshold for statistical significance for all analyses, unless otherwise specified.

Results

A total of 108 participants consented to genetic analyses. Three participants were excluded due to missing baseline glucose data for one of the treatment oils and four individuals were identified as outliers when analysing their fasting blood glucose values. Therefore, a total of 101 participants (fifty-nine females, forty-two males) were included in the present analysis (Table 2, Fig. 1). For the primary outcome, no significant differences ($P = 0·74$) were observed in Δglucose with the consumption of any of the treatment oils. This was confirmed with an endpoint-to-endpoint comparison, that is, Control oil final time point (5·1 (SEM 0·05) mmol/l) *v.* RCO final time point (5·1 (SEM 0·04) mmol/l) *v.* HOCO final time point (5·2 (SEM 0·05) mmol/l). Additionally, the consumption of the treatment oils did not influence either Δinsulin ($P = 0·21$) or ΔHOMA-IR ($P = 0·22$).

For our secondary outcome, we conducted an exploratory nutrigenetics analysis to determine if common variants in *SCD* influenced a participant's response to treatment oils varying in SFA/MUFA content. To this end, we analysed seven SNP in *SCD*. All SNPs were in Hardy Weinberg equilibrium except rs10883463, for which no minor allele homozygotes were detected in our study population (Table 3). Thus, this SNP was not considered further. We first examined the remaining six SNPs using an additive genetic model and found statistically significant gene-by-treatment interactions (P_{int}) on Δglucose for three SNPs (Fig. 2(a), (c) and (e); online Supplementary Table S1): rs1502593 ($P_{int} = 0·01$), rs3071 ($P_{int} = 0·02$) and rs522951 ($P_{int} = 0·03$). No interactions were observed with rs11190480, rs7849 and rs3829160. No sex effects were detected across any SNPs. These significant gene-by-treatment interactions were confirmed with an endpoint-to-endpoint analysis (not shown). To obtain further insight into these gene-by-treatment interactions, we next examined the three significant SNPs with dominant and recessive genetic models.

For rs1502593, weak statistical significance was found with the recessive model ($P_{int} = 0·04$; Fig. 2(b)) and a trend was seen in the dominant ($P_{int} = 0·051$, data not shown) model. For rs522951, the recessive model was not significant ($P_{int} = 0·43$) and a trend was seen in the dominant model ($P_{int} = 0·052$, Fig. 2(f)). However, *post hoc* Tukey analyses did not yield any significance for gene-by-treatment interactions for rs1502593 (recessive model) or rs522951 (dominant model).

For rs3071, statistical significance was observed with the recessive model ($P_{int} = 0·005$, Fig. 2(d)), while the dominant model was not significant ($P_{int} = 0·13$). Importantly, the outcome of this recessive model remained statistically significant even when corrected for multiple testing by Bonferroni. *Post hoc* Tukey analysis revealed that overall significance was driven by a significant difference between genotypes in response to the Control oil. Specifically, the group of individuals with the CC genotype had an increase in Δglucose (+0·14 (SEM 0·09) mmol/l) in response to the Control

