

Supplemental Table S1. Diabetes treatment stratified longitudinal associations between fasting KB and annual HbA1c change in linear mixed models in ZODIAC

	Diet alone (n=29)	<i>p</i>	OBGLD (n=152)	<i>p</i>	Insulin (n=21)	<i>p</i>	OBGLD and insulin (n=18)	
	KB <i>per doubling</i>		KB <i>per doubling</i>		KB <i>per doubling</i>		KB <i>per doubling</i>	
	B (95% CI)		B (95% CI)		B (95% CI)		B (95% CI)	
Crude	-0.27 (-0.79 – 0.26)	0.31	-0.11 (-0.20 - -0.01)	0.03	0.17 (-0.05 – 0.39)	0.15	-0.08 (-0.42 – 0.25)	0.61
Model 1	-0.19 (-0.75 – 0.38)	0.51	-0.11 (-0.21 - -0.01)	0.03	0.15 (-0.10 – 0.40)	0.24	-0.08 (-0.45 – 0.29)	0.67
Model 2	-0.22 (-0.80 – 0.35)	0.44	-0.11 (-0.21 - -0.01)	0.03	0.18 (-0.15 – 0.51)	0.28	-0.07 (-0.46 – 0.31)	0.70
Model 3	-0.30 (-0.92 – 0.32)	0.33	-0.10 (-0.20 - -0.00)	0.05	0.19 (-0.14 – 0.53)	0.25	-0.06 (-0.58 – 0.45)	0.81
Model 4	-0.37 (-1.02 – 0.28)	0.26	-0.11 (-0.21 - -0.00)	0.05	0.21 (-0.19 – 0.61)	0.30	-0.08 (-0.53 – 0.37)	0.72

Crude

Model 1: adjusted for age and gender and baseline HbA1c

Model 2: Model 1 + BMI and systolic blood pressure

Model 3: Model 2 + eGFR, smoking and total cholesterol/HDL ratio

Model 4: Model 3 + T2D duration + C-reactive protein

Linear mixed model analyses were performed in all individuals with ≥ 2 HbA1c measurements. A p-value of <0.05 was considered statistically significant. All models were adjusted for time as main fixed factor in linear mixed model analyses. The estimates and p-values for the interactions of KB with time are depicted. Coefficients represent the yearly change in HbA1c (%) levels per doubling of KB.

KB: ketone bodies; *HbA1c* glycated haemoglobin; *T2D*: type 2 diabetes; *BMI*: body mass index; *eGFR*: estimated glomerular filtration rate; *HDL*: high density lipoprotein.

Supplemental Table S2. Longitudinal associations between fasting plasma KB and annual fasting glucose change in linear mixed model analyses in PREVEND

	Total ketone bodies <i>Per doubling</i>	p	β-OHB <i>Per doubling</i>	p	Acetoacetate <i>Per doubling</i>	p	Acetone <i>Per doubling</i>	p
	B (95% CI)		B (95% CI)		B (95% CI)		B (95% CI)	
Model 1	-0.09 (-0.15 – -0.02)	0.01	-0.08 (-0.15 - -0.02)	0.01	-0.06 (-0.11 - -0.01)	0.02	-0.04 (-0.09 – 0.01)	0.12
Model 2	-0.09 (-0.16 – -0.02)	0.02	-0.08 (-0.15 - -0.02)	0.02	-0.06 (-0.11 - -0.01)	0.03	-0.03 (-0.09 – 0.02)	0.20
Model 3	-0.09 (-0.14 – -0.01)	0.02	-0.08 (-0.13 - -0.01)	0.03	-0.05 (-0.10 - -0.00)	0.04	-0.02 (-0.07 – 0.03)	0.39
Model 4	-0.09 (-0.16 – -0.02)	0.01	-0.08 (-0.15 - -0.02)	0.01	-0.06 (-0.11 - -0.01)	0.02	-0.04 (-0.09 – 0.01)	0.11
Model 5	-0.09 (-0.15 – -0.02)	0.01	-0.08 (-0.14 - -0.01)	0.02	-0.06 (-0.11 - -0.01)	0.02	-0.04 (-0.09 – 0.01)	0.13

Model 1: adjusted for age and gender and baseline glucose

Model 2: Model 1 + time-updated T2D therapy and baseline plasma insulin concentration

Model 3: Model 2 + time-updated eGFR, systolic blood pressure and use of antihypertensive drugs

Model 4: Model 2 + time-updated BMI, smoking and alcohol use

Model 5: Model 2 + time updated total cholesterol/HDL ratio

Linear mixed model analyses were performed in all individuals with ≥ 2 fasting glucose measurements. A p-value of <0.05 was considered statistically significant. All models were adjusted for time as main fixed factor in linear mixed model analyses. The estimates and p-values for the interactions of KB with time are depicted. Coefficients represent the yearly change in fasting glucose levels (mmol/L) per doubling of KB.

KB: ketone bodies; *HbA1c* glycated haemoglobin; *β-OHB*: β-hydroxybutyrate; *T2D*: type 2 diabetes; *BMI*: body mass index; *eGFR*: estimated glomerular filtration rate; *HDL*: high density lipoprotein.

Supplemental Figure S1. Graphical illustration of the association between KB according to tertiles at baseline and HbA1c at baseline and over time (average).

