SUPPLEMENTARY DATA

Supplementary Table 1. Botnia Study: plasma aminoacid profile. #

	Non-progressors	**Progressors**	***p***
N	412	130	-
Women (%)	76	76	ns
Age (years)	48 ± 14	53 ± 13	0.002
BMI (kg/m^2)	26.0 ± 3.8	28.5 ± 4.5	<0.0001
eM ($ml \cdot min^{-1} \cdot kg^{-1}$)	8.74 [2.33]	7.01 [3.93]	<0.0001
α-HB (µg/ml)	**3.60 [1.41]**	**3.96 [1.64]**	**<0.01**
L-GPC (µm/ml)	**16.02 [5.74]**	**14.07 [3.27]**	**<0.0001**
Leucine (µmol/l)	134 [39]	145 [51]	0.004
Isoleucine (µmol/l)	69 [20]	72 [23]	<0.003
Valine (µmol/l)	209 [50]	217 [69]	0.003
Alanine (µmol/l)	350 [123]	371 [128]	<0.001
Arginine (µmol/l)	67 [24]	71 [23]	0.01
Asparagine (µmol/l)	4.4 [3.6]	4.1 [3.2]	ns
Aspartate (µmol/l)	44 [10]	45 [10]	ns
Citrulline (µmol/l)	31 [11]	31 [12]	ns
Glutamine (µmol/l)	15 [20]	11 [11]	0.001
Glutamate (µmol/l)	640 [225]	675 [368]	<0.004
Glycine (µmol/l)	184 [61]	174 [60]	0.01
Histidine (µmol/l)	43 [10]	41 [13]	ns
Lysine (µmol/l)	157 [33]	156 [35]	ns
Methionine (µmol/l)	1.3 [1.0]	1.3 (1.6)	ns
Ornitine (µmol/l)	61 [14]	59 [23]	ns
Phenylalanine (µmol/l)	55 [11]	55 [15]	ns
Proline (µmol/l)	160 [56]	169 [56]	ns
Serine (µmol/l)	100 [14]	99 [14]	ns
Threonine (µmol/l)	112 [32]	118 [32]	ns
Tryptophan (µmol/l)	55 [13]	54 [13]	ns
Tyrosine (µmol/l)	57 [15]	61 [12]	<0.01

entries are mean±SD or median [IQR]; Progressors = subjects who progressed to type 2 diabete

