Response of serum LDL cholesterol to oatmeal consumption depends on CYP7A1_rs3808607 genotype in Chinese

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Running title: Gene–diet interaction in lipid regulation of oat

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ABSTRACT

Background and Objectives: Notable inter-individual differences in cholesterol-lowering effects following oatmeal consumption have been previously reported. Genetic variations may among the reasons for the heterogeneous response to lipid modulations. And to determine whether SNP of cytochrome P450 family 7 subfamily A member 1 gene rs3808607 and isoforms of apolipoprotein E are associated with the inter-individual variations in cholesterol-lowering effects of oatmeal consumption, we did this study. **Methods and Study Design:** Data in this study were extracted from a parallel, controlled trial, in which 62 medication-naive hypercholesterolemic patients provided with staple food substitute of either 80 g/d oatmeal (n=31) or 80 g/d refined white rice (n=31) for 45 days. Fasting blood samples were collected at baseline and endpoint of the study for lipid profiling, glycemic testing, and genotyping. **Results:** Totally, 56 of 62 participants completed the study and were thus included. Genotype–diet interactions were observed between oatmeal consumption and SNP in the cytochrome P450 family 7 subfamily A member 1 gene rs3808607 in regulating LDL cholesterol (p=0.04); rs3808607-TT homozygotes exhibited significantly higher responsiveness to oatmeal (reduction in LDL cholesterol) than G allele carriers (GG/GT) (p=0.02). However, obvious genotype–diet interactions were not observed between oatmeal consumption and apolipoprotein E isoforms in cholesterol and glycemic modulation (p>0.05). **Conclusions:** SNP in cytochrome P450 family 7 subfamily A member 1 gene rs3808607 was associated with the extent of LDL cholesterol reduction following oatmeal consumption. Trials with larger sample sizes are required to confirm the findings.

Key Words: oatmeal, lipid profile, SNP, cytochrome P450 family 7 subfamily A member 1, apolipoprotein E

INTRODUCTION

Oatmeal has been widely known for its considerable cholesterol-lowering effect;[1,2] however, notable interindividual variations in the aforementioned effect have been reported.[3,4] Data from genotype–diet interaction studies have provided a new perspective for understanding individual heterogeneity in cholesterol-lowering responses after oatmeal consumption.[5,6] Apolipoprotein E (APOE) isoforms, which have gained considerable attention because of their associations with lipoprotein metabolism and plasma lipid phenotypes, have been reported to be related to the extent of cholesterol reduction in response to oatmeal and plant sterol consumption.[7-9] Furthermore, the SNP in the rs3808607 locus of the cytochrome P450

family 7 subfamily A member 1 gene (CYP7A1 rs3808607), which encodes cholesterol 7 α-hydroxylase, was also reported to affect the responsiveness of individuals to oatmeal consumption in terms of reductions in LDL cholesterol following plant sterol consumption.[9,10]

Considering the limited evidence available on the relationships between the heterogenous response to oatmeal-induced cholesterol reduction and genetic variations, we explored whether changes in lipid profiles following oatmeal consumption differed according to the genotypes of CYP7A1_rs3808607 or isoforms of APOE. Besides, glycemic parameters were also reported to be regulated after oatmeal consumption. Genotype–diet interactions of oatmeal consumption in glycemic modulation were also evaluated in this study.

MATERIALS AND METHODS

Participants and Study Design

Data of lipid profiles, anthropometric measurements, dietary intakes and physical activity in this study were all extracted from an open-labelled, parallel, placebo-controlled trial conducted in Shanghai, which mainly focused on the cholesterol-lowering effect of oatmeal consumption. Informed consent was obtained from all qualified participants before the beginning of the trial and the protocol was approved by the Institutional Review Board of Huadong Hospital (No.20180059). The study was registered at Chinese Clinical Trial Registry as ChiCTR180001864. Relevant study details are provided in supplementary File 1.

In brief, 62 medication-naive hypercholesterolemic men and women with elevated total cholesterol (TC) (5.2 mmol/L≤TC≤6.8 mmol/L; triglyceride [TG] <2.3 mmol/L) aged 18 to 65 years were recruited from the general population by using a questionnaire (containing a total of 17 simple questions, including some regarding basic contact information and the primary inclusion and exclusion criteria) for preliminary screening. The preliminarily qualified participants then visited the nutrition department of Huadong Hospital in a fasting state for further anthropometric, hematological, and biochemical measurements. Additional inclusion criteria included willingness to take no hypocholesterolemic drugs for the duration of the study. Principal exclusion criteria were as follows: (a) having diabetes, having heart, liver, kidney, gastrointestinal, or hematopoietic system diseases, or being mentally ill; (b) body mass index (BMI) ≥28 kg/m^2; (c) being currently pregnant or in lactation; (d) having a history of using any lipid-lowering drugs in the past 3 months; (e) having had a regular intake (≥ 3 times per week) of oats or other foods rich in β -glucan in the past 6 months; (f) having a history of excessive smoking or alcoholism; (g) being allergic or intolerant to oat; (h) having

special eating habits such as vegetarianism, a weight loss diet, or a ketogenic diet; (i) showing a likelihood of poor compliance.

Interventions and measurements

Participants were equally randomized to either the oatmeal group or control group. According to evidences provided by meta-analyses, consumption of 3 g/d oatmeal β-glucan can cause a notable reduction in serum cholesterol,[1] thus, in this study, the oatmeal group was required to replace part of their daily staple food with 80 g of oatmeal (providing 3 g of β-glucan) per day at breakfast and dinner (40 g per meal) for 45 days, whereas the control group was provided with an equal amount of refined white rice (containing no β-glucan) instead. Both the oatmeal and refined white rice were provided in packages of 40 g per individual. The participants were instructed to boil the oatmeal or refined white rice in hot water before consumption. The compositions of the two food were presented in Table 1. All participants were required to maintain their original habitual diet and physical activities throughout the study. Weekly follow-ups were carried out by telephone to record the corresponding food consumption, adverse reactions, and drug use. The oatmeal and refined white rice were provided in an amount that was sufficient for 2 weeks (during the last visit, the provided amount was expected to last for 17 days) each time. Thus, participants were required to visit Huadong Hospital every 2 weeks throughout the study to replenish the eaten-up corresponding food and in addition, attending face-to-face follow-up sessions. If participants completely stopped eating the oatmeal or refined white rice for 2 days consecutively or if the amount consumed was less than half of the specified amount (40 g/d) for 6 days within a week, then the participants were categorized as having poor compliance; and the researchers were allowed to withdraw them from the experiment. Fasting venous blood samples were collected while fasting at the baseline and the endpoint. Serum was extracted and stored at −80℃ until further lipid testing and genotype analysis. Lipid profiles testing involved the assessment of TC, TG, LDL cholesterol, HDL cholesterol, small dense LDL (sdLDL) cholesterol, apolipoprotein B (apoB), fasting blood glucose (FBG) and glycated albumin (GA), which were tested using commercial kits with the help of fully automated analyzer. Non-high-density lipoprotein (non-HDL) cholesterol were calculated as the absolute difference of concentration between TC and HDL cholesterol.

