Gene–diet interactions on plasma lipid levels in the Inuit population

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Abstract
The Inuit population is often described as being protected against CVD due to their traditional dietary patterns and their unique genetic background. The objective of the present study was to examine gene–diet interaction effects on plasma lipid levels in the Inuit population. Data from the Qanuippitaa Nunavik Health Survey (n 553) were analysed via regression models which included the following: genotypes for thirty-five known polymorphisms (SNP) from twenty genes related to lipid metabolism; dietary fat intake including total fat (TotFat) and saturated fat (SatFat) estimated from a FFQ; plasma lipid levels, namely total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C) and TAG. The results demonstrate that allele frequencies were different in the Inuit population compared with the Caucasian population. Further, seven SNP (APOA1 – 75G/A (rs670), APOB XbaI (rs693), AGT M235T (rs699), LIPC 480C/T (rs1800588), APOAI 847C/T (rs5070), PPARG2 – 618G/C (rs10865710) and APOE 219G/T (rs405509)) in interaction with TotFat and SatFat were significantly associated with one or two plasma lipid parameters. Another four SNP (APOC3 3238C > G (rs5128), CETP 1405V (rs5882), CYP1A1 A4899G (rs1048943) and ABCA1 Arg219Lys (rs2230806)) in interaction with either TotFat or SatFat intake were significantly associated with one plasma lipid variable. Further, an additive effect of these SNP in interaction with TotFat or SatFat intake was significantly associated with higher TC, LDL-C or TAG levels, as well as with lower HDL-C levels. In conclusion, the present study supports the notion that gene–diet interactions play an important role in modifying plasma lipid levels in the Inuit population.

Key words: Saturated fat; Total fat; Total cholesterol; LDL-cholesterol; HDL-cholesterol; TAG; Polymorphisms

The Inuits are frequently described as being somehow protected from CVD through their traditional diet and lifestyle11. Yet, the recent adoption of a Westernised lifestyle has been associated with an increase in the prevalence of obesity and other diet-related disorders, including type 2 diabetes, hypertension and CVD1–3. Blood lipid levels play a causal role in the development of CVD. A meta-analysis has shown that LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C) are independently associated with CVD risk4. Moreover, there is evidence that an increase in blood TAG concentration is also an independent risk factor for CVD5. Further, there exists strong evidence to suggest that plasma lipid response to dietary fat content is, to a large extent, genetically controlled6. Thus, common genetic polymorphisms may render an individual more or less responsive to changes in dietary fat intake. Moreover, an individual’s response to dietary fat is probably due to a combination of polymorphisms from various genes rather than a single polymorphism69. Overall, gene–diet interactions may provide important insights into the inter-individual variability observed in plasma lipid levels and thus on the risk of CVD.

The genetic background of the Inuit population has also been shown in previous studies to be protective; however, others have reported potentially detrimental effects for CVD susceptibility50. The interactions between polymorphisms, dietary fat intake and plasma lipid levels in the Inuit population may thus be different from those previously observed in other populations. Therefore, the main objective of the present study was to examine the associations between thirty-five known polymorphisms (SNP) in twenty candidate genes related to lipid metabolism, the intake of total fat (TotFat) or saturated fat (SatFat), and plasma lipid levels (total cholesterol (TC), LDL-C, HDL-C and TAG) in the Inuit population.

Abbreviations: HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SatFat, saturated fat; TC, total cholesterol; TotFat, total fat.
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Subjects and methods

Subjects

Data were collected in the framework of the Nunavik Inuit Health Survey ‘Qanuippitaaq? How are we?’ conducted among the Inuit of Nunavik in 2004. The survey covered all fourteen Nunavik communities. In the winter of 2009, participants from the Qanuippitaaq Nunavik Health Survey in 2004 were revisited for the additional genetic component. The present study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Ethics Committee on Research of Laval University and the Quebec Public Health Ethics review board. Written informed consent was obtained from all subjects.

Anthropometric measurements

Height was measured using a rigid square and a measuring tape in a standardised standing position, with the participant’s back against the wall looking straight ahead, with arms hanging down freely. Body weight was measured with a scale (Tanita TBF-300; Tanita Corporation). BMI was calculated as body weight (kg)/height (m²), and internationally recommended cut-offs were used.

