Supplemental information

The secondary bile acid isoursodeoxycholate

correlates with post-prandial lipemia, inflammation,

and appetite and changes post-bariatric surgery

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The secondary bile acid isoursodeoxycholate (isoUDCA) modulates postprandial lipaemia, inflammation and appetite, and changes post bariatric surgery

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Supplementary tables, and figures

Supplementary Table 1. Descriptive characteristics of participants

	TwinsUK (n = 2,382)		ZOE PREDICT-1 (n = 327)		Omega-3 Study (n = 65)		BARIA (n = 116)			
							Pre-surgery (n = 116)		*Post-surgery (n = 71)*	
	n	%	n	%	n	%	n	%	n	%
Females	2,037	85.5	327	100	61	93.9	91	78.5	68	95.8
Type-2 diabetes	67	2.8	0	0	0	0	26	28.6	19	26.8
	mean	sd	mean	sd	mean	sd	mean	sd	Mean	sd
Age, years	58.9	14.6	53.8	7.0	65.9	9.4	46.0	10.3	47	9.6
BMI, kg/m^2	26.0	5.0	26.3	5.6	26.5	4.4	39.6	4.5	26.0	2.9
Fasting										
Triglycerides	1.0	0.6	1.1	0.57			1.3	0.7		
GlycA			1.35	0.19						
Postprandial										
Triglycerides			2.33	1.2			1.5	0.7		
GlycA			1.4	0.3						
Dietary indices										
HEI	61.8	9.9	57.1	9.4						

aMED	4.8	1.9	4.5	1.8
oPDI	56.1	5.6	53.3	6.1
hPDI	58.5	6.7	58.9	6.2
uPDI	58.9	7.0	59.4	6.2

Supplementary Table 2. Bile acids detected in >80% of the serum and stool samples.

Bile acid	Pathway	Serum	Stool
Cholate	Primary	Yes	Yes
Glycocholate	Primary	Yes	Yes
Glycochenodeoxycholate	Primary	Yes	Yes
Taurocholate	Primary	Yes	No
Glyco-beta-muricholate	Primary	Yes	No
Glycochenodeoxycholate 3-sulfate	Primary	Yes	No
Glycochenodeoxycholate glucuronid	Primary	Yes	No
Taurochenodeoxycholate	Primary	Yes	No
Isoursodeoxycholate	Secondary	Yes	Yes
Deoxycholic acid 12 sulfate	Secondary	Yes	No
Deoxycholic acid glucuronide	Secondary	Yes	No
Glycocholenate sulfate	Secondary	Yes	No
Glycodeoxycholate 3 sulfate	Secondary	Yes	No
Glycolithocholate sulfate	Secondary	Yes	No
Glycoursodeoxycholate	Secondary	Yes	No
Glycoursodeoxycholicacid sulfate 1	Secondary	Yes	No
Lithocholatesulfate1	Secondary	Yes	No
Taurocholenatesulfate	Secondary	Yes	No
Taurolithocholate 3 sulfate	Secondary	Yes	No
Dehydrodeoxycholate	Secondary	No	Yes
Dehydrolithocholate	Secondary	No	Yes
Deoxycholate	Secondary	No	Yes
Glycodeoxycholate	Secondary	No	Yes
Hyocholate	Secondary	No	Yes
Isohyodeoxycholate	Secondary	No	Yes
Ketodeoxycholate	Secondary	No	Yes
Ketolithocholate	Secondary	No	Yes
Lithocholate	Secondary	No	Yes
Oxolithocholate	Secondary	No	Yes
Ursocholate	Secondary	No	Yes

