Content

ESM Methods

Search terms

Pubmed database was searched using the following search terms: (("Diabetes Mellitus, Type 2"[MeSH] OR (type 2 diabete[tiab] OR type 2 diabetes[tiab] OR type 2 diabetes,[tiab] OR type 2 diabetic[tiab] OR type 2 diabetics[tiab]) OR "hemoglobin A, Glycosylated"[MeSH] OR hbac1[tiab] OR fasting glucose[tiab]) AND ("DNA Methylation"[MeSH] OR DNA methylation[tiab] OR EWAS[tiab] OR Epigenome-wide association study[tiab] OR methylome[tiab])) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms]) The Embase database was searched using: ((((('non insulin dependent diabetes mellitus'/exp OR 'hemoglobin a1c'/exp OR 'fasting glucose') AND ('dna methylation'/exp OR 'dna methylation assay'/exp OR 'ewas' OR 'epigenome wide association study')) NOT ([animals]/lim NOT [humans]/lim)) restricted to articles only (not reviews, letter, comments, conference posters). Both searches were performed until April 26, 2017. Of each publication, both title and abstract were examined to evaluate its usefulness for review by two independent reviewers (EW; JvVO). We identified 580 relevant publications in PubMed and Embase. EWASs investigating DNA methylation patterns associated with T2D or glycaemic traits were included. We excluded candidate-gene approach studies, studies that focused on epigenetic mechanisms other than DNA methylation, studies determining only global methylation, studies not related to T2D or glucose metabolism, intervention studies, animal studies, studies in neonates, case reports, promoter methylation, EWAS replication studies, co-morbidities (e.g. dementia in elderly with T2D, Parkinson, Alzheimer), T2D complications (e.g. nephropathy, patient-derived diabetic foot ulcer fibroblasts) and articles published in other languages than English. Disagreements between the two reviewers were solved through discussion and with help of an arbitrator (HS). Full texts of included studies were retrieved.

Quality control and normalization

Methylumi R package was used to extract the data from the raw IDAT files. We performed quality control checks on the probes and samples. Two samples were excluded from the control group for sex-mismatch. After having performed a principal component analysis (PCA), we checked for outliers using the first two principal components (PCs). Next, we performed background correction and probe type normalization based on the Touleimat and Tost pipeline[1], using the dasen normalization strategy[2]. We remapped the 450K probes to the human genome reference (HG19). Details on this procedure can be found in Bonder et al [3]. Next, we removed probes with a known Single Nucleotide Polymorphism (SNP) from “Genome of the Netherlands” (GoNL), minor allele frequency (MAF) > 0.01) at the single base extension (SBE) site or CpG site. Lastly, we removed

all probes on the sex chromosomes, resulting in 423,289 high quality methylation sites for subsequent analyses.

Assessing the quality of included publications

We evaluated bias and quality of included publications using the Newcastle-Ottawa Scale, a scale designed to evaluate the quality of case-control and cohort studies [4]. Two independent reviewers (EW; JvVO) assessed the study quality based on the three categories: selection of individuals, comparability of cases and controls and outcome assessment. A maximum of nine stars could be granted. Studies with a score of eight or nine stars were judged to be at low risk of bias, studies with a score of six to seven stars were considered to be at medium risk of bias, whereas studies with a score of five or less stars were considered to be at high risk of bias.

ESM Box 1 Functions of 5 top CpG sites from our replication study in Lifelines T2D EWAS sub study.

