

## Evidence of increased intestinal absorption of cholesterol after the replacement of dietary saturated with unsaturated fats. Findings from the RISSCI-1 study

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We have previously shown that replacement of dietary saturated fat (SFA) with unsaturated fat (UFA) lowers serum LDL-cholesterol and increases the gene expression of LDL-receptors (LDL-R) in peripheral blood mononuclear cells, in the RISSCI-1 (Reading Imperial Surrey Saturated fat Cholesterol Intervention) study<sup>(1)</sup>. This dietary-induced upregulation of LDL-R gene expression has been reported to occur in response to a reduction in endogenous cholesterol synthesis and intra-cellular free cholesterol. The latter, in part, is regulated by a reciprocal ‘push-pull’ relationship between the endogenous synthesis and intestinal absorption of cholesterol<sup>(2)</sup>. The aim of the present investigation was to evaluate the effects of exchanging SFA for UFA on markers of intestinal absorption and endogenous synthesis of cholesterol. RISSCI-1 was a non-randomised, sequential dietary intervention study, in which 109 healthy men (age 48, SD 11y, BMI 25.1 kg/m<sup>2</sup> SD 3.3) followed two iso-energetic diets; a high SFA (18% total energy (TE)) - lower UFA (15% TE) diet, followed by a lower SFA (10% TE) - high UFA (24% TE) diet, for 4 weeks each. Plasma non-cholesterol sterols, standardised for total cholesterol and expressed as ratios of non-cholesterol sterol to total cholesterol, were used as validated biomarkers of intestinal cholesterol absorption ( $\beta$ -sitosterol, cholestanol, campesterol), and endogenous cholesterol synthesis (lathosterol, desmosterol)<sup>(3)</sup>. Non-cholesterol sterols were measured in plasma samples collected at the end of each diet, using GC-MS and epicoprostanol (5 $\beta$ -cholestan-3 $\alpha$ -ol) as an internal standard. Data was analysed by a linear mixed model, with age, BMI, baseline visit, diets (high SFA, low SFA), and study centre included as fixed effects, and participants as a random effect (R version 4.1.2). Replacement of dietary SFA with UFA produced increases of between 15 to 35% in all three plasma biomarkers of intestinal cholesterol absorption (high vs lower SFA diet). Mean cholesterol-standardised ratios (95% CI) were as follows:  $\beta$ -sitosterol 0.95 (0.94–1.01) vs 1.31 (1.27–1.34); cholestanol 1.25 (1.22–1.28) vs 1.44 (1.41–1.47); campesterol 0.91 (0.87–0.94) vs 1.14 (1.11–1.18) all  $p < 0.0001$ . Plasma desmosterol increased (0.61 (0.59–0.63) vs 0.66 (0.65–0.68))  $p < 0.0001$ , while plasma lathosterol showed no significant change. In conclusion, the consistent increase in biomarkers of intestinal cholesterol absorption is in accord with the replacement of dietary SFA with UFA reducing the endogenous synthesis of cholesterol. However, since there was no evidence of a consistent dietary effect on the biomarkers of endogenous cholesterol synthesis, this fails to support a reciprocal relationship between cholesterol synthesis and absorption. Further insight into these effects will be gained through the stable isotope trace-labelling of dietary saturated fat in a follow-up study (RISSCI-2).

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### References

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