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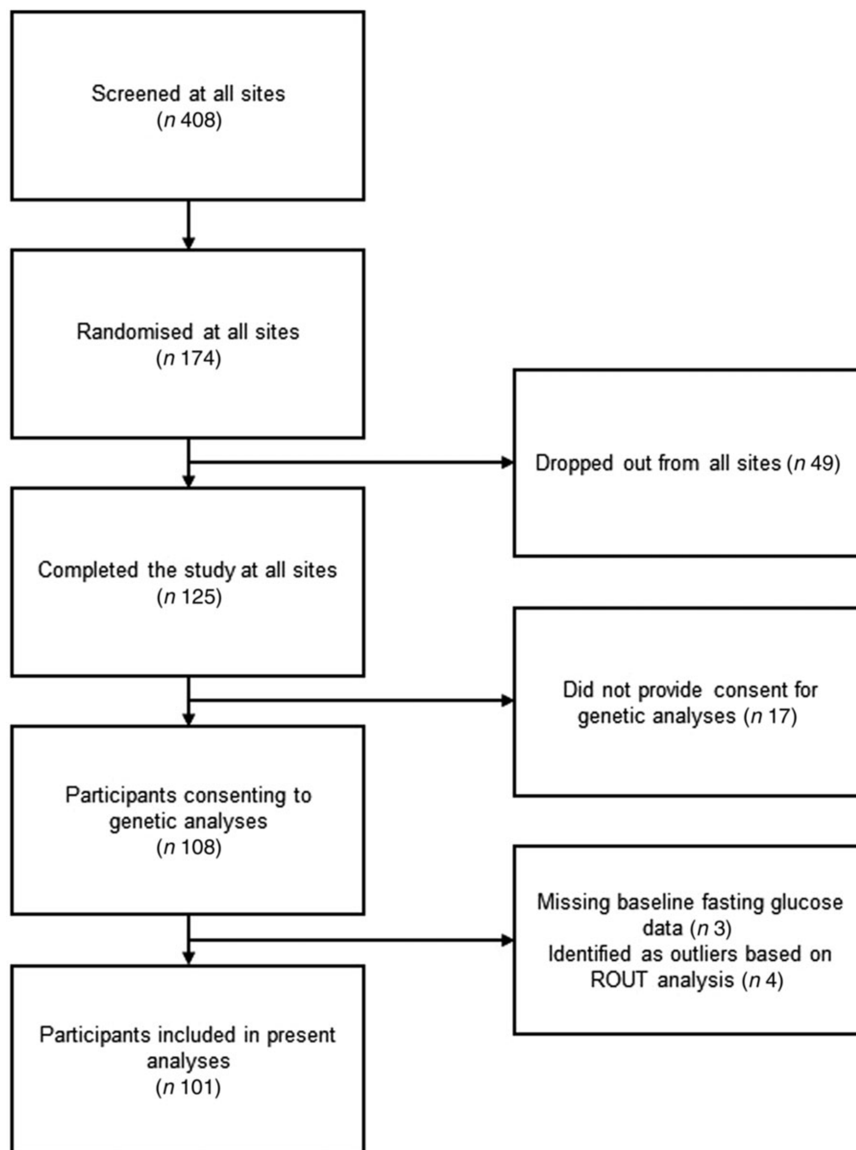

Fig. 1. Consort diagram. Flow chart of participating adults in the Canola Oil Multi-Centre Intervention Trial II trial and the present study.

oil, while the group of individuals carrying the more common AA and AC genotypes showed a reduction in Δglucose (–0·20 (SEM 0·03) mmol/l). When the group of individuals with the CC genotype consumed either of the high MUFA treatment oils, they experienced reductions in Δglucose (RCO: –0·20 (SEM 0·1) mmol/l; HOCO: –0·21 (SEM 0·1) mmol/l) that were of similar magnitude to that observed in carriers of the AA and AC genotype (RCO: –0·15 (SEM 0·04) mmol/l; HOCO: –0·11 (SEM 0·04) mmol/l).

Using a statistical approach identical to that performed with Δglucose, a subsequent analysis of changes (Δ) in fasting blood insulin ($P = 0·27$), HOMA-IR ($P = 0·45$), fructosamine ($P = 0·93$) and adiponectin ($P = 0·82$) in response to the different treatment oils in individuals stratified by their rs3071 genotype according to a recessive model revealed no effect with the different treatment oils. This was further confirmed with an endpoint-to-endpoint comparison (not shown).

Discussion

The present exploratory nutrigenetics study revealed that changes in blood glucose in response to treatment oils varying in SFA/MUFA content are modified by common variants in the *SCD* gene in individuals with obesity and at least one additional characteristic of the MetS. Specifically, individuals with the CC genotype in rs3071 experienced a 0·14 (SEM 0·09) mmol/l increase in fasting blood glucose following the 6-week consumption of a diet containing high SFA/low MUFA compared to individuals with the AA and AC genotypes. However, when these same individuals consumed diets containing high MUFA (either RCO or HOCO), they showed reductions in blood glucose comparable to individuals with the AA and AC genotypes. Interestingly, the comparable changes in blood glucose seen with RCO and HOCO in individuals with the CC genotype suggest that α-linolenic acid is not driving this response since these

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Table 3. Genotype and allelic distribution of *SCD* polymorphisms in COMIT II participants, and compared with the 1000 Genomes European population