Supplementary Table 3. Bile acids correlations with the gut microbiome

	TwinsUK								ZOE PREDICT-1							
	Serum				Stool				Serum				Stool			
Bile acid	AUC (%)	95% CI	Rho	95% CI	AUC (%)	95% CI	Rho	95% CI	AUC (%)	95% CI	Rho	95% CI	AUC (%)	95% CI	Rho	95% CI
Cholate	80.7	80.5, 80.9	0.42	0.42, 0.42	83.4	83.3, 83.5	0.48	0.48, 0.48	80.9	79.8, 82.0	0.43	0.42, 0.44	84.1	83.1, 85.2	0.46	0.45, 0.47
glycocholate	49.2	48.6, 49.8	0.06	0.06, 0.06	72.9	72.5, 73.4	0.35	0.35, 0.35	56.9	55.5, 58.3	0.04	0.03, 0.05	80.7	79.6, 81.9	0.40	0.39, 0.41
glycochenodeoxycholate	60.3	59.9, 60.6	0.12	0.12, 0.12	75.2	74.7, 75.6	0.37	0.37, 0.37	63.1	61.9, 64.4	0.23	0.22, 0.24	79.2	79.6, 80.4	0.42	0.41, 0.43
isoursodeoxycholate	75.4	75.0, 75.8	0.39	0.39, 0.39	85.2	84.8, 85.6	0.51	0.50, 0.52	85.0,	84.4, 86.0	0.47	0.45, 0.49	87.3	87.3, 87.8	0.48	0.47, 0.49
deoxycholic acid 12-sulfate	69.3	68.8, 69.9	0.27	0.27, 0.27					79.4	78.7, 80.2	0.43	0.42, 0.44				
deoxycholic acid glucuronide	68.8	68.4, 69.3	0.34	0.33, 0.35					60.2	60.2, 61.4	0.16	0.15, 0.17				
glyco-beta-muricholate	61.3	61.1, 61.5	0.20	0.19, 0.21					70.4	68.2, 72.7	0.16	0.15, 0.17				
glycochenodeoxycholate 3-sulfate	51.4	50.9, 52.0	0.09	0.09, 0.09					58.4	57.7, 59.1	0.19	0.18, 0.20				

glycochenodeoxycholate glucuronide	55.6	55.2, 56.1	0.09	0.09, 0.09					59.9	58.6, 61.3	0.24	0.23, 0.25				
glycocholenate sulfate	60.8	60.3, 61.3	0.10	0.10, 0.10					61.4	60.1, 62.6	0.09	0.08, 0.10				
glycodeoxycholate 3-sulfate	66.8	66.6, 67.1	0.21	0.21, 0.21					69.1	67.5, 70.7	0.25	0.24, 0.26				
glycolithocholate sulfate	66.6	66.1, 67.2	0.28	0.28, 0.28					71.9	70.3, 73.4	0.32	0.31, 0.33				
glycoursodeoxycholate	75.8	75.3, 76.3	0.40	0.40, 0.40					73.0	72.2, 73.9	0.33	0.32, 0.34				
glycoursodeoxycholic acid sulfate	79.0	78.4, 79.6	0.42	0.42, 0.42					65.7	63.0, 68.3	0.27	0.26, 0.28				
lithocholate sulfate	72.0	71.6, 72.5	0.30	0.30, 0.30					71.3	70.0, 72.8	0.32	0.31, 0.33				
taurochenodeoxycholate	61.8	61.3, 62.3	0.11	0.11, 0.11					53.6	53.0, 54.2	0.14	0.12, 0.16				
taurocholate	52.0	51.4, 52.7	0.01	0, 0.02					52.1	51.4, 52.9	0.06	0.05, 0.07				
taurocholenate sulfate	62.2	61.5, 62.9	0.14	0.14, 0.14					60.6	59.2, 61.9	0.11	0.10, 0.12				
taurolithocholate 3-sulfate	72.3	71.7, 72.9	0.33	0.33, 0.33					71.6	70.6, 72.7	0.33	0.32, 0.34				
12-ketolithocholate					72.0	71.7, 72.4	0.33	0.33, 0.33					81.2	80.3, 82.2	0.40	0.39, 0.41

