ABSTRACT
Background: The response of plasma lipids to dietary fat manipulation is highly heterogeneous, with some indications that APOE genotype may be important.
Objective: The objective was to use a prospective recruitment approach to determine the effect of dietary fat quantity and composition on both lipid and nonlipid cardiovascular disease biomarkers according to APOE genotype.
Design: Participants had a mean (±SD) age of 51 ± 9 y and a BMI (in kg/m²) of 26.0 ± 3.8 (n = 44 E3/E3, n = 44 E3/E4) and followed a sequential dietary intervention (the SATgen study) in which they were assigned to a low-fat diet, a high-fat high-SFA (HSF) diet, and the HSF diet with 3.45 g DHA/d (HSF-DHA), each for 8 wk. Fasting blood samples were collected at the end of each intervention arm.
Results: An overall diet effect was evident for all cholesterol fractions (P < 0.01), with no significant genotype × diet interactions observed. A genotype × diet interaction (P = 0.033) was evident for plasma triglycerides, with 17% and 30% decreases in APOE3/E3 and APOE3/E4 individuals after the HSF-DHA diet relative to the low-fat diet. A significant genotype × diet interaction (P = 0.009) was also observed for C-reactive protein (CRP), with only significant increases in concentrations after the HSF and HSF-DHA diets relative to the low-fat diet in the APOE3/E4 group (P < 0.015).
Conclusions: Relative to the wild-type APOE3/E4 group, our results indicate a greater sensitivity of fasting triglycerides and CRP to dietary fat manipulation in those with an APOE3/E4 genotype (25% population), with no effect of this allelic profile on cholesterol concentrations. The SATgen study was registered at clinicaltrials.gov as NCT01384032.

INTRODUCTION
Manipulation of dietary fat composition represents one of the main dietary strategies aimed at reducing the incidence and progression of cardiovascular disease (CVD). Typical population recommendations suggest an SFA intake of <10% to 11% of dietary food energy with a <7% cutoff for those with primary hypercholesterolemia (1). A minimum of 450 to 500 mg/d of the long-chain n-3 PUFAs EPA and DHA is recommended to the general population (2), rising to 1 g/d for those with a diagnosis of CVD and to a suggested 2–4 g/d as an effective hypotriglyceridemic intake (3). Although generic population dietary recommendations are provided, the responsiveness to dietary fat manipulation is known to be highly heterogeneous. For example, in the Reading Imperial Surrey Cambridge and King study (n = 548), replacement of an average of 7.3% SFAs with carbohydrates resulted in a mean reduction in LDL cholesterol of 7%, with CIs ranging from 4.8% to −9.2% (4); in the FINGEN trial (n = 312), supplementation with 1.8 g EPA+DHA/d resulted in a mean reduction in triglycerides of 11%, representing a response of −240 to +150% and triglyceride reduction in only 61% of participants (5). The etiological basis of these highly variable responses is relatively unknown, but is of wide interest in an era of a move toward the provision of more targeted dietary advice. Although pleiotropic, the best described function of apolipoprotein E is as a central regulator of lipoprotein metabolism. Carriers of the APOE4 allele (20–25% whites) are at increased risk of CVD, in part attributable to the modestly higher plasma LDL-cholesterol and triglyceride concentrations in this subgroup (6, 7). This genotype has also been widely investigated as a potential modulator of the plasma lipid response to altered dietary fat composition. Findings to date have been highly inconsistent but provide some evidence of a greater sensitivity in APOE4 individuals to altered dietary cholesterol, total fat, and SFA intakes (8, 9). Available data are almost exclusively derived from cohort studies or interventions in which genotyping was conducted retrospectively, often resulting in small group sizes in the rare allele subgroups and a lack of power to conclusively study APOE genotype × dietary lipid × phenotype associations. Also, we have reported that the commonly observed LDL-cholesterol-raising effect of high-dose fish oils, particularly DHA (10, 11), is most evident in APOE4 carriers. A significant 10% increase in LDL cholesterol was observed in this subgroup after supplementation with a DHA-rich oil (3.7 g DHA/d) as was a modest reduction evident in the wild-type APOE3/E3 group (12), which was broadly consistent with the findings of an earlier study (13). Although high-dose fish oils (2–4 g EPA and DHA/d) are often