FFQ

A validated FFQ was administered to the participants. The FFQ covered sixty-nine food items and beverages. Foods were divided into two major groups. The first group, ‘country foods’, refers to food items derived from fishing, hunting and gathering, recorded for each of the four seasons of the year before the interview. The second group, ‘store-bought foods’, refers to most store-bought foods imported from southern regions and consumed during the month before the survey. Pre-defined serving sizes were included in the questionnaire and a corresponding food model was shown in the survey. Pre-defined serving sizes were included in the questionnaire and a corresponding food model was shown to the respondents. Analysis of the FFQ data provided estimates of consumption frequency and the usual intake in grams of country foods on a daily, weekly, monthly, seasonal or annual basis. Daily food intakes were calculated on an annual basis by multiplying food consumption frequency by intake in grams for each food.

Plasma blood sampling

Blood samples were collected from an antecubital vein into vacutainer tubes containing EDTA. Plasma was separated by centrifugation (2500 g for 10 min at 4°C) and samples were portioned and frozen for subsequent measurements. Plasma TC and TAG levels were determined using enzymatic methods using a Hitachi 917 autoanalyser and reagents from Roche Diagnostics. The HDL-C fraction was obtained directly using a Hitachi 917 autoanalyser and reagents from Roche Diagnostics. LDL-C was calculated with the Friedewald formula.

DNA extraction and genotyping

DNA was extracted from 100 μl of buffy coat using the QiAamp 96 DNA Blood Kit (Qiagen, Inc.). The Quant-iT PicoGreen dsDNA Assay Kit (Invitrogen) was used to quantify DNA. DNA was analysed with TaqMan Pre-Designed SNP Genotyping Assays according to the manufacturer’s instructions at the McGill University/Génomique Québec Innovation Center (Montreal, Canada).

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From a literature review, thirty-five polymorphisms in twenty genes relating to lipid metabolism were identified, namely: angiotensin I-converting enzyme (ACE) I/D alleles (rs4343), rs4341; angiotensinogen (AGT) M235T (rs699), T74M (rs4762), A-20C (rs5050), A-6G (rs5051); apoA-I (APOAI) G-75A (rs670), 84T/C (rs5070); apoA-IV (APOA4) Asn147Ser (rs5104); apoA-V (APOA5) T-1131C (rs662799), -3A/G (rs651821), S19W (rs3135506), Gly185Cys (rs2075291); apoB (APOB) Xbal (rs693); apoC-III (APOC3) 328C>G (rs5128), T-455C (rs2854116); apoE (APOE) Cys112Arg (rs429358), Arg158Cys (rs7412), G-219T (rs4050509); ATP-binding cassette, subfamily A, member 1 (ABCA1), member 1 (ABCA1), Arg219Lys (rs2230806); cholesterol ester transfer protein (CEPT) TaqIB (rs708272), C-629A (rs1800775), C-4502T (rs183130), G-971A (rs4783961), Ile-405Val (rs5882); cytochrome P450, family 1, subfamily A, polypeptide 1 (CYP1A1) Msp1 (rs4649093), A4889G (rs1048943); fat mass and obesity associated (FTO) rs9939609; glucokinase (hexokinase 4) regulator (GCKR) rs780009; insulin-induced gene 2 (INSIG2) rs7566605; lipoprotein lipase (LPL) HindIII (rs320), Ser447Ter (rs328); hepatic lipase (HL or LIPC) C-514T (rs1800588), G-250A (rs2070895); methylenetetrahydrofolate reductase (NADPH) (MTHFR) C677T (rs1801133); paraoxonase 1 (PON1) E55M (rs854560), Gln192Arg (rs662), C-107T (rs705739); PPPARy2 (PPARG2) Pro12Ala (rs1801282), −681C/G (rs10865710); transcription factor 7-like 2 (TCF7L2) C47835T (rs7903146).

Statistical analysis

Hardy–Weinberg equilibrium was tested with the Allele Procedure in SAS, version 9.2 (SAS Institute, Inc.). Distribution of alleles was compared between the Inuit and Caucasian populations using the CEU data from the National Center for Biotechnology Information (NCBI; www.ncbi.nlm.nih.gov/) and analysed using the Fisher exact test.