ABCG1 is involved in lipid homeostasis, especially promoting cholesterol efflux into HDL[5]. Cholesterol homeostasis is known to be essential modulator of insulin secretion, which is reflected in the phenotype of the *ABCG1*-/- mice, characterized by impaired glucose tolerance and insulin secretion[6].
LOXL2 gene, a member of lysyl oxidase family and an important regulator of tumour progression[7]. It has been shown that *LOXL2* expression is glucose-sensitive in eye and can be related to diabetic retinopathy[8]. In mice, *LOXL2* inhibitor has a profitable effect on glomerular structure in kidney, implicating that *LOXL2* can be a potential therapeutic target for diabetic nephropathy[9].
TXNIP (Thioredoxin-interacting protein) expression is induced by glucose in β-cells as well as in other tissues and also inhibits glucose uptake via enhanced endocytosis of glucose-transporter 1 (GLUT1)[10].
SREBF1 gene located on chromosome 17 encodes two protein - SREBP-1a and SREBP-1c, both participating in the synthesis of cholesterol, fatty acids and triglycerides. In liver overexpressed SREBP-1c induces the secretion of glucokinase, an enzyme involved in glucose utilization. Moreover, in obese mice with insulin resistance and hyperinsulinemia, SREBP-1c levels are elevated[11]
SLC1A5 gene- its protein belongs to different solute carriers (SLC) family of amino-acids transporters. Overexpression of *SLC1A5* increases glutamine uptake especially in cancer cells, therefore represents a potential target in cancer as well as in pathologies such as obesity, type 2 diabetes and neurodegeneration[12]

ESM Table 1 List of CpG sites associated with T2D and glycaemic traits used for replication analysis (100 unique CpGs).

CpG site	Gene name	Study, year	Effect sizes		p-values	Tissue	Correction	Trait
			β	OR				
cg19693031	TXNIP	Chamber et. al, 2015		RR=0.92	$1x10^{-13}$	Blood	Bonferroni	T2D
cg19693031	TXNIP	Sorriano-Tarraga et. al, 2016	-0.13		$7.3x10^{-16}$	Blood	Bonferroni	T2D
cg19693031	TXNIP	Florath et. Al, 2016	-0.03		$4.5x10^{-7}$	Blood	Bonferroni	T2D
cg19693031	TXNIP	Kulkarni et.al, 2015*	-0.58		$1.53x10^{-19}$	Blood	Bonferroni	T2D
cg06500161	ABCG1	Kulkarni et.al, 2015	0.39		$9.43x10^{-10}$	Blood	Bonferroni	T2D
cg06500161	ABCG1	Chamber et. al, 2015		RR=1.08	$2.2x10^{-13}$	Blood	Bonferroni	T2D
cg11024682	SREBF1	Chamber et. al, 2015		RR=1.06	8.4×10^{-9}	Blood	Bonferroni	T2D
cg06721411	DOX1	Al Muftah et al. 2016	5.79		$1.18x10^{-9}$	Blood	Bonferroni	T2D
cg02650017	PHOSPHO1	Chamber et. al, 2015		RR=0.94	$2.1x10^{-9}$	Blood	Bonferroni	T2D
cg00076653	C1QTNF7	Kulkarni et.al, 2015	-0.4		$6.38x10^{-9}$	Blood	Bonferroni	T2D
cg00277397	CALN1	Kulkarni et.al, 2015	0.43		$3.4x10^{-8}$	Blood	Bonferroni	T2D
cg00574958	CPT1A	Kulkarni et.al, 2015	0.38		$4.29x10^{-9}$	Blood	Bonferroni	T2D
cg01657995	C6orf48;SNORD52	Kulkarni et.al, 2015	0.48		$9.3x10^{-8}$	Blood	Bonferroni	T2D
cg18181703	SOCS3	Chamber et. al, 2015		RR=0.95	$2.1x10^{-7}$	Blood	Bonferroni	T2D
cg02560388		Kulkarni et.al, 2015	0.46		$5.85x10^{-8}$	Blood	Bonferroni	T2D
cg02711608	SLC1A5	Kulkarni et.al, 2015	0.45		$4.17x10^{-10}$	Blood	Bonferroni	T2D
cg03497652	ANKS3	Kulkarni et.al, 2015	-0.41		$2.61x10^{-8}$	Blood	Bonferroni	T2D
cg03699074	FAM38A	Kulkarni et.al, 2015	0.39		$1.1x10^{-8}$	Blood	Bonferroni	T2D
cg03725309	SARS	Kulkarni et.al, 2015	0.73		$4.68x10^{-11}$	Blood	Bonferroni	T2D
cg04344749	LDLRAP1	Kulkarni et.al, 2015	-0.35		$1x10^{-7}$	Blood	Bonferroni	T2D
cg04645070		Kulkarni et.al, 2015	0.70		$6.08x10^{-9}$	Blood	Bonferroni	T2D
cg04727071	ZBTB7A	Kulkarni et.al, 2015	0.60		$3.45x10^{-8}$	Blood	Bonferroni	T2D
cg04816311	C7orf50	Kulkarni et.al, 2015	-0.50		$5.47x10^{-8}$	Blood	Bonferroni	T2D
cg04973995		Kulkarni et.al, 2015	0.45		$4.32x10^{-8}$	Blood	Bonferroni	T2D
cg04992150	NUP210	Kulkarni et.al, 2015	0.60		$1.1x10^{-7}$	Blood	Bonferroni	T2D
cg05400498		Kulkarni et.al, 2015	-0.46		$1.12x10^{-9}$	Blood	Bonferroni	T2D

