

Supplementary Data

Supplementary Tables

Supplementary Table 1

Cross-imputation of missing variables (N=1045)

Variable	Missing rate
MRI subcutaneous fat volume	0.39
MRI total fat volume	0.39
MRI visceral fat volume	0.39
MR spectroscopy liver fat	0.17
Fat percentage (bioimpedance)	0.05
Fasting insulin	0.02
Post-challenge insulin 120 min	0.02
Insulin sensitivity (Matsuda-index)	0.02
Insulin secretion (C-peptide based)	0.02
Glycemia (AUC glucose)	0.01
Hip circumference	0.01
Waist circumference	0.01
BMI	0
Fasting glucose	0
Post-challenge glucose 120 min	0
Alanin-aminotransferase	0
Sex	0
Triglycerides	0

Supplementary Table 2

Participants of the Prediabetes Lifestyle Intervention Study (PLIS) at baseline stratified to previously established metabolic clusters. Differences were tested with ANOVA.

Cluster	1	2	3	4	5	6	p-value
Metabolic risk*	Low	Very Low	High	Low	High	High	
Key features*			Low insulin secretion without pronounced insulin resistance	Metabolically healthy obesity	Prominent insulin resistance with insulin secretion failure	Insulin resistance with compensatory hyperinsulinemia	
n	88	93	399	8	229	228	
Intervention group (%)							<0.001
conventional	43 (48.9)	40 (43.0)	194 (48.6)	6 (75.0)	111 (48.5)	128 (56.1)	
control	36 (40.9)	29 (31.2)	30 (7.5)	1 (12.5)	0 (0.0)	20 (8.8)	
intensive	9 (10.2)	24 (25.8)	175 (43.9)	1 (12.5)	118 (51.5)	80 (35.1)	
Sex = male (%)	49 (55.7)	45 (48.4)	183 (45.9)	2 (25.0)	77 (33.6)	81 (35.5)	<0.001
Age (mean (SD))	57.37 (11.78)	59.52 (11.38)	60.17 (9.80)	51.30 (11.23)	56.42 (9.55)	56.62 (11.09)	<0.001
BMI (kg/m²) (mean (SD))	27.59 (4.84)	24.62 (2.68)	29.07 (4.43)	32.69 (3.60)	34.45 (5.57)	35.28 (5.48)	<0.001
eGFR (ml/min/1.73m²) (mean (SD))	90.88 (15.53)	90.72 (13.36)	89.33 (12.99)	102.33 (12.24)	91.22 (13.86)	91.20 (15.37)	0.082
AUC glucose (mean (SD))	894.20 (93.36)	936.37 (138.93)	1158.91 (143.98)	824.27 (71.25)	1198.05 (154.10)	1006.56 (134.60)	<0.001
Insulin secretion (AUC₀₋₁₂₀ C-peptide/AUC₀₋₁₂₀ glucose) (AU) (mean (SD))	309.09 (79.65)	209.59 (58.59)	229.21 (60.43)	241.60 (46.43)	293.29 (76.21)	343.06 (80.92)	<0.001
insulin sensitivity (AU) (mean (SD))	7.97 (3.34)	13.78 (5.16)	7.09 (3.01)	10.15 (2.49)	3.83 (1.85)	4.59 (1.93)	<0.001
HDL [mmol/l] (mean (SD))	1.34 (0.32)	1.98 (0.76)	1.45 (0.36)	1.35 (0.24)	1.25 (0.28)	1.31 (0.33)	<0.001
subcutaneous fat volume (l) (mean (SD))	9.58 (3.19)	8.23 (3.94)	12.41 (4.73)	18.36 (7.31)	17.69 (6.79)	20.49 (13.27)	<0.001
visceral fat volume (l) (mean (SD))	3.89 (1.58)	2.84 (1.53)	4.92 (1.97)	4.94 (1.51)	6.14 (2.17)	6.96 (3.75)	<0.001
liver fat content (%) (mean (SD))	3.23 (2.91)	2.28 (2.59)	5.47 (4.10)	3.67 (2.63)	20.62 (6.94)	8.81 (4.58)	<0.001
polygenic risk score (mean (SD))	-0.31 (0.95)	0.00 (0.93)	0.24 (1.01)	-0.56 (1.03)	0.02 (0.92)	-0.10 (1.00)	<0.001

*see Ref. 1 (Wagner et al, Nature Medicine 2021)

Supplementary Table 3

Between-cluster comparison of key anthropometric and metabolic measures (two-sided ANOVA with post-hoc test using Tukey's method)

