Supplementary Table 1: Summary statistics of the obesity and glycemic traits analyzed

Outcome Trait	PubMed ID	Phenotype transformation	Units of effect size	Description
Body mass index (BMI)	25673413	quantile transformation	standard deviations	Body mass index
Waist-Hip ratio adj. BMI	25673412	quantile transformation	standard deviations	Waist-hip ratio, adjusted for BMI
Fasting glucose	22581228	none	log(mmol/L)	Fasting glucose
Fasting insulin (adj. BMI)	22581228	log	log(pmol/L)	Fasting insulin adjusted for BMI
Fasting proinsulin	21873549	log	log(pmol/L)	Fasting pro-insulin
HOMA-IR	20081858	log	$\log(\text{(mU/L)}*\text{(mmol/L)})$	HOMA IR
HOMA-B	20081858	log	$\log(\text{(mU/L)}/\text{(mmol/L)})$	HOMA B
HbA1c	20858683	none	%	Glycated hemoglobin
Insulin secretion (IS) - Insulin sensitivity Index (ISI)	24699409	none	mg/dL	Insulin Sensitivity Index: 10,000/sqrt(fasting plasma glucose (mg/dl) x fasting insulin x mean glucose during OGTT)
IS AUC $_{Insulin}$/AUC $_{glucose}$	24699409	none	mU/mmol	ratio of the area under the curve (AUC) for AUC $_{insulin}$/AUC $_{glucose}$ after OGTT
IS Increase at 30 minutes	24699409	none	mU/L	Insulin increase at 30 min: insulin at 30 min (during OGTT) – fasting insulin
IS AUC$_{insulin}$	24699409	none	mU×min/L	area under the curve (AUC) of insulin levels during OGTT
IS Correct Insulin Response (adj. ISI)	24699409	none	original	Correct Insulin Response: (100 x insulin at 30 min)/(glucose at 30 min*(glucose at 30 min–3.89)), adjusted for Insulin secretion ISI
IS Disposition Index (DI)	24699409	none	original	Disposition index: CIR x ISI
IS Insulin at 30 minutes (adj. BMI)	24699409	none	original	Insulin at 30 min/ (glucose at 30 min x BMI)
2hr Glucose (adj. BMI)	20081857	none	mmol/L	Glucose after 2 hours of OGTT, adjusted for BMI
Type 2 diabetes	28566273	none	Odds Ratio	Type 2 Diabetes

Supplementary Table 2: Microbiome features that correlate with obesity and glycemic traits at FDR<0.1.

The table lists microbiome features that correlate with obesity and glycemic traits in the LL-DEEP cohort at FDR <0.1. The number of individuals used for each microbiome feature-trait pair is given in column N. Spearman correlation value and corresponding two-sided pvalue were calculated in R using the *cor.test()* function; pvalues were subsequently adjusted for multiple-testing using the *p.adjust()* function.

 (Included as a separate excel file)

Supplementary Table 3: Short chain fatty acid levels that correlate with obesity and glycemic traits at FDR <0.1

The table lists fecal short chain fatty acid levels that correlate with obesity and glycemic traits in the LL-DEEP cohort at FDR <0.1. The number of individuals used for each microbiome feature-trait pair is given in column N. Spearman correlation value and corresponding two-sided pvalue were calculated in R using the *cor.test()* function; pvalues were subsequently adjusted for multiple-testing using the *p.adjust()* function in R.

Trait	Short chain fatty acid	Spearman Correlation	*P*	N	FDR *P*
Body mass index (BMI)	Propionate	0.10	3.24E-03	934	9.87E-02
BMI	Butyrate	0.10	2.75E-03	935	9.87E-02
Waist-Hip ratio (WHR)	Propionate	0.09	4.23E-03	934	9.87E-02

Supplementary Table 4: Genetic predictors of PWY-5022 and their association coefficients estimated by GWAS analysis

The table lists the genetic predictors of PWY-5022 and their association coefficient derived from the genome-wide association analysis in 952 normo-glycemic LifeLines individuals. For each genetic predictor, both HGVS and dbSNP identifiers are given. The (two-sided) pvalue was calculated using the linear mixed model implemented in EPACTS (Kang, H.M. et al. Nat Genet 42, 348-54 (2010)) as described in the Methods section.

