

Table S2.

Response to dietary plant sterols/stanols in subjects according to *APOE* polymorphism

Reference	Experimental Protocol	Subjects	Response	Remarks
Vanhanen et al. (1993) ^{S1}	Parallel, 6 weeks: 3.4 g/d sitostanol (n=34) vs. controls (n=33)	Moderate hypercholesterolemia (n = 67) Controls: E3E3 (n=22) E3E4 (n=10) E4E4 (n=1); M/F: 26/7, 43 years, BMI=25.8kg/m ² Sitostanol: E2E2 (n=1) E3E2 (n=16) E4E3 (n=12) E4E4 (n=5); M/F: 21/13; 48 years; BMI=25.2kg/m ²	Total cholesterol: -0.44 mmol/L (-7.5%), LDL-C: -0.37 mmol/L (-10%). E4 carriers: -11.8% LDL-C (<i>P</i> <0.05); E3E3: -6% LDL-C (NS). Decrease in absorption (plasma sitosterol and campesterol) and increase in cholesterol synthesis, both greater in E4 carriers than E3E3.	Changes in LDL-C correlated to changes in plasma plant sterol. Relatively large number of E4E4. Significant response in E4 carriers but not in E3E3, no significant difference between the two responses.
Miettinen & Vanhanen (1994) ^{S2}	Parallel, 6 weeks: mayonnaise colza, mayonnaise colza + 700 mg/d sitosterol, mayonnaise colza+	Moderate hypercholesterolemia >6 mmol/L (n=31) M/F: 22/9, age=45±3 years, BMI=25.2±1.2 kg/m ²	Small effects, plant sterols/stanols combined: -5% (<i>P</i> <0.05). E4 (n=8): -0.28 mmol/L (-8%) LDL-C (<i>P</i> <0.05); E3E3 (n=15): -0.06 mmol/L (NS).	Decrease in absorption (plasma sitosterol and campesterol) and increase in cholesterol synthesis both greater in E4 than E3E3. Same research group as above

	700 mg/d sitostanol, mayonnaise colza + 800 mg/d sitostanol esters			ref ⁷⁴ .
Ishiwata et al. (2002) ^{S3}	Parallel, 4 weeks: placebo (n = 35) 2.0 g/d stanols (n = 34) 3.0 g/d stanols (n = 36)	Healthy subjects Control: E3 (n=19), E4 (n=11) Group 2.0 g/d: E3 (n=21), E4 (n=10) Group 3.0 g/d: E3 (n=25), E4 (n=6)	No difference in changes in total cholesterol or LDL-C between E3 (-8.9%) and E4 (-10.4%).	Low fat and low cholesterol diet at baseline.
Tammi et al. (2002) ^{S4}	STRIP study Crossover, 2 x 3 months, margarine rich in stanol esters (1.6 g/d) vs. control margarine	Healthy children (n=81, M/F: 45/36, age 6 years) E4 carriers (E4E4 or E3/E4) (n=24) vs. non carriers (E2E3 or E3E3) (n=54)	No difference in total cholesterol and LDL-C changes. In E4 carriers, -0.24 mmol/L (-8.4%) LDL-C; in non-carriers, -0.20 mmol/L (-7.6%) LDL-C. Absorption decreased in both groups but cholesterol synthesis increased only in E4 carriers.	Baseline concentration correlated with response. Decreases in plasma plant sterols were similar in boys and girls, but cholesterol synthesis precursors increased more in girls.
Geelen et	Crossover, 3	Healthy subjects E3E4 or	No influence of <i>APOE</i> genotype.	Young healthy subjects.