cg06007201	FAM38A	Kulkarni et.al, 2015	0.49	$2.73x10^{-8}$	Blood	Bonferroni	T2D
cg06178887	POU2F2	Kulkarni et.al, 2015	-0.51	$3.26x10^{-8}$	Blood	Bonferroni	T2D
cg07092212	DGKZ	Kulkarni et.al, 2015	0.67	$9.52x10^{-8}$	Blood	Bonferroni	T2D
cg07960624	SAMD12	Kulkarni et.al, 2015	0.45	$1.55x10^{-9}$	Blood	Bonferroni	T2D
cg08309687		Kulkarni et.al, 2015	0.47	$2.45x10^{-9}$	Blood	Bonferroni	T2D
cg08788930	DENND3	Kulkarni et.al, 2015	-0.35	$4.76x10^{-8}$	Blood	Bonferroni	T2D
cg09247619	PTPRC	Kulkarni et.al, 2015	0.66	$1.85x10^{-8}$	Blood	Bonferroni	T2D
cg10508317	SOCS3	Kulkarni et.al, 2015	0.36	$7.42x10^{-9}$	Blood	Bonferroni	T2D
cg10919522	C14orf43	Kulkarni et.al, 2015	0.46	$5x10^{-10}$	Blood	Bonferroni	T2D
cg13199639	KIFC1	Kulkarni et.al, 2015	0.38	$2.95x10^{-8}$	Blood	Bonferroni	T2D
cg13640297	WDR27	Kulkarni et.al, 2015	-0.71	$6.66x10^{-8}$	Blood	Bonferroni	T2D
cg14204586	ARHGEF2	Kulkarni et.al, 2015	0.63	$1.16x10^{-8}$	Blood	Bonferroni	T2D
cg14597545	ADPGK	Kulkarni et.al, 2015	-0.69	$1.5x10^{-8}$	Blood	Bonferroni	T2D
cg15585213	PRDM2	Kulkarni et.al, 2015	-0.32	$2.57x10^{-8}$	Blood	Bonferroni	T2D
cg15962267	SNHG4;SNORA74A; MATR3	Kulkarni et.al, 2015	0.55	$3.09x10^{-8}$	Blood	Bonferroni	T2D
cg16809457	MDN1	Kulkarni et.al, 2015	-0.48	$6.01x10^{-9}$	Blood	Bonferroni	T2D
cg17058475	CPT1A	Kulkarni et.al, 2015	0.43	$3.89x10^{-9}$	Blood	Bonferroni	T2D
cg17315426	CDH24	Kulkarni et.al, 2015	0.56	$6.52x10^{-8}$	Blood	Bonferroni	T2D
cg17666418		Kulkarni et.al, 2015	0.61	$6.31x10^{-8}$	Blood	Bonferroni	T2D
cg19266329		Kulkarni et.al, 2015	0.50	$9.98x10^{-11}$	Blood	Bonferroni	T2D
cg21699330	NFE2L3	Kulkarni et.al, 2015	0.47	$8.56x10^{-8}$	Blood	Bonferroni	T2D
cg21766592	SLC1A5	Kulkarni et.al, 2015	0.53	$1.97x10^{-9}$	Blood	Bonferroni	T2D
cg22909677	ARMC2	Kulkarni et.al, 2015	-0.38	$1.84x10^{-9}$	Blood	Bonferroni	T2D
cg24531955	LOXL2	Kulkarni et.al, 2015	0.37	$9.29x10^{-9}$	Blood	Bonferroni	T2D
cg26546155	RSPRY1	Kulkarni et.al, 2015	-0.57	$5.92x10^{-8}$	Blood	Bonferroni	T2D
cg26712428	CALHM1	Kulkarni et.al, 2015	-0.39	$2.71x10^{-8}$	Blood	Bonferroni	T2D
cg26804423	ICA1	Kulkarni et.al, 2015	-0.56	$5.76x10^{-9}$	Blood	Bonferroni	T2D
cg26836479	DEDD2	Kulkarni et.al, 2015	0.56	$1.05x10^{-7}$	Blood	Bonferroni	T2D
cg13725826		Dayeh et.al, 2014	Delta(%) -5.24	$1x10^{-7}$	Pancreatic islets	Bonferroni	T2D