SNP	Position	Genotype	Count (*n*)	Allele	Count	Frequency	1000 Genomes (EUR) frequency	Fisher's exact test (*P*)	HWE (*P*)
rs1502593	Intron	GG	32	G	114	0·56	0·56	1·00	0·95
		GA	50	A	88	0·44	0·44		
		AA	19						
rs11190480	Intron	AA	79	A	179	0·89	0·92	0·63	0·76
		AG	21	G	23	0·11	0·08		
		GG	1						
rs7849	UTR	TT	70	T	168	0·83	0·85	0·85	0·91
		TC	28	C	34	0·17	0·15		
		CC	3						
rs3071	Intron	AA	46	A	136	0·67	0·67	1·00	0·77
		AC	44	C	66	0·33	0·33		
		CC	11						
rs522951	Intron	CC	39	C	119	0·59	0·55	0·67	0·09
		CG	41	G	83	0·41	0·45		
		GG	21						
rs3829160	Intron	GG	39	G	122	0·61	0·53	0·32	0·34
		GA	44	A	80	0·39	0·47		
		AA	18						
rs10883463	Intron	TT	92	T	194	0·95	0·95	1·00	–
		TC	10	C	10	0·05	0·05		
		CC	0						

SCD, stearoyl-CoA desaturase; COMIT, Canola Oil Multi-Centre Intervention Trial; HWE, Hardy Weinberg equilibrium.

two oils differ in the levels of this important FA (i.e., 8·3 % in RCO *v.* 2·2 % in HOCO). Given that the prevalence of the C allele is estimated to be ~33 % of the general population of European descent, this result identifies a common SNP that could potentially be used by healthcare practitioners considering personalised nutrition approaches involving genetics as a means to help manage blood glucose levels in their patients. For individuals with the AA or AC genotypes, further research is necessary to identify effective replacement options for SFA, such as diets rich in *n*-3 PUFA or fibre-rich whole grains, as means to modify their blood glucose levels.

The *SCD* gene encodes the Δ9-desaturase, which converts SFA into MUFA through the insertion of a *cis* double-bond between carbons 9 and 10 of the acyl chain. The role of SCD, and particularly the SCD1 isoform, on cardiometabolic endpoints has been studied extensively in cell and rodent models, but how this knowledge translates to humans remains unclear. Interestingly, the global *Scd1-/-* mouse has reduced MUFA but is resistant to diet-induced obesity and has improved insulin sensitivity(21,22). Subsequent investigations using global and liver-specific *Scd1-/-* mice suggested that the improved insulin sensitivity in these mice stems from greater glucose utilisation in several tissues, including skeletal muscle and heart, as well as reduced hepatic gluconeogenesis (reviewed in[23]). While these past findings paradoxically imply that lower MUFA may be metabolically beneficial, results from feeding studies in *Scd1-/-* mice have led to the suggestion that MUFA produced by SCD and MUFA consumed in the diet may constitute different cellular pools of FA and therefore have different metabolic outcomes(23–25). Although further investigations regarding the potentially distinct roles of dietary *v.* endogenously produced MUFA are necessary, past studies such as these highlight the profound influence of SCD on whole-body metabolism that extends beyond the simple desaturation of SFA into MUFA.

The functional significance of polymorphisms in the human *SCD* gene remains elusive. Results to date suggest that *SCD* polymorphisms may modify enzyme activity, but whether this stems from changes in *SCD* gene expression, mRNA stability or protein function is unknown. In all the studies discussed below, SCD enzyme activity was estimated with product-to-precursor desaturation indices based on blood FA, that is, palmitoleate/palmitate (16:1*n*-7/16:0) and oleate/stearate (18:1*n*-9/18:0). While the use of desaturation indices based on blood FA as a proxy for SCD enzyme activity is common in human research, an important caveat with the interpretation of these estimates is that they are strongly impacted by dietary fat composition[26].

Gong *et al.*[8] reported a significant association between rs1502593 and prevalence of the MetS in Costa Rican adults. Moreover, Costa Rican women with the minor allele in this SNP had higher fasting blood glucose compared with the common allele; however, no significance was observed between rs1502593 and SCD desaturation indices. A significant association with rs1502593 was also found in the present study, where individuals with the AA genotype experienced a smaller reduction in fasting blood glucose following the Control oil compared with individuals carrying at least one copy of the major G allele. However, these differences failed to attain significance in *post hoc* analysis. Martín-Núñez *et al.*[4] measured serum phospholipid FA composition and genotyped nine SNPs in *SCD* in over 800 Spanish adult men and women. Interestingly, several SNPs (rs508384, rs2167444 and rs7849) in *SCD* were significantly associated with desaturation indices, suggesting that polymorphisms may affect SCD activity. Specifically, the minor alleles of all three SNPs were associated with a reduced 18:1*n*-9/18:0 desaturation index. Although rs3071 was examined in this past study, it was not found to be associated with desaturation indices. Finally, Rudkowska *et al.*[7] reported a significant genotype effect between rs2234970 and the 18:1*n*-9/18:0 ratio in French