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3-dehydrodeoxycholate	71.8	71.3, 72.3	0.36	0.36, 0.36	84.0	82.8, 85.2	0.51	0.50, 0.52
6-oxolithocholate	67.3	66.8, 67.8	0.23	0.22, 0.24	71.6	70.8, 72.3	0.29	0.28, 0.30
7-ketodeoxycholate	82.4	82.1, 82.1	0.46	0.45, 0.47	83.0	82.3, 83.7	0.45	0.44, 0.46
dehydrolithocholate	81.7	81.5, 82.0	0.47	0.47, 0.47	79.6	78.5, 80.8	0.48	0.46, 0.50
Deoxycholate	83.7	83.5, 84.0	0.48	0.48, 0.48	86.5	85.8, 87.2	0.51	0.50, 0.52
glycodeoxycholate	76.1	75.7, 76.5	0.37	0.37, 0.37	76.6	75.1, 78.2	0.36	0.35, 0.37
hyocholate	80.5	80.1, 80.9	0.43	0.42, 0.44	78.8	78.8, 79.9	0.40	0.39, 0.41
isohyodeoxycholate	74.4	73.5, 75.2	0.35	0.35, 0.35	58.1	56.6, 59.6	0.04	0.03, 0.05
lithocholate	75.9	75.3, 76.5	0.38	0.38, 0.38	75.2	74.1, 76.2	0.39	0.38, 0.4
ursocholate	82.1	81.5, 82.8	0.50	0.50, 0.50	83.7	82.8, 84.6	0.47	0.46, 0.48

Supplementary Table 4. Correlation of primary and secondary bile acids measured from serum and stool samples and postprandial lipaemia in PREDICT.

Bile acid	Pathway	Serum			Stool		
		Beta	95% CI	p value	Beta	95% CI	p value
Cholate	Primary	-0.04	-0.17, 0.1	0.59	0.12	-0.02, 0.26	0.09
Glycocholate	Primary	0.1	-0.06, 0.26	0.21	0.01	-0.12, 0.14	0.89
Glycochenodeoxycholate	Primary	0.12	-0.05, 0.29	0.18	0.06	-0.09, 0.21	0.41
Taurocholate	Primary	0.06	-0.10, 0.21	0.46	NA	NA	NA
Glyco-beta-muricholate	Primary	0.03	-0.13, 0.18	0.73	NA	NA	NA
Glycochenodeoxycholate 3-sulfate	Primary	-0.05	-0.19, 0.09	0.5	NA	NA	NA
Glycochenodeoxycholate glucuronide	Primary	0.12	-0.02, 0.27	0.1	NA	NA	NA
Taurochenodeoxycholate	Primary	0.02	-0.15, 0.19	0.8	NA	NA	NA
Isoursodeoxycholate	Secondary	0.32	0.18, 0.46	$7.36 \times 10{-6}$	0.23	0.10, 0.36	$5.52 \times 10{-4}$
Deoxycholic acid 12-sulfate	Secondary	0.14	-0.01, 0.30	0.06	NA	NA	NA
Deoxycholic acid glucuronide	Secondary	0.17	0.02, 0.32	0.02	NA	NA	NA
Glycocholenate sulfate	Secondary	0.03	-0.10, 0.16	0.65	NA	NA	NA
Glycodeoxycholate 3-sulfate	Secondary	-35.6	-0.15, 0.14	0.97	NA	NA	NA

