

SUPPLEMENTARY DATA

Supplementary Table 1. Characteristics of the participants included in the METSIM study

Variable	Baseline	Follow-up
Number of subjects	9398	4335
Normal Glucose Tolerance (NGT)	3034	1446
Impaired Fasting Glucose (IFG)	4344	2031
Impaired Glucose Tolerance (IGT)	312	148
IFG+IGT	1059	434
New type 2 diabetes	649	276
Age, years	57.3±7.1	63.1±7.0
BMI, kg/m ²	27.0±4.0	26.7±3.7
Smoking, %	58.6	55.4
Physically inactive, %	35.6	30.5
Acetoacetate, mmol/L	0.06±0.04	NA
β-hydroxybutyrate, mmol/L	0.14±0.11	NA
Matsuda ISI	6.7±4.2	6.5±4.3
InsAUC ₀₋₃₀ /GlucAUC ₀₋₃₀	30.7±21.3	33.6±22.8

Mean values ± SD or percentages. NA=not available.

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Supplementary Table 2. Association of baseline levels of acetoacetate and β -hydroxybutyrate as predictors of glucose AUC and with incident type 2 diabetes at 5-year follow-up. Statistical analyses were performed with glucose AUC as a continuous variable and as the highest quartile (Q4) vs. the three lowest quartiles (Q1-Q3) combined and type 2 diabetes as a categorical variable (yes/no).

Glucose AUC at follow-up as a continuous variable	B	SE	<i>P</i> *	B	SE	<i>P</i> †	B	SE	<i>P</i> §
Acetoacetate, mmol/L	39.5	10.1	2.3x10⁻⁴	46.1	9.0	9.9x10⁻⁷	35.3	10.1	9.3x10⁻⁴
β -hydroxybutyrate, mmol/L	51.6	11.1	5.7x10⁻⁶	59.9	9.9	2.7x10⁻⁹	45.3	11.0	6.2x10⁻⁵
Glucose AUC at follow-up as a categorical variable (Q4 vs. Q1-Q3)	OR	95% CI	<i>P</i> *	OR	95% CI	<i>P</i> †	OR	95% CI	<i>P</i> §
Acetoacetate, mmol/L	1.56	1.33-1.84	7.9x10⁻⁸	1.79	1.50-2.13	9.1x10⁻¹¹	1.52	1.29-1.79	5.5x10⁻⁷
β -hydroxybutyrate, mmol/L	1.46	1.25-1.72	3.4x10⁻⁶	1.64	1.38-1.95	2.1x10⁻⁸	1.42	1.21-1.67	1.8x10⁻⁵
No diabetes vs. Newly diagnosed type 2 diabetes	OR	95% CI	<i>P</i> *	OR	95% CI	<i>P</i> †	OR	95% CI	<i>P</i> §
Acetoacetate, mmol/L	1.32	1.00-1.74	0.047	1.55	1.10-2.17	0.012	1.30	0.93-1.82	0.125
β -hydroxybutyrate, mmol/L	1.03	0.77-1.36	0.864	1.35	0.96-1.89	0.085	1.18	0.84-1.64	0.345

*P**, adjustment for age, BMI, smoking and physical activity

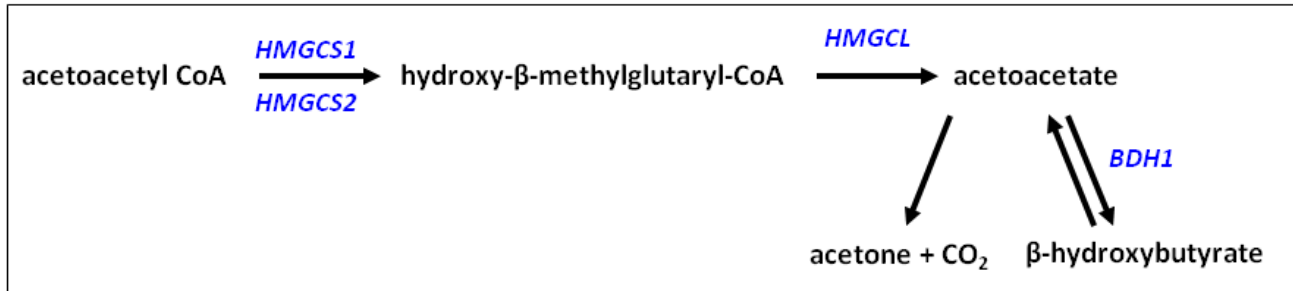
P†, adjustment for age, BMI, smoking, physical activity and Matsuda ISI

P§, adjustment for age, BMI, smoking, physical activity and InsAUC₀₋₃₀/GlucAUC₀₋₃₀

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Supplementary Figure 1. Pathways of ketogenesis and ketolysis. HMGCS1 = 3-hydroxy-3-methylglutaryl- CoA synthase 1 (soluble), HMGCS2 = 3-hydroxy-3-methylglutaryl-CoA synthase 2 (mitochondrial), HMGCL= 3-hydroxymethyl-3-methylglutaryl-CoA lyase, BDH1 = 3-hydroxybutyrate dehydrogenase, type 1, OXCT1 = 3-oxoacid CoA transferase 1, ACAT1 = acetyl-CoA acetyltransferase 1, ACSS2 = acyl-CoA synthetase shortchain family member 2. 254x190mm (96 x 96 DPI)

KETOGENESIS



KETOLYSIS