Of 62 participants, 56 (29 and 27 from the oatmeal and control groups, respectively) completed the trial; thus, they were included in this study for further genotype testing. Two

participants dropped out, one because of time constraints and one because of loss of interest. Four participants were suspended because of noncompliance with the intervention. Six participants (four and two from the oatmeal and control groups, respectively) reported various degrees of gastrointestinal reactions, such as bloating, which were basically relieved within 3 weeks. Only one participant from the oatmeal group reported persistent yet tolerable bloating throughout the entire study. The flow chart was shown in the Figure 1.

DNA extraction and genotyping

DNA was extracted from the serum samples by applying the proteinase K cleavage method, and CYP7A1_rs3808607, APOE_rs429358 and APOE_rs7412 were specifically amplified by a polymerase chain reaction (PCR) with suitable primers.[11,12] The PCR product was sequenced using Sanger's method with the help of ABI PRISM 3730XL analyzer (PE Applied Biosystems, USA) and Clone Manager software (version 7.11) for used for further sequence alignment and target SNP analysis. CYP7A1 rs_3808607 genotypes were presented as GG, GT, and TT, whereas, APOE isoforms, mainly were mainly decided by SNPs in rs429358 and rs7412 with six possible genotypes, which were presented as APOE E2 (sum of ε2/ε2 and ε2/ε3 genotypes), E3 (sum of ε3/ε3 and ε2/ε4 genotypes), and E4 (sum of ε3/ε4 and ε4/ε4 genotypes). Details of the primers, amplification conditions, and results of Sanger's sequencing analysis were summarized in Supplementary File 1.

Statistical analysis

The statistician was blinded to the group allocations. All data were presented as the mean ± standard error (SE). The chi‐square test or Fisher's exact test was used to verify the Hardy-Weinberg equilibrium. To minimize the effects of disequilibrium at baseline, dietary intakes and physical activity during the study period were evaluated by comparing the alterations from baseline. For data of baseline characteristics, dietary intakes and physical activity, ANOVA was used when analyzing quantitative variables with normal distribution and homogenous variance; otherwise, the Kruskal Wallis test was used. For lipid profiles, ANCOVA was used for comparison of their changes from baseline during study period where baseline lipid concentrations, gender and age were used as covariates into the linear model, along with post hoc test carried out by Bonferroni test in the situation of multigroup comparisons. Data were all analyzed by using SPSS (version 23.0). A value of $p<0.05$ (two-tailed) was considered significant. The pwr package in R (Version 1.2.1335) was used to

conduct post-hoc power calculations for the genotype–diet interaction, which was based on ANOVA test (two-tailed) with the significance level set to 0.05. The results were presented in the Supplementary Table 1.

RESULTS

Genotype Distributions

All 29 participants in the oatmeal group (10 men and 19 women) and 27 participants in the control group (11 men and 16 women) were successfully genotyped. The genotypes of all three tested genes were in the Hardy–Weinberg equilibrium (CYP7A1_rs3808607 [G allele=43.8%]: $X^2 = 0.15$, p=0.93; APOE_rs429358 [C allele=13.4%]: $X^2 = 1.78$, p=0.41; APOE_rs7412 [T allele=4.5%]: p=0.72 [Fisher's exact test]). The detailed distribution was provided in the Supplementary Table 2. Regarding APOE isoforms, only two participants had the APOE E2 isoform in the oatmeal group and no participant had APOE E2 isoform in the control group. Considering that compared with populations who have the APOE E2 and E3 isoforms, those with the APOE E4 isoform have been reported to exhibit unfavorable lipid profiles and a higher risk of cardiovascular diseases;[13,14] thus, data of participants with APOE isoforms E2 and E3 were combined to form a single group for further analysis (n=22 and n=24 in the oatmeal and control groups, respectively).

Baseline Characteristics of Participants

The daily intake of the corresponding food was 78.0±0.8 g/d (97.5%) and 75.0±1.2 g/d (93.8%) in the oatmeal and control groups, respectively, indicating a satisfactory compliance of participants. On the basis of groupings in CYP7A1_rs3808607 genotypes and interventions, significant imbalances of the baseline concentration of HDL cholesterol (p=0.02), non-HDL cholesterol (p=0.03), sdLDL cholesterol (p=0.01) and apoB (p<0.01) were observed between groups. Besides, other indicators were comparable between the groups at baseline (p>0.05) (Table 2). However, all indicators were comparable at baseline between the groups categorized according to APOE isoforms and interventions (Supplementary table 3).

Changes in dietary intakes and physical activity

Results of comparing changes of dietary intakes and physical activity for groups categorized according to CYP7A1_rs3808607 genotypes and interventions were presented in the Supplementary Table 4. Briefly, except for a significant difference in the change of fiber

intake (p<0.01), no significant difference was observed in the other indicators between the groups (p>0.05). Similarly, significant difference in change of fiber intake between groups was also observed on the basis of groups categorized according to APOE isoform groups and interventions (p<0.01). Besides, significant differences of changes in energy and fat intakes between four groups were observed (p<0.05 and p=0.04, respectively) (Supplementary table 4). Thus, when evaluating the genotype–diet interaction effect based on APOE isoforms groups and interventions, changes in energy and fat intakes were also included in the linear model as covariates.