Data are presented as means with their standard errors. Further, variables were checked for normality of distribution using skewness and the kurtosis values. TAG levels were log-transformed before analyses to normalise their distribution. A regression model was used to evaluate the effect of each polymorphism, the fat intake (either TotFat or SatFat as a continuous variable) and the polymorphism *fat intake interaction effect, adjusted for the effects of age, sex and BMI on each of the lipid variables. Second, a regression model adjusted for the effects of age, sex, BMI as well as
energy intake was carried out on each of the lipid variables. Then, the regression $\beta$-coefficient ($\beta$) was derived to estimate the phenotypic difference imparted by each of the genotype $X$ fat intake interaction effects. In addition, to test for the additive effects of multiple polymorphisms, a ‘risk score’ was calculated based on the number of risk genotypes an individual carried from all the significant polymorphism $X$ fat intake interactions for each lipid parameter. A statistical model was used to evaluate the effect of the ‘risk score’, fat intake (either TotFat or SatFat as a continuous variable) and the risk score $X$ fat intake interaction effect, adjusted for the effects of age, sex and BMI on each of the lipid variables. Again, the regression $\beta$ was calculated to estimate the phenotypic difference contributed by the number of risk genotypes and fat intake interaction effects. Statistical analyses were performed with SAS statistical software, version 9.2 (SAS Institute, Inc.). Statistical significance was defined as $P<0.05$.

## Results

### Subject characteristics

In total, 677 households were contacted, of which 521 agreed to participate including 1056 individuals who signed a consent form and 917 who agreed to the collection of blood samples. In addition, 769 participants completed the FFQ. For the additional genetic component, 658 of the original participants gave consent. Consequently, statistical analyses were done for all individuals where plasma lipid levels, nutritional intake and genotypes were available. Therefore, 553 participants, including 251 men and 302 women, with an average age of 37 (SEM 0.8) years and with an average BMI of 28 (SEM 0.3) kg/m$^2$ were included. Collectively, the Inuit population had a relatively favourable plasma lipid profile (Table 1) compared with an optimal profile\(^{(15)}\). Comprehensive results from blood lipid levels in the whole Inuit population have been published previously\(^{(1)}\). Further, FFQ data demonstrate that the average total dietary fat intake was 76 and 63 g/d (approximately 26% of energy intake per d) in men and women, respectively, including 27 and 22 g/d of SatFat (approximately 9% of energy intake per d) in men and women, respectively, for this particular subset of the population.

### Genotypic characteristics

Genotype frequencies did not deviate from those predicted by the Hardy–Weinberg equilibrium except for the following three SNP: \texttt{LPL} HindIII (rs320), \texttt{LPL} Ser474Ter (rs328) and \texttt{TCF7L2} C47833T (rs7903146), which were excluded from the statistical analyses. The minor alleles of the SNP \texttt{AGT} T174M (rs4762), \texttt{AGT} A-20C (rs5050), \texttt{APOA5} Gly185Cys (rs2075291), \texttt{APOA5} S19W (rs3135506), \texttt{APOE} Cys112Arg (rs429358), \texttt{FTO} (rs9939609) and \texttt{TCF7L2} C47833T (rs7903146) had low frequencies ($<0.10$) in the Inuit population and were also excluded from the analyses.

In addition, allele frequencies were significantly different ($P<0.05$) in the Inuit population compared with the Caucasian population for the following eighteen SNP: \texttt{ABCA1} Arg219Lys (rs2230806); \texttt{AGT} M235T (rs699); \texttt{APOA1} G-75A (rs670); \texttt{APOA4} Asn147Ser (rs5104); \texttt{APOE} -3A/G (rs651821); \texttt{APOE} T-1131C (rs662799); \texttt{APOB} XbaI (rs670); \texttt{APOC3} 3238C>G (rs5128); \texttt{APOE} -219T (rs405509); \texttt{APOE} Cys112Arg (rs429358); \texttt{CETP} TaqIB (rs708272); \texttt{CETP} C-629A (rs1800775); \texttt{CYP1A1} A889G (rs1048943); \texttt{FTO} (rs9939609); \texttt{MTHFR} C677T (rs1801133); \texttt{PONI} 155M (rs854560); \texttt{PPARG2} G-302C (rs10865710); \texttt{TCF7L2} C47833T (rs7903146) (see Supplementary material 1, available online).