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Glycolithocholate sulfate	Secondary	5×10^{-3}	-0.13, 0.14	0.94	NA	NA	NA
Glycoursodeoxycholate	Secondary	0.26	0.10, 0.42	1.6×10^{-3}	NA	NA	NA
Glycoursodeoxycholic acid sulfate	Secondary	0.18	0.03, 0.34	0.02	NA	NA	NA
Lithocholate sulfate	Secondary	0.01	-0.14, 0.15	0.94	NA	NA	NA
Taurocholenate sulfate	Secondary	-0.12	-0.27, 0.03	0.12	NA	NA	NA
Taurolithocholate 3-sulfate	Secondary	-0.09	-0.22, 0.05	0.22	NA	NA	NA
3-Dehydrodeoxycholate	Secondary	NA	NA	NA	0.19	0.06, 0.31	4.47×10^{-3}
Dehydrolithocholate	Secondary	NA	NA	NA	0.04	-0.10, 0.17	0.6
Deoxycholate	Secondary	NA	NA	NA	0.21	0.08, 0.33	1.10×10^{-3}
Glycodeoxycholate	Secondary	NA	NA	NA	0.13	-0.02, 0.28	0.09
Hyocholate	Secondary	NA	NA	NA	0.2	0.06, 0.34	0.01
Isohyodeoxycholate	Secondary	NA	NA	NA	0.12	-0.02, 0.26	0.1
7-Ketodeoxycholate	Secondary	NA	NA	NA	0.12	-0.02, 0.26	0.1
12-Ketolithocholate	Secondary	NA	NA	NA	0.15	0.01, 0.28	0.03
Lithocholate	Secondary	NA	NA	NA	0.13	0.00, 0.26	0.05
6-Oxolithocholate	Secondary	NA	NA	NA	4.45×10^{-3}	-0.12, 0.13	0.95
Ursocholate	Secondary	NA	NA	NA	0.26	0.12, 0.39	1.86×10^{-4}
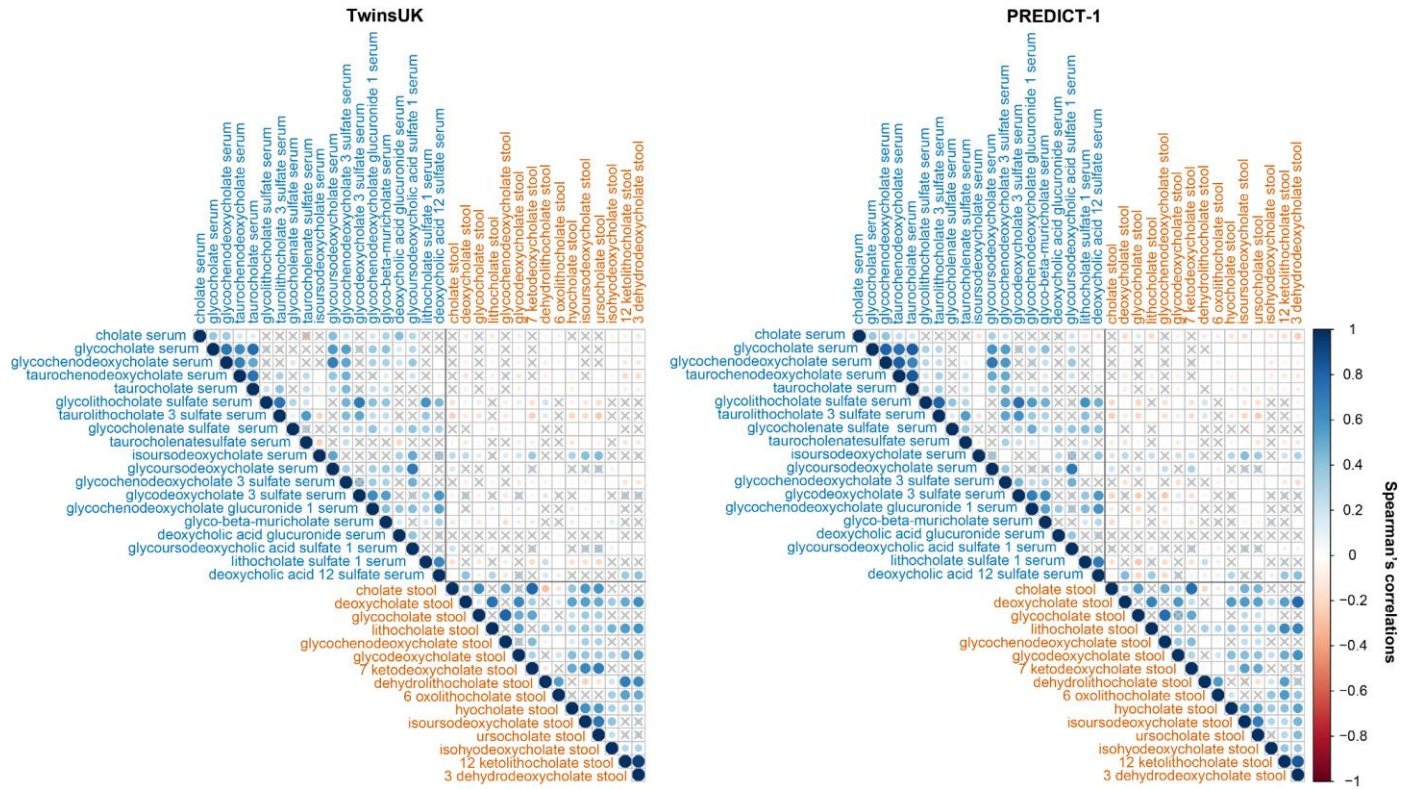
