

Supplementary information

Epigenome-wide Meta-Analysis Reveals Associations between Dietary Glycemic Index and Glycemic Load and DNA methylation in Children and Adolescents with Different Body Size

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Supplemental Tables

Table S1. Individual cohort overview of array preprocessing and normalization steps

Cohort	Illumina array type	Preprocessing R package	Filter threshold for sub-optimal probes (p-value threshold)	Normalization method	Additional batch adjustment	N autosomal probes
ATHEROBESITY	EPIC	Champ	0.01	Beta mixture quantile dilation	ComBat	665623
INMA	450K	Minfi	10E-16	Functional normalization	ComBat	368485
LIFE Child	EPIC	Champ	0.01	Beta mixture quantile dilation	ComBat	665623
NFBC1986	450K	Minfi	10E-16	Functional normalization	-	369518
Raine Study Gen2	450K	MethylAid	0.05	Beta mixture quantile dilation	-	367786
TEENDIAB	EPIC	Minfi	0.01	Quantile normalization	ComBat	651659

Table S2. Individual cohort post-bacon-corrected model estimates

Cohort	“classical λ ”	λ	μ	Post-bacon median SE
Glycemic index (whole group)				
INMA	1.01	1.00	-0.002	3.84E-04
TEENDIAB	1.02	1.01	-0.001	1.63E-04
LIFE Child	1.00	1.00	0.001	4.02E-04
ATHEROBESITY	1.02	1.00	-0.003	3.82E-04
Raine Study Gen2	1.30	1.00	0.000	2.86E-04
NFBC1986	1.14	1.00	0.000	2.25E-04
Glycemic load (whole group)				
INMA	0.89	0.99	0.005	7.03E-05
TEENDIAB	1.02	1.00	0.001	1.94E-05
LIFE Child	1.02	1.01	-0.000	6.54E-05
ATHEROBESITY	1.49	1.16	-0.156	9.01E-05
Raine Study Gen2	3.24	0.98	-0.039	3.22E-05
NFBC1986	0.96	0.98	0.018	2.33E-05
Glycemic index (normal-weight)				
INMA	1.03	1.00	-0.002	4.22E-04
TEENDIAB	1.02	1.00	-0.001	1.91E-04
LIFE Child	1.09	1.00	0.001	7.40E-04
ATHEROBESITY	1.06	1.01	-0.003	6.22E-04
Raine Study Gen2	3.28	0.98	-0.071	2.80E-04
NFBC1986	1.12	1.00	-0.000	2.45E-04
Glycemic index (overweight/obese)				
INMA	1.10	1.01	-0.002	7.52E-04
TEENDIAB	1.05	1.01	0.001	3.25E-04
LIFE Child	1.03	1.01	0.001	4.91E-04
ATHEROBESITY	1.05	1.02	-0.004	5.46E-04
Raine Study Gen2	1.05	0.99	0.004	3.20E-04
NFBC1986	1.10	0.99	-0.002	3.95E-04
Glycemic load (normal-weight)				
INMA	0.89	1.00	-0.001	7.42E-05
TEENDIAB	1.01	1.00	-0.000	2.13E-05
LIFE Child	1.13	1.03	-0.020	1.61E-04
ATHEROBESITY	1.12	1.02	-0.013	1.48E-04
Raine Study Gen2	3.00	0.98	-0.036	4.10E-05
NFBC1986	1.00	1.00	0.003	2.99E-05
Glycemic load (overweight/obese)				
INMA	1.07	1.01	-0.011	1.98E-04
TEENDIAB	1.05	1.01	0.005	5.60E-05
LIFE Child	1.03	1.01	0.001	6.82E-05
ATHEROBESITY	1.07	1.02	0.008	1.44E-04
Raine Study Gen2	1.07	1.00	0.001	5.31E-05
NFBC1986	1.07	1.00	0.005	5.27E-05

Classical genomic inflation factor (λ) obtained from *QCEWAS* R package. Inflation/deflation (λ) and bias (μ) obtained from *bacon* R package. Median of all standard errors (SE) obtained from *QCEWAS* R package.

Table S3. Genomic inflation factor (λ) and bias (μ) of the meta-analysis models

Meta-analysis model	Total n	Genomic inflation factor (λ)*	Bias (μ)*
Glycemic index	1187	0.99	0.001
Glycemic load	693	1.00	-0.000
Glycemic index normal-weight	801	1.00	0.001
Glycemic index overweight/obese	386	1.01	-0.000
Glycemic load normal-weight	481	1.00	0.000
Glycemic load overweight/obese	209	1.00	-0.000

*Genomic inflation factor (λ) and bias (μ) obtained from *bacon* R package.

Supplemental tables S4-S18 are included in a separate excel file.

Supplemental Figures

Supplemental Figure S1: QQ-plots of Cochran's heterogeneity test p-values derived from the full group meta-analyses with glycemic load and different included cohorts