Genotype–diet interaction on blood lipid profile

Compared to the control group, significant improvements were observed in the LDL cholesterol (−0.26±0.08 mmol/L vs 0.08±0.06 mmol/L, p<0.01), non-HDL cholesterol (−0.83±0.09 mmol/L vs −0.55±0.07 mmol/L, p=0.02), sdLDL cholesterol (−0.06±0.05 mmol/L vs 0.14±0.04 mmol/L, p=0.03) and apoB (−0.11±0.02 mmol/L vs −0.01±0.02 mmol/L, p<0.01) after oatmeal consumption (Table 3). A notable genotype–diet interaction was observed between oatmeal consumption and CYP7A1_rs3808607 genotypes in regulating LDL cholesterol (p=0.04 and p=0.02 from the genotype–diet interaction model and addictive model, respectively). The results of further analysis indicated that compared with G allele carriers (GG/GT), participants with the TT homozygous genotype exhibited significantly greater reductions in LDL cholesterol after oatmeal consumption (p=0.02); whereas GG homozygous individuals exhibited no significant difference in LDL cholesterol reduction after oatmeal intervention compared with TT homozygote individuals (p=0.37) (Table 3). However, no significant genotype–diet interaction was observed between oatmeal consumption and APOE isoforms in lipid and glycemic modulations (p>0.05) (Supplementary table 5).

DISCUSSION

Our study indicated that genotype–diet interaction was observed for the CYP7A1_rs3808607 genotypes in the response of oatmeal consumption in LDL cholesterol regulation. The efficacy of the oatmeal consumption in reducing LDL cholesterol was associated with CYP7A1_rs3808607-G allele acting in a dominant fashion, with its G allele carriers (GG/GT) being less responsive to oatmeal consumption in reducing LDL cholesterol than TT homozygous individuals.

Cholesterol 7α-hydroxylase, coded by the CYP7A1 gene, is the rate-limiting enzyme in the classic bile acid biosynthesis process,[15] which is the principal pathway for cholesterol excretion in body, and the locus rs_3808607 is located in the promoter region of the CYP7A1gene. A previous study reported a positive role of CYP7A1_rs3808607 G allele in responding to β-glucan-induced improvements of TC and LDL cholesterol.[16] It was supported by some reporter gene assays, which implicated that the CYP7A1 gene with the G allele in this SNP locus exhibited higher transcriptional activity than that with the T allele.[10,17] However, the results of our study indicated that the presence of CYP7A1_rs3808607 G allele potentially flattened the reduction in LDL cholesterol after oatmeal consumption. The result is similar to those reported in several statin-interventional studies, which showed that the rs3808607 G allele was associated with lower statin-induced LDL cholesterol reduction[18] and that a high activity of cholesterol 7α-hydroxylase status was associated with a lower likelihood of reaching the optimal cholesterol goal.[19] The underlying mechanism of this phenomenon remains unknown. Nevertheless, our data suggest that an individual's genetic pattern may serve as potentially predictive markers for identifying the most responsive hypercholesterolemic individuals who would benefit from oatmeal consumption, and pave the way for personalized nutritional recommendations and treatments. Simultaneously, the question of whether oatmeal and statin have any common effects on cholesterol metabolism involving cholesterol 7α-hydroxylase should be explored because oatmeal and statin exhibit similar intervention–genotype interactions.

The receptor-binding ability and lipoprotein clearance rate of APOE showed an isoform-specific characteristic; thus, APOE isoforms are related to the heterogeneity of cholesterol metabolizing ability.[20,21] The relationship between APOE isoforms and interindividual variations in cholesterol reduction following oatmeal consumption remains complicated; some reports have suggested a greater responsiveness of the E2 or E3 allele to oatmeal consumption in terms of cholesterol modulation,[8,22] whereas others have reported contrasting results.[17] In the present study, a genotype–diet interaction was not observed between APOE isoforms and oatmeal consumption in serum lipid regulation; thus, the findings of the present study support the idea that differences in responsiveness in cholesterol and glycemic modulation following oatmeal consumption are not related to APOE isoforms.[17] However, there was no denying that the quite small sample size (n=56), with an even smaller sample size in subgroup (only 3 participants were found to have the E4 isoform of APOE), had limited the ability to detect such higher order interactive effects in this study. Similar problems were encountered while exploring the relationships between CYP7A1_rs3808607

genotypes and differential responsiveness in terms of cholesterol-lowering and glycemic-modulation following oatmeal consumption in this study. Consequently, additional studies with larger sample sizes are required to confirm the current findings.

In conclusion, the genotype of CPY7A1_ rs3808607 was associated with the extent of reduction in LDL cholesterol following oatmeal consumption, with its G allele potentially being a passivate factor of oatmeal-induced improvements in LDL cholesterol. However, clinical trials with larger sample sizes were needed to further verify and support this finding.

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AUTHOR DISCLOSURE

The authors declare no competing interests.

REFERENCES

1. Ho HV, Sievenpiper JL, Zurbau A, Blanco Mejia S, Jovanovski E, Au-Yeung F, Jenkins AL, Vuksan V. The effect of oat beta-glucan on LDL-cholesterol, non-HDL-cholesterol and apoB for CVD risk reduction: a systematic review and meta-analysis of randomised-controlled trials. Br J Nutr. 2016;116:1369-82. doi: 10.1017/s000711451600341x.
2. Whitehead A, Beck EJ, Tosh S, Wolever TM. Cholesterol-lowering effects of oat beta-glucan: a meta-analysis of randomized controlled trials. Am J Clin Nutr. 2014;100:1413-21. doi: 10.3945/ajcn.114.086108.
3. Torronen R, Kansanen L, Uusitupa M, Hanninen O, Myllymaki O, Harkonen H, Malkki Y. Effects of an oat bran concentrate on serum lipids in free-living men with mild to moderate hypercholesterolaemia. Eur J Clin Nutr. 1992;46:621-7.
4. Queenan KM, Stewart ML, Smith KN, Thomas W, Fulcher RG, Slavin JL. Concentrated oat beta-glucan, a fermentable fiber, lowers serum cholesterol in hypercholesterolemic adults in a randomized controlled trial. Nutr J. 2007;6:6. doi: 10.1186/1475-2891-6-6.
5. Vazquez-Vidal I, Desmarchelier C, Jones PJH. Nutrigenetics of Blood Cholesterol Concentrations: Towards Personalized Nutrition. Curr Cardiol Rep. 2019;21:38. doi: 10.1007/s11886-019-1124-x.
6. Abdullah MM, Jones PJ, Eck PK. Nutrigenetics of cholesterol metabolism: observational and dietary intervention studies in the postgenomic era. Nutr Rev. 2015;73:523-43. doi: 10.1093/nutrit/nuv016.

