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RESEARCH PAPER

The -308 G/A polymorphism of the tumour necrosis factor-α gene modifies the association between saturated fat intake and serum total cholesterol levels in white South African women

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Abstract This study explored interactions between dietary fat intake and the tumour necrosis factor-α gene (*TNFA*) -308 G/A polymorphism on serum lipids in white South African (SA) women. Normal-weight ($N = 88$) and obese ($N = 60$) white SA women underwent measurements of body composition, fat distribution, fasting serum lipids, glucose, insulin concentrations and dietary intake. Subjects were genotyped for the functional -308 G/A polymorphism within the *TNFA* gene. There were no significant differences in the genotype or allele frequencies between groups, and no significant genotype associations were found for body fatness or distribution, or serum lipid concentrations. However, there was a significant interaction effect between dietary saturated fat (SFA) intake (%E) and *TNFA* -308 genotypes on serum total cholesterol concentrations ($P = 0.047$). With increasing SFA intake (%E), serum total cholesterol levels decreased for the GG genotype and increased for the GA plus AA genotypes. The *TNFA* -308 G/A polymorphism appears to modify the relationship between dietary fat intake and serum total cholesterol concentrations in white SA women.

Keywords Cholesterol · Dietary fat · Fatty acids · Tumour necrosis factor-α · White women

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Introduction

Excess adipose tissue associated with obesity has been linked with a low-grade, chronic inflammatory response, characterised by altered production of adipokines and raised inflammatory markers such as tumour necrosis factor-α (TNFα) [27, 14].

The proinflammatory cytokine TNFα has been shown to have important effects on whole-body lipid metabolism. Raised circulating levels of TNFα have been associated with increased serum triglycerides (TG), very low-density lipoprotein cholesterol (VLDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C) [24]. Moreover, circulating soluble tumour necrosis factor receptor levels, a surrogate marker of previous TNFα effects, have been shown to circulate in proportion to low-density lipoprotein cholesterol (LDL-C) concentrations in apparently healthy subjects [7]. Consequently, TNFα has been associated with obesity [17–19, 20, 21, 32] and dyslipidaemia [24, 32]. The link between obesity, inflammation and dyslipidaemia may be mediated through different pathways; one of which may include interactions between dietary fat intake and polymorphisms within the *TNFA* gene, potentially modulating the phenotype [9, 8, 29].

The A allele of the functional *TNFA* -308 G/A polymorphism has been shown to increase transcription and subsequently increase TNFα production [38]. In addition, the *TNFA* -308 A allele has been shown to modulate the

relationship between dietary fat intake and obesity risk and dyslipidemia in different populations. Nieters et al. found that white German men and women with the *TNFA* -308 A allele, who were in the highest tertile for intake of the n-6 fatty acids linoleic acid (LA) and arachidonic acid (AA) as a percentage of total energy (%E), had significantly increased risk of obesity [29]. In a mixed Canadian population, Fontaine-Bisson showed that dietary polyunsaturated fat (PUFA) intake (%E) was inversely associated with HDL-C concentration in carriers of the *TNFA* -308 A allele, but not in those with the GG genotype [9].

More recently, in black South African (SA) women, we found that the odds of obesity for women with the *TNFA* -308 A allele increased with total dietary fat intake (%E), whereas the risk of obesity was not altered in women with the GG genotype [23]. Further, we found significant interactions between dietary intake of α-linolenic acid (ALA) (%E) and the total cholesterol : HDL-cholesterol ratio (T-C:HDL-C) ($P = 0.036$), as well as between dietary PUFA (%E) intake and serum LDL-C concentrations ($P = 0.026$), with subjects carrying the *TNFA* -308 A allele being more responsive to changes in relative fat intake.

Importantly, there are differences in the distribution of inflammatory gene polymorphisms, inflammatory gene expression and dietary fat intake between black and white populations [2, 6, 11]. Genetic studies have shown that African American and sub-Saharan populations are more likely to carry allelic variants that up-regulate inflammation compared with white women [28], and in a SA population, black women had higher subcutaneous adipose tissue (SAT) TNFα gene expression than white SA women [6]. Further, white SA women have been reported to have lower dietary fat intake, but a higher relative intake of saturated fat (SFA) and lower intake of PUFA than black women [11]. Given these reported differences, it is important to investigate these diet–genotype interactions in white SA women, who have also been shown to have a higher prevalence of dyslipidaemia and cardiovascular disease (CVD) compared with black women [26].