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4 Abbreviations used: CO, control oil; CRP, C-reactive protein; CVD, cardiovascular disease; HSF, high-fat high-SFA; HSF-DHA, HSF + DHA diet (3.45 g/d); NEFA, nonesterified fatty acid; RQUICKI, revised quantitative insulin-sensitivity check index; sLDL-C, small, dense LDL cholesterol; TC, total cholesterol.

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recommended as a triglyceride-lowering strategy (3) for individuals who may have a high habitual SFA intake, the interactive effect of DHA and SFA on LDL cholesterol in APOE4 carriers is unknown.

In view of these knowledge deficits, our primary aim was to use an adequately powered prospective genotyping approach to examine the effects of dietary fat composition on LDL cholesterol and other associated lipid risk markers in individuals according to APOE genotype. Because this genotype has also been identified as a genetic determinant of C-reactive protein (CRP) concentration (a marker of inflammation linked to CVD), an investigation of the influence of dietary fat manipulation on CRP according to APOE genotype was included as a secondary aim of the current study.

### SUBJECTS AND METHODS

#### Study subjects

The SATgene study is a chronic intervention designed to determine the effects of dietary fat quantity and composition on LDL-cholesterol concentrations and other CVD risk factors in men and women aged 35–70 y [BMI (in kg/m²): 20–32] prospectively recruited by APOE genotype (APOE3/E3 and APOE3/E4). Exclusion criteria included anemia (hemoglobin: <12.5 g/L in men and <11.5 g/L in women); hyperlipidemia [triglycerides: >4.0 mmol/L; total cholesterol (TC): >8 mmol/L]; diabetes or fasting glucose >7 mmol/L; liver or endocrine dysfunction; medication use for blood pressure, lipid, or endocrine disorders; pregnancy or breastfeeding; alcohol intakes >21 units/wk for men and >14 units for women (1 UK unit defined as 10 mL or 8 g pure alcohol); or unwillingness to change their habitual diet. A total of 246 subjects were screened to fulfill the study recruitment target of 90 total subjects, equally distributed as 45 subjects with the APOE3/E3 genotype and 45 with the APOE3/E4 (wild-type) subjects. The genotype groups were matched for age, BMI, male:female ratio, and menopausal status. The study was given a favorable ethical opinion for conduct by the University of Reading Research Ethics committee and before participation in the study; all subjects gave written informed consent.

#### Study design and capsules

A sequential dietary intervention design was used, whereby subjects followed 3 isonenergetic diets, each of 8 wk in duration in the same order. Full details of how the dietary targets were achieved were previously reported (14). Briefly, target diet compositions were as follows: low-fat diet (24% of energy from fat, 8% of energy from SFA, 59% of energy from carbohydrate), high-fat high-SFA (HSF) diet (38% of energy from fat, 18% of energy from SFA, 45% of energy from carbohydrate), and the HSF diet supplemented with 3.45 g DHA/d (HSF-DHA). Before commencing the test diets, volunteers underwent a 1-wk run-in period during which time they consumed their habitual diet with the addition of 2 × 1 g/d of control oil (CO) capsules. The CO consisted of palm olein and soybean oil (80:20 ratio) (AarhusKarlsmann United) and provided a fatty acid mixture representative of the typical UK diet (44% SFA, 39% MUFA, and 17% PUFA). The CO capsules (2 g/d) were also consumed during the subsequent low-fat and HSF diets. During the HSF-DHA diet, subjects consumed 6 × 1 g DHA-enriched fish oil capsules/d (Incromega 500TG DHA; Croda Europe Ltd). The DHA-enriched oil had the following fatty acid profile: 5.7% SFA, 11.6% MUFA, and 82% PUFA (8.3% EPA, 3.1% DPA, and 57.5% DHA), which provided the target 3.45 g DHA/d (see Table 1 under “Supplemental data” in the online issue).