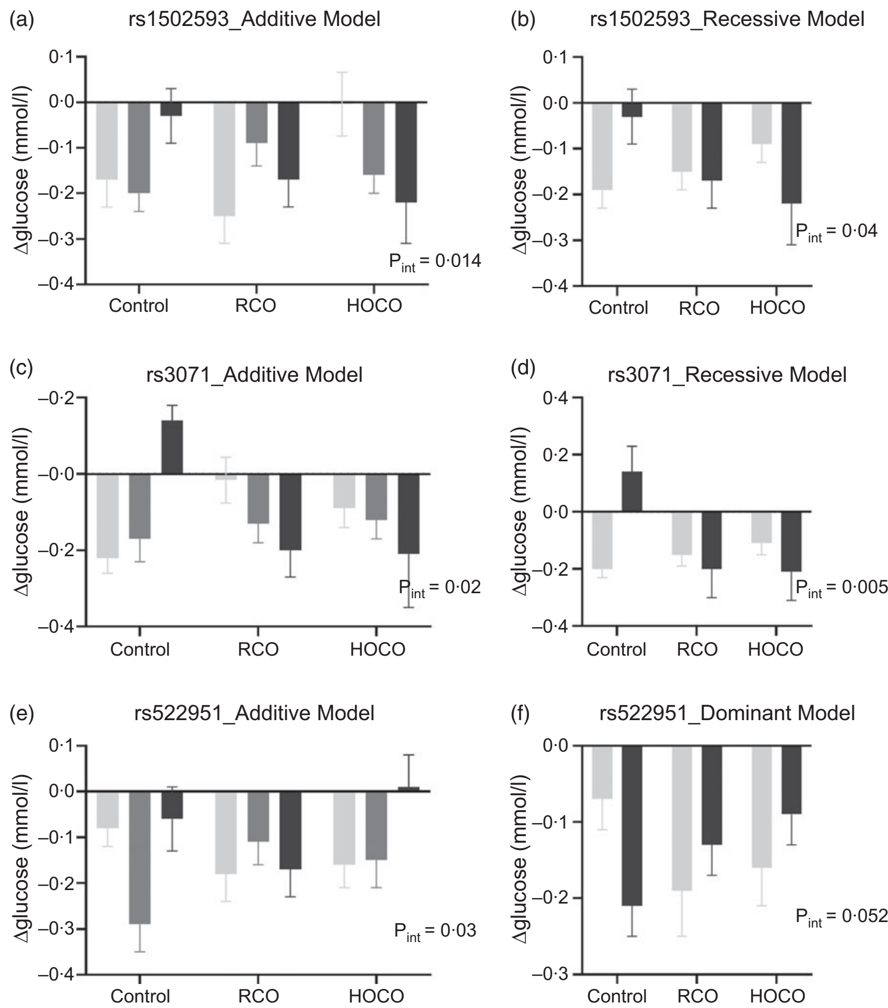

Fig. 2. *SCD* genotypes modify blood glucose response to treatment oils. Changes in fasting blood glucose (Δglucose) were calculated by subtracting baseline value from its corresponding 6-week endpoint value. Repeated measures mixed models were used to assess the effect of genotype on Δglucose in response to the three treatment oils. Treatment, sex, age, ethnicity, BMI, baseline fasting glucose and genotype were included as fixed effects, and treatment sequence, clinical site and participants were included as random effects. Participant was a repeated factor. *P*-values reflecting the interaction (P_{int}) between genotype–treatment are indicated for each model. See Table 3 for the number of participants with each genotype. *SCD*, stearoyl-CoA desaturase; RCO, regular canola oil; HOCO, high-oleic acid canola oil. (a) , GG; , AG; , AA. (b) , GG + AG; , AA. (c) , AA; , AC; , CC. (d) , AA + AC; , CC. (e) , CC; , CG; , GG. (f) , CC; , CG + GG.