Therefore, the aim of this study was to explore interactions between dietary fat intake and the *TNFA* -308 G/A polymorphism on obesity risk and serum lipids in white SA women.

Subjects and methods

Subjects

A convenience sample of 88 normal-weight (BMI $\leq$ 25 kg/m^2) and 60 obese (BMI $\geq$ 30 kg/m^2) white SA women between the ages of 18 and 45 years were recruited as part of a larger study in the greater Cape Town area. Inclusion criteria were the following: (1) normal-weight or obese; (2) no previous diagnosis or undergoing therapy for diabetes, hypertension, HIV or other metabolic diseases; and (3) not currently pregnant or lactating.

Approval was obtained from the Human Research Ethics Committee of the Faculty of Health Sciences at the University of Cape Town, and written informed consent was obtained from all participants prior to participation. The study was performed in accordance with the principles of the Declaration of Helsinki, ICH Good Clinical Practice (GCP).

Measurements

Basic anthropometric measurements including weight, height and waist and hip circumferences were taken, as well as whole-body composition using dual-energy X-ray absorptiometry (Hologic QDR 4500 Discovery-W dual-energy X-ray absorptiometer, software version 4.40, Hologic). Blood sampling and analysis, and DNA extraction and genotype analysis have been previously described in detail [23]. In brief, blood samples were drawn from the antecubital vein after an overnight (10–12 h) fast for the determination of serum TG, total cholesterol (T-C), HDL-C and LDL-C concentrations, and for DNA extraction. Fasting plasma glucose concentrations were measured using the glucose oxidase method (Glucose Analyzer 2, Beckman Instruments) and serum insulin concentrations by a micro particle enzyme immunoassay (AxSym Insulin kit). Serum TG, T-C and HDL-C concentrations were measured on the Roche Modular Auto Analyzer using enzymatic colorimetric assays. LDL-C was calculated using the Friedewald equation [10]. Serum concentration of high-sensitivity C-reactive protein (hsCRP; Immun Diagnostik AG, Bensheim, Germany) was analysed using a commercially available ELISA kit according to the manufacturer's protocol. DNA was extracted using the method of Lahiri and Nurnberger [25]. The functional -308 G/A polymorphism (rs1800629) within the proximal promoter of the *TNFA* gene was detected by nested PCR amplification and digested with the NcoI restriction enzyme, as previously described [37].

Dietary intake

Dietary intake was estimated using a quantified food frequency questionnaire (QFFQ) [33, 4] as described in detail previously [23]. The questionnaire comprised 100 food items with food photographs to determine portion size. Nutrient intake was calculated by means of the software program FoodFinder, III (South African Medical Research Council) [12]. Energy intake reporting status was assessed using the method of Black [1]. After applying the cut-off

points (<1.05 and >2.28), subjects included: 22 (15%) under-reporters, 121 (82%) adequate reporters, and 5 (3%) over-reporters. There were no significant differences between the over- and under-reporters, and the adequate reporters for body composition or metabolic outcomes (results not shown). Where dietary intake was reported, only 74 normal-weight and 47 obese adequate reporters were included in the analysis.

Statistical analysis

Data were transformed (adding a constant, then taking the natural log), when required, to approximate normality, for analysis. The obese women were significantly older than the normal-weight women, and therefore all analyses were age-adjusted. There were very few women with the *TNFA* -308 AA homozygous genotype, so they were grouped with those with a GA genotype for all analyses. Linear regression was used to model baseline, lipid and insulin variables as functions of body mass index (BMI) group and *TNFA* -308 G/A genotype, including their interaction, while covarying for age. We modelled dietary variables as a function of BMI group, adjusted for age (no genotype interaction).

Linear regression was similarly used to model BMI and lipids as functions of the interaction between specific dietary variables and genotype while covarying for age and BMI. Dietary fats were the focus of the analysis because of their interaction with inflammation and serum lipids. A binomial model with logit link was used to model the risk of obesity (i.e. probability of belonging to the normal-weight or obese group) as a function of the interaction between dietary variables and genotype while covarying for age. When we found significant interactions, we present graphs to aid in their interpretation, because interaction effects, especially between transformed variables, are difficult to describe.