7. Uusitupa MI, Ruuskanen E, Makinen E, Laitinen J, Toskala E, Kervinen K, Kesaniemi YA. A controlled study on the effect of beta-glucan-rich oat bran on serum lipids in hypercholesterolemic subjects: relation to apolipoprotein E phenotype. J Am Coll Nutr. 1992;11:651-9. doi: 10.1080 / 07315724.1992.10718264
8. Jenkins DJ, Hegele RA, Jenkins AL, Connelly PW, Hallak K, Bracci P et al. The apolipoprotein E gene and the serum low-density lipoprotein cholesterol response to dietary fiber. Metabolism. 1993;42:585-93. doi: 10.1016/0026-0495(93)90217-c.
9. MacKay DS, Eck PK, Gebauer SK, Baer DJ, Jones PJ. CYP7A1-rs3808607 and APOE isoform associate with LDL cholesterol lowering after plant sterol consumption in a randomized clinical trial. Am J Clin Nutr. 2015;102:951-7. doi: 10.3945/ajcn.115.109231.
10. De Castro-Oros I, Pampin S, Cofan M, Mozas P, Pinto X, Salas-Salvado J et al. Promoter variant -204A > C of the cholesterol 7alpha-hydroxylase gene: association with response to plant sterols in humans and increased transcriptional activity in transfected HepG2 cells. Clin Nutr. 2011;30:239-46. doi: 10.1016/j.clnu.2010.07.020.
11. Kim SK, Yim SV, Lee BC. Association between cytochrome P450 promoter polymorphisms and ischemic stroke. Exp Ther Med. 2012;3:261-8. doi: 10.3892/etm.2011.388.
12. Yuan L, Liu J, Dong L, Cai C, Wang S, Wang B, Xiao R. Effects of APOE rs429358, rs7412 and GSTM1/GSTT1 Polymorphism on Plasma and Erythrocyte Antioxidant Parameters and Cognition in Old Chinese Adults. Nutrients. 2015;7:8261-73. doi: 10.3390/nu7105391.
13. Liu S, Liu J, Weng R, Gu X, Zhong Z. Apolipoprotein E gene polymorphism and the risk of cardiovascular disease and type 2 diabetes. BMC Cardiovasc Disord. 2019;19:213. doi: 10.1186/s12872-019-1194-0.
14. Dankner R, Ben Avraham S, Harats D, Chetrit A. ApoE genotype, lipid profile, exercise, and the associations with cardiovascular morbidity and 18-year mortality. J Gerontol A Biol Sci Med Sci. 2019. doi: 10.1093/gerona/glz232.
15. Chiang JY. Bile acids: regulation of synthesis. J Lipid Res. 2009;50:1955-66. doi: 10.1194/jlr.R900010-JLR200.
16. Wang Y, Harding SV, Eck P, Thandapilly SJ, Gamel TH, Abdel-Aal el SM et al. High-Molecular-Weight beta-Glucan Decreases Serum Cholesterol Differentially Based on the CYP7A1 rs3808607 Polymorphism in Mildly Hypercholesterolemic Adults. J Nutr. 2016;146:720-7. doi: 10.3945/jn.115.223206.
17. Inamine T, Higa S, Noguchi F, Kondo S, Omagari K, Yatsuhashi H, Tsukamoto K, Nakamura M. Association of genes involved in bile acid synthesis with the progression of primary biliary cirrhosis in Japanese patients. J Gastroenterol. 2013;48:1160-70. doi: 10.1007/s00535-012-0730-9.
18. Li Q, Hong J, Wu J, Huang ZX, Li QJ, Yin RX, Lin QZ, Wang F. The role of common variants of ABCB1 and CYP7A1 genes in serum lipid levels and lipid-lowering efficacy of statin treatment: a meta-analysis. J Clin Lipidol. 2014;8:618-29. doi: 10.1016/j.jacl.2014.07.010.

19. Wang D, Hartmann K, Seweryn M, Sadee W. Interactions between regulatory variants in CYP7A1 (Cholesterol 7alpha-Hydroxylase) promoter and enhancer regions regulate CYP7A1 expression. Circ Genom Precis Med. 2018;11:e002082. doi: 10.1161/circgen.118.002082.
20. Mahley RW, Rall SC, Jr. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet. 2000;1:507-37. doi: 10.1146/annurev.genom.1.1.507.
21. Weintraub MS, Eisenberg S, Breslow JL. Dietary fat clearance in normal subjects is regulated by genetic variation in apolipoprotein E. J Clin Invest. 1987;80:1571-7. doi: 10.1172/jci113243.
22. Uusitupa MI, Miettinen TA, Sarkkinen ES, Ruuskanen E, Kervinen K, Kesaniemi YA. Lathosterol and other non-cholesterol sterols during treatment of hypercholesterolaemia with beta-glucan-rich oat bran. Eur J Clin Nutr. 1997;51:607-11. doi: 10.1038 / sj.ejcn.1600453.

Table 1. Composition of oatmeal and refined white rice (per 80 g)

Nutrients	Oatmeal	Control
Energy (Kcal)	304	311
Protein (g)	8.8	5.3
Fat (g)	7.4	1.5
Carbohydrate (g)	48.4	67.7
Total Fiber (g)	9.6	0.7
β-glucan (g)	3.0	0.0

Table 2. Baseline Characteristics based on groupings in CYP7A1_rs3808607 genotypes and interventions