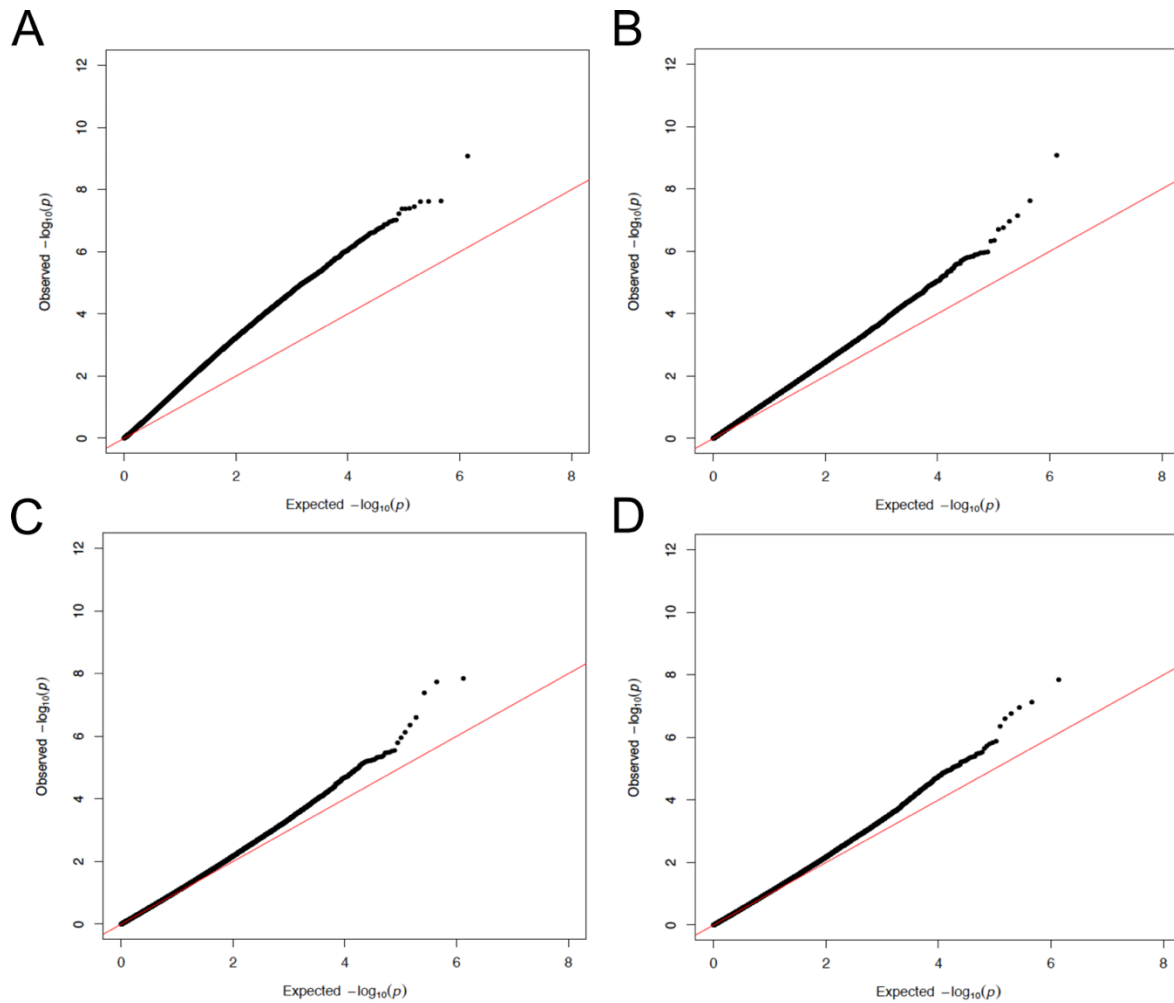


Figure S1. QQ-plots of Cochran's heterogeneity test p-values derived from the full group meta-analyses with glycemic load and different included cohorts. Overall heterogeneity of meta-analyses models was checked by evaluating the QQ-plots of Cochran's heterogeneity test p-values. Including all studies, i.e., INMA, TEENDIAB, LIFE Child, ATHEROBESITY and Raine, except NFBC1986 showed high heterogeneity (A; $\lambda=2.03$). Heterogeneity decreased much after exclusion of Raine, i.e. keeping INMA, TEENDIAB, LIFE Child, ATHEROBESITY, (B; $\lambda=1.40$) and decreased further after exclusion of ATHEROBESITY (C; $\lambda=1.05$). Addition of NFBC1986 to the cohorts used in C, did not introduce heterogeneity (D; $\lambda=1.05$). The final models for glycemic load thus included INMA, TEENDIAB, LIFE and NFBC1986 (D).

Supplemental Figure S2: QQ-plots of Cochran's heterogeneity test p-values derived from meta-analyses before and after the inclusion of the NFBC1986 cohort

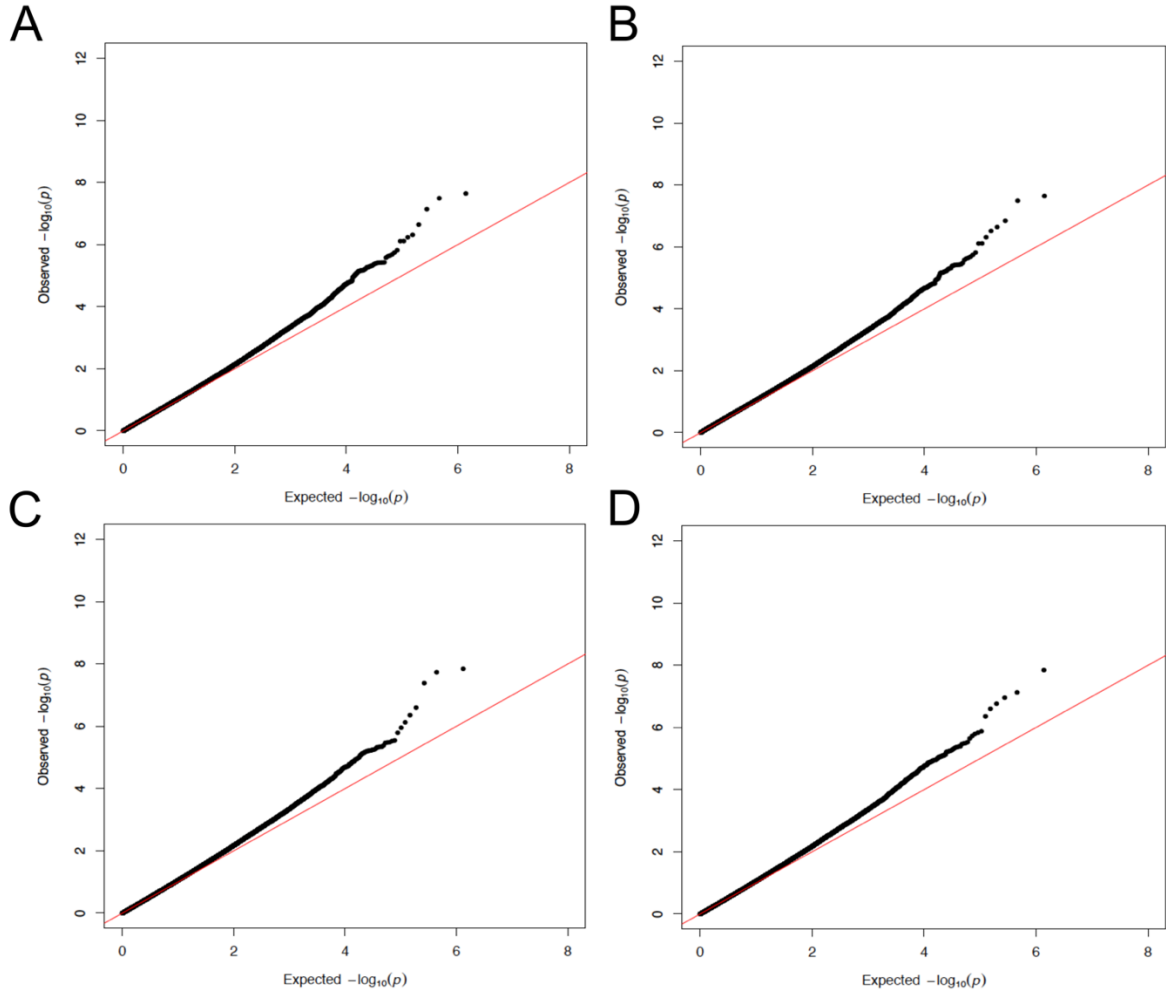


Figure S2. QQ-plots of Cochran's heterogeneity test p-values derived from the full group meta-analyses with glycemic index or glycemic load without or with NFBC1986. To evaluate if the addition of NFBC introduced heterogeneity to the meta-analysis models, QQ-plots were checked before and after the inclusion of NFBC to glycemic index analysis (A: without NFBC1986 $\lambda=1.09$, B: with NFBC1986 $\lambda=1.12$) and glycemic load analysis (C: without NFBC1986 $\lambda=1.05$, D: with NFBC1986 $\lambda=1.05$). As the inclusion of NFBC1986 did not introduce heterogeneity, we included it in the final models.

Supplemental Figure S3: Forest plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic index normal weight meta-analysis