We did not adjust for multiple testing because it has been suggested that the Bonferroni correction is too conservative when several associations are tested in the same group of individuals [30] and might not be appropriate in a situation such as this, where there is prior evidence that such effects exist [31].

Analyses were done in R, a language and environment for statistical computing, freely available from www.r-project.org. The R package genetics was also used.

Results

Genotype distribution

There were no significant differences in the *TNFA* -308 G/A genotype ($P = 0.345$) or allele ($P = 0.453$) frequencies between the normal-weight (48 GG, 55%; 38 GA, 43%, and 2 AA, 2%) and obese (35 GG, 58%; 24 GA, 40%, and 1 AA, 2%) women. Similarly, when the GA and the rare AA genotypes were combined, there were no significant differences in genotype ($P = 0.146$) between the normal-weight and obese groups. The *TNFA* genotype distributions of the normal-weight ($P = 0.138$) and obese ($P = 0.264$) groups were in Hardy–Weinberg equilibrium.

Body composition and metabolic outcomes according to BMI and genotype

As expected, all obesity measures (Table 1) and metabolic outcomes (Table 2) were significantly different between the normal-weight and obese groups, after adjusting for age and *TNFA* -308 genotype. The only genotype–obesity interaction effect was for BMI; there was a significantly larger increase from normal-weight to obese in GA + AA than in GG women (Table 1). However, this was not supported by DXA-derived measures of body fatness. There were no independent effects of the *TNFA* -308 genotypes on serum lipid or hsCRP concentrations.

Dietary intake according to BMI and genotype

Table 3 describes the dietary intake of the normal-weight and obese groups by genotype (including only adequate reporters). As expected, the obese group reported consuming more kJ than the normal-weight group, and although the observed difference in total fat intake (%E) between BMI groups was not significant, there was a difference in the amount of AA (%E) consumed (Table 3).

Diet–genotype interactions

We assessed in adequate reporters whether *TNFA* -308 G/A genotypes modified the association between dietary fat intake and BMI group, as well as serum lipid concentrations, after adjusting for age and BMI.

We detected a significant interaction between dietary SFA intake (%E) and *TNFA* -308 G/A genotypes on serum T-C concentrations ($P = 0.047$) (Fig 1). After adjusting for age and BMI, serum T-C levels decreased for the GG genotype and increased for the GA + AA genotype with increasing SFA intake (%E).

Discussion

The main finding of the study was that *TNFA* -308 G/A genotypes modulated the relationship between SFA intake (%E) and serum T-C concentrations in apparently healthy white SA women. Specifically, with increasing SFA intake

Table 1 Physical characteristics and body fat distribution of normal-weight and obese women according to *TNFA* -308 G/A genotype

	Normal-weight, $n = 88$		Obese, $n = 60$		*P*-values[a]		
	GG	GA + AA	GG	GA + AA	BMI group	Genotype	Interaction
n	48	40	35	25			
Age, years	29.8 ± 7.5	29 ± 7.1	33.4 ± 8.7	36.1 ± 7.8	0.034	0.652	0.191
Height, cm	1.67 ± 0.07	1.68 ± 0.07	1.67 ± 0.06	1.66 ± 0.07	0.739	0.403	0.458
Weight, kg	61.5 ± 7.0	62.2 ± 5.8	94.8 ± 12.3	101.3 ± 16.4	<0.001	0.732	0.130
BMI, kg/m^2	21.6 ± 1.8	21.6 ± 1.9	33.9 ± 3.8	36.4 ± 4.6	<0.001	0.931	0.020
Body fat, %	27.7 ± 5.1	27.5 ± 5.3	46.2 ± 3.2	44.6 ± 4.3	<0.001	0.897	0.346
Waist, cm	77.6 ± 6.4	77.2 ± 6.0	106.1 ± 10.6	108.6 ± 11.1	<0.001	0.858	0.355
WHR	0.79 ± 0.05	0.78 ± 0.05	0.86 ± 0.07	0.85 ± 0.05	<0.001	0.569	0.855
VAT, cm^2	64.1 ± 23.7	61.5 ± 17.9	152.7 ± 67.6	161.7 ± 55.9	<0.001	0.826	0.960
SAT, cm^2	163 ± 67	169 ± 63	567 ± 140	516 ± 104	<0.001	0.833	0.131

