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The APOLIPOPROTEIN E genotype impacts on the responsiveness of fasting lipids and gut peptides to functional interventions - findings from the CABALA study

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Beneficial effects of dietary fibres, polyphenols, and probiotics (referred to as functional interventions) on cardiometabolic health may be mediated by changes in gut microbiota composition leading to reductions in low-density lipoprotein cholesterol (LDL-C) concentration[(1)]. The *APOLIPOPROTEIN* (*APO*)*E* genotype has been shown to impact on the responsiveness of the fasting lipid profile and cardiovascular disease risk to dietary fat intake. However, little is known about other nutrient-gene interactions, with one study reporting a greater LDL-C lowering effect in *APOE4* carriers than wild- type *APOE3*/*E3* group after chronic intake of plant sterols[(2)]. Our aim was to investigate the association of the *APOE* genotype with fasting cardiometabolic disease risk markers following chronic consumption of functional interventions known to impact on the gut microbiota.

In this secondary analysis from the CABALA study[(3)], data for participants assigned to the oats, apples and probiotic interventions (n = 46/61, mean ± SD, age 52 ± 11y and BMI 24.9 ± 3.1kg/m^2), were combined. In brief, healthy volunteers [randomised based on age, sex, BMI and serum total cholesterol (TC)] were assigned to one of three interventions: two placebo capsules and i) 40g/day of porridge oats (n = 14) or ii) two Renetta Canada apples/day (n = 16), or iii) two *Lactobacillus reuteri* capsules with 40g/day of cornflakes (n = 15) for 8 weeks. At weeks 0 and 8, a fasting blood sample was taken for the measurement of the lipid profile, glucose and gut peptides. *APOE* genotyping was performed retrospectively (rs429358 and rs7412) [*E2* carriers (*E2*/*E2* and *E2*/*E3*, n = 7), *E3*/*E3* group (wild-type, n = 28) and *E4* carriers (*E3*/*E4* and *E4*/*E4*, n = 10)]. A linear mixed-model was used to determine the impact of genotype on the cardiometabolic outcomes in response to the functional interventions.

Prior to the start of the interventions (week 0), fasting LDL-C concentrations were higher in *E4* carriers compared with the *E3*/*E3* group and *E2* carriers (p£0.026) TC) concentrations were also higher in the *E4* carriers than *E3*/*E3* group ($p = 0.034$), with a tendency for a similar effect evident on apoB and non- high-density lipoprotein-cholesterol ($p = 0.051$–0.078) concentrations. Following the chronic interventions, significant visit*genotype interactions were found for fasting TC, LDL-C, apoB, glucose and peptide YY (PYY)(p£0.032). Relative to week 0, there was a reduction in TC, LDL-C and apoB at week 8 in the *E4* carriers whereas there was an increase in glucose and PYY in the *E2* carriers, relative to the other genotype groups.

In conclusion, baseline associations between the *APOE* genotype and fasting lipids confirm previous findings. Data from our exploratory analyses indicate that *APOE* genotype had an impact on fasting cardiometabolic risk markers in response to daily consumption of the functional interventions. Further studies are needed to confirm these associations.

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