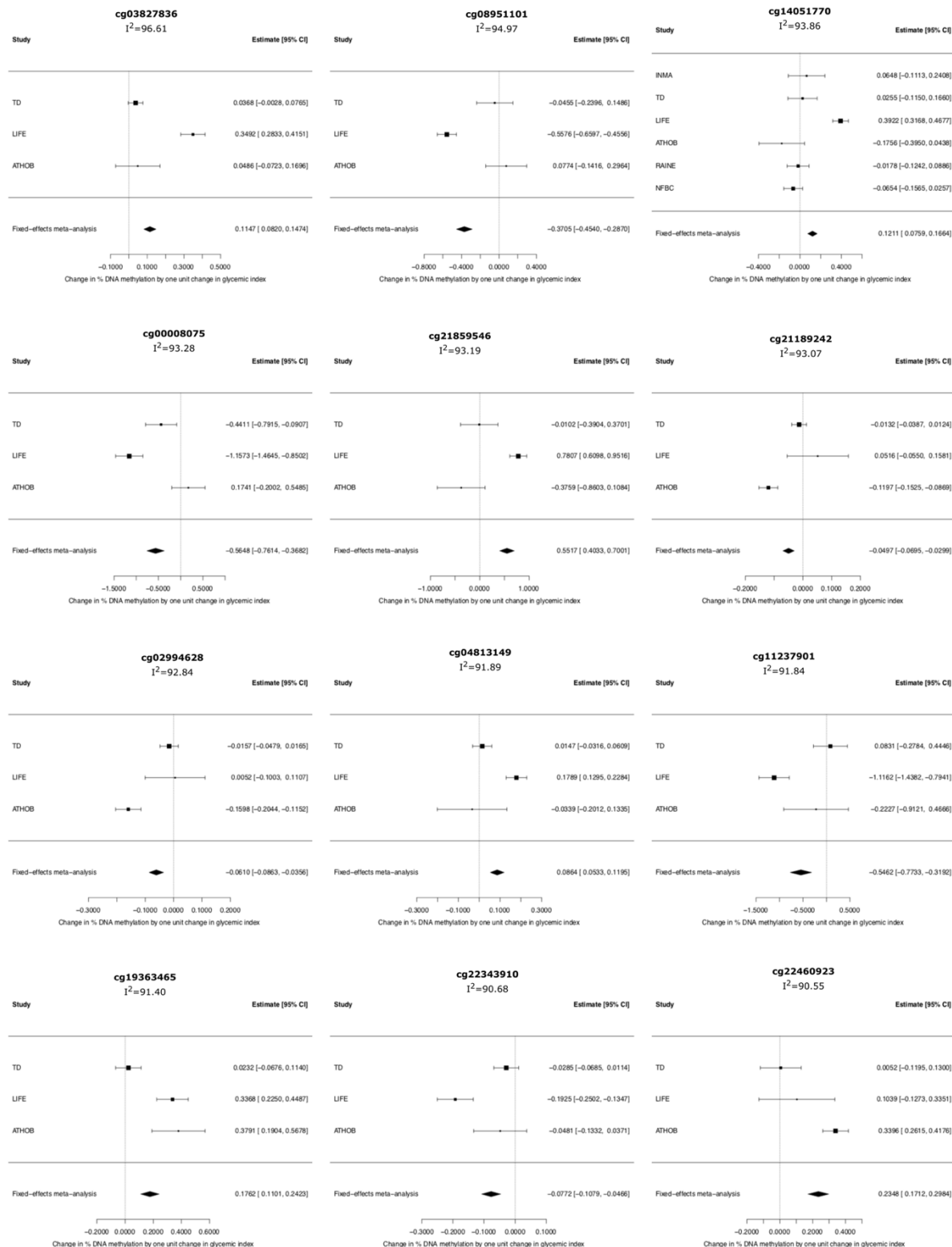


Figure S3. Forest plots of the meta-analysis results with highest heterogeneity based on I^2 -value of the glycemic index normal weight model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; ATHOB, Atherobesity; RAINE, the Raine study, NFBC, NFBC1986.

Supplemental Figure S4: Forest plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic load normal weight meta-analysis

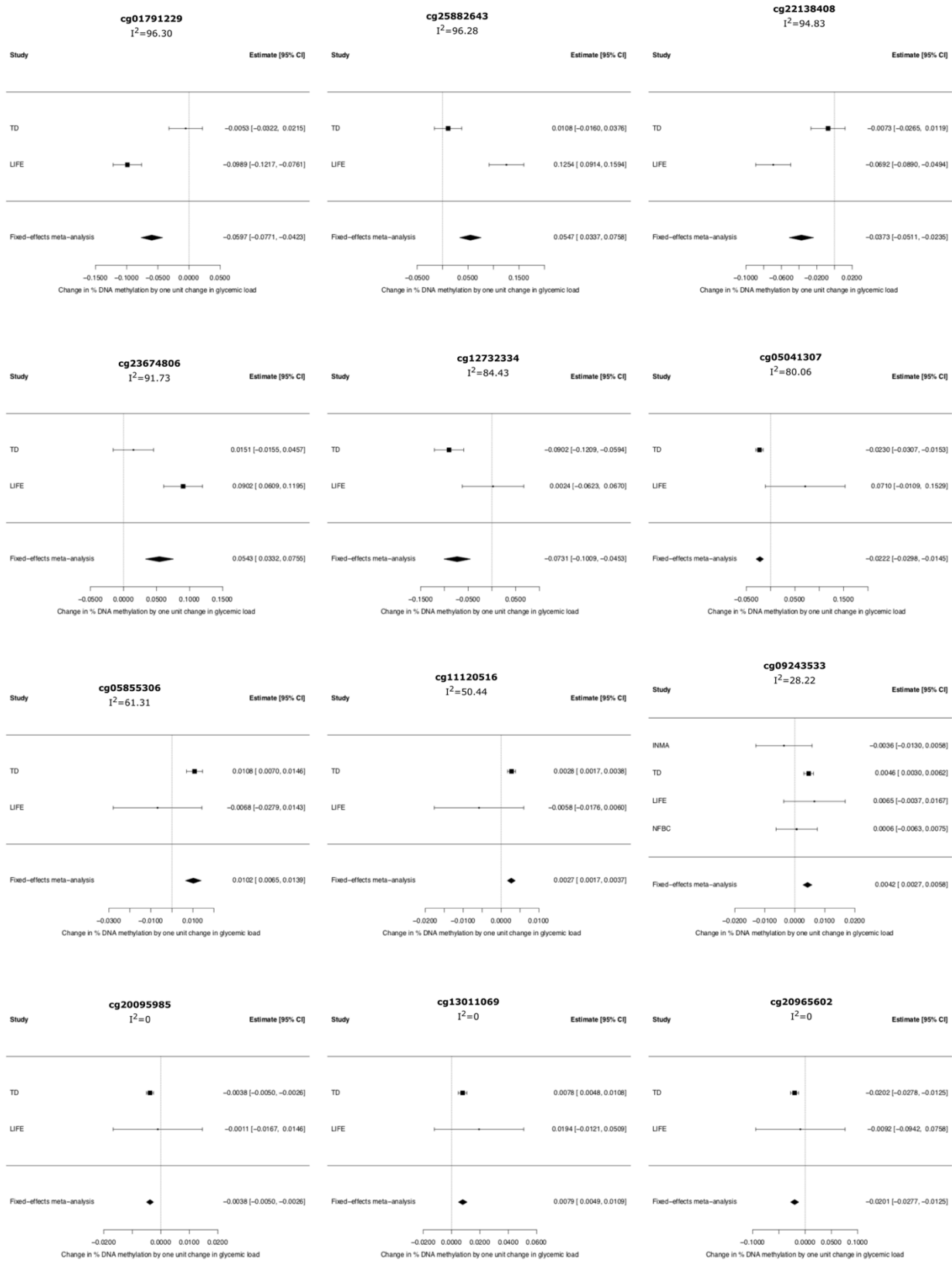


Figure S4. Forest plots of the meta-analysis results with highest heterogeneity based on I^2 -value of the glycemic load normal weight model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; NFBC, NFBC1986.

Supplemental Figure S5: Forest plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic index overweight/obesity meta-analysis