Values are mean ± standard deviation

WHR waist-to-hip ratio, *VAT* visceral adipose tissue, *SAT* subcutaneous adipose tissue

[a] *P*-values are from a linear model testing the interaction between BMI group and *TNFA* -308 G/A genotype, adjusted for age

Table 2 Metabolic outcomes of normal-weight and obese women according to *TNFA* -308 G/A genotype

	Normal-weight, $n = 88$		Obese, $n = 60$		*P*-values[a]		
	GG	GA + AA	GG	GA + AA	BMI group	Genotype	Interaction
n	48	40	35	25			
Glucose, mmol/L	4.56 (4.30–4.80)	4.48 (4.28–4.70)	4.78 (4.51–4.99)	4.84 (4.63–5.05)	0.007	0.716	0.647
Insulin, mU/L	5.79 (4.15–8.02)	5.30 (4.22–6.35)	10.70 (8.42–15.55)	12.51 (9.10–18.76)	<0.001	0.558	0.195
HOMA-IR	0.73 (0.52–1.01)	0.67 (0.53–0.81)	1.34 (1.08–1.98)	1.61 (1.19–2.33)	<0.001	0.572	0.203
TG, mmol/L	0.80 (0.60–1.05)	0.75 (0.60–1.03)	1.20 (0.65–1.60)	1.00 (0.90–1.50)	0.003	0.974	0.965
T–C, mmol/L	4.30 (3.85–4.95)	4.50 (4.08–5.10)	4.90 (4.40–5.80)	5.00 (4.40–5.70)	0.023	0.827	0.956
HDL–C, mmol/L	1.80 (1.60–2.00)	1.70 (1.60–2.00)	1.50 (1.35–1.85)	1.40 (1.10–1.60)	0.014	0.659	0.096
LDL-C, mmol/L	2.30 (1.85–2.70)	2.30 (1.85–2.80)	2.70 (2.25–3.50)	3.20 (2.60–3.50)	0.006	0.991	0.348
T-C/HDL-C ratio	2.53 (2.17–2.90)	2.67 (2.20–2.82)	3.29 (2.58–4.06)	3.82 (3.15–4.82)	<0.001	0.799	0.122
hsCRP, mg/L	1.6 (0.7–4.2)	1.4 (0.7–2.6)	8.1 (2.9–11.7)	6.3 (3.7–7.4)	<0.001	0.144	0.3403

Values are median (interquartile range)

HOMA-IR homeostasis model assessment–insulin resistance, *TG* triglycerides, *T-C* total cholesterol, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *T-C:HDL-C ratio* total cholesterol:high-density lipoprotein cholesterol ratio, *hsCRP* high-sensitivity C-reactive protein

[a] *P*-values are from a linear model testing the interaction between BMI group and *TNFA* -308 G/A genotype, adjusted for age

(%E), T-C concentrations increased for the GA + AA genotype and decreased for the GG genotype. This finding has potentially important implications for dietary recommendations in white SA women, who have previously been shown to have a high prevalence of dyslipidaemia and ischaemic heart disease [26].

The results of this study are supported by our previous study in black SA women [23] in which we identified significant diet–genotype interactions on serum lipid levels. Specifically, with increasing PUFA intake (%E, largely the pro-inflammatory n-6 fatty acid LA), LDL-C concentrations increased in those with the GA + AA genotype and decreased in those with the GG genotype. Similarly, in a Canadian population of mixed ethnicity, Fontaine-Bisson and colleagues found that dietary PUFA intake (%E) was inversely associated with HDL-C concentration in carriers of the *TNFA* -308 A allele, but not in those with the GG genotype [9]. Together these studies suggest that individuals with the pro-inflammatory *TNFA* -308 A allele are more responsive to changes in dietary fat intake (%E) than those with the GG genotype (33). These results are particularly relevant to the SA population. Raised serum lipids are an established risk factor for coronary artery disease (CAD), especially in the white SA population, which presents with a higher T-C and LDL-C concentrations than the black SA population [11, 26]. Understanding how this

Table 3 Dietary characteristics of normal-weight and obese adequate reporter women according to *TNFA* -308 G/A genotype