Variable	Oatmeal group (n=29)			Control group (n=27)			*p* value
	TT (n=9)	GT (n=11)	GG (n=9)	TT (n=10)	GT (n=14)	GG (n=3)	
Age, year	47.3±2.5	47.6±3.0	48.9±3.8	43.7±3.9	47.6±1.8	54.7±3.3	0.627
Gender, (% for men)	33.3%	36.4%	33.3%	30.0%	42.9%	66.7%	0.896†
Body weight, kg	65.6±2.9	62.3±3.1	62.6±2.3	66.2±3.7	64.2±2.6	62.0±5.2	0.916
BMI, kg/m^2	23.5±0.6	23.7±0.7	22.4±0.8	24.4±0.7	22.8±0.7	22.5±1.4	0.417
Waistline, cm	82.9±1.8	83.0±2.4	82.8±2.3	84.4±1.9	81.2±2.0	79.6±3.9	0.861
Hip Circumference, cm	98.1±1.7	95.5±1.8	97.0±1.9	97.0±1.6	95.1±1.3	95.5±4.4	0.807
Blood pressure, mmHg							
Systolic	120.2±4.3	117.0±4.1	122.1±3.6	119.7±6.3	119.3±3.5	118.8±0.4	0.984
Diastolic	73.7±2.2	68.5±2.8	70.1±1.4	70.7±5.2	72.9±2.4	65.7±4.8	0.730
Serum measurement, mmol/L							
T^C	6.03±0.16	5.80±0.09	5.89±0.11	5.85±0.05	5.72±0.11	5.80±0.13	0.441
TG	1.50±0.19	1.46±0.14	1.14±0.12	1.19±0.14	1.09±0.11	1.08±0.22	0.178‡
LDL ^{c}holesterol	3.71±0.19	3.43±0.15	3.28±0.15	3.50±0.06	3.26±0.15	3.31±0.13	0.283
HDL ^{c}holesterol	1.60±0.09^{ab}	1.67±0.07^{ab}	1.98±0.13^{a}	1.58±0.06^{b}	1.77±0.08 ^{ab}	1.91±0.17 ^{ab}	0.022
non-HDL ^{c}holesterol	4.43±0.16	4.13±0.11	3.91±0.15	4.28±0.07	3.95±0.11	3.89±0.07	0.029
sdLDL cholesterol	1.14±0.17^{a}	0.96±0.08^{abc}	0.67±0.04^{b}	0.85±0.07 ^{abc}	0.72±0.06^{bc}	0.64±0.05^{abc}	0.011‡
apoB	1.22±0.05^{a}	1.13±0.04^{abc}	0.99±0.03^{b}	1.11±0.03^{abc}	1.03±0.04^{bc}	1.04±0.02^{abc}	0.002
FBG	5.30±0.13	5.25±0.14	5.14±0.10	5.25±0.14	4.91±0.10	5.00±0.15	0.172
GA, %	13.4±0.6	13.1±0.6	13.9±0.4	13.1±0.4	13.7±0.3	13.3±0.3	0.656‡

CYP7A1: cytochrome P450 family 7 subfamily A member 1 gene; TC: total cholesterol; TG: triglyceride, LDL: low-density lipoprotein; HDL: high density lipoprotein; non-HDL: non-high-density lipoprotein; sdLDL: small dense low-density lipoprotein; apoB: apolipoprotein B; FBG: fasting blood glucose; GA: glycated albumin.
Values labeled without a common superscript letter differ from each other in the same row, $p<0.05$.
†Chi-square test; ‡Kruskal-Wallis Test; otherwise, One-way ANOVA is used. Bonferroni was used for post Hoc tests.

Table 3. Differences in cholesterol-lowering and glycemia-modulation effect following oatmeal consumption between different CYP7A1_rs3808607 genotypes in hypercholesterolemic adults

Variable	Genotype				*p* Value				
	TT	GT	GG	Total	Diet	Genotype-diet interaction	TT+GG vs GT†	G allele vs. TT‡	GG vs. TT§
Control group, mmol/L									
TC	-0.49±0.11	-0.63±0.11	-0.69±0.06	-0.57±0.07	-	-	-	-	-
TG	0.05±0.14	0.18±0.13	-0.26±0.15	0.08±0.09	-	-	-	-	-
LDL cholesterol	0.18±0.11	0.01±0.08	0.07±0.25	0.08±0.06	-	-	-	-	-
HDL cholesterol	0.05±0.05	-0.07±0.06	-0.06±0.11	-0.02±0.04	-	-	-	-	-
non-HDL cholesterol	-0.55±0.10	-0.56±0.12	-0.55±0.15	-0.55±0.07	-	-	-	-	-
sdLDL cholesterol	0.17±0.07	0.12±0.05	0.13±0.13	0.14±0.04	-	-	-	-	-
apoB	0.00±0.03	-0.01±0.02	-0.04±0.06	-0.01±0.02	-	-	-	-	-
FBG	0.26±0.10	0.29±0.11	0.40±0.10	0.29±0.07	-	-	-	-	-
GA, %	0.30±0.26	0.00±0.26	0.00±0.58	0.11±0.17	-	-	-	-	-
Oatmeal group, mmol/L									
TC	-1.03±0.17	-0.63±0.10	-0.77±0.18	-0.79±0.09	0.126	0.084	0.070	0.030	0.215
TG	-0.18±0.19	-0.13±0.16	-0.10±0.15	-0.14±0.09	0.222	0.572	0.617	0.903	0.446
LDL cholesterol	-0.45±0.16	-0.10±0.11	-0.27±0.15	-0.26±0.08	0.002	0.038	0.016	0.024	0.368
HDL cholesterol	0.04±0.09	0.03±0.05	0.05±0.07	0.04±0.04	0.255	0.756	0.666	0.347	0.573
non-HDL cholesterol	-1.06±0.19	-0.65±0.09	-0.81±0.15	-0.83±0.09	0.018	0.118	0.059	0.086	0.324
sdLDL cholesterol	-0.22±0.12	-0.02±0.08	0.05±0.05	-0.06±0.05	0.026	0.217	0.185	0.080	0.415
apoB	-0.18±0.05	-0.08±0.02	-0.07±0.03	-0.11±0.02	0.003	0.088	0.102	0.047	0.301
FBG	0.24±0.15	0.36±0.14	0.24±0.17	0.28±0.09	0.361	0.346	0.125	0.242	0.857
GA, %	0.00±0.24	0.18±0.40	-0.56±0.24	-0.10±0.19	0.335	0.823	0.596	0.770	0.999

CYP7A1: cytochrome P450 family 7 subfamily A member 1 gene; TC: total cholesterol; TG: triglyceride, LDL: low-density lipoprotein; HDL: high density lipoprotein; non-HDL: non-high-density lipoprotein; sdLDL: small dense low-density lipoprotein; apoB: apolipoprotein B; FBG: fasting blood glucose; GA: glycated albumin.
Values are shown as changes of lipid profiles (difference of lipid concentrations of Endpoint and Baseline).
p values were from ANCOVA, age, gender and baseline concentrations were taken as covariates.
†Addictive model, the difference of homozygote (GG homozygote and TT homozygote) to the GT heterozygote in oatmeal group was compared with the corresponding difference in the control group.
‡Dominant model, the difference of G allele genotypes (GG homozygote and GT heterozygote) to the TT genotype in oatmeal group was compared with the corresponding difference in the control group.
§Homozygote model, the difference of GG genotypes to the TT genotype in oatmeal group was compared with the corresponding difference in the control group.