HGVS	dbSNP	Effect Allele (EA)	EA Frequency	Beta (95%CI)	P
NC_000010.10:g.5608741A>T	rs9423658	C	0.86	0.33 (0.19,0.48)	5.7E-06
NC_000011.9:g.34314176T>C	rs881390	C	0.11	0.40 (0.23,0.57)	5.7E-06
NC_000012.11:g.117002658G>A	rs2089222	A	0.04	0.56 (0.32,0.79)	3.7E-06
NC_000017.10:g.78461406A>G	rs9904981	G	0.77	0.25 (0.14,0.36)	6.0E-06
NC_000022.10:g.22726968C>T	rs10483112	T	0.03	0.59 (0.34,0.84)	5.2E-06
NC_000002.11:g.75683350C>T	rs12994030	T	0.27	0.24 (0.14,0.34)	3.5E-06
NC_000002.11:g.76969378C>T	rs2056208	T	0.24	0.24 (0.14,0.35)	9.1E-06
NC_000004.11:g.14808039T>C	rs10019739	C	0.27	0.24 (0.13,0.34)	8.2E-06
NC_000006.11:g.115184297A>G	rs7743827	G	0.80	0.27 (0.15,0.38)	4.9E-06

Supplementary Table 5: Results of Mendelian Randomization analysis testing the causal effect of microbiome pathway PWY-5022 on obesity and glycemic traits

The table lists the results from the inverse-variance weighted (IVW) Mendelian Randomization analysis testing the causal effect of microbiome pathway PW-5022 on all traits listed in **Supplementary Table** 1. The column #SNPs indicates the number of genetic predictors that were used for the analysis of each trait (out of the 9 predictors selected for this pathway). The two-sided IVW pvalue was calculated as $P=2* (1- \Phi(Z))$, where $\Phi(Z)$ is the standard normal cumulative distribution function and Z is ratio of the combined (using inverse variance weights) causal effect and its standard error (see the Methods section). Beta represent changes in the outcome units per each standard deviation change in relative abundance of PWY-5022 – for outcome units, see **Supplementary Table 1** (for Type 2 Diabetes, changes are log (OR))

Outcome	#SNPs	Causality by IVW	
		Beta (95%CI)	*P*
Insulin secretion (IS) $AUC_{insulin}$ /$AUC_{glucose}$	8	0.16 (0.08,0.24)	9.8E-05
IS Insulin at 30 minutes (adj. BMI)	8	0.12 (0.04,0.2)	2.4E-03
IS AUC Insulin	8	0.11 (0.03,0.19)	6.3E-03
IS Correct Insulin Response (adj. insulin sensitivity index [ISI])	8	0.10 (0.02,018)	1.4E-02
IS Increase at 30 minutes	8	0.09 (0.01,0.17)	1.5E-02
IS Disposition Index	8	0.08 (0,,0.16)	3.4E-02
Waist-hip ratio (adj. BMI)	8	-0.02 (-0.03,0.004)	6.4E-02
2hr Glucose (adj. BMI)	8	-0.03 (-0.11,0.05)	4.1E-01
IS ISI	8	-0.03 (-0.11,0.05)	4.3E-01
HOMA-B	8	-0.003 (-0.02,0.02)	6.2E-01
Fasting glucose	8	0.003 (-0.02,0.02)	6.3E-01
HbA1c	8	0.003 (-0.02,0.02)	6.4E-01
BMI	7	0.003 (-0.02,0.02)	7.2E-01
Type 2 diabetes	7	0.02 (-0.06,0.09)	7.4E-01
Fasting proinsulin	8	0.003 (-0.02,0.02)	8.3E-01
HOMA-IR	8	0.001 (-0.02,0.02)	9.0E-01
Fasting insulin (Adj. BMI)	8	-0.001 (-0.02,0.02)	9.0E-01