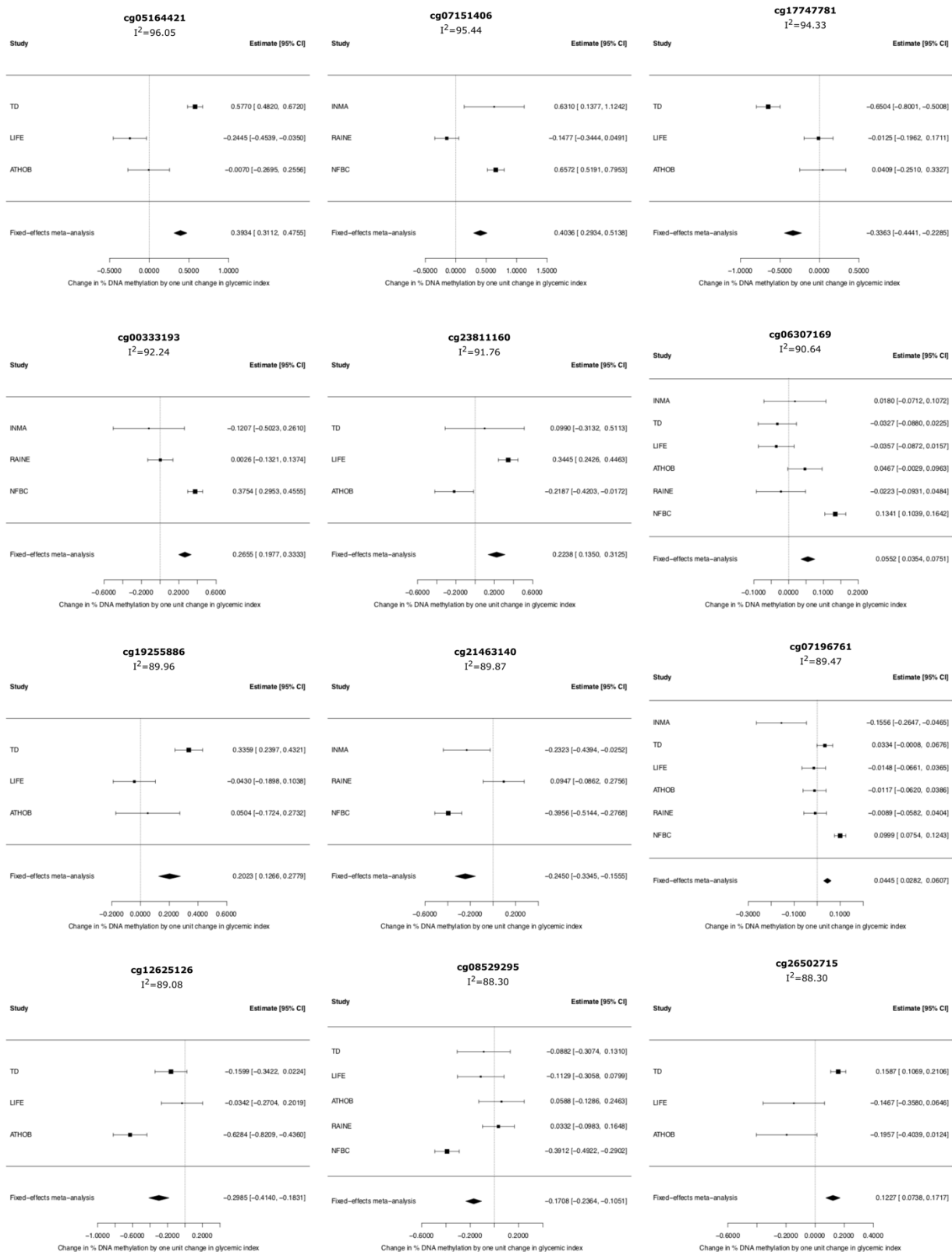


Figure S5. Forest plots of the meta-analysis results with highest heterogeneity based on I^2 -value of the glycemic index overweight/obesity model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; ATHOB, Atherobesity; RAINE, the Raine study, NFBC, NFBC1986.

Supplemental Figure S6: Forest plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic load overweight/obesity meta-analysis

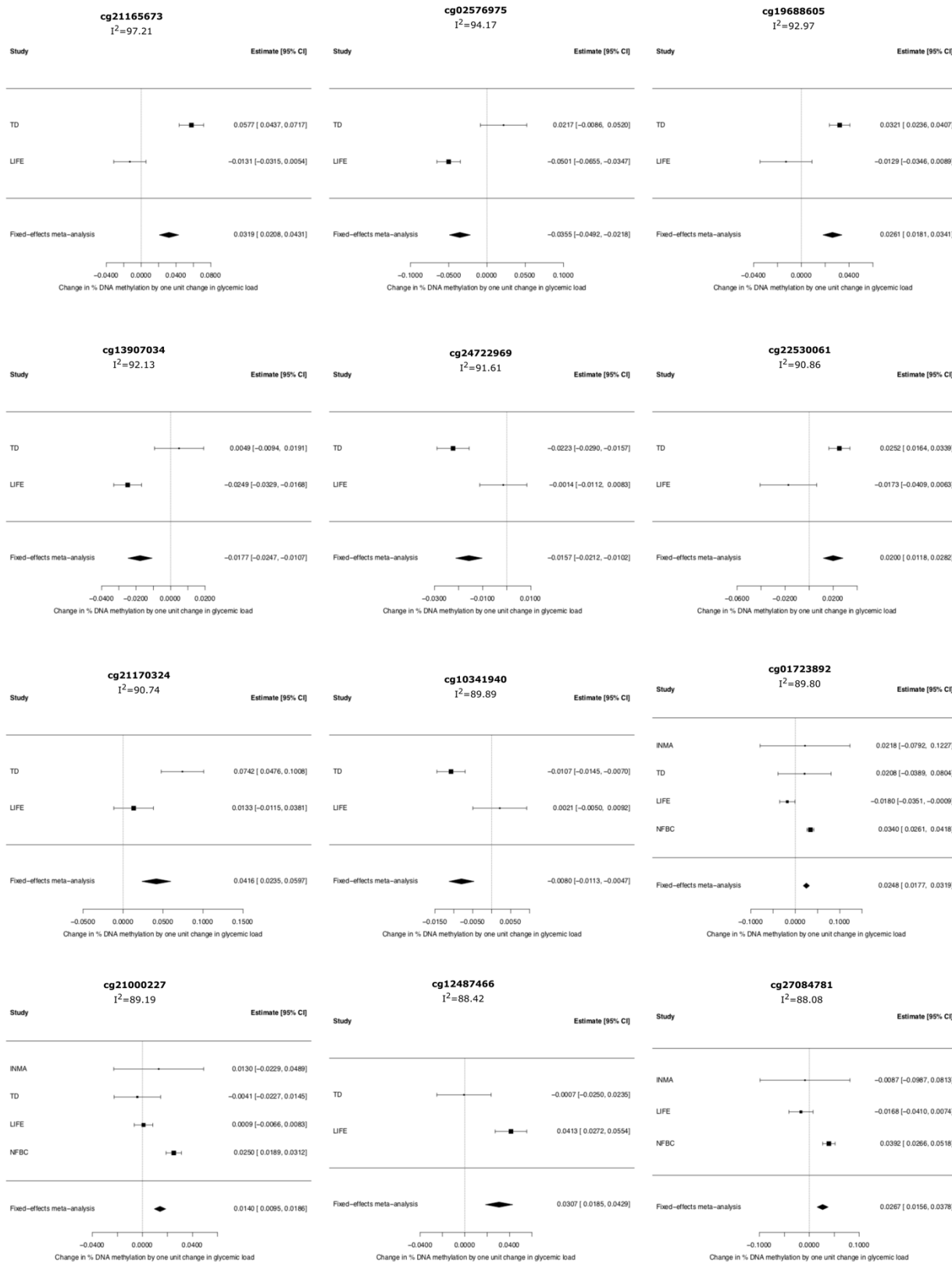


Figure S6. Forest plots of the meta-analysis results with highest heterogeneity based on I^2 -value of the glycemic load overweight/obesity model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; NFBC, NFBC1986.

Supplemental Figure S7: Leave study out plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic index normal weight meta-analysis