	Normal-weight, $n = 74$		Obese, $n = 47$		*P*-values[a]
	GG	GA + AA	GG	GA + AA	BMI group
n	41	33	24	23	
Energy intake, kJ/d	8899 (7276–9446)	9305 (8087–10295)	8860 (8081–10511)	10604 (8323–11768)	0.007
Protein, %E	15.2 (13.5–16.9)	13.6 (11.0–15.8)	16.0 (14.4–18.1)	14.8 (13.2–16.6)	0.111
CHO, %E	50.5 (47.4–56.5)	52.1 (49.6–55.8)	50.5 (47.7–54.5)	48.5 (44.3–52.1)	0.332
Fat, %E	29.5 (26.1–32.5)	30.9 (26.1–34.0)	30.8 (27.2–33.2)	33.2 (30.0–36.6)	0.128
SFA, %E	9.5 (8.3–11.8)	10.1 (8.5–12.2)	11.3 (9.7–13.0)	11.6 (10.4–12.5)	0.089
MUFA, %E	10.5 (8.5–11.9)	10.1 (8.9–11.5)	9.9 (9.2–11.5)	11.6 (10.3–13.1)	0.564
PUFA, %E	5.7 (4.7–7.8)	6.4 (4.5–8.0)	6.0 (5.1–8.0)	6.6 (5.3–7.7)	0.150
P:S ratio	0.57 (0.46–0.74)	0.59 (0.42–0.82)	0.55 (0.47–0.79)	0.58 (0.50–0.67)	0.889
(n-3) PUFA. %E	0.33 (0.27–0.41)	0.32 (0.27–0.37)	0.31 (0.27–0.39)	0.33 (0.27–0.41)	0.292
(n-6) PUFA, %E	5.3 (4.1–7.5)	5.7 (4.0–7.6)	5.5 (4.6–7.6)	6.1 (4.8–7.3)	0.134
(n-6):(n-3) PUFA ratio	15.4 (11.7–20.6)	17.1 (12.4–25.0)	16.5 (13.2–29.1)	17.1 (12.9–24.9)	0.088
ALA, %E	0.25 (0.22–0.28)	0.26 (0.21–0.30)	0.24 (0.21–0.27)	0.26 (0.21–0.33)	0.503
LA, %E	5.3 (4.1–7.4)	5.7 (4.0–7.6)	5.4 (4.5–7.6)	6.1 (4.8–7.3)	0.139
AA, %E	0.030 (0.020–0.040)	0.020 (0.020–0.030)	0.035 (0.030–0.043)	0.030 (0.030–0.040)	0.020

Values are median (interquartile range)

%E percentage of total energy intake, *CHO* carbohydrate, *SFA* saturated fat, *MUFA* monounsaturated fat, *PUFA* polyunsaturated fat, *P:S ratio* polyunsaturated fat : saturated fat ratio, *(n-3) PUFA* omega-3 polyunsaturated fatty acid, *(n-6) PUFA* omega-6 polyunsaturated fatty acid, *(n-6):(n-3) PUFA ratio* omega-6 : omega-3 polyunsaturated fatty acid ratio, *ALA* α-linolenic acid, *LA* linoleic acid, *AA* arachidonic acid

[a] *P*-values are from a linear model testing the association with BMI group, adjusted for age

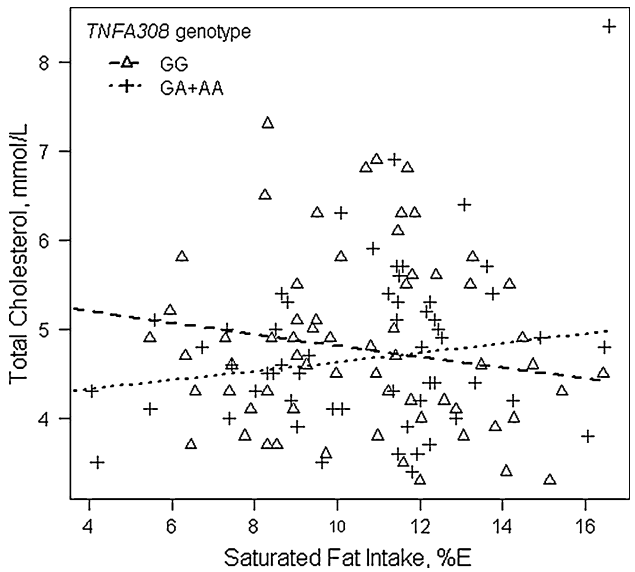

Fig. 1 The relationship between dietary saturated fat intake, serum total cholesterol and *TNFA* -308 G/A genotype in normal-weight and obese women. The modelled relationship is for white women adequate reporters with mean age (30.6 years) and BMI (26.7 kg/m^2). With increasing dietary saturated fat intake (%E), total cholesterol concentration decreases in those with the GG genotype and increases in those with the GA + AA genotype. The difference in rates of change is statistically significant ($P = 0.047$). *Curves* (because of the logs being modelled) will shift up or down according to age and BMI