cg15599668	SYNPO	Dayeh et.al, 2014	-10.45	$2.9x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg22610620		Dayeh et.al, 2014	-10.26	$7.1x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg24327307	SSBP3	Dayeh et.al, 2014	-9.14	$7.7x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg19296305	LEF1	Dayeh et.al, 2014	-9.14	$1.1x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg16782117		Dayeh et.al, 2014	-8.45	$6.6x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg01649611	THADA;THADA	Dayeh et.al, 2014	-7.81	$5.4x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg15275625		Dayeh et.al, 2014	-7.46	$1.8x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg17328407		Dayeh et.al, 2014	-7.13	$8.7x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg09225373		Dayeh et.al, 2014	-6.86	$4.3x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg07820189		Dayeh et.al, 2014	-6.59	$3.2x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg22378252	GCNT2	Dayeh et.al, 2014	-6.38	$6.2x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg21449597		Dayeh et.al, 2014	-6.18	$9.7x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg04071398	IL20RA	Dayeh et.al, 2014	-5.99	$5.4x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg12458003	NFASC	Dayeh et.al, 2014	-5.91	$3.7x10^{-8}$	Pancreatic islets	Bonferroni	T2D
cg08125242		Nilsson et. al, 2015	-0,53	$1,04x10^{-9}$	liver	Bonferroni	T2D
cg07088414		Nilsson et. al, 2015	-0,50	$5,83x10^{-8}$	liver	Bonferroni	T2D
cg27402634		Nilsson et. al, 2015	-0,77	$8,08x10^{-8}$	liver	Bonferroni	T2D
cg00574958	CPT1A	Kriebel et al., 2016	-0.10	$9.8x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg06500161	ABCG1	Kriebel et al., 2016	0.04	$4.2x10^{-10}$	Blood	Bonferroni	Fasting glucose
cg11024682	SREBF1	Kriebel et al., 2016	0.06	$2.5x10^{-10}$	Blood	Bonferroni	Fasting glucose
cg06500161	ABCG1	Kulkarni et al., 2015	0.20	$3.7x10^{-9}$	Blood	Bonferroni	Fasting glucose
cg00138407	KLHL18	Kulkarni et al., 2015	0.27	$4.44e^{-08}$	Blood	Bonferroni	Fasting glucose
cg00552753		Kulkarni et al., 2015	0.20	$7.97x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg01676795	POR	Kulkarni et al., 2015	0.31	$2.94x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg02059849	PTP4A3	Kulkarni et al., 2015	0.21	$5.91x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg02079413	SNORA54;NAP1L4	Kulkarni et al., 2015	0.22	$1.94x10^{-9}$	Blood	Bonferroni	Fasting glucose
cg02436098	TNFAIP8L1	Kulkarni et al., 2015	-0.19	$4.03x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg04816311	C7orf50	Kulkarni et al., 2015	0.29	$4.61x10^{-9}$	Blood	Bonferroni	Fasting glucose
cg06715330	CCDC57	Kulkarni et al., 2015	0.19	$7.65x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg07136133	PRR5L	Kulkarni et al., 2015	-0.25	$4.77x10^{-10}$	Blood	Bonferroni	Fasting glucose