### Gene–diet interaction in plasma lipid levels

A total of fourteen interactions between SNP and TotFat intake were observed. Individuals with the T/T genotype of \texttt{AGT} M235T (rs699), the T/T genotype of \texttt{CETP} Ile405Val (rs5882), the G allele of \texttt{PPAR2} −681C/G (rs10856710) and the T allele of \texttt{APOB} XbaI (rs693) increased their TC to a greater extent than the other genotype groups with higher TotFat intake (Table 2). Similarly, higher LDL-C levels were associated with a higher dietary TotFat in individuals bearing the T/T genotype of \texttt{AGT} M235T (rs699), the T/T genotype of \texttt{APOE} G-219T (rs405509), the G allele of \texttt{APOA1} G-75A (rs670), the C allele of \texttt{APOC3} 3238C>G (rs5128), the C allele of \texttt{APOC1} G-302C (rs10865710) and the T allele of \texttt{APOB} XbaI (rs693) increased their LDL-C to a greater extent than the other genotype groups with higher TotFat intake (Table 2).

- **Total cholesterol** (mmol/l) 4.94 (SEM 0.06) 5.04 (SEM 0.05)
- **HDL-cholesterol** (mmol/l) 1.48 (SEM 0.02) 1.79 (SEM 0.03)
- **LDL-cholesterol** (mmol/l) 2.89 (SEM 0.06) 2.74 (SEM 0.05)
- **Total/HDL-cholesterol** 3.52 (SEM 0.07) 2.96 (SEM 0.05)
- **apoB100** (mmol/l) 0.97 (SEM 0.03) 0.93 (SEM 0.01)
- **apoA1** (mmol/l) 1.62 (SEM 0.02) 1.77 (SEM 0.02)

#### Table 1. Baseline characteristics of the study subjects

(Mean values with their standard errors)

<table>
<thead>
<tr>
<th></th>
<th>Men (n 251)</th>
<th>Women (n 302)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthropometrics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>37.1 0.9</td>
<td>37.3 0.8</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.5 1.0</td>
<td>65.9 0.9</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.8 0.4</td>
<td>154.0 0.3</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>27 0.3</td>
<td>28 0.4</td>
</tr>
<tr>
<td><strong>Hypercholesterolaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>22 9</td>
<td>21 7</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Plasma lipids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>4.94 0.06</td>
<td>5.04 0.05</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.48 0.02</td>
<td>1.79 0.03</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>2.89 0.06</td>
<td>2.74 0.05</td>
</tr>
<tr>
<td>Total/HDL-cholesterol</td>
<td>3.52 0.07</td>
<td>2.96 0.05</td>
</tr>
<tr>
<td>apoB100 (mmol/l)</td>
<td>0.97 0.03</td>
<td>0.93 0.01</td>
</tr>
<tr>
<td>apoA1 (mmol/l)</td>
<td>1.62 0.02</td>
<td>1.77 0.02</td>
</tr>
<tr>
<td><strong>Daily intake</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total energy intake (kJ)</td>
<td>10932 352</td>
<td>9291 301</td>
</tr>
<tr>
<td>Total fat intake (g)</td>
<td>76.1 2.7</td>
<td>63.4 2.5</td>
</tr>
<tr>
<td>Total saturated fat intake (g)</td>
<td>27.2 1.0</td>
<td>22.2 0.9</td>
</tr>
</tbody>
</table>
significantly higher TC, LDL-C or TAG levels, as well as lower HDL-C levels (Figs. 1–3).