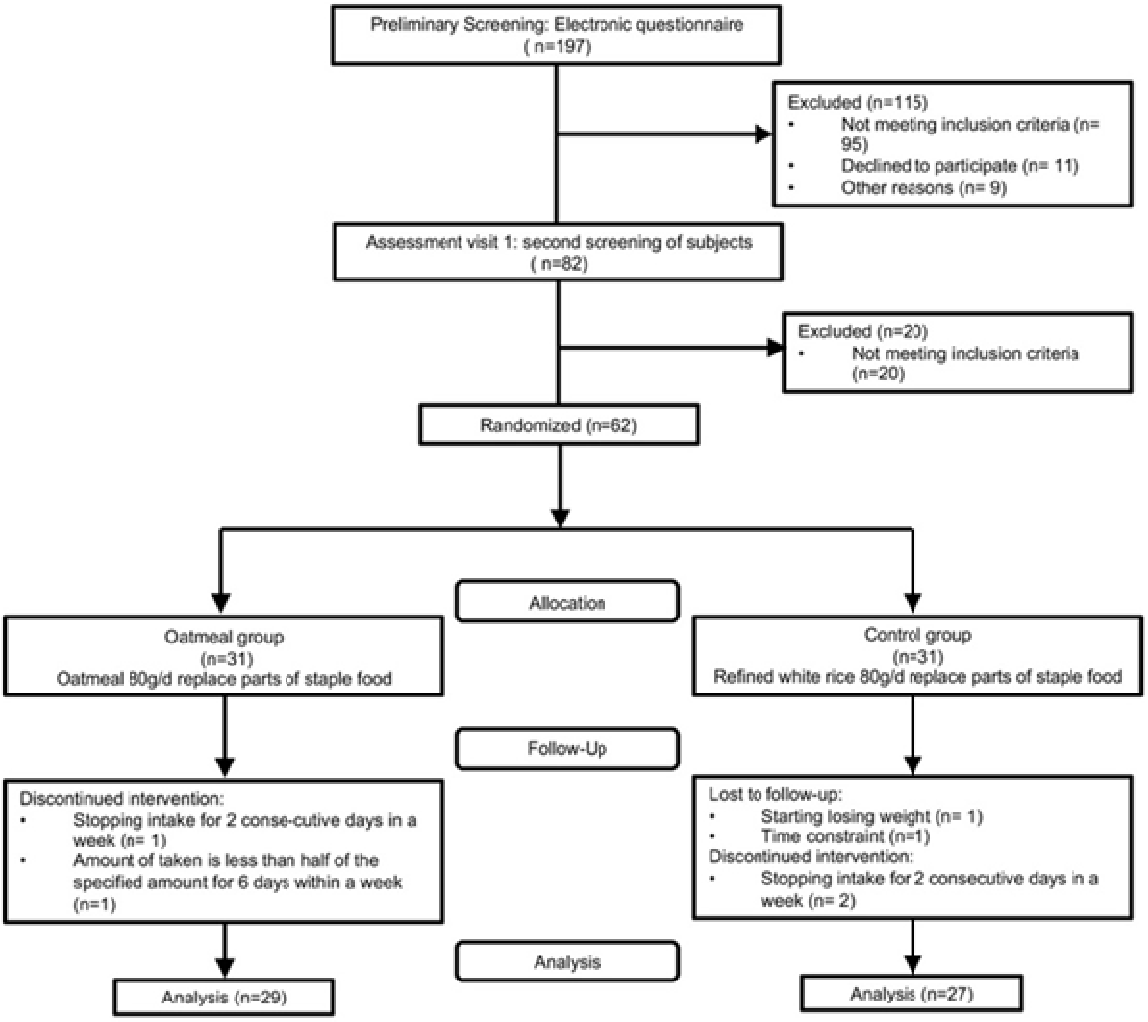

Figure 1. Flow chart.

Supplementary table 1. Results of post-hoc power calculations

Variables	CYP7A1 (Genotype-diet interaction)		CYP7A1 (Addictive model)		CYP7A1 (Dominant model)		APOE (E2+E3 vs. E4)	
	Effect-size	Power	Effect-size	Power	Effect-size	Power	Effect-size	Power
TC	0.1	5.53%	0.066	6.04%	0.092	6.64%	0.000078	5.00%
TG	0.023	5.03%	0.005	5.01%	0.000308	5.00%	0.002666	5.00%
LDL cholesterol	0.13	5.90%	0.113	8.18%	0.099	6.91%	0.020549	5.02%
HDL cholesterol	0.012	5.01%	0.004	5.00%	0.018	5.06%	0.020429	5.02%
non-HDL cholesterol	0.087	5.40%	0.071	6.21%	0.059	5.66%	0.00659	5.00%
sdLDL cholesterol	0.063	5.21%	0.036	5.30%	0.061	5.71%	0.000244	5.00%
apoB	0.098	5.51%	0.054	5.69%	0.078	6.17%	0.002505	5.00%
FBG	0.044	5.10%	0.047	5.52%	0.028	5.15%	0.001788	5.00%
GA, %	0.0082	5.00%	0.006	5.01%	0.002	5.00%	0.000799	5.00%

CYP7A1: cytochrome P450 family 7 subfamily A member 1; APOE: apolipoprotein E; TC: total cholesterol; TG: triglyceride: LDL: low-density lipoprotein; HDL: high density lipoprotein; non-HDL: non-high-density lipoprotein; sdLDL: small dense low-density lipoprotein; apoB: apolipoprotein B; FBG: fasting blood glucose; GA: glycated albumin.

Supplementary table 2. The distribution of classified genotypes

Group	CYP7A1_rs3808607			APOE_rs429358			APOE_rs7412			APOE isoform		
	TT	GT	GG	TT	TC	CC	TT	TC	CC	E2	E3	E4
Oatmeal	9	11	9	21	5	3	1	2	26	2	20	7
Control	10	14	3	23	4	0	0	1	26	0	24	3

Supplementary table 3. Baseline Characteristics based on groupings in APOE isoforms and interventions