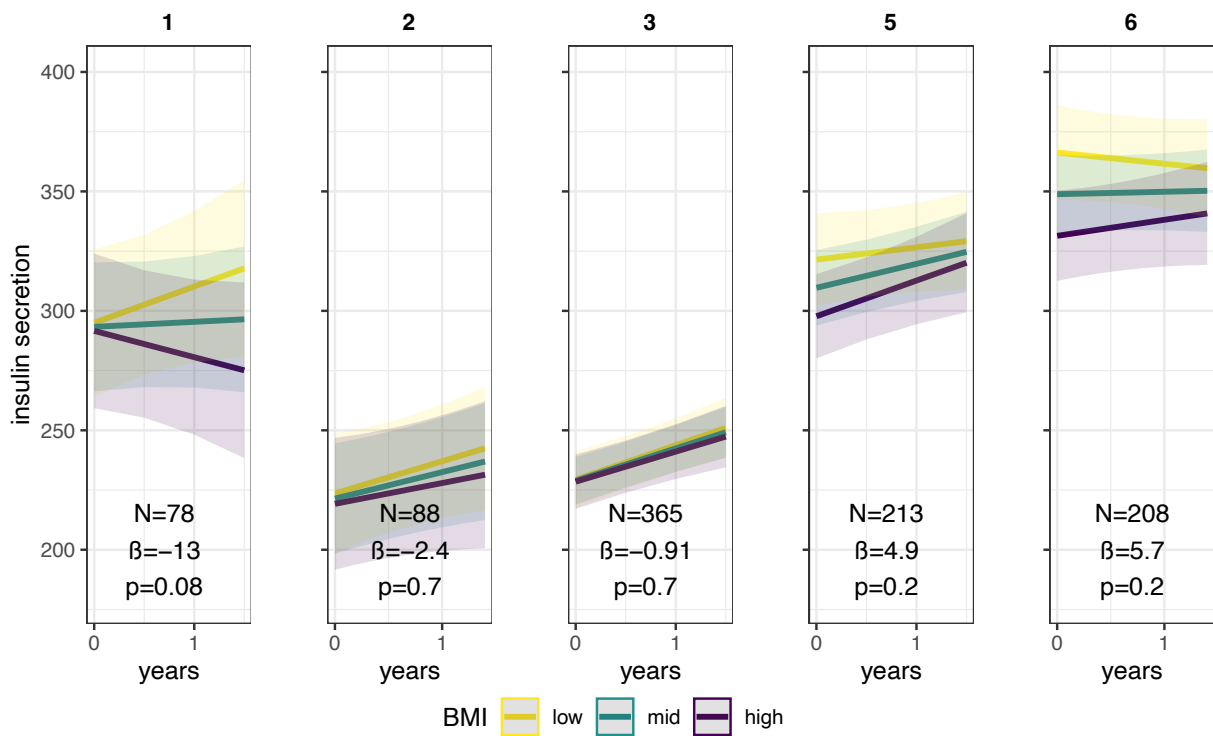
	2-1	3-1	3-2	5-1	5-2	5-3	6-1	6-2	6-3	6-5
Age	0.63	0.15	0.98	0.95	0.11	1.33*10 ⁻⁰⁴	0.98	0.16	3.82*10 ⁻⁰⁴	1
BMI (kg/m ²)	4.06*10 ⁻⁰⁴	0.074	4.97*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	0.36
AUC glucose	0.26	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	0.0071	2.64*10 ⁻⁰⁹	4.92*10 ⁻⁰⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴
Insulin secretion (AU)	1.49*10 ⁻¹³	1.48*10 ⁻¹³	0.12	0.39	1.47*10 ⁻¹³	1.38*10 ⁻¹³	0.0014	1.01*10 ⁻¹³	1.01*10 ⁻¹³	1.77*10 ⁻¹²
Insulin secretion adjusted (AU)*	0.0092	3.28*10 ⁻¹³	4.09*10 ⁻¹³	4.32*10 ⁻¹³	3.83*10 ⁻⁰⁴	3.69*10 ⁻⁰⁶	0.99	0.0045	3.28*10 ⁻¹³	3.76*10 ⁻¹³
insulin sensitivity (AU)	6.22*10 ⁻¹⁴	0.08	6.22*10 ⁻¹⁴	7.46*10 ⁻¹⁴	6.22*10 ⁻¹⁴	6.22*10 ⁻¹⁴	1.12*10 ⁻¹³	6.22*10 ⁻¹⁴	1.10*10 ⁻¹³	0.044
HDL (mmol/l)	<1*10 ⁻¹⁴	0.092	<1*10 ⁻¹⁴	0.4	<1*10 ⁻¹⁴	8.36*10 ⁻⁰⁹	0.98	<1*10 ⁻¹⁴	1.04*10 ⁻⁰⁴	0.52
subcutaneous fat volume (l)	0.84	0.059	4.10*10 ⁻⁰⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	2.78*10 ⁻¹⁰	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	0.019
visceral fat volume (l)	0.093	0.022	3.54*10 ⁻⁰⁹	1.43*10 ⁻⁰⁸	<1*10 ⁻¹⁴	1.61*10 ⁻⁰⁵	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	0.045
liver fat content (%)	0.71	0.0021	4.17*10 ⁻⁰⁷	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	<1*10 ⁻¹⁴	7.06*10 ⁻¹³	<1*10 ⁻¹⁴
polygenic risk score	0.19	2.23*10 ⁻⁰⁵	0.24	0.051	1	0.065	0.4	0.92	4.33*10 ⁻⁰⁴	0.69

*adjusted for insulin sensitivity

Supplementary Figures

Supplementary Figure 1

Cluster-wise interactions between BMI and time in generalized linear mixed models are shown as marginal effects by plotting the modelled change of insulin secretion for low (mean-SD), mid (mean) and high (mean+SD) BMI. Effect sizes (β) and p-values are provided for the interaction between BMI and time.



Supplementary Figure 2. A-B

Sensitivity analysis investigating cluster-specific change of insulin secretion (A) and time x liver fat interaction (B) using AUC_{0-30} C-peptide/ AUC_{0-30} glucose as insulin secretion index (outcome). Otherwise, these models feature the same exposure variables as the models shown in Figure 1. A, D