Similarly, thirteen interactions between SNP and SatFat intake were observed. The pattern of association with SatFat intake was similar to the pattern obtained with TotFat intake (eleven out of fourteen interactions); however, there were a few differences. The individuals with the T/T genotype of AGT M235T (rs699), the C allele of PPARG2 2681C/G (rs10865710) and the T allele of APOB XbaI (rs693) had higher TC levels with a higher SatFat intake (Table 2). In addition, APOA1 G-75A (rs670) SNP and SatFat determined the TC levels (Table 2). Similarly (except for one SNP),

<table>
<thead>
<tr>
<th>SNP</th>
<th>Genotype</th>
<th>n</th>
<th>β† SEM</th>
<th>β† SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>APOA1 G-75A (rs670)§</td>
<td>G/G</td>
<td>382</td>
<td>0.0018 a,b</td>
<td>0.0034</td>
</tr>
<tr>
<td></td>
<td>G/A</td>
<td>149</td>
<td>0.0065 b</td>
<td>0.0036</td>
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<tr>
<td></td>
<td>A/A</td>
<td>22</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td>APOB XbaI (rs693)§</td>
<td>C/C</td>
<td>360</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>171</td>
<td>0.0025 a,b</td>
<td>0.0017</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>22</td>
<td>0.0089 b</td>
<td>0.0035</td>
</tr>
<tr>
<td>CYP1A1 A4889G (rs1048943)§</td>
<td>A/A</td>
<td>166</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td></td>
<td>A/G</td>
<td>271</td>
<td>0.0031 a,b</td>
<td>0.0020</td>
</tr>
<tr>
<td></td>
<td>G/G</td>
<td>116</td>
<td>0.0061 b</td>
<td>0.0024</td>
</tr>
<tr>
<td>CETP Ile405Val (rs5882)</td>
<td>C/C</td>
<td>144</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>265</td>
<td>−0.0029 a</td>
<td>0.0023</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>144</td>
<td>0.0024 b</td>
<td>0.0026</td>
</tr>
<tr>
<td>PPARG2 – 681C/G (rs10865710)§</td>
<td>C/C</td>
<td>360</td>
<td>0*</td>
<td>0*</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>171</td>
<td>0.0025 a,b</td>
<td>0.0017</td>
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<tr>
<td></td>
<td>T/T</td>
<td>22</td>
<td>0.0089 b</td>
<td>0.0035</td>
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<tr>
<td></td>
<td>A/A</td>
<td>166</td>
<td>0*</td>
<td>0*</td>
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<td>0.0020</td>
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<tr>
<td></td>
<td>G/G</td>
<td>116</td>
<td>0.0061 b</td>
<td>0.0024</td>
</tr>
</tbody>
</table>

Table 2. Impact of SNP, dietary fat intake and the interaction SNP x dietary fat intake on total cholesterol levels* (β coefficients with their standard errors)

* The model includes SNP, fat intake and the interaction term (SNP x fat intake) with adjustment for the effects of age, sex and BMI.
† The β regression coefficients are derived from absolute values.
‡ P values are calculated with normalised values.
§ Genotype frequency is different between the Inuit and Caucasian populations.

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higher LDL-C levels were associated with a higher SatFat intake for the T/T genotype of APOC3 T589G (rs660, the G allele of APOC3 T589G (rs660), the C allele of APOC3 G589A (rs5128), the C allele of RR2R2 −681C/G (rs10865710) and the T allele of APOC3 XbaI) (rs6953) (Table 3). Lower HDL-C levels were associated with a higher SatFat intake for individuals with the C/C genotype of APOC3 T589G (rs5128) and the T/T genotype of APOC3 XbaI (rs6953) (Table 4). Higher TAG levels were associated with a higher SatFat intake in carriers of the C/T genotype of LIPC C514T (rs1800588) as well as with the C/C genotype of ABCA1 Arg219Lys (rs2230806) (Table 5). Again, the same SNP × SatFat interactions were seen when energy intake was included in the model, in addition to age, sex and BMI (data not shown). Similarly to the SNP × TotFat data, a higher number of these aforementioned risk alleles and higher SatFat intake were associated with significantly higher TC, LDL-C and TAG levels, as well as with lower HDL-C levels (data not shown).

Similar statistical analyses were done with apoB100 (apoB) and apoA1 levels, which yielded the same interaction results as seen for LDL-C and HDL-C levels, respectively (data not shown).