cg08309687		Kulkarni et al., 2015	-0.24	$1.5x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg11467506		Kulkarni et al., 2015	-0.27	$1.34x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg16097041	FLAD1;LENEP	Kulkarni et al., 2015	0.27	$4.57x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg16809457	MDN1	Kulkarni et al., 2015	0.25	$4.98x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg19048360	PFDN6;WDR46	Kulkarni et al., 2015	-0.19	$9.05x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg19693031	TXNIP	Kulkarni et al., 2015	-0.27	$1.55x10^{-15}$	Blood	Bonferroni	Fasting glucose
cg22887911	TMEM42	Kulkarni et al., 2015	-0.18	$9.85x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg23906191	C7orf50	Kulkarni et al., 2015	0.20	$3.51x10^{-8}$	Blood	Bonferroni	Fasting glucose
cg25217710		Kulkarni et al., 2015	0.31	$8.88x10^{-11}$	Blood	Bonferroni	Fasting glucose
cg26666886	ANKRD11	Ronn et. al, 2015	-0,05	$2,3x10^{-9}$	Adipose tissue	Bonferroni	HbA1c
cg07973479	*ATP8A2*	Ronn et. al, 2015	-0,06	$3,1x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg08242859	*IMPDH1*	Ronn et. al, 2015	-0,04	$2,8x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg09308803	*LOC256880;H2AFZ*	Ronn et. al, 2015	-0,03	$2,1x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg14178899	*ERRFI1*	Ronn et. al, 2015	-0,06	$1,4x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg18083764		Ronn et. al, 2015	0,05	$3,4x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg27405128		Ronn et. al, 2015	-0,05	$1,8x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg01722584	*LOC643406*	Ronn et. al, 2015	-0,05	$4,8x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg18161036		Ronn et. al, 2015	-0,04	$5,1x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg08146372		Ronn et. al, 2015	-0,03	$8,0x10^{-8}$	Adipose tissue	Bonferroni	HbA1c
cg11111226	*SH3TC1*	Ronn et. al, 2015	-0,08	$9,7x10^{-8}$	Adipose tissue	Bonferroni	HbA1c

*Kulkarni et al: For discrete traits SOLAR returns regression coefficients that are inverted in direction. Hence, for T2D, negative regression coefficient indicates increased risk; Different colours mark the same CpG sites (duplicates).

ESM Table 2 Baseline characteristics of the study sample of T2D patients and healthy controls from Lifelines, divided into four groups.