Variable	Oatmeal group		Control group		*p* value
	E2/E3 (n=22)	E4 (n=7)	E2/E3 (n=24)	E4 (n=3)	
Age, year	47.9±2.2	48.0±2.7	46.5±1.9	50.7±5.8	0.880
Gender, % for men	36.4%	28.6%	41.7%	33.3%	0.937†
Body weight, kg	62.5±1.9	66.3±2.5	65.8±2.1	55.8±2.6	0.242
BMI, kg/m^2	23.1±0.5	24.0±0.7	23.6±0.5	21.4±1.1	0.383
Waistline, cm	82.3±1.4	84.9±2.6	83.0±1.4	75.7±1.3	0.247
Hip Circumference, cm	96.0±1.3	99.3±1.3	96.3±1.0	92.0±3.6	0.234
Blood pressure, mmHg					
Systolic	120.4±2.9	116.9±2.8	119.8±3.2	116.5±3.1	0.920
Diastolic	70.4±1.7	71.4±2.3	71.3±2.6	70.7±1.8	0.977‡
Serum measurement, mmol/L					
TC	5.83±0.01	6.13±0.10	5.78±0.06	5.74±0.19	0.116
TG	1.44±0.11	1.17±0.11	1.16±0.09	0.84±0.11	0.079‡
LDL cholesterol	3.39±0.11	3.70±0.16	3.39±0.09	3.03±0.12	0.199
HDL cholesterol	1.70±0.07	1.87±0.13	1.67±0.05	2.00±0.17	0.168
non-HDL cholesterol	4.12±0.10	4.25±0.16	4.11±0.07	3.74±0.24	0.379
sdLDL cholesterol	0.96±0.09	0.83±0.09	0.77±0.05	0.67±0.09	0.311‡
apoB	1.10±0.03	1.16±0.06	1.07±0.02	0.98±0.05	0.238
FBG	5.23±0.08	5.24±0.15	5.01±0.08	5.33±0.27	0.204
GA, %	13.5±0.4	13.4±0.5	13.3±0.2	14.3±0.3	0.523‡

APOE: apolipoprotein E; TC: total cholesterol; TG: triglyceride; LDL: low-density lipoprotein; HDL: high density lipoprotein; non-HDL: non-high-density lipoprotein; sdLDL: small dense low-density lipoprotein; apoB: apolipoprotein B; FBG: fasting blood glucose; GA: glycated albumin.
†Fisher's exact test; ‡Kruskal-Wallis Test; otherwise, One-way ANOVA is used. Bonferroni was used for post Hoc tests.

Supplementary table 4. Changes of dietary intakes and physical activity during the study period based on genotypes

Variable	Subgroup by CYP7A1_rs3808607 genotypes						*p* value
	Oatmeal group			Control group			
	TT (n=9)	GT (n=11)	GG (n=9)	TT (n=10)	GT (n=14)	GG (n=3)	
Weight (kg)	-0.68±0.29	0.01±0.36	-0.48±0.33	-0.50±0.48	0.29±0.33	-0.77±0.15	0.802
BMI (kg/m^2)	-0.23±0.10	-0.01±0.15	-0.17±0.12	-0.19±0.16	-0.08±0.12	-0.28±0.05	0.838
Waistline (cm)	-1.62±1.05	-0.10±0.95	-1.41±1.84	-1.09±0.92	0.04±1.01	-0.63±1.77	0.872
Hip Circumference (cm)	-0.84±0.45	0.26±0.92	0.13±0.77	-0.57±0.57	0.01±0.62	-1.40±2.43	0.799
Blood pressure (mmHg)							
Systolic	-1.67±5.15	-1.27±3.44	-0.06±3.16	2.90±3.11	-0.18±1.95	-8.5±11.56	0.757
Diastolic	-2.11±4.76	3.18±3.04	1.72±2.40	2.40±3.48	0.32±2.03	-4.83±3.37	0.742
Energy (kcal/d)	18.2±84.0	137.6±84.1	121.2±124.4	-4.7±135.8	154.8±94.3	153.7±69.9	0.833
Carbohydrate (g/d)	-1.9±15.1	20.6±13.3	23.7±17.1	7.0±26.4	32.0±16.2	42.9±10.9	0.718
Fat (g/d)	0.68±4.07	7.98±2.60	4.75±4.65	-1.56±2.23	2.45±2.69	-3.02±3.58	0.304
Protein (g/d)	4.94±4.17	-4.20±6.44	-4.09±7.03	-4.68±6.40	1.18±4.62	2.31±2.82	0.828†
Fiber (g/d)	6.40±1.80	7.49±1.20	7.51±3.52	-0.17±0.87	-1.43±2.97	-0.17±0.50	0.007†
Cholesterol (mg/d)	-4.5±40.9	-98.0±67.2	-14.2±30.7	-11.8±43.5	-26.4±46.4	-19.7±83.5	0.978†
Staple food (g/d)	14.6±14.0	-2.0±15.6	19.3±26.7	-2.5±36.5	-9.7±20.3	-16.1±56.2	0.852†
Fruit & Vegetables (g/d)	41.2±31.9	-22.4±22.2	-18.8±41.6	-48.4±33.5	-44.4±31.4	-67.8±26.3	0.368†
Meat (g/d)	23.5±29.3	-27.1±17.6	3.6±16.3	-19.5±24.9	20.9±15.2	8.8±44.4	0.407
Eggs & Dairy products (g/d)	-59.6±68.0	-12.3±20.7	5.7±23.3	-42.7±27.0	-18.8±25.7	-26.7±20.4	0.906†
Beans (g/d)	3.0±8.4	2.4±11.3	1.1±13.9	-3.2±10.6	8.5±9.0	22.8±11.4	0.890
Aquatic products (g/d)	8.1±19.6	-35.5±14.7	-3.7±17.0	-24.8±15.7	-15.0±13.7	-27.8±98.8	0.747†
Working day (d/week)	0.11±0.11	0.09±0.15	0.06±0.13	0.05±0.16	-0.07±0.07	0.67±0.67	0.656†
Daily working time (h/d)	-0.33±0.22	-0.18±0.23	-0.11±0.42	-0.10±0.28	0.21±0.16	0.33±0.33	0.329†
Sitting time (h/d)	0.11±0.58	-0.91±0.54	0.39±0.69	-0.75±0.50	-0.36±0.47	-1.17±0.17	0.484
Daily Commuting time (min/d)	-18.3±9.1	-8.2±5.8	-12.2±10.6	-12.0±9.8	-11.4±7.6	-8.3±27.2	0.942†
Frequency of medium intensity exercise per week	0.009±0.056	-0.383±0.140	-0.023±0.016	-0.021±0.063	-0.091±0.092	-0.573±0.143	0.069†
Frequency of high intensity exercise per week	-0.040±0.04	-0.065±0.065	0.016±0.016	-0.079±0.53	-0.097±0.045	-0.097±0.097	0.324†
house work (min/d)	-23.0±8.0	1.8±3.2	-5.6±9.3	-0.5±10.6	11.1±13.3	-6.7±12.0	0.140†
sleep time (h/d)	0.33±0.17	-0.23±0.17	0.00±0.08	0.05±0.16	-0.14±0.06	0.17±0.17	0.115†

p value are from Kruskal Wallis test, otherwise, it was from ANOVA. Bonferroni was used for post Hoc tests. Values labeled without a common superscript letter differ from each other in the same row, $p<0.05$.