Participants attended a clinical visit at the end of each 8-wk dietary period (low-fat, HSF, and HSF-DHA), at which time blood pressure was measured in triplicate with an automated monitor (OMRON 705IT; Omron Health Care UK), anthropometric measures were performed, and a fasting (12-h fast) blood sample was collected. In the 24 h before the clinical visits, participants were asked to refrain from alcohol consumption and strenuous exercise and to consume a low-fat evening meal (<10 g fat). Blood samples were collected into tubes containing potassium EDTA [for the analysis of small, dense LDL cholesterol (sdLDL-C)], lithium heparin tubes [for the analysis of nonesterified fatty acids (NEFAs), glucose, insulin, and triglycerides], and serum-separating tubes (for the analysis of apolipoprotein B, apolipoprotein CIII, apolipoprotein E, TC, LDL cholesterol, HDL cholesterol, and CRP) and centrifuged at 1700 × g for 10 min at 4°C. Plasma and serum samples were stored at −20°C until analyzed, with the addition of a preservative cocktail to appropriate tubes before the addition of serum samples (final concentration: 5% vol:vol) to protect the apolipoproteins from proteolytic cleavage (15).

#### DNA extraction and genotyping

DNA was isolated from the buffy coat layer of 10 mL blood collected into a tube containing potassium EDTA by using the Qiagen DNA Blood Mini Kit (Qiagen Ltd). APOE genotype was determined by allelic discrimination by using “Assay-on-Demand” single nucleotide polymorphism genotyping assays (rs7412 and rs429358) (Applied Biosystems).

#### Biochemical analysis

An ILAB600 clinical chemistry analyzer (Instrumentation Laboratory Ltd) was used to determine lipid and glucose concentrations by using enzyme-based kits supplied by Instrumentation Laboratory Ltd (triglyceride, TC, HDL cholesterol, and LDL cholesterol), Alpha Laboratories (NEFA), and Randox (sdLDL-C). Immunoturbidimetric assays were used to quantify serum apo concentrations (Kamiya Biomedical Ltd) and CRP (Instrumentation Laboratory). Insulin was assayed by using a specific ELISA (Dako Ltd). The mean intra-assay CV for the automated assays and insulin ELISA were <5%.

HOMA and the revised quantitative insulin sensitivity check index (RQUICKI) were calculated from fasting concentrations of NEFA, glucose, and triglyceride as previously reported by Brady et al (16) using the following equations:

\[
\text{RQUICKI} = 1/ [\log \text{glucose}_0 (\text{mg/dL}) + \log \text{insulin}_0 (\mu \text{U/mL}) + \log \text{NEFA}_0 (\text{mmol/L})] \\
(1)
\]

\[
\text{HOMA-IR} = (\text{insulin}_0 (\mu \text{U/mL}) \times \text{glucose}_0 (\text{mmol/L})/22.5 \\
(2)
\]

#### Statistical analyses

Sample size was calculated by least standardized difference with LDL cholesterol and TC as the primary phenotypic
outcomes. On the basis of a 5% significance level and a power of 80%, the sample size required to detect a mean (±SD) average difference in LDL-cholesterol concentration of $-0.39 \pm 0.61$ mmol/L and in TC concentration of $-0.55 \pm 0.87$ mmol/L between the $APOE3/E3$ and $E3/E4$ genotype groups (based on data from previous studies) is 39 per genotype group. Forty-five per genotype group were recruited to allow for a 15% dropout rate.

The data were analyzed by using the SPSS statistical analysis software version 17 (SPSS Inc). Before analysis, data distribution and normality (skewness and kurtosis) were checked. The transformations included log10 (triglyceride, sdLDL-C, apolipoprotein E, and insulin), natural log (NEFA), and square root (percentage body fat and CRP). To determine the independent and interactive effect of genotype and diet, an ANOVA with repeated measures was used with diet as a within-subject factor and genotype as a between-subjects factor. When a significant diet $\times$ genotype interaction was found, data were split by genotype group and analyzed further by using repeated-measures ANOVA with post hoc Bonferroni correction to determine which dietary groups were significantly different ($P < 0.017$) within each genotype group. If a significant overall diet effect was found, paired $t$ tests (with Bonferroni corrections) were used to analyze the data with the genotype groups combined. Results are presented as means $\pm$ SEMs. $P < 0.05$ was considered significant.