Supplementary Figure 1. Correlation between concentrations of bile acids in serum and stool in TwinsUK and ZOE PREDICT-1. Colours represent Spearman's rho values, x signifies a p value > 0.05.
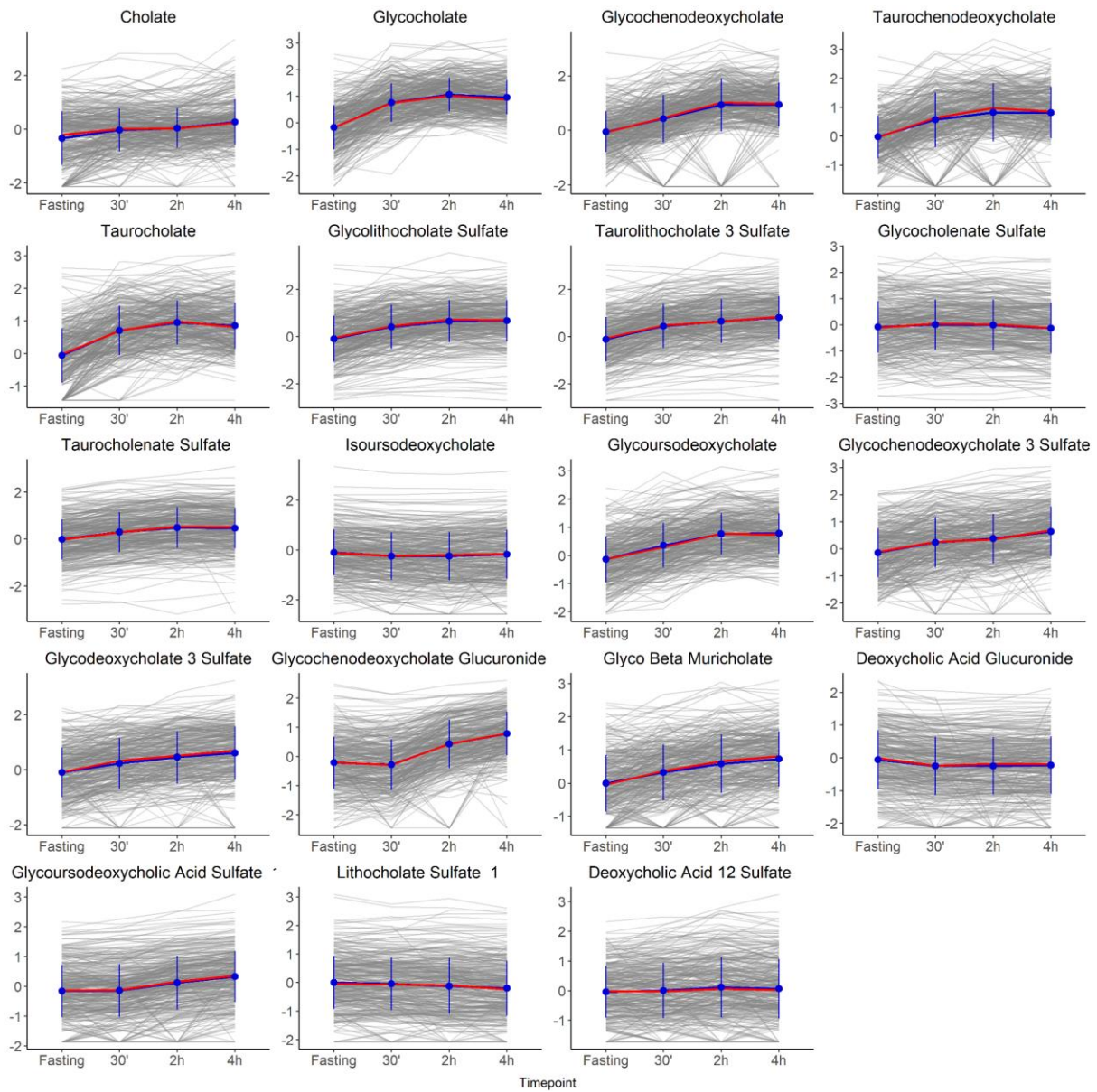
Supplementary Figure 2. Line plot of serum bile acid concentrations at fasting and in response to test meal challenge in ZOE PREDICT-1. Each grey line represents an individual participant, the blue line the mean and the red line the median.
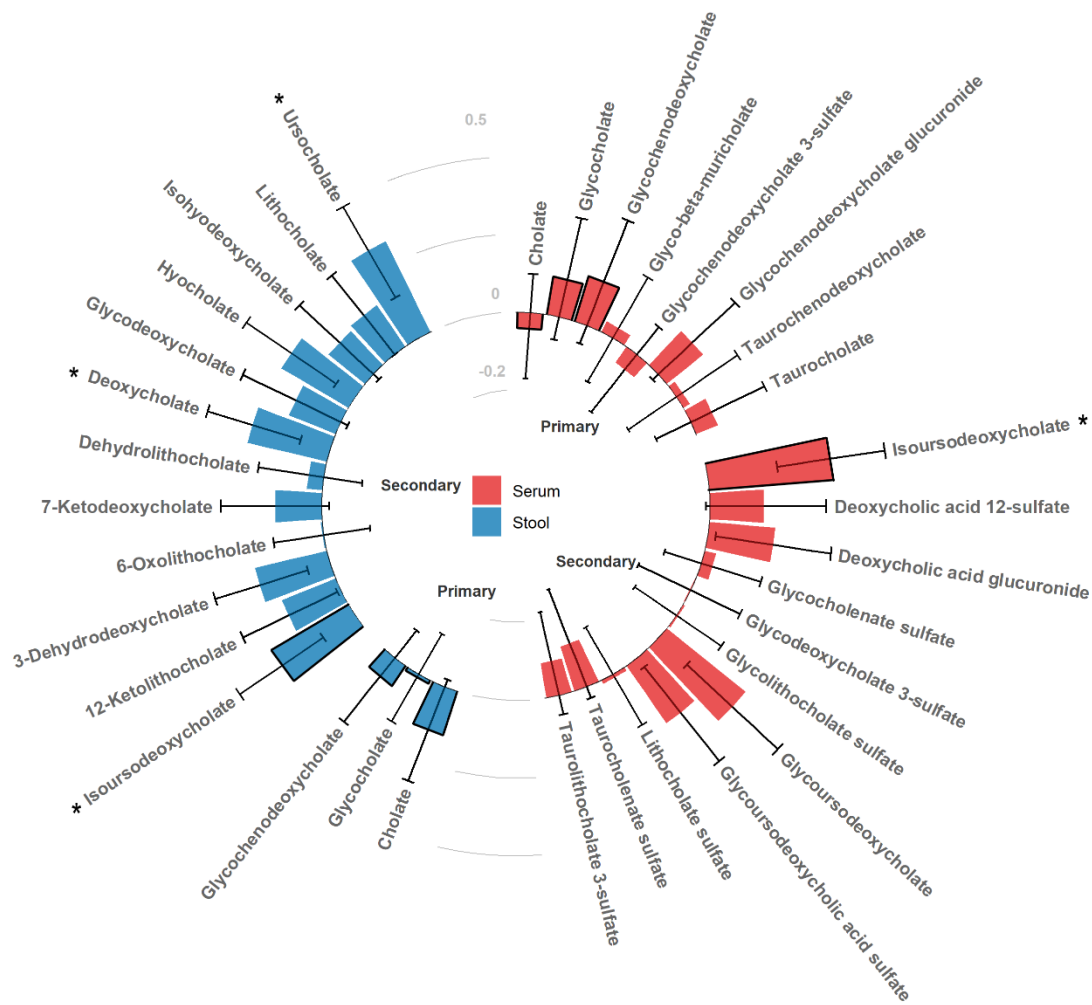