Discussion

The present study confirms that there are genetic differences between the Inuit and Caucasian populations; even so, interactions between polymorphisms, dietary fat intake and plasma lipid levels also exist in the Inuit population. More specifically, seven SNP, namely APOB XbaI (rs693), APOA1 −75G/A (rs670), APOE 219G/T (rs405509), LIPC 480C/T (rs1800588), AGT M235T (rs66099), APOA1 84T/C (rs5070) and PPARG2 −618C/G (rs10865710), in interaction with TotFat and SatFat intake were associated with plasma levels of at least one of the following risk factors for CVD: TC, HDL-C, LDL-C and TAG.

Participants who had the minor allele of APOB XbaI (rs693) demonstrated higher plasma TC and LDL-C levels when consuming a high TotFat and SatFat diet. Numerous studies have previously demonstrated that carriers of the minor allele had elevated LDL-C levels and a less pronounced plasma lipid response to changes in dietary fat intake (20–22). Thus, individuals who carry the minor allele for rs693 in the APOB gene combined with a higher dietary fat intake may be at risk of hypercholesterolaemia.

Similarly, higher TotFat and SatFat intakes were associated with higher plasma LDL-C levels, as well a higher SatFat intake was associated with higher plasma TC, in heterozygotes for APOA1 −75G/A (rs670). A previous study showed that subjects carrying the mutated allele had higher TC, LDL-C and TAG levels than homozygotes for the wild-type allele (23). In addition, a diet rich in PUFA has been shown to induce greater plasma TC and LDL-C decreases in heterozygotes compared with a high SatFat intake was associated with higher plasma LDL-C levels and a less pronounced plasma lipid response to changes in dietary fat intake (20–22). Thus, individuals who carry the minor allele for rs693 in the APOB gene combined with a higher dietary fat intake may be at risk of hypercholesterolaemia.
diet (23). In contrast, an earlier study showed no differences between genotype groups for any lipid variables; yet, the -75G/A polymorphism appears to have an effect on plasma TC, LDL-C and HDL-C responsiveness to increased PUFA in the diet (24). Further, the presence of the A allele has previously been associated with increased promoter activity in vitro (25).

Overall, studies have shown that the response to dietary fat intake may be modified by the 

\[ 75G/A (rs670) \] mutation.

Moreover, in the present study, participants with the T/T genotype of APOE 219G/T (rs405509) exhibited higher plasma LDL-C and lower plasma HDL-C levels when consuming a high-TotFat and -SatFat diet. Similarly, a study demonstrated that carriers of the T allele had higher LDL-C and apoB plasma levels after the SatFat diet compared with G/G homozygotes (26). In addition, carriers of the T allele had a greater decrease in LDL-C and apoB levels when they modified their diet from a SatFat diet to a carbohydrate diet (26). These results suggest that the 219G/T polymorphism may also partially explain inter-individual differences in plasma lipid response to dietary fat intake.

In the Inuit population, carriers of the minor allele of LIPC C-514T (rs1800588) had higher TAG levels when they consumed a high-TotFat and -SatFat diet. Fan et al. (27) also showed that serum TC, HDL-C and TAG levels increased according to the rs1800588 genotype in the order C/C, C/T and T/T in the Finnish population. Further, studies have suggested that the effects of C-514T polymorphism on HDL-C levels were modified by TotFat and SatFat intake (28–30). Clearly, there exists a gene–diet interaction between plasma lipid levels, dietary fat intake and LIPC C-514T polymorphism.

Further, higher TotFat and SatFat intakes were related to higher TC and LDL-C in carriers of the minor allele of AGT M235T (rs699). Previously, the M235T polymorphism (rs699) in the AGT gene has been related to an increased risk of CVD (31) via the presence of hypercholesterolaemia. Overall, these results for AGT (rs699) are supported by previous epidemiological studies (31); however, this gene–diet interaction should be reconfirmed.