	T2D patients with complications (n=50)	**T2D patients without complications (n=50)**	**Age, sex matched to T2D patients controls (n=49)**	**Second control group (n=49)**
Sex (M) (n, %)	29 (58%)	23 (46%)	27 (55.1%)	17 (34.7%)
Age (years)	65 (52-71)	62 (53-68)	60 (49-65)	48 (40-51)
BMI (kg/m^2)	31.5 (5.8)	30.1 (3.0)	28 (3.4)	22.6 (1.6)
Waist (cm)	106.7 (14.7)	103.9 (9.5)	97 (8.5)	81.5 (7.5)
Waist –Hip ratio	0.99 (0.08)	0.98 (0.07)	0.94 (0.07)	0.87 (0.07)
HbA1c (%)	6.9 (6.3-7.3)	6.6 (6.3-7.1)	5.6 (5.4-5.7)	5.5 (5.3-5.7)
Fasting glucose (mmol/L)*	7.5 ()	7.1 (6.2-8.4)	5 (4.7-5.3)	4.8 (4.5-5.2)
Triglycerides (mmol/L)	1.4 (1.1-1.9)	1.4 (1.1-1.9)	1.1 (0.8-1.5)	0.9 (0.7-1.1)
HDL cholesterol (mmol/L)	1.21 (0.3)	1.26 (0.3)	1.4 (0.3)	1.67 (0.4)
LDL cholesterol (mmol/L)	2.6 (0.8)	3.0 (1.0)	3.7 (0.9)	3.2 (0.8)
Total cholesterol (mmol/L)	4.3 (0.8)	4.7 (1.1)	5.5 (1.0)	5.1 (1.0)
SBP (mm Hg)	137 (19)	133 (17)	124 (8)	121 (14)
DBP (mm Hg)	74 (9)	77 (9)	74 (7)	71 (8)
Education level (n, %)*				
1- Low	1-29 (58%)	1- 26 (55%)	1-21 (46%)	1-13 (28%)
2- Intermediate	2-11 (22%)	2- 11 (23%)	2-11 (24%)	2-17 (36%)
3- High	3- 10 (20%)	3 -10 (22%)	3-13 (30%)	3-17 (36%)
Insulin intake (n, %)	9 (18%)	1 (2%)	0 (0%)	0 (0%)
Oral anti-glycaemic drugs (n, %)	26 (52%)	25 (50%)	0 (0%)	0 (0%)
Lipids lowering drugs (n,%)	36 (72%)	24 (48%)	1 (2%)	0 (0%)

ESM Table 3 Significant differentially methylated CpG sites for T2D replicated in the Lifelines T2D EWAS subsample (n=198) – additional models.

CpG site	CHR	MAPINFO	Gene name	Mean methylation (%)	Model 1		Model 1 + BMI		Model 1+ newly diagnosed + medication use		Model 1 +Education + Smoking		Model 1 + complications		Model 1 + BMI + Education	