Supplementary Table 6: Results of reverse Mendelian Randomization analysis testing the causal effect of glucose-stimulated insulin response (measured by several parameters) to PWY-5022

The table lists the results from the inverse-variance weighted (IVW) Mendelian Randomization analysis testing the causal effect of glucose-stimulated insulin response parameters on microbiome pathway PW-5022. The column #SNPs used indicates the number of genetic predictors that were used for the analysis of each trait. The (two-sided) pvalue was calculated as described in **Supplementary Table 5**. Beta represent the changes in the relative abundance of PWY-5022 (in standard deviation units) per change in the exposure units – for units, see **Supplementary Table 1** (for Type 2 Diabetes, changes are log (OR))

Trait (exposure)	#SNPs	Causality by IVW	
		Beta (95%CI)	*P*
Insulin secretion (IS) Disposition Index	9	0.20 (0.05,0.45)	0.13
IS Correct Insulin Response (adj. ISI)	13	0.12 (0.04,0.35)	0.33
IS Insulin 30 minutes (adj. BMI)	7	0.28 (0.14,0.62)	0.11
IS $AUC_{insulin}/AUC_{glucose}$	3	-0.02(-0.29,0.47)	0.93
IS $AUC_{insulin}$	4	0.26 (0.25,0.71)	0.26
IS index	11	-0.01(-0.0001,0.19)	0.90
IS Inc30	4	0.01 (0.20,0.41)	0.95

Supplementary Table 7: Results of Mendelian Randomization analysis on the UK Biobank testing the causal effect of PWY-5022

The table lists the results of Mendelian Randomization analyses (four statistical tests: IVW, MR-PRESSO, MR-EGGER and Weighted Median) testing the causal effect of microbiome pathway PW-5022 on 7 traits using summary statistics from UK Biobank. The column N indicates the number of UK Biobank samples for which summary statistics were generated. For each Mendelian Randomization test the effect size (Beta), 95% confidence intervals and two-sided pvalues are given. Beta represents the change in the outcome units per each standard deviation change in fecal propionate levels. For Type 2 Diabetes and Obesity, beta is equivalent to log (OR). The last two columns indicate the (two-sided) pvalues for MR-PRESSO Global test and Rücker's Q' (modified) test which, if significant, indicate presence of pleiotropy.

		IVW		MR-PRESSO		MR-Egger		Weighted Median		MR-PRESSO	Rücker's Q'
Outcome	N	Beta (95%C.I.)	*P*	Beta* (95%C.I.)	*P*	Beta (95%C.I.)	*P*	Beta (95%C.I.)	*P*	Global test *P*	(mod.) *P*
Quantitative traits											
BMI	441355	0.004(-0.002,0.01)	0.22	0.004(-0.004,0.01)	0.35	-0.007(-0.03,0.02)	0.64	0.002(-0.007,0.01)	0.66	0.16	0.10
BF%	434823	0.005(-0.001,0.01)	0.08	0.005(0,0.01)	0.10	-0.005(-0.03,0.02)	0.63	0.004(-0.004,0.01)	0.29	0.53	0.47
SAT	4728	-0.005(-0.07,0.06)	0.88	-0.005(-0.05,0.04)	0.83	0.03(-0.18,0.24)	0.78	0.004(-0.07,0.08)	0.93	0.86	0.78
VAT	4728	-0.02(-0.08,0.04)	0.49	-0.02(-0.1,0.06)	0.61	-0.23(-0.44,-0.02)	0.11	0.04(-0.04,0.13)	0.33	0.12	0.32
WHR	441941	0.005(-0.001,0.01)	0.08	0.005(-0.002,0.01)	0.18	-0.002(-0.02,0.02)	0.89	0.008(0.001,0.01)	0.02	0.19	0.10
Binary traits											
Obesity	340039[#]	0.001(0,0.003)	**0.04**	0.001(0,0.003)	0.07	-0.001(-0.006,0.003)	0.57	0.001(0,0.003)	0.12	0.53	0.51
T2D	442817[$]	-0.02(-0.05,0.008)	0.14	-0.02(-0.05,0.007)	0.17	-0.07(-0.18,0.04)	0.24	-0.03(-0.07,0.01)	0.18	0.51	0.49