Supplementary Table 4. Changes of dietary intakes and physical activity during the study period based on genotypes (cont.)

Variable	Subgroup by APOE isoforms				*p* value
	Oatmeal group		Control group		
	ε2/ε3 (n=22)	ε4 (n=7)	ε2/ε3 (n=24)	ε4 (n=3)	
Weight (kg)	-0.49±0.23	0.07±0.33	-0.50±0.25	0.17±0.98	0.546
BMI (kg/m^2)	-0.18±0.09	0.04±0.12	-0.17±0.09	0.06±0.38	0.505
Waistline (cm)	-0.80±0.72	-1.54±2.15	-0.80±0.51	2.30±4.49	0.950†
Hip Circumference (cm)	-0.07±0.49	-0.27±1.04	-0.54±0.43	1.07±2.27	0.706
Blood pressure (mmHg)					
Systolic	-0.84±2.83	-1.57±2.42	-0.56±2.11	4.83±4.48	0.752†
Diastolic	2.11±2.45	-2.14±2.83	1.50±1.70	-7.33±6.21	0.363
Energy (kcal/d)	186.0±48.6a	-189.1±123.5b	75.6±77.2ab	255.6±123.6ab	0.048
Carbohydrate (g/d)	26.9±8.2	-24.2±19.1	20.8±14.3	49.5±14.7	0.065†
Fat (g/d)	7.31±2.02	-3.46±5.48	0.00±1.75	3.17±6.57	0.035
Protein (g/d)	3.11±3.23	-15.27±8.84	-1.88±3.66	7.26±6.53	0.202†
Fiber (g/d)	8.75±1.25a	2.13±2.82ab	-0.78±1.74b	-1.22±0.43ab	<0.01†
Cholesterol (mg/d)	-20.4±21.4	-114.1±1067.0	-36.7±31.3	111.4±27.1	0.264†
Staple food (g/d)	14.2±11.9	-4.0±25.4	-3.8±19.3	-39.4±28.7	0.658
Fruit & Vegetables (g/d)	8.3±18.8	-32.5±49.6	-59.9±21.2	42.7±40.4	0.095
Meat (g/d)	10.6±13.2	-41.1±28.0	5.7±13.5	-4.0±56.3	0.357†
Eggs & Dairy products (g/d)	8.4±14.1	-115.0±79.8	-35.2±18.1	25.0±19.5	0.109†
Beans (g/d)	7.8±7.0	-15.5±13.4	4.1±6.7	19.4±18.1	0.285†
Aquatic products (g/d)	-14.2±10.9	-5.2±25.3	-22.2±14.4	-2.8±10.3	0.946†
Working day (d/week)	0.11±0.10	0.00±0.00	-0.02±0.08	0.67±0.67	0.538†
Daily working time (h/d)	-0.34±0.19	0.21±0.31	0.13±0.15	0.00±0.00	0.251†
Sitting time (h/d)	-0.64±0.36	1.21±0.71	-0.69±0.33	0.17±0.73	0.055
Daily Commuting time (min/d)	-15.0±5.9	-5.0±6.8	-8.8±6.1	-31.7±15.9	0.444†
Frequency of medium intensity exercise per week	-0.15±0.07	-0.16±0.14	-0.12±0.07	-0.14±0.14	0.990†
Frequency of high intensity exercise per week	-0.04±0.04	0.00±0.00	-0.10±0.03	0.00±0.00	0.141†
house work (min/d)	-6.23±3.66	-14.3±14.3	5.42±8.79	0.00±17.32	0.543†
sleep time (h/d)	-0.05±0.11	0.21±0.15	0.00±0.07	-0.33±0.33	0.378†

p value are from Kruskal Wallis test, otherwise, it was from ANOVA. Bonferroni was used for post Hoc tests. Values labeled without a common superscript letter differ from each other in the same row, $p<0.05$.

Supplementary table 5. Differences in cholesterol-lowering and glycemia-modulation effect following oatmeal consumption between different APOE isoforms

Variable (mmol/L)	isoforms		*p* value	
	E2/E3	E4	Genotype-diet interaction	E2/3 vs E4[†]
Control Group				
TC	-0.59±0.08	-0.43±0.23	-	-
TG	0.08±0.10	0.05±0.11	-	-
LDL cholesterol	0.05±0.07	0.33±0.15	-	-
HDL cholesterol	-0.02±0.04	-0.02±0.12	-	-
non-HDL cholesterol	-0.57±0.08	-0.41±0.20	-	-
sdLDL cholesterol	0.14±0.04	0.12±0.10	-	-
apoB	-0.01±0.02	0.00±0.06	-	-
FBG	0.33±0.06	-0.03±0.33	-	-
GA, %	0.17±0.18	-0.33±0.67	-	-
Oatmeal Group				
TC	-0.78±0.11	-0.84±0.17	0.934	0.952
TG	-0.13±0.12	-0.17±0.08	0.722	0.725
LDL cholesterol	-0.21±0.08	-0.41±0.21	0.332	0.326
HDL cholesterol	0.00±0.04	0.15±0.11	0.333	0.327
non-HDL cholesterol	-0.78±0.09	-0.98±0.21	0.582	0.579
sdLDL cholesterol	-0.07±0.07	-0.04±0.04	0.910	0.915
apoB	-0.09±0.02	-0.16±0.06	0.737	0.733
FBG	0.32±0.10	0.16±0.19	0.762	0.773
GA, %	-0.09±0.25	-0.14±0.14	0.890	0.847

APOE: apolipoprotein E; TC: total cholesterol; TG: triglyceride; LDL: low-density lipoprotein; HDL: high density lipoprotein; non-HDL: non-high-density lipoprotein; sdLDL: small dense low-density lipoprotein; apoB: apolipoprotein B; FBG: fasting blood glucose; GA: glycated albumin.
Values are shown as change of lipid profiles (lipid concentrations of Endpoint−Baseline). *p* values were from ANCOVA, age, gender, change of energy and fat intakes as well as baseline concentrations were taken as covariates.
[†]The difference of E2 and E3 isoforms to the E4 isoforms in oatmeal group was compared with the corresponding difference in the control group.