**RESULTS**

A total of 88 volunteers ($n = 44$ $APOE3/3$ and $n = 44$ $APOE3/E4$) completed all 3 diets successfully. As previously reported, 4-d weighed diet diaries and plasma phosphatidylcholine concentrations indicated that the SATgenetic dietary targets were broadly met (14). A significant increase in plasma phosphatidylcholine DHA was evident after DHA supplementation (4.1% compared with 8.2% of total fatty acids with the HSF and HSF-DHA diets, respectively; $P < 0.001$); no diet $\times$ genotype interactions were evident for any of the phosphatidylcholine fatty acid classes (14).

**Dietary and genotype effects on anthropometric measures and blood pressure**

No significant independent or interactive effects of genotype were found for anthropometric measures or for blood pressure (Table 1). Although significant diet effects on BMI, waist circumference, percentage body fat, and fat mass were evident ($P < 0.01$), the effects were modest: 0–5% increases after the HSF interventions compared with the low-fat diet.

**The effect of diet and genotype on fasting lipids, CRP, and markers of insulin sensitivity**

An overall diet effect was evident for all fasting cholesterol fractions ($P < 0.01$; Table 2): 6%, 6%, 13%, and 9% increases in TC, LDL cholesterol, sdLDL-C, and HDL cholesterol, respectively, were observed after the HSF intervention and no further changes after DHA supplementation (HSF-DHA), except for a modest 3% increase in HDL cholesterol. Fifteen percent and 23–25% lower NEFA and triglyceride concentrations were observed after the HSF-DHA than after the low-fat and HSF
**Table 2**

Effect of the APOE genotype and chronic dietary fat manipulation on fasting serum and plasma profiles in healthy UK adults.

<table>
<thead>
<tr>
<th>APOE</th>
<th>Diet</th>
<th>Genotype</th>
<th>Diet × genotype</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LF</td>
<td>HSF</td>
<td>HSF-DHA</td>
<td></td>
</tr>
<tr>
<td>TC (mmol/L)</td>
<td>5.45 ± 0.68</td>
<td>5.79 ± 0.88</td>
<td>5.43 ± 0.10</td>
<td>0.85b 5.83</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>1.38 ± 0.60</td>
<td>1.51 ± 0.60</td>
<td>1.56 ± 0.42</td>
<td>0.85b 5.46</td>
</tr>
<tr>
<td>sMDL-C (mmol/L)</td>
<td>0.68 ± 0.24</td>
<td>0.68 ± 0.18</td>
<td>0.73 ± 0.17</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>apo A1 (mg/mL)</td>
<td>0.97 ± 0.22</td>
<td>0.98 ± 0.16</td>
<td>0.97 ± 0.16</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>apo A2 (mg/mL)</td>
<td>0.70 ± 0.16</td>
<td>0.70 ± 0.16</td>
<td>0.70 ± 0.16</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>apo A3 (mg/mL)</td>
<td>0.66 ± 0.14</td>
<td>0.64 ± 0.12</td>
<td>0.64 ± 0.12</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>apo E (mg/mL)</td>
<td>0.52 ± 0.14</td>
<td>0.52 ± 0.14</td>
<td>0.52 ± 0.14</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>NEFAs (mEq/L)</td>
<td>1.23 ± 0.70</td>
<td>1.23 ± 0.70</td>
<td>1.23 ± 0.70</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.09 ± 0.05</td>
<td>0.09 ± 0.05</td>
<td>0.09 ± 0.05</td>
<td>0.85b 5.82</td>
</tr>
<tr>
<td>RQUICKI</td>
<td>0.43 ± 0.09</td>
<td>0.43 ± 0.09</td>
<td>0.43 ± 0.09</td>
<td>0.85b 5.82</td>
</tr>
</tbody>
</table>