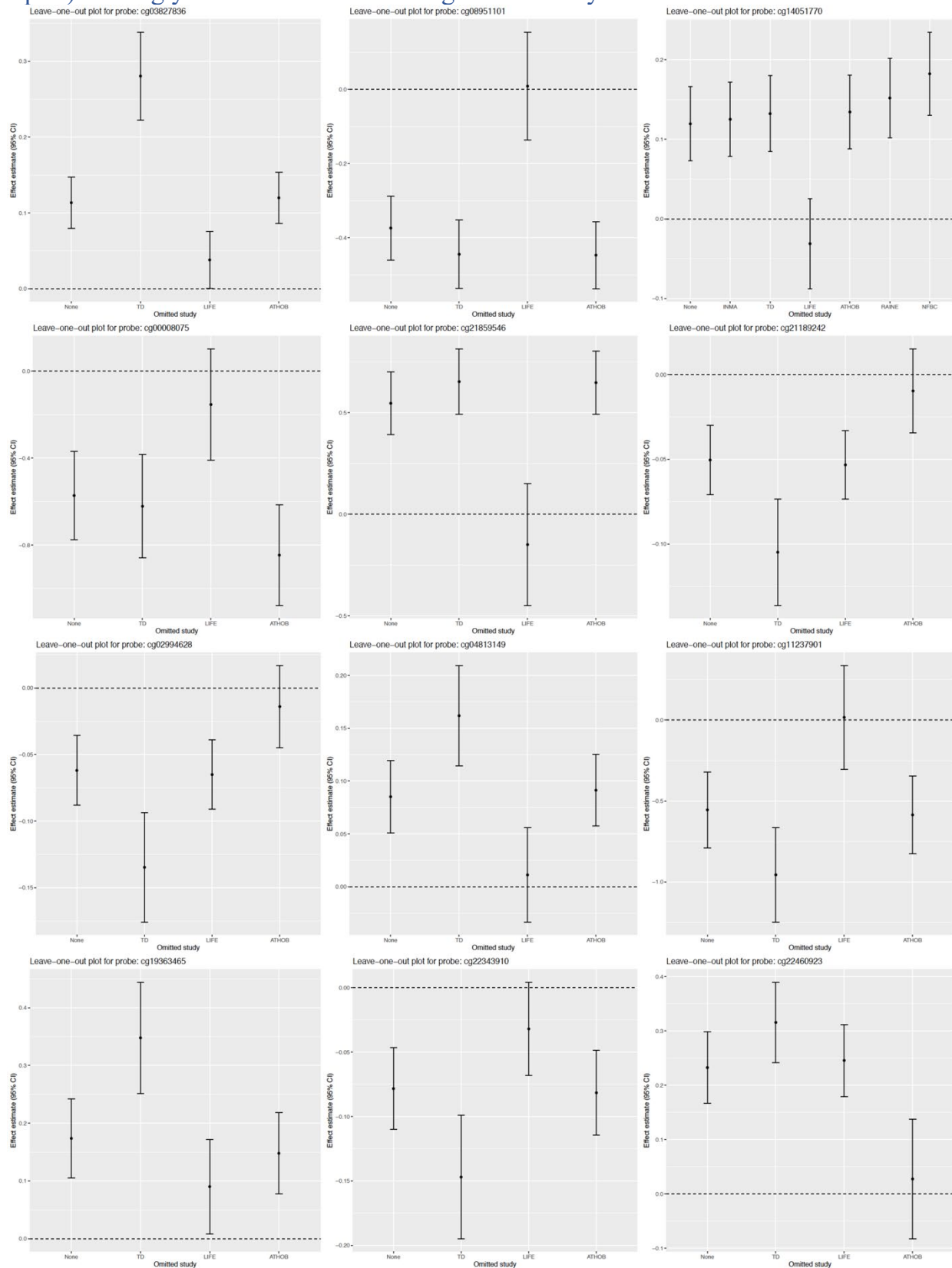


Figure S7. Leave study out meta-analysis effect estimates (95% CI) of the probes with highest heterogeneity based on I^2 -value of the glycemic index normal weight model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; ATHOB, Atherobesity; RAINE, the Raine study, NFBC, NFBC1986.

Supplemental Figure S8: Leave study out plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic load normal weight meta-analysis

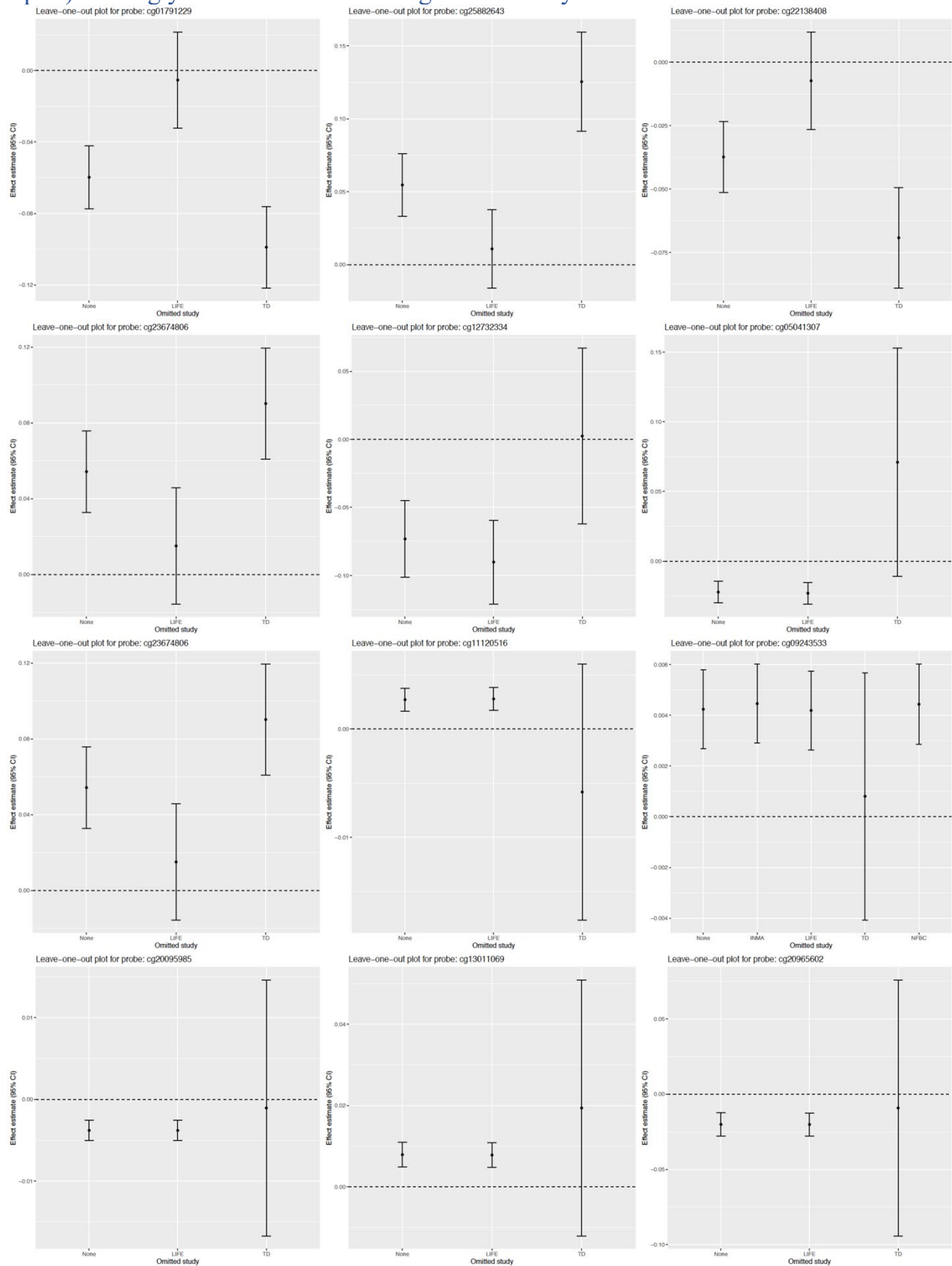


Figure S8. Leave study out meta-analysis effect estimates (95% CI) of the probes with highest heterogeneity based on I^2 -value of the glycemic load normal weight model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; NFBC, NFBC1986.

Supplemental Figure S9: Leave study out plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic index overweight/obese meta-analysis