population responds to specific dietary variables may contribute towards interventions that may reduce risk and elucidate differences in CAD risk between white and black SA women.

The validity of the diet–genotype interactions shown in these studies is supported by the known impact of dietary fatty acids on the release of different cytokines [34]. Saturated fatty acids have been shown to have a pro-inflammatory action; increasing TNFα concentration, macrophage NFkB activity, expression of IL-6, circulating C-reactive protein and expression of cellular adhesion molecules [35, 36]. In general, n-6 fatty acids have been shown to reduce CVD prevalence, but may in some cases promote inflammation, whereas cell culture and human studies have demonstrated that n-3 fatty acids act in an anti-inflammatory manner, inhibiting the production of a number of cytokines, including TNFα, by monocytes, macrophages and endothelial cells [34].

In addition to the effects on serum lipid levels, several studies have reported that carriers of the pro-inflammatory A allele (AA and GA genotype) of the *TNFA* -308 G/A polymorphism have a higher BMI and/or percent body fat than those with the GG genotype [3, 15, 16], contrary to this we showed no association with obesity in this study, nor in our recently published report in black SA women. However, when dietary fat intake was included in the

analyses, black SA women, as well as another Caucasian cohort [29] showed a significant diet–genotype interaction that altered obesity risk. We did not, however, show a similar relationship in our current study of white SA women.

A possible explanation for the disparate findings may be differences in the underlying inflammatory phenotype between populations studied and/or differences in dietary fat intake. Dietary fat intake between the white women sampled in the present study and our previous study in black women differed for most dietary intake variables, which is in agreement with previous findings in other SA cohorts [11]. White and black women consumed the same absolute amount of saturated fat (27 g/day); however, white women consumed a greater relative amount of saturated fat than black women (11.2 and 9.2%E, respectively). White women also consumed less absolute total fat and less n-6 PUFAs than black women (68 g and 79 g vs. 104 g and 126 g, and 5.8 g and 6.0 g vs. 8.6 g and 9.2 g, for normal-weight and obese groups in white and black women, respectively). Similarly, although relative total dietary fat intake was higher in the German white men and women [29], their n-6:n-3 ratio was almost 3 times lower (7.29 and 6.91 vs. 19.9 and 21.1 for normal-weight and obese groups, in the German study and this study, respectively). Further, their reported n-3 (%E) intake was two times greater than in the white SA women in the present study [29]. Numerous studies have highlighted the contribution of different dietary fatty acids to inflammation and other disease conditions [34]. Specifically, saturated fats may unfavourably affect the inflammatory environment. This is of particular relevance as it has been suggested that the inherent underlying inflammatory status of a population may alter the impact of different dietary fats on inflammation [13]. Despite this, we found no associations with hsCRP in this study. Additional SNPs within the *TNFA* gene, as well as SNPs in other genes involved in inflammation, may also be involved and these should be investigated. Further, it has been shown that there is constancy in TNFα production in post-menopausal women and men but not pre-menopausal women, suggesting that TNFα production may be regulated by sex hormones [22]. This study included only pre-menopausal women, which may also affect the study results. Furthermore, our study group was small, and we therefore may not have been able to detect differences that may exist in the white population.

In conclusion, we did not detect any association between the *TNFA* -308 G/A polymorphism and obesity risk, or serum lipid concentrations in this group of white SA women. The *TNFA* -308 G/A polymorphism did, however, modify the relationship between dietary SFA intake (E%) on serum T-C concentrations, further supporting previous studies showing modulation of lipids by diet and inflammatory gene polymorphisms. Future studies should explore these interactions in larger groups of men and women of different ethnic origin in order to inform dietary recommendations for individuals and populations.

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