					Delta (%)	*p*-value	Delta (%)	*p*-value	Delta (%)	*p*-value	Delta (%)	*p*-value	Delta (%)	*p*-value	Delta (%)	*p-value*
cg06500161	21	43656587	ABCG1	60.9	3	**$2{,}9\times10^{-7}$**	2.39	**3×10^{-4}**	2.55	2.3×10^{-3}	3.08	**1.2×10^{-6}**	2.56	**1×10^{-4}**	2.4	0.1
cg24531955	8	23154691	LOXL2	25.4	-1.99	**1.6×10^{-4}**	-1.63	6×10^{-3}	-1.91	3.8×10^{-3}	-1.79	1×10^{-3}	-1.92	1.2×10^{-3}	-1.6	0.03
cg19693031	1	145441552	TXNIP	69.5	-3.6	**2.6×10^{-4}**	-2.68	0.02	-3.70	0.07	-2.49	5×10^{-3}	-3.70	7×10^{-3}	-2	0.3
cg02711608	19	47287964	SLC1A5	20.1	-1.81	**3.2×10^{-4}**	-1.26	0.03	-1.93	1.6×10^{-3}	-1.92	3×10^{-3}	-1.93	8×10^{-3}	-1.3	0.07
cg11024682	17	17730094	SREBF1	44.6	1.88	**5.5×10^{-4}**	1.04	0.08	1.80	0.18	1.83	2×10^{-3}	1.8	3×10^{-3}	1	0.36
cg07960624	8	119208486	SAMD12	39.7	-2.3	4.8×10^{-3}	-1.59	0.09	-2.86	0.04	-2.49	4×10^{-3}	-2.87	1.6×10^{-3}	-1.9	0.22
cg03497652	16	4751569	ANKS3	55.5	1.86	9.7×10^{-3}	1.79	0.03	1.55	0.23	1.59	0.03	1.55	0.05	1.8	0.17
cg19266329	1	145456128	POLR3GL	60.9	-1.77	0,01	-0.98	0.20	-1.85	5×10^{-3}	-1.98	8×10^{-3}	-1.85	0.02	-1.1	0.32
cg22909677	6	109172312	ARMC2	80.4	1.11	0,01	1.04	0.07	1.25	0.14	1.27	5×10^{-3}	1.25	0.01	1.1	0.01
cg08309687	21	35320596	ATP5O	56.7	-2.61	0,01	-0.92	0.36	-3.32	0.13	-2.69	0.02	-3.32	6×10^{-3}	-1.3	0.67
cg26804423	7	8201134	ICA1	63.8	1.39	0,02	0.78	0.23	1.15	0.11	1.47	0.02	1.15	0.08	0.9	0.38
cg13199639	6	33360495	KIFC1	11.7	-0.91	0,02	-0.49	0.34	-0.9	0.24	-0.93	0.03	-0.9	0.04	-0.5	0.87
cg15962267	5	138612986	SNHG4	69.9	-1.29	0,03	-0.79	0.22	-1.42	0.42	-1.5	0.02	-1.42	0.03	-1	0.95
cg03725309	1	109757585	SARS	17.9	-1.06	0,03	-0.72	0.19	-0.98	0.42	-1.4	0.01	-0.99	0.1	-0.9	0.64
cg10919522	14	74227441	C14orf43	31.4	-1.42	0,04	-0.42	0.56	-1.27	0.04	-1.39	0.06	-1.27	0.1	-0.7	0.77