al. (2002) ^{S5}	weeks, control margarine vs. plant sterol rich margarine (3.2 g/d)	E4E4 (n=31), E3E3 (n=57); 25 ±11 years	Total cholesterol: -0.36 mmol/L (7.4%) in E3 vs. -0.31 (5.7%) in E4 (NS). LDL-C:-0.34 mmol/L (12.2) in E3/3 vs. 0.32 (9.8%) in E4 (NS).	
Plat & Mensink (2002) ^{S6}	Parallel, 8 weeks, 3 groups: controls, 3.8±0.6 g/d stanols from vegetable oil, 4.0±1.8 g/d stanols from wood	Normocholesterolemic (n=112 [41M, 71F], BMI= 23±2.8 kg/m ² , age=33±16 years) With stanols, n=70 (E3=E3E3, n=41; E2=E2E2+E2E3+ E2E4 , n=11; E4=E3E4+E4E4, n=10)	Differences between genotypes not significant. In E2: -0.31 mmol/L LDL-C; in E3: - 0.41 mmol/L LDL-C; in E4: -0.49 mmol/L LDL-C.	No difference in campesterol decrease. Lower increase in lathosterol for E3. Other gene polymorphisms without significant effect: <i>APOA4, SCARB1, HMGCR,</i> <i>CETP</i>
Lottenberg et al. (2003) ^{S7}	Crossover, 4 weeks, margarine providing or not 1.68 g/d plant sterols	Moderate hypercholesterolemia (7 mmol/L on average, n=60 M+F, 20-60 years). E3E3 (n=35), E3E4 (n=16)	No difference between E3E3 and E3E4 for changes in total cholesterol and LDL-C (-6.3% and -6.8% for E3E3 and E3E4 respectively), but response significant only in E3E3.	E4E3 sample is less than half the E3E3 group.
Sanchez- Muniz et al.	Parallel, 5 weeks, control spread (n=87), 1.1 g/d or	Hypercholesterolemic subjects (M+F, n=217, 21 to 75 years)	In E2 carriers: -12.7% LDL-C (<i>P</i> <0.01); in E3: -5.5% LDL-C (<i>P</i> <0.001); in E4: -5.6% LDL-C (NS).	At baseline, LDL-C higher in E4 and E3 than in E2. Similar changes in E3 and E4, but

(2009) ^{S8}	2.2 g/d plant sterols (n=120)	E2E3+E2E2 (n=26), E3E4+E4E4 (n=51), E3E3 (n=130); E2E4 (n=10) excluded	TG lowering in E2 carriers. Serum carotenoid decrease in E4.	since there were fewer E4 subjects, the NS response in E4 might be a statistical power issue. High response in E2, only due to the fact that E2 subjects with control spread had an increase in LDL-C. The LDL-C change in E2 carriers when compared only to baseline levels is much lower (figure 2).
Banuls et al. (2011) ^{S9}	Parallel, 3 months, NCEP-ATIII diet + low fat milk with (n=41) or without (n=34) 2.0 g/d plant sterols (sitosterol 70%, campesterol 15%, sitostanol 10%, Unilever)	Moderate hypercholesterolemic subjects (M/F: 22/53, 18-76 years, BMI=28 kg/m ²). In the group eating plant sterols, E3 (n=24), E4 (n=13), E2 (n=4).	No difference in response according to <i>APOE</i> . Average effect: -8.1% LDL-C.	Response not correlated with LDL particle size at baseline. Diet does not change LDL particle size. Statistical power issue.

MacKay et al. (2015) ^{S10}	Crossover, 4 weeks, 25g margarine with 2.0 g/d plant sterols or without	Mildly hypercholesterolemic subjects (M/F: 24/39, age: 55.2 years, BMI=28.8 kg/m ²); preselected as possessing either high endogenous cholesterol synthesis (n=24) or low endogenous cholesterol synthesis (n=39); E3 (E3E3, n=36 + E2E3, n = 4), E4 (=E4E3, n=18 + E4E4, n=5)	In E3: -0.13 mmol/L LDL-C; in E4: -0.31 mmol/L LDL-C. Significant effects in both groups, but significantly higher in E4.	Borderline interaction with <i>CYP7A1</i> rs3808607, in such a way that carriers of <i>CYP7A1</i> -rs3808607 T/T and <i>APOE</i> E3 (n=14) were the only group who did not benefit from the intervention (LDL-C change: +0.09 mmol/L). <i>ABCG8</i> rs4148217 (T400K) and <i>CETP</i> rs5882 (I405V) polymorphisms: no effect on the response.
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Abbreviations: ABCG5/G8, ATP-binding cassette subfamily G member 5/8; APOA4, apolipoprotein A-IV; APOE, apolipoprotein E; CETP, cholesterol ester transfer protein; CYP7A1, cholesterol 7 α -hydroxylase; F, females; HMGCR, hydroxyl-methyl-glutaryl coenzyme A reductase; LDL-C: low-density lipoprotein cholesterol; M, males; NPC1L1, Niemann-Pick C1 Like 1 protein; NS, not significant; SCARB1, scavenger receptor BI; STRIP, Special Turku Coronary Risk Factor Intervention Project; TG, triglycerides

References

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