[#] Total number consists of 11708 cases and 328331 controls
[$] Total number consists of 19119 cases and 423698 controls

Supplementary Table 8: Genetic predictors of fecal propionate levels and their association coefficients estimated by GWAS analysis

The table lists the genetic predictors of fecal propionate and their association coefficients derived from a genome-wide association analysis in 898 normo-glycemic LL-DEEP individuals for which fecal propionate levels were available. For each genetic predictor, both HGVS and dbSNP identifiers are given. The (two-sided) pvalue was calculated using the linear mixed model implemented in the software EPACTS (Kang, H.M. et al. Nat Genet 42, 348-54 (2010)) as described in the **Methods** section.

HGVS	dbSNP	Effect Allele (EA)	EA Frequency	Beta (95%CI)	*P*
NC_000014.8:g.79482379A>G	rs7142308	G	0.61	0.24 (0.14,0.34)	2.1E-06
NC_000015.9:g.48088204A>C	rs12050534	C	0.14	0.31 (0.18,0.44)	6.4E-06
NC_000003.11:g.29178581T>G	rs1400566	G	0.45	-0.22 (-0.31,-0.12)	9.6E-06

Supplementary Table 9: Results of Mendelian Randomization analysis testing the causal effect of fecal propionate levels to obesity and glycemic traits

The table lists the results of the inverse-variance weighted (IVW) Mendelian Randomization analysis testing the causal effect of fecal propionate on all traits listed in **Supplementary Table 1**. The column #SNPs indicates the number of genetic predictors that were used for the analysis of each trait (out of the 3 predictors selected for this pathway). The (two-sided) pvalue was calculated as detailed in **Supplementary Table 5**. Beta represents the change in the outcome scale per each standard deviation change in fecal propionate levels.

Trait (outcome)	Scale	#SNPs	Causality by IVW	
			Beta (95%CI)	P
Body Mass Index (BMI)	SD	3	0.03 (0.01,0.05)	6.8×10^{-03}
Type 2 diabetes	log(OR)	3	0.14 (-0.05,0.33)	4.0×10^{-03}
HOMA-IR	log	3	-0.01 (-0.04,0.01)	0.26
Insulin secretion (IS) AUC $_{insulin}$	original	3	0.06 (-0.07,0.19)	0.36
Waist-Hip ratio (adj. BMI)	SD	3	-0.01 (-0.03,0.01)	0.38
Fasting Insulin (adj. BMI)	original (*pmol/L*)	3	-0.01 (-0.02,0.01)	0.39
HbA1c	original	3	0.01 (-0.01,0.03)	0.55
HOMA-B	log	3	0.01 (-0.01,0.03)	0.58
IS index (ISI)	original	3	-0.03 (-0.17,0.10)	0.64
IS AUC $_{insulin}$/AUC $_{glucose}$	original	3	0.03 (-0.10,0.17)	0.66
IS lnc30	original	3	0.02 (-0.10,0.15)	0.71
2hr Glucose (adj. BMI)	original (*mmol/L*)	3	-0.01 (-0.12,0.10)	0.88
Fasting pro-insulin	log	3	0.00 (-0.04,0.05)	0.89
IS Correct Insulin response (Adj. ISI)	original	3	-0.01 (-0.14,0.12)	0.90
IS Disposition Index	original	3	0.00 (-0.12,0.12)	1.00
IS Insulin 30 minutes (adj. BMI)	original	3	0.00 (-0.13,0.13)	1.00
Fasting Glucose	original (*mmol/L*)	3	0.00 (-0.02,0.02)	0.98