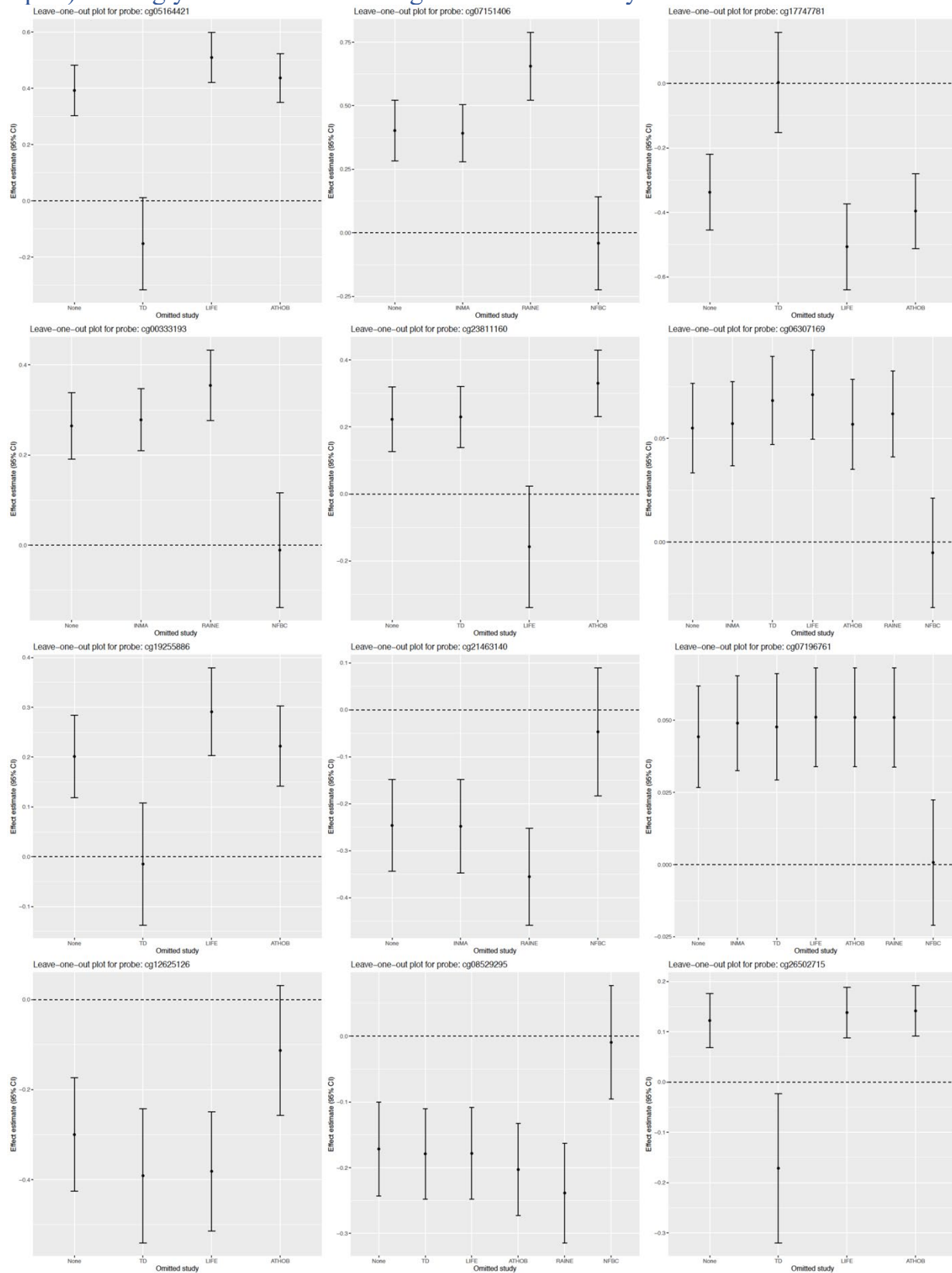


Figure S9. Leave study out meta-analysis effect estimates (95% CI) of the probes with highest heterogeneity based on I^2 -value of the glycemic index overweight/obese model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; ATHOB, Atherobesity; RAIN, the Raine study, NFBC, NFBC1986.

Supplemental Figure S10: Leave study out plots of the probes with highest I^2 -value (first 12 CpGs) of the glycemic load overweight/obese meta-analysis

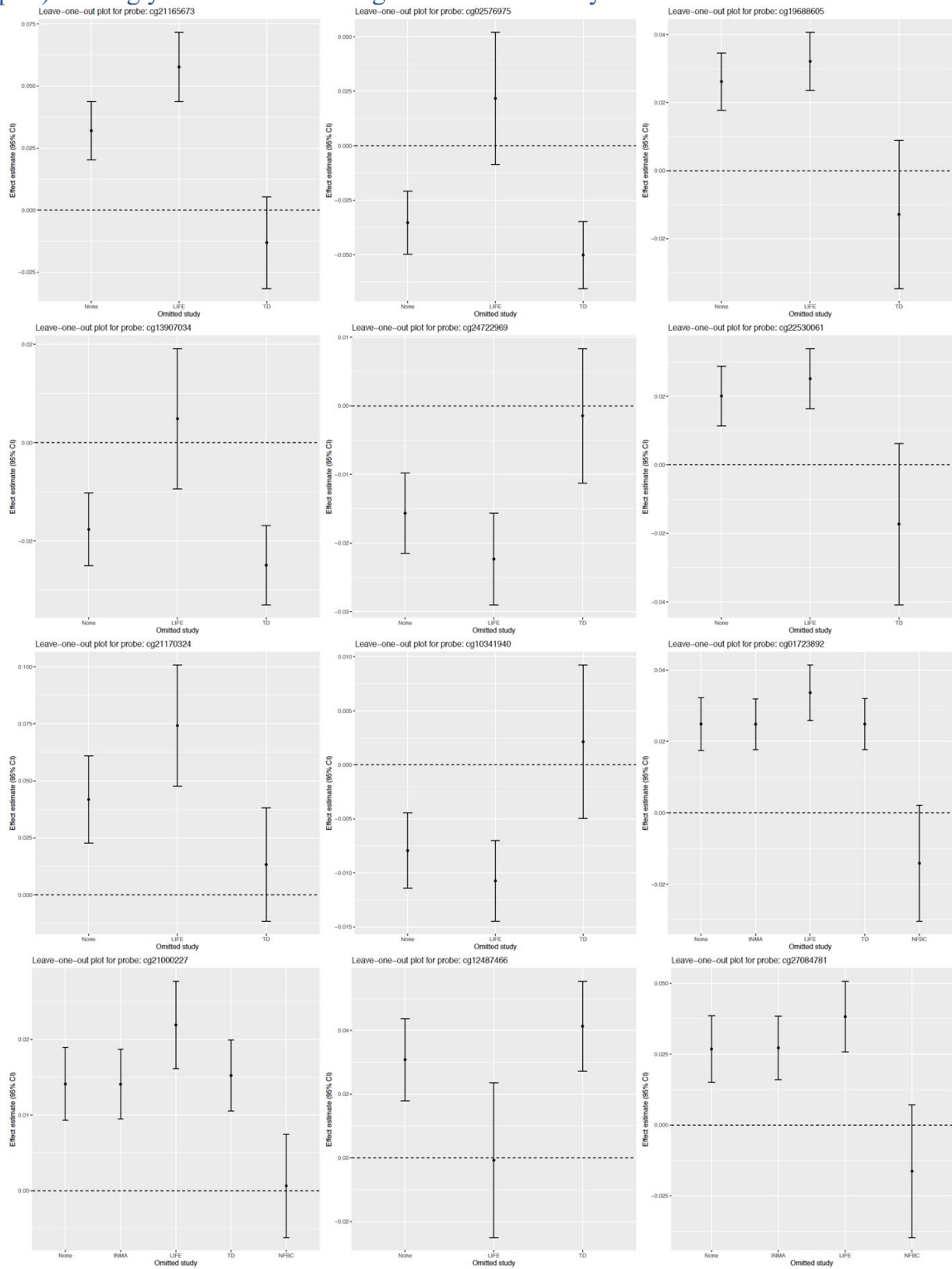


Figure S10. Leave study out meta-analysis effect estimates (95% CI) of the probes with highest heterogeneity based on I^2 -value of the glycemic load overweight/obese model. Shown are the 12 most heterogenous probes. Cohort abbreviations: TD, Teendiab; LIFE, Life Child; ATHOB, Atherobesity; RAINE, the Raine study, NFBC, NFBC1986.

Additional cohort information

INMA

Design and study population

The INMA -Infancia y Medio Ambiente- (Environment and Childhood) Project is a network of birth cohorts in Spain that aim to study the role of environmental pollutants in air, water and diet during pregnancy and early childhood in relation to child growth and development (1). Data for this study came from INMA Sabadell cohort (children born between 2004 and 2007). The selected only the European ancestry children. Study website: <http://www.proyectoinma.org/>.

Ethics statement

The study has been approved by Ethical Committee of each participating centre and written consent was obtained from participating parents.

TEENDIAB

Design and study population

The TEENDIAB study investigates the period of puberty and adolescence in the natural course of type 1 diabetes development (2). Between 2009 and 2015, a total of 610 children and adolescents aged 6-16 years with at least one first degree relative with type 1 diabetes and who were free of any diabetes-associated antibodies have been enrolled in this prospective observational cohort study. Follow-up visits took place every 6 months (on average) until the age of 18 years by 2016. The primary aims are to explore the roles of anthropometric, metabolic and genetic factors, as well as diet, physical activity, psychosocial factors and pubertal status in the development of islet autoimmunity and type 1 diabetes.

Ethics statement

The study was conducted according to the Declaration of Helsinki and approved by the ethical committee of the Technical University Munich (No. 2149/08) and Medizinische Hochschule Hannover (No. 5644). Written informed consent was obtained from children's parents.

ATHEROBESITY

Design and study population

77 lean children and 112 children with overweight or obesity aged 6 to 18 years were recruited between 2007 and 2015 from the area around Leipzig and underwent detailed cardiovascular and metabolic characterization. The participants were subsequently invited to follow-up visits after 2, 5, 7 and 10 years. More details on the study population have been described elsewhere (3,4).