Bonferroni threshold: $0.05/52= 9.6\times10^{-4}$ (in bold); delta methylation is based on beta-values, *p*-values are from analyses based on M-values
*Closest gene was *POLR3GL* (108bp downstream) and ATP5O (32438bp upstream)
Model 1 is adjusted for age, sex, measured blood cell composition, position on the plate and position on the chip
Abbreviations: CHR- chromosome; IllmID- Illumina ID; MAPINFO- position on the chromosome; Shores - 0-2 kb from CpG island; Shelves - 2-4 kb from CpG island; Open sea- more than 4kb from CpG island

ESM Table 4 Methylation difference between diabetic patients with and without history of CVD from the Lifelines sample.

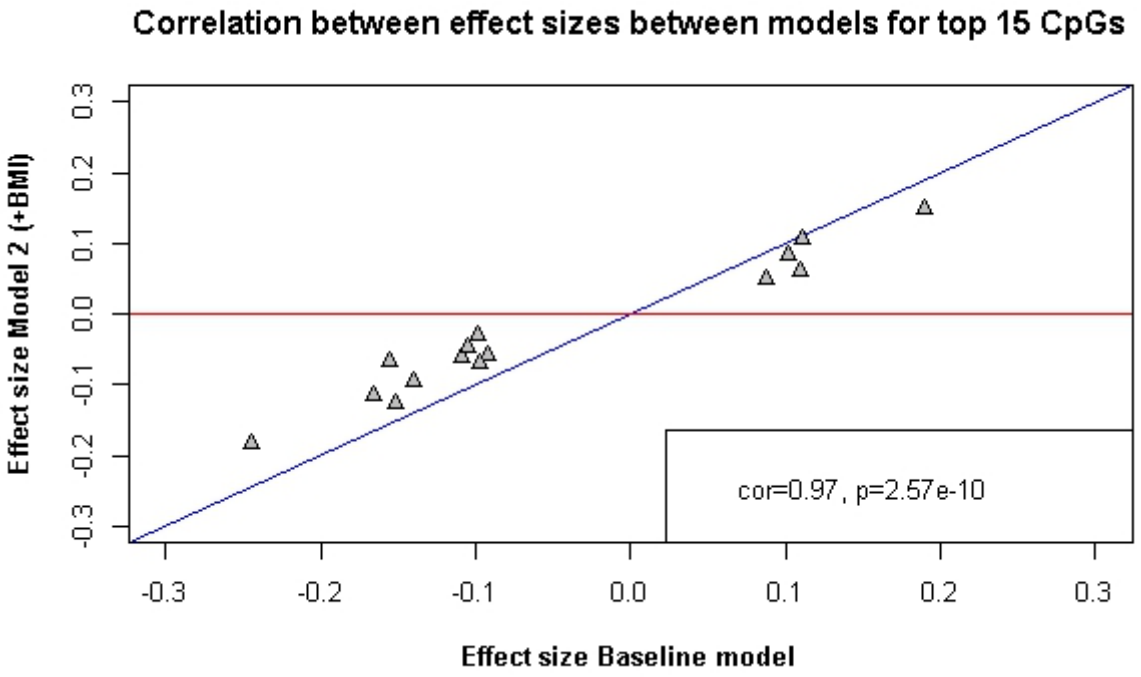
CpG site	CHR	MAPINFO	Gene name	Mean methylation patients without complications (%)	Mean methylation patients with complications (%)	*p*-value
cg06500161	21	43656587	*ABCG1*	62.3	63.7	0.059
cg24531955	8	23154691	*LOXL2*	24.2	24.5	0.63
cg19693031	1	145441552	*TXNIP*	67.2	67.7	0.75
cg02711608	19	47287964	*SLC1A5*	19.1	19.0	0.91
cg11024682	17	17730094	*SREBF1*	46.0	46.2	0.81
cg07960624	8	119208486	*SAMD12*	37.6	38.1	0.63
cg03497652	16	4751569	*ANKS3*	56.6	57.1	0.54
cg19266329	1	145456128	*POLR3GL*	59.6	60.4	0.30
cg22909677	6	109172312	*ARMC2*	81.1	80.4	0.21
cg08309687	21	35320596	*ATP5O*	54.2	56.5	0.1
cg26804423	7	8201134	*ICA1*	64.5	64.2	0.7
cg13199639	6	33360495	*KIFC1*	11.4	11.3	0.79
cg15962267	5	138612986	*SNHG4*	68.8	69.8	0.25
cg03725309	1	109757585	*SARS*	17.3	16.3	0.07
cg10919522	14	74227441	*C14orf43*	30.3	30.4	0.98

ESM Table 5 Overlap between CpGs that are significantly associated with T2D and fasting glucose (from Table S1) and CpGs significantly associated with lipids and BMI.

CpG site	Gene name	Trait	BMI	TG		HDL		LDL	
			Wahl	Dekker	Pfeifer	Dekker	Pfeifer	Dekker	Pfeifer
cg19693031	*TXNIP*	T2D, fasting glucose	✓	✓	✓				
cg06500161	*ABCG1*	T2D, fasting glucose	✓	✓	✓	✓	✓		
cg11024682	*SREBF1*	T2D, fasting glucose	✓	✓	✓				
cg02650017	*PHOSPHO1*	T2D	✓						
cg00574958	*CPT1A*	T2D, fasting glucose	✓	✓	✓				
cg18181703	*SOCS3*	T2D	✓						
cg02560388	*LPIN1*	T2D	✓						
cg02711608	*SLC1A5*	T2D	✓	✓					
cg03725309	*SARS*	T2D	✓						
cg10919522	*C14orf43*	T2D	✓						
cg17058475	*CPT1A*	T2D		✓					
cg24531955	*LOXL2*	T2D	✓						
cg26804423	*ICA1*	T2D	✓						
cg07136133	*PRR5L*	Fasting glucose	✓						
cg08309687		Fasting glucose	✓						

The comparison was made based on published studies[13-15]. Green check marks indicate a directionally consistent overlap.

ESM Figure 1 Correlation between effect sizes based on baseline model 1 and model 2 (Model 1 +BMI).



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