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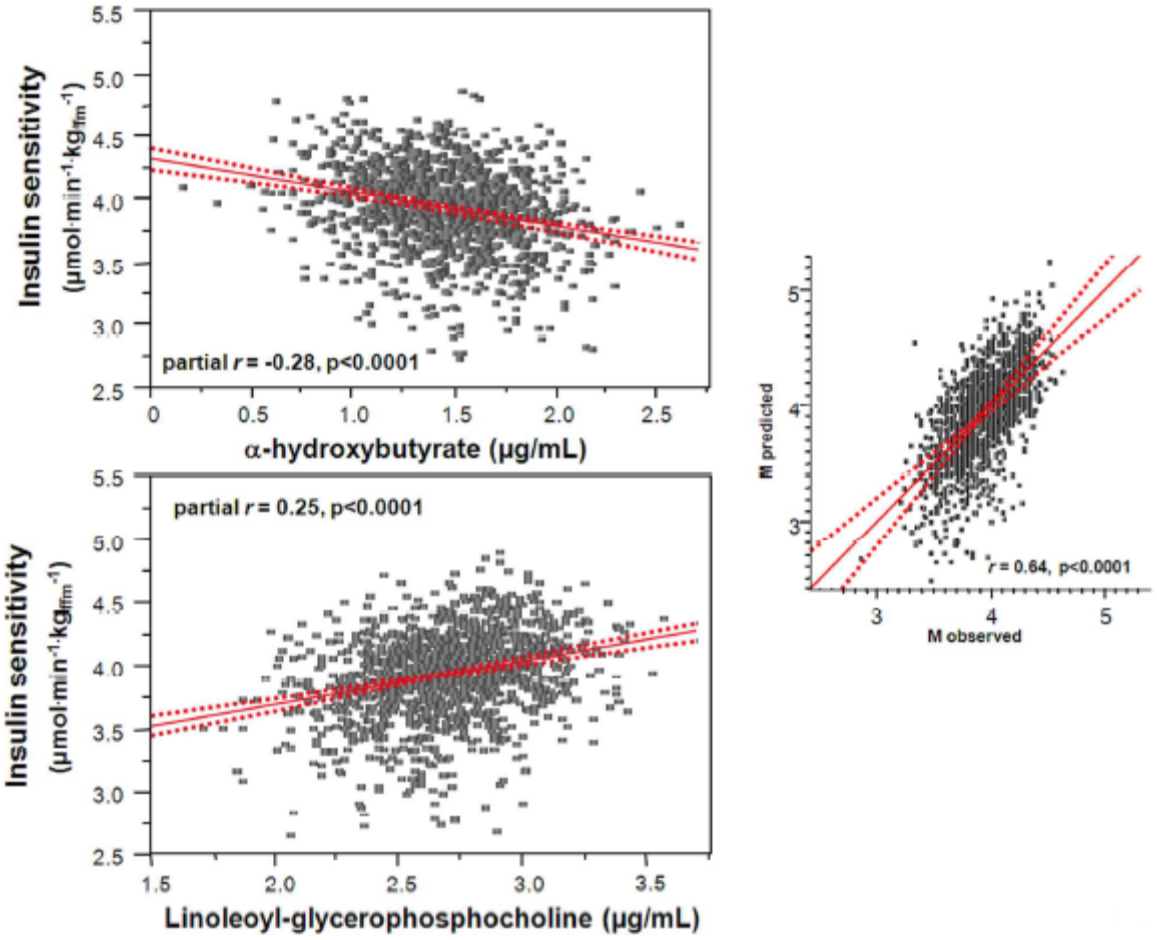
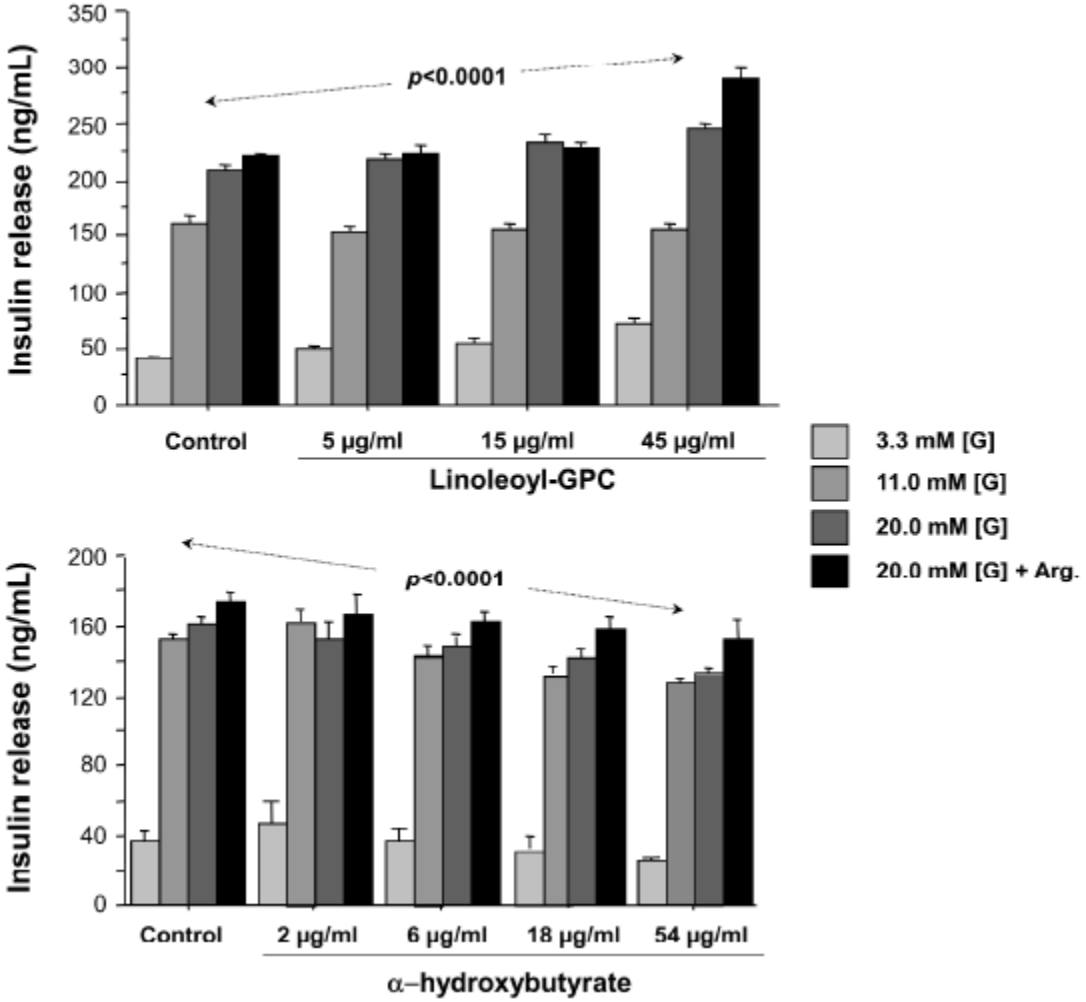
Supplementary Figure 1. α-HB and L-GPC are novel fasting markers of insulin sensitivity identified in RISC. Association between insulin sensitivity (as the M, or insulin-mediated glucose disposal rate from the clamp) and plasma concentrations of α-HB (*top*) and L-GPC (*bottom*) in the RISC cohort (NGT and IGR subjects). Data plots are natural logarithms of the original values, and the relationships (*full lines*) and their 95% confidence intervals (*dotted lines*) are adjusted for center, sex, age, and BMI (adjusted r^2's = 0.33 and 0.34, respectively). The inset shows the relationship between observed and predicted M value from a multivariate model using center, sex, age, BMI, α-HB, and L-GPC as predictors.



SUPPLEMENTARY DATA

Supplementary Figure 2. α-HB and L-GPC modulate glucose- and arginine-induced insulin release in pancreatic beta cells. Physiological concentrations of α-HB and L-GPC were tested for their effect on glucose-induced insulin secretion in rat INS1-e cells *in vitro*. *p* values are for the interaction term (glucose *x* metabolite concentrations) by 2-way ANOVA.



SUPPLEMENTARY DATA

Supplementary Figure 3. Reciprocal association between plasma L-GPC and oleate concentrations. In 542 subjects from the Botnia cohort, targeted concentrations of oleate and L-GPC were measured by UPLC-MS/MS isotope dilution assays. Note the log-log scale. The line is a power function fit, with its 95% confidence intervals (dotted lines).