Ethics statement

The study meets the ethical standards of the Declaration of Helsinki as revised in 2008 and has been approved by the institutional review board of the Medical Faculty of the University Leipzig, Germany (registration number at institutional review board: 029-2006; registration number at clinicaltrials.gov: NCT01605123). Written informed consent was provided by the legal guardians as well as the subjects themselves from the age of 12 years.

LIFE Child

Design and study population

The LIFE Child study is a large population-based longitudinal childhood cohort study conducted in the city of Leipzig, Germany. As a part of LIFE, a research project conducted at the Leipzig Research Center for Civilization Diseases, it aims to monitor healthy child development from birth to adulthood and to understand the development of lifestyle diseases such as obesity. The study consists of three interrelated cohorts; the birth cohort, the health cohort, and the obesity cohort. Depending on age and cohort, the comprehensive study program comprises different medical, psychological, and sociodemographic assessments as well as the collection of biological samples. Optimal data acquisition, process management, and data analysis are guaranteed by a professional team of physicians, certified study assistants, quality managers, scientists and

statisticians. Due to the high popularity of the study, more than 5000 children have already participated so far, and most of them participate continuously. The large quantity of acquired data allows LIFE Child to gain profound knowledge on the development of children growing up in the twenty-first century. The LIFE Child study has been described in more details elsewhere (5)

Ethics statement

The study meets the ethical standards of the Declaration of Helsinki as revised in 2008 and has been approved by the institutional review board of the Medical Faculty of the University Leipzig, Germany (registration number at institutional review board: 264-10-19042010; registration number at clinicaltrials.gov: NCT 02550236). Written informed consent was provided by both parents as well as the subjects themselves from the age of 12 years.

NFBC1986

Design and study population

The Northern Finland Birth Cohort 1986 (NFBC1986) is a longitudinal, population-based birth cohort comprising all births with an expected date of delivery between July 1, 1985 and June 30, 1986 in the Finnish provinces of Oulu and Lapland. 9,203 live-born individuals entered the study from which 7,182 answered the questionnaire and 6,795 completed the clinical examination at 16 years-of age (6).

Ethics statement

Approval for the studies was granted by the ethics committee of the Northern Ostrobothnia Hospital District in Oulu, Finland in accordance with the declaration of Helsinki.

Raine Study Gen2

Design and study population

The Raine Study is a prospectively recruited longitudinal pregnancy cohort that recruited 2900 mothers between 1989 and 1991 from Western Australia's major perinatal centre, King Edward Memorial Hospital, and nearby private practices. Women (Gen1) who had sufficient English language skills, an expectation to deliver at King Edward Memorial Hospital, and an intention to reside in Western Australia to allow for future follow-up of their child (Gen2) were eligible for the study (7).

Ethics statement

Informed consent was provided by all participants. Participant assent and parental consent was provided for minors. The Raine Study has ethics approval from The University of Western Australia Human Research Ethics Committee.

Additional cohort information on covariables

INMA

During the post-partum visit, age and sex of the child was collected by maternal self-report using a standardized questionnaire. None of the children smoke and therefore, smoking was not included into the models. Maternal education was collected by standardized questionnaires and categorized into three groups (low, medium and high) using the highest education level of the mothers. Child BMI was calculated using the height and weight measured at study visit by trained personal.

TEENDIAB

At each visit, age, sex and smoking status of the child/adolescent was collected by self-report using a standardized questionnaire. None of the included children reported smoking and therefore, smoking was not included into the models. Parental education was collected standardized questionnaires and categorized into three groups (low, medium and high) using the highest education level of the parents. Child BMI was calculated using the height and weight measured at study visit by trained personal.

ATHEROBESITY

At each visit, age, sex and smoking status of the child was collected by self-report using a standardized questionnaire. Only very few children smoked and therefore, smoking was not included into the models. Parental education was collected by standardized questionnaires and categorized into three groups using the highest education level of the parents (“low” = no professional education at all, “medium” = vocational training, “high” = academic degree). Child BMI was calculated using the height and weight measured at study visit by trained personal.

LIFE Child

At each visit, age, sex and smoking status of the child was collected by self-report using a standardized questionnaire. Only very few children smoked and therefore, smoking was not included into the models. As a measure of parental education, the socioeconomic status was calculated based on information regarding school education, professional education, profession and income, which were collected by standardized questionnaires (8). Hereby, the socioeconomic status could potentially range from 3 to 21 points and was divided into three categories: “low” (< 8.5), “medium” (8.5 up to 15.4) and high (> 15.4). Child BMI was calculated using the height and weight measured at study visit by trained personal.

NFBC1986

Age and sex were collected from birth records. At the clinical 16-year follow-up visit weight (kg) and height (cm) was measured, and BMI was calculated. At the time of follow-up visit, participants filled in a postal questionnaire about current smoking status with which was dichotomized (also “occasionally smoking” was categorized as smoking). Parental highest education was obtained via postal questionnaire from parents and was categorized from 1 to 6: 1. no professional training (low); 2. Vocational school or college 6-12 months (low); 3. Vocational school or college > 1 years (medium); 4. College-level training (medium); 5. University of applied sciences (high); 6. University degree (high).

Raine Study Gen2

To calculate BMI, trained researchers conducted weight and height measurements at the 14-year follow-up. Weight was measured to the nearest 100 g, using a Wedderburn Digital Chair Scale, and height was measured to the nearest 0.1 cm, with a Holtain stadiometer. Parental education was assessed using a self-report parental questionnaire. Age was determined using date of birth and date of assessment. Date of birth and sex were collected from birth records.

Additional cohort information on dietary assessment

INMA

The 105 item semi-quantitative food frequency questionnaire (FFQ) was administered to the parents to evaluate child’s usual dietary intake for the last 12 months at the 4-year assessment. The FFQ was previously validated by interviewing twice the parents or care-givers of children over a 9-month period. Reproducibility was explored by comparing intake of nutrients by the FFQs, while validity was examined by comparing the nutrient values from the FFQs with the average nutrient values of three 24-hour dietary recall (24hDR) taken in the period, and also, with the concentration in blood specimens for several vitamins (carotenoids, folate, vitamin B12, vitamin C and α -tocopherol). Pearson correlation coefficients and de-attenuated correlation coefficients were calculated and we also evaluated misclassification by quintile distribution. More details of the validation can be found elsewhere (9)

TEENDIAB

Habitual dietary intake was assessed at first study visit using the modified computer-assisted Diet Interview Software for Health Examination Studies Junior (DISHES Junior; Robert Koch Institute, Berlin, Germany). The standardized questionnaire was performed by face-to-face interview with trained staff and collected detailed data on the consumed frequency, type and quantity of foods and beverages of the last four weeks (10).

ATHEROBESITY

Patients had to fill out a dietary protocol as detailed as possible over 3-5 days. Data were matched with the software EBISpro 2016 to the item of the “Bundeslebensmittelschlüssel”. Overall, 761 different food items were specified by participants.

LIFE Child

In the LIFE Child study, dietary data was collected in children and adolescents aged six years and older. The FFQ used in the LIFE Child study is described in more detail in Stiegler et al. (11).

NFBC1986

At the 16-year visit, a FFQ was filled out by each subject. The FFQ contained food items generally consumed in Finland and was not designed for a specific trait. The collection of dietary data and blood sampling was completed during one year.

Raine Study Gen2

Adolescents who attended the 14-year follow-up assessment at the Telethon Institute for Child Health Research in Perth, Western Australia, were given a 3-day food record to complete, with parental assistance allowed if required. Metric measuring cups and spoons were provided to assist with quantification of serve sizes. Adolescents indicated whether each day was representative of their usual eating habits. As the food records were returned, they were checked by a dietitian who clarified details over the telephone where necessary. Data were analysed using Food Works (Professional Version 4.00, Xyris Software, Brisbane, Queensland, Australia) and a customized GI database (12).