In the Inuit population, two polymorphisms, namely APOAI 84T/C (rs5070) and PPARG2 –618C/G (rs10865710), had opposite effects than described previously in epidemiological studies, which did not take dietary fat intake into consideration. First, carriers of the minor allele of APOAI 84T/C (rs5070) had lower HDL-C levels with a higher TotFat or SatFat intake. In contrast, other studies have shown that the minor C allele was protective: higher HDL-C and lower TAG levels observed in the Japanese population (32,33). Second, participants with the wild-type allele of PPARG2 –618C/G (rs10865710) had higher TC and LDL-C levels when consuming a higher-TotFat and -SatFat diet. Contrary to the present results, the carrier of the mutated allele of PPARG2...
– 618C/G was previously associated with a deteriorated lipid profile in a Caucasian population.\(^{(34)}\) Thus, the addition of dietary fat intake with genetic variations may explain discrepancies in plasma lipids levels. In summary, these results suggest that the interaction with dietary fat may determine the risk allele with these two polymorphisms.

Additionally, four SNP, including \(APOC3\) 3238C > G (rs5128), \(CETP\) I405V (rs5882), \(CYP1A1\) A4889G (rs1048943) and \(ABCA1\) Arg219Lys (rs2230806), showed an interaction with either TotFat or SatFat intake to modulate one plasma lipid variable. A higher TotFat intake was associated with higher plasma LDL-C levels in individuals who carry the wild-type allele of \(APOC3\) 3238C > G (rs5128). Previously, the carrier of the mutated allele of \(APOC3\) 3238C > G has been associated with elevated plasma TC and TAG levels.\(^{(35,36)}\) Lopez-Miranda et al.\(^{(37)}\) also demonstrated a decrease in plasma LDL-C concentration in heterozygous subjects after consumption of a diet high in MUFA compared with an increase in plasma LDL-C concentration in wild-type subjects. Additionally, carriers of the I405V (rs5882) polymorphism in the \(CETP\) gene had higher plasma TC levels when consuming a high-TotFat diet. Previously, Darabi et al.\(^{(38)}\) showed that subjects carrying the mutated allele had a greater reduction in plasma HDL-C levels without changes in TC compared with subjects with the other genotype after a diet low in PUFA:SatFat ratio.\(^{(38)}\) Thus, these genetic variations may modulate the effect of dietary fat on blood lipids in the Inuit and other populations; yet, more studies are needed to validate these gene–diet interaction effects.

Furthermore, the \(CYP1A1\) A4889G polymorphism (rs1048943) was associated with higher plasma TC levels with a higher TotFat intake. Studies have shown that \(CYP1A1\) is involved in the bioactivation and detoxification of environmental toxins.\(^{(39)}\) The biological significance of this interaction needs to be validated; however, it might be of interest to examine the interaction between polymorphisms, dietary fat intake and environmental toxins in the Inuit population as factors influencing plasma lipid levels.

A higher SatFat intake was related to higher plasma TAG levels in carriers of the C allele of \(ABCA1\) Arg219Lys (rs2230806). Genetic variants of \(ABCA1\) have been associated with altered atherosclerosis progression and fasting lipid concentration; however, results from different studies have been inconsistent.\(^{(40–42)}\) Therefore, the impact of this polymorphism may be altered by gene–diet interactions.

Further, a combination of SNP coupled with dietary fat intake generated additive effects on lipid traits, which increases the risk of CVD. Overall, these risk alleles in interaction with dietary fat intake, including TotFat and SatFat, may significantly influence the risk of CVD, especially when the risk allele is in a greater proportion in the Inuit population compared with the Caucasian population. Thus, these results suggest that the environment, such as dietary fat consumed, interacts with genes to produce phenotypic differences. Similar to previous reports,\(^{(43)}\) each genetic variant had a small-to-moderate effect; however, the combined effect of all significant variants explained a modest extent of lipid variation.

In conclusion, the findings indicate that genetic variants involved in the modulation of lipid metabolism may play an important role in the modulation of cardiovascular health of the Inuit population. The inclusion of environmental factors, such as TotFat and SatFat, to the genetic association study can help to better predict inter-individual variations in plasma lipid levels. Yet, many other SNP exist in lipid metabolism that have not yet been examined. Further, the present study also supports the notion that the multiple-gene approach might provide a better prediction of lipid variations in the population, but this needs to be investigated in a large-scale study. Overall, the assessment of gene–diet interactions may be a valuable tool to predict the impact of dietary changes on plasma lipid levels in order to reduce the risk of CVD.

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Supplementary material is available online at http://www.journals.cambridge.org/bjn

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