Canadian adults, with minor allele carriers showing a higher estimated enzyme activity. These authors did examine rs3071 and although they reported a significant association with plasma IL-6 levels, with the minor CC genotype having lower IL-6 compared with the AA and AC genotypes, no relationship between rs3071 and the 18:1*n*-9/18:0 ratio was found. Together, these three studies show conflicting results regarding the associations between *SCD* polymorphisms and estimated desaturation enzyme activity. However, this is not surprising given the different populations in these studies would have been consuming dramatically different background diets that would undoubtedly affect the blood FAs used to calculate desaturation indices. Further, the allele frequency for *SCD* variants differs between populations; thus, associations from one population may not necessarily translate to other populations with different genetic backgrounds. Nevertheless, these past studies, in addition to findings from *Scd1-/-* mice, allow us to speculate a potential mechanism of action related to the rs3071 SNP. We hypothesise that rs3071 may have modified SCD enzyme activity in our participants, thereby altering endogenous MUFA production. The difference in SCD enzyme activity between genotypes coupled with differences in the SFA/MUFA composition of the diet could alter the relative proportions of the different cellular pools of MUFA (i.e., diet-derived *v.* endogenous produced), ultimately leading to differences in the regulation of glucose homoeostasis. Therefore, we propose that individuals carrying the CC genotype for rs3071 may have lower endogenous MUFA production via the SCD enzyme and therefore benefit from higher MUFA intake with RCO and HOCO. Future examination of the rs3071 SNP should consider using stable FA isotopes (e.g., ^{13}C-palmitic acid[27]) to measure desaturase activity to verify or reject this hypothesised mechanism of action. It would also be of interest to perform glucose tolerance tests in individuals stratified according to their rs3071 genotype to obtain greater insight into glycaemic control.

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To the best of our knowledge, no studies have examined whether SNPs in *SCD* can modify blood glucose responses to diets varying in SFA/MUFA content. However, two prior studies have investigated if blood glucose response following *n*-3 FA intake is modified by SNPs in *SCD*. Lemas *et al.*[18] reported no interactions between SNPs in *SCD* and *n*-3 intake on fasting glucose and other markers of glycaemic control in Yup'ik individuals. In contrast, Rudkowska *et al.*[7] found a significant gene-by-*n*-3 supplement interaction on fasting glucose. Individuals with the AA genotype in rs508384 experienced a reduction in fasting plasma glucose levels following 6-week *n*-3 supplementation compared with increased plasma glucose levels in CA and CC genotypes. In the present study, we examined the rs7849 SNP, which is in high linkage disequilibrium with rs508384 ($r^2 > 0{\cdot}99$); however, we did not detect a gene-by-treatment interaction with this SNP. Despite the different dietary oils used between past studies and the present one, these findings collectively support the need for additional investigations examining the role of *SCD* variants.

The present study is limited by its small sample size (in particular, for our exploratory nutrigenetics analyses) and the unequal distribution of different ethnicities. However, we accounted for ethnicity in our statistical models and the rs3071-by-treatment interaction in the recessive model was significant even after accounting for multiple testing, which strengthens our confidence in the results. Nevertheless, further investigation in larger cohorts that includes a more diversified group of individuals ranging from normoglycaemia to type 2 diabetes is necessary. An important strength of the present study relates to design of the multi-centre clinical trial, where participants received all three treatment oils as part of fully controlled isoenergetic diets in a randomised and blinded manner. Furthermore, the consumption of test oils delivered in smoothies helped to ensure a high degree of compliance during the study.

In summary, we did not observe a general effect of high MUFA oils on blood glucose compared with an SFA-rich Control oil. However, we did identify a common SNP in *SCD* that modifies blood glucose response to treatment oils that vary in SFA/MUFA composition. Although numerous variants have been reported in the literature to associate with the individual components of the MetS[28], few have been shown to elicit different responses in cardiometabolic risk factors following the consumption of different diets. Thus, the findings of this exploratory study are valuable for the field of nutrigenetics and identify a potential variant for personalised nutrition using genetics.

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D. E. L., M. R. and D. M. M. performed the laboratory work, data analysis and wrote the manuscript related to this exploratory nutrigenetics study. J. S., S. S. H., C. G. T., P. Z., S. G. W., K. B., P. M. K.-E., B. L., P. C., V. G., D. J. A. J. and P. J. H. J. designed and supervised the COMIT II trial and were involved in data collection and sample handling. J. S. conducted fatty acid analyses. P. W. C. performed biochemical analyses. P. E. assisted with genotyping analyses. All authors read and approved the final manuscript.

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Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521001264

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