All values are means ± SEMs. Data were analyzed by using a general linear model with repeated measures with one within-subject (diet) and one between-subject (genotype) factor. *P* < 0.05 indicates a significant diet or genotype effect, while *P* < 0.01 indicates a significant diet × genotype effect. All post hoc comparisons were made with Bonferroni correction. apo, apolipoprotein; HDL-C, HDL cholesterol; HSF, high-SFA diet; HSF-DHA, HSF + DHA diet (3.45 g/d); LDL-C, LDL cholesterol; LF, low-fat diet; NEFAs, nonesterified fatty acids; RQUICKI, revised quantitative insulin-sensitivity check index; sMDL-C, small, dense LDL cholesterol; TC, total cholesterol.

**DISCUSSION**

Establishment of the main genetic determinants of the response to key dietary fat recommendations, such as reductions in SFA and increases in long-chain n–3 PUFA intakes, would allow the identification of population subgroups that would specifically benefit from targeted interventions. Although there is an extensive literature reporting on possible common gene variants, with APOE genotype emerging as a potential candidate, robust evidence from adequately powered studies, in which an investigation of response to genotype is a primary study aim, are distinctly lacking. To our knowledge, this was the first study to prospectively recruit according to genotype (which provides groups at baseline matched by not only genotype but also sex, BMI, and age) to examine the effect of the common APOE genotype on the response to dietary fat manipulation in normolipidemic individuals.

Whereas the diets were isoenergetic by design (14), the shift from the low-fat to the HSF and HSF-DHA diets was associated with significant increases in total energy intake, which was reflected in the overall 2% increase in BMI. Comparable observations have been reported in the Reading Imperial Surrey Cambridge and King and Lipid and Genetics study studies in subjects after isoenergetic low- and high-fat diets (4, 17). Although relatively modest, the observed weight gain may have contributed to the changes in the fasting cholesterol profile in the group as a whole when switching to the HSF diet, which were broadly in line with the predicted cholesterol responses to the dietary fat manipulation derived from available logarithms, such as the equations of Mensink et al (18).

Even though an effect of APOE genotype on the fasting cholesterol response to altered total fat and saturated fat intakes
A SFA diet. Significant diet 8% from SFA), HSF diet (38% of energy from fat, 18% from SFA), and intervention trials, of the reported 36 included studies showed and Nutrition–Norfolk group or in the Costa Rican cohort However, these observations were not confirmed in the larger follow-up European Prospective Investigation into Cancer and Nutrition–Norfolk cohort or in the Costa Rican cohort. In the 2003 Masson et al (8) systematic review of intervention trials, 11 of the reported 36 included studies showed significant genotype × dietary fat interactions for the plasma cholesterol responses, with typically greater responses in APOE4 carriers (8). However, in many of the included studies, small group size (often $n = 10$) was found in the rarer allele subgroups, genotype was measured retrospectively, and investigation of the LDL cholesterol response according to genotype was not a primary study aim, which collectively makes drawing definitive conclusions difficult because of the lack of study power. In the current study, no genotype × diet interactions were evident with comparable increases in TC, LDL-cholesterol, and HDL-cholesterol concentrations in both the wild-type APOE3/E3 group and in APOE4 carriers after increased total fat and SFA intakes. Although very underinvestigated [with only 6 of 42 studies in the Masson et al review having a separate APOE4/E4 group and only 1–15 per group (8)] and therefore somewhat speculative, it is likely that the effect of the APOE allele is dependent on heterozygosity (APOE3/E4, 20–25% whites) or homozygosity (APOE4/E4, 1–2% whites). In agreement with our observations, Tikkanen et al (22) observed no differences in responses between the APOE3/E4s and wild-type genotypes, with significantly greater cholesterol responses in the APOE4/E4 subgroup after the switch to a lower-fat, lower-SFA diet, which is consistent with the observations of Sarkkinen et al (23) in subjects with familial hypercholesterolemia (23).