Supplementary Figure 3. Correlation of primary and secondary bile acids measured from serum and stool samples and postprandial lipaemia in PREDICT. * denotes bile acids that passed multiple testing (FDR <0.05). Bars with thick black borders represent bile acids detected in both serum and stool samples.
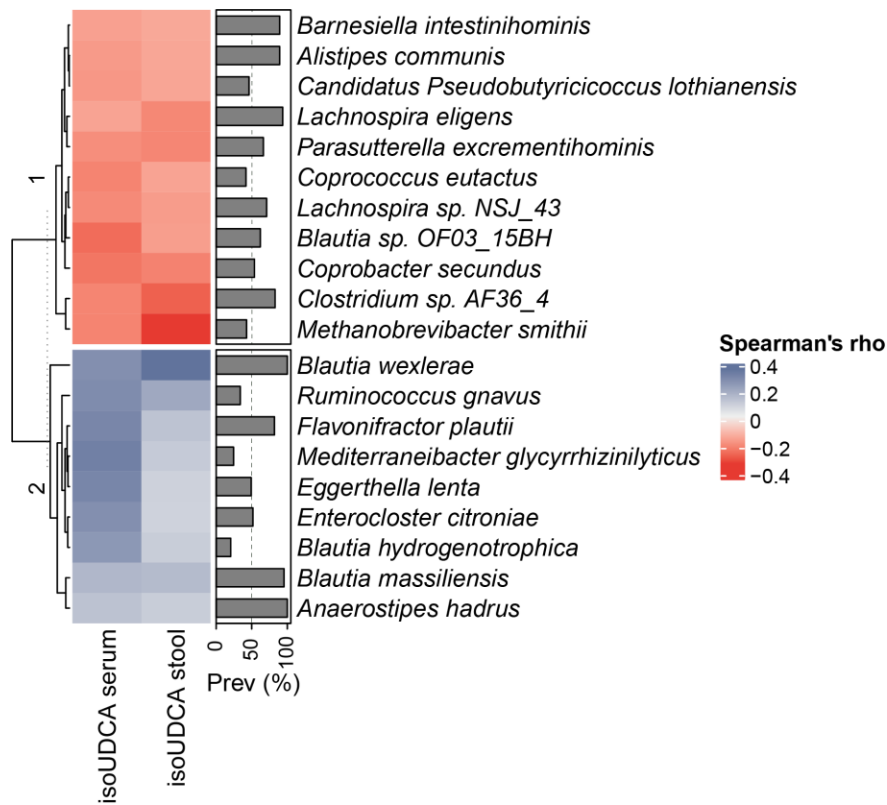
Supplementary Figure 4. Partial Spearman's correlations adjusted for age and BMI between isoUDCA levels in serum and stool, and single microbial species in 327 women from ZOE PREDICT-1. Only the characterised species with a prevalence >20% that had significant correlations (p-value<0.05), and