Supplementary Table 10: Results of reverse Mendelian Randomization analysis testing the causal effect of BMI and T2D to fecal propionate levels

The table lists the results of the inverse-variance weighted (IVW) Mendelian Randomization analysis testing the causal effect of BMI and T2D on fecal propionate levels. The column #SNPs indicates the number of genetic predictors that were used for the analysis of each trait. The (two-sided) pvalue was calculated as in **Supplementary Table 5**. Beta represent the standard deviation (SD) change in fecal propionate levels for each SD change in BMI or T2D risk (log(OR) scale)

Trait (Exposure)	#SNPs	Causality IVW	
		Beta (95%CI)	*P*
Body mass index	96	-0.17 (-0.56,0.22)	0.39
Type 2 diabetes	10	-0.13 (-0.35,0.09)	0.25

Supplementary Table 11: Results of Mendelian Randomization analysis on the UK Biobank testing the causal effect of fecal propionate levels

The table lists the results of Mendelian Randomization analyses (four statistical tests: IVW, MR-PRESSO, MR-EGGER and Weighted-Median) testing the causal effect of fecal propionate levels on 7 traits using summary statistics from UK Biobank. The column N indicates the number of UK Biobank samples for which summary statistics were generated. For each Mendelian Randomization test the effect size (Beta), 95% confidence intervals and two-sided pvalues are given. Beta represents the change in the outcome units per each standard deviation change in fecal propionate levels. For Type 2 Diabetes and Obesity, beta is equivalent to log (OR). The last two columns indicate the (two-sided) pvalues for MR-PRESSO Global test and Rücker's Q' (modified) test which, if significant, indicate presence of pleiotropy.

| | | IVW | | MR-PRESSO | | MR-Egger | | Weighted Median | | MR-PRESSO | Rücker's Q' |
Outcome	N	Beta (95%C.I.)	P	Beta (95%C.I.)	P	Beta (95%C.I.)	P	Beta (95%C.I.)	P	Global test P	(mod.) P
		Quantitative traits									
BMI	441355	0.02(0.005,0.03)	**0.003**	0(-0.001,0.002)	0.79	-0.01(-0.08,0.06)	0.96	0(-0.01,0.02)	0.61	**0.001**	**1e-4**
Body Fat%	434823	0.02(0.007,0.03)	**0.001**	0.01(-0.003,0.02)	0.42	-0.03(-0.10,0.04)	0.83	0.01(-0.01,0.03)	0.18	**0.02**	**0.02**
SAT	4728	-0.04(-0.15,0.06)	0.36	-0.05(-0.12,0.02)	0.30	-0.07(-0.79,0.65)	0.87	-0.03(-0.17,0.10)	0.62	0.60	0.35
VAT	4728	-0.13(-0.23,-0.03)	**0.01**	-0.13(-0.16,-0.10)	0.01	-0.24(-0.97,0.49)	0.52	-0.12(-0.25,0.01)	0.06	0.91	0.80
WHR	441941	0.01(-0.002,0.02)	0.15	0.01(-0.009,0.022)	0.49	-0.06(-0.12,0.002)	0.37	0(-0.01,0.01)	0.82	0.09	0.52
		Binary traits									
Obesity	340039[#]	0(-0.002,0.002)	0.98	0(-0.002,0.002)	0.98	-0.01(-0.02,0.007)	0.25	0(-0.002,0.003)	0.75	0.51	0.92
T2D	442817[$]	0.07(0.02,0.12)	**0.01**	0.07(0.06,0.08)	**0.007**	0.01(-0.36,0.38)	0.95	0.07(0.004,0.13)	**0.04**	0.97	0.99

[#] Total number consists of 11708 cases and 328331 controls
[$] Total number consists of 19119 cases and 423698 controls