In contrast with our previous findings (12, 13), in the current study (against a background diet high in total fat and SFA) we observed no increase in total and LDL cholesterol in the APOE3/E4 group after high-dose DHA supplementation. Considering these studies collectively, it appears that the penetrance of APOE genotype on the responsiveness of LDL cholesterol to DHA is not homogeneous and is dependent on the DHA dose, the plasma lipid profile, and the habitual fat intake of the individual. After intakes of DHA that could be achieved through high oily fish consumption (up to 2 g DHA/d), no negative effect on LDL cholesterol in APOE4 carriers was evident (FINGEN Study) (5). However, in APOE4 carriers, the addition of higher supplemental doses recommended for triglyceride lowering (2–4 g/d) to the habitual diet resulted in increases in LDL cholesterol that may, in part, counteract the antiatherogenic effects of DHA (12, 13), particularly in those with mild to moderate hypertriglyceridemia.

The 24% overall mean reduction in triglyceride agrees with the 21% reduction we previously reported (12) with the use of a comparable 3.7 g DHA/d intervention and with the 25% study mean reduction reported in normolipidemic groups (derived from 32 data sets) in the above-mentioned review by Harris (24). The greater responsiveness of triglycerides to DHA in APOE4 carriers was likely due, in part, to the higher baseline triglyceride concentrations in this subgroup. ApoE acts as a high-affinity ligand for the removal of VLDL remnants by the liver. The selective affinity of the apoE4 protein isoform for VLDL in contrast with the E2 and E3 isoforms, which have a preference for more lipid-poor large HDLs, may help explain the apparently greater triglyceride lowering in APOE4 carriers (25). The HSF-DHA diet resulted in a significant, albeit small, difference by genotype for plasma apolipoprotein E. The lack of any striking genotype-mediated differences in serum apolipoprotein E concentrations in response to the dietary intervention treatment does not preclude a differential effect of diet in the genotype subgroups in hepatic apolipoprotein E production or recycling, and therefore availability in the Space of Disse for VLDL removal which would influence circulating triglyceride concentrations (26).

In the group as a whole, the HSF intervention resulted in a significant increase in serum CRP concentrations (compared with post–low-fat), which may in part account for the increased CVD risk associated with high SFA intakes (27, 28). Although no effect of dietary fat manipulation on CRP was evident in the LIPGENE study (29), the elevation in CRP associated with increased dietary total fat and SFA observed here is consistent with associations reported in the US National Diet and Nutrition Survey Cohort (30) and those in a limited number of randomized controlled trials (31). We observed no effect of DHA intervention on CRP concentrations, which agrees with most studies included in a recent review that examined associations between marine n-3 fatty acid intake and many inflammatory indicators.
(32). We provide novel evidence of a divergent CRP response to SFA according to APOE genotype, with a significant increase in CRP concentrations after increased SFA intake evident only in APOE4 carriers. CRP is largely liver derived via the mevalonate pathway, which influences hepatic CRP production (33). The mechanistic basis of APOE genotype–CRP associations and how it can be manipulated by alterations in habitual fat intake is currently unknown, but it is likely a result of the effect of genotype and diet on hepatic lipid composition and metabolism.

Study limitations included the use of a single high dose of DHA supplementation, the unblinded nature of the intervention, and the relatively short 8-wk intervention periods. The study design, namely a sequential intervention with no washout period between the intervention arms, may be considered a limitation. However, this design has been used in previous dietary studies (23) and was specifically chosen because of inherent difficulties encountered during fat-manipulation studies when volunteers returned to their habitual diet during washout periods.

In conclusion, our data indicate, that in normolipidemic individuals, heterozygous APOE4 status is unlikely to be a major population determinant of the fasting cholesterol responses to DHA. APOE4/4 carriers may represent a population subgroup with high sensitivity to dietary fat composition. Robust investigations in this subgroup are lacking, which is largely because of the low population prevalence of the genotype.

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