presented the same directional effects in TwinsUK and ZOE PREDICT-1 are shown. Species are hierarchically clustered (complete linkage, Euclidean distance).
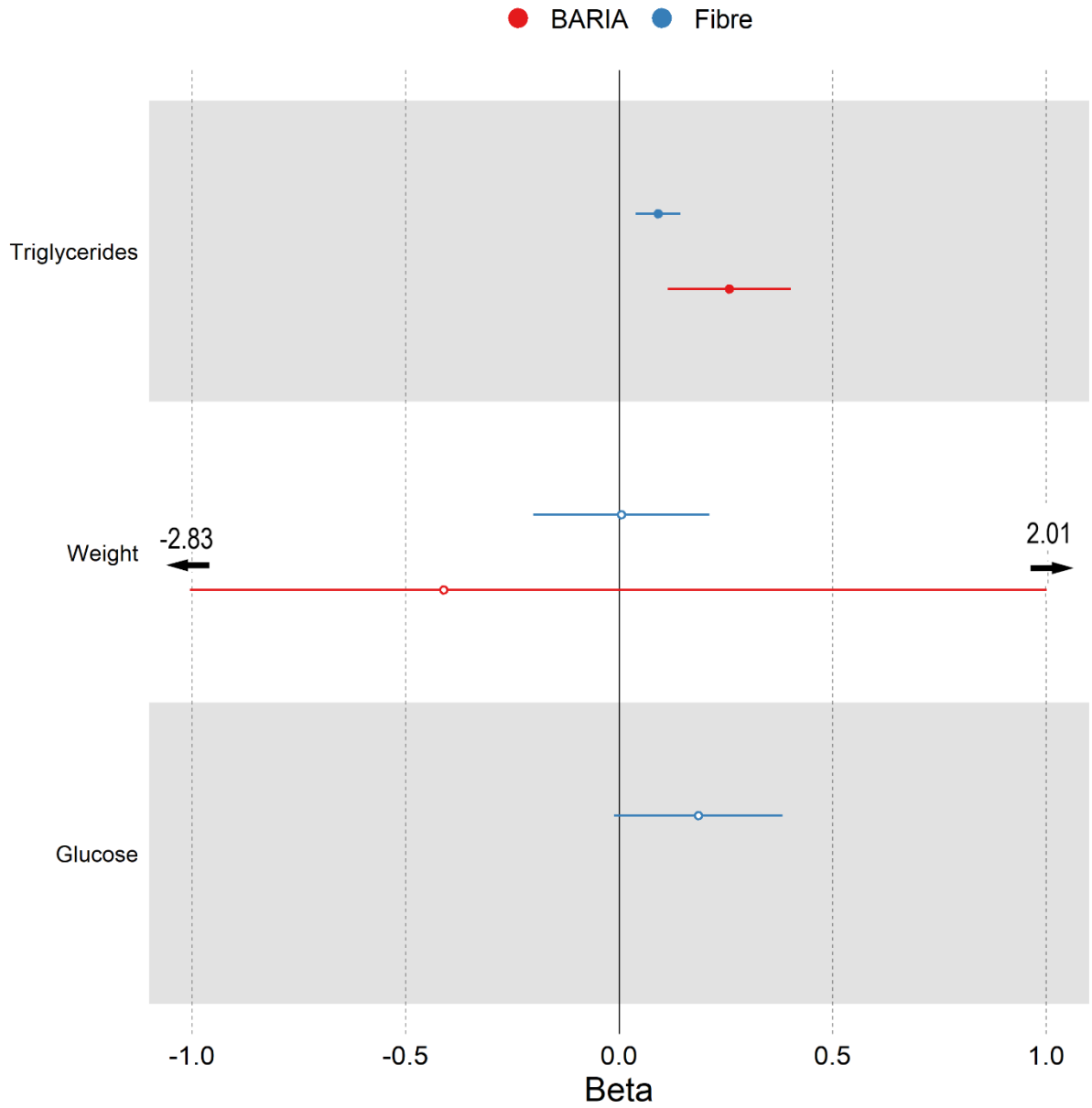
Supplementary Figure 5. Correlation between change in isoUDCA and changes in triglycerides, body weight, and glucose, in the BARIA trial and in the fibre arm of the Omega-3 and Fibre Intervention Study to Improve Metabolic Health study. Points represent regression coefficients (solid if statistically significant) adjusting for age, and BMI, and tails illustrate 95% confidence intervals.