Additional cohort information on DNA methylation analyses

INMA

Child blood collected at the age of 4 years was extracted using the Chemagen kit (Perkin Elmer). DNA concentration was determined by NanoDrop spectrophotometer (Thermo Scientific) and with the Quant-iT PicoGreen dsDNA Assay Kit (Life Technologies). Methylation data was produced in two different laboratories as part of two different projects: in the Genome Analysis Facility of the University Medical Center Groningen (UMCG) in Holland, and in the Bellvitge Biomedical Research Institute (IDIBELL, Barcelona). Both laboratories used the recommended Illumina protocol for the Infinium HumanMethylation450 beadchip. Briefly, 500 ng of DNA was bisulfite-converted using the EZ 96-DNA methylation kit following the manufacturer's standard protocol, and DNA methylation measured using the Illumina Infinium HumanMethylation450 beadchip. DNA methylation data were quality controlled and preprocessed using the minfi package (13). A series of steps were completed for quality control and data analysis. The first step was low quality sample removal. First, 2 samples with bad overall quality or with low detection p-value according to the output of the MethylAid package (14) were removed. Then, we removed 3 samples whose sex was wrongly predicted using shinyMethyl were eliminated (15). Following guidelines of Lehne work (16), we increased the stringency of the detection p-value threshold to 10E-16 and we filtered 18 samples with a call rate lower than 98%. Data was normalized with the functional normalization method. Correlation between SNPs in replicates replicated samples was checked and probes not measuring SNPs were discarded. 7,136 probes with a call rate lower than 95% were also removed. Probes in sexual chromosomes, crosshybridizing or containing SNPs were flagged but not removed at this point. ComBat was applied to remove laboratory batch effect (17). Finally, duplicated samples were removed, prioritizing MeDALL samples over BREATHE samples. In this current study we used samples collected at 4 years: 182 samples and 476,946 CpGs. Child blood cell proportions were estimated using the Reinius reference panel (18) with the pickCompProbes method (minfi) for CpG selection, and the Houseman algorithm (19) for deconvolution of 6 main blood cell types.

TEENDIAB

DNA was extracted from whole blood. Bisulfite conversion of genomic DNA was performed and bisulfite-converted DNA was subjected to a genome-wide DNA methylation analysis performed using the Illumina Infinium MethylationEPIC 850k Bead-Chip array (San Diego, CA). All samples were randomized across the chips and analyzed on the same machine by the same technician to reduce batch effects. After single-base extension and staining, the BeadChips were imaged with the Illumina iScan. Raw fluorescence intensities of the scanned images were extracted with the GenomeStudio Methylation module (Illumina). The fluorescence intensity ratio was used to calculate the β -value. All samples had high bisulfite conversion efficiency (signal intensity >4,000) and were included for further analysis based on GenomeStudio quality control. Quality control was performed using R software (version 4.0.3). The DNA methylation IDAT files were imported using the R package *minfi* for pre-processing and quality control (13). The following probes were excluded from further analysis: probes with a detection P value ≥ 0.01 for at least one sample, cross-hybridizing probes, probes with a bead count less than three in at least 5% of the samples, non-CpG probes, and probes that lie near single nucleotide polymorphisms. Probes on chromosomes X and Y were used for sex estimation and then excluded from downstream analyses. Samples with <99% probes with a detection P value <0.01 were excluded. Probe design biases and batch effects were normalized using R packages ENmix and sva (20), respectively. After quality control, cell composition was estimated from a reference panel using the R package FlowSorted.Blood.EPIC.

To remove unwanted variation/batch effects, Combat method was applied as implemented in the R package (17).

ATHEROBESITY

Preprocessing was done applying Bioconductor packages ChAMP 2.18.3 (21) jointly with the samples of the LIFE Child Study. Only probes present in all samples were considered. Preprocessing included k-nearest neighbor imputing of missing values (with parameter $k=3$), filtering of methylation probes at detection p-value threshold 0.01, filtering probes with a bead count of less than three in 5 or more percent of samples, removing non-CG probes, filtering probes which fall near SNPs and which align to multiple locations, both as defined by Nordlund et al. (22) and filtering probes with missingness higher than 10%. Samples identified as outlier in multi-dimensional-scaling, with high proportion of failed detection-p-value (>10%), and irregular distribution of density distribution of methylation values were removed ($n=4$). Data was normalized using the BMIQ (Beta MIXture Quantile dilation) method (23). Initial batch-adjustment was done applying ComBat on expression-chip batches without protecting any contrasts (20). Finally, 12 samples were removed, as reported sex and sex imputed from methylation data was conflicting. Cell type proportions were estimated applying previously reported reference data (19). The Satrix ID was used for batch correction.

LIFE Child

Preprocessing was done applying Bioconductor packages ChAMP 2.18.3 (21) jointly with the samples originating from the Leipzig Atherobesity Childhood Cohort. Only probes present in all samples were considered. Preprocessing included k-nearest neighbor imputing of missing values (with parameter $k=3$), filtering of methylation probes at detection p-value threshold 0.01, filtering probes with a bead count of less than three in 5 or more percent of samples, removing non-CG probes, filtering probes which fall near SNPs and which align to multiple locations, both as defined by Nordlund et al. (22), and filtering probes with missingness higher than 10%. Samples identified as outlier in multi-dimensional-scaling, with high proportion of failed detection-p-value (>10%), and irregular distribution of density distribution of methylation values were removed ($n=2$). Data was normalized using the BMIQ (Beta MIXture Quantile dilation) method (23). Initial batch-adjustment was done applying ComBat on expression-chip batches without protecting any contrasts (20). Finally, 6 samples were removed, as reported sex and sex imputed from methylation data was conflicting. Cell type proportions were estimated applying previously reported reference data (19). The Satrix ID was used for batch correction.

NFBC1986

Offspring DNA methylation was assayed using Infinium HumanMethylation450 BeadChip (Illumina, Inc., San Diego, CA, USA) for 546 randomly selected subjects. Bisulphite conversion of genomic DNA was performed using the EZ DNA methylation kit according to manufacturer's instructions (Zymo Research,

Orange, CA). From these, 24 technical replicates, 18 samples that did not reach a call rate of >95% applying a detection P-value filter of 10-16 and 7 samples with gender inconsistency were excluded. DNA methylation data of 517 samples were used in the analysis. DNA methylation data was normalised by functional normalisation (24) and potential confounding effects of blood cell subtypes were estimated by the Houseman method (25).

Raine Study Gen2

Clinical examination of the offspring at the age of 16 years was conducted between April 2007 and February 2008. Offspring DNA methylation was assayed using Infinium HumanMethylation450 BeadChip (Illumina, Inc., San Diego, CA, USA) for 546 randomly selected subjects. Bisulphite conversion of genomic DNA was performed using the EZ DNA methylation kit according to manufacturer's instructions (Zymo Research, Orange, CA). Processing of the Illumina Infinium HumanMethylation450 BeadChips was carried out by the Centre for Molecular Medicine and Therapeutics (CMMT) (<http://www.cmmt.ubc.ca>). Two packages were used to perform QC checks of the samples; shinyMethyl (15) and MethylAid (14). Samples that were evident as outliers based on the output from shinyMethyl and MethylAid were removed. Gender discrepancy was inferred using the RnBeads package (26), and samples showing discrepancies were excluded. Samples that were run in duplicate or triplicate present on the Bead-Chip were used to assess genetic similarity between these individuals as a check for sample mix-ups. Samples showing signs of contamination based on heatmap produced by the RnBeads package were excluded. Intentional SNP probes, sex chromosome probes and probes with a detection p-value greater than 0.05 in any sample were removed. Probes with low bead counts (bead count < 3 in more than 5% of samples) were also removed. Methylation data were normalized and batch effects accounted by using functional normalization method (24). Potential confounding effects of blood cell subtypes were estimated by the Houseman method (19). Plate was used as technical variable in the models. In addition, we adjusted for time difference between time of dietary questionnaire and time of blood sampling.

Material and methods – Mendelian randomization (two-sample) analysis

We evaluated the overlap between the CpGs significantly associated with GI/GL in the meta-analysis and mQTLs of the ARIES data at childhood (834 Europeans; 39,833 cis- and trans-mQTLs, 8282911 input SNPs, 395625 input CpGs) (27). Next, we queried the public GWAS catalog (<https://www.ebi.ac.uk/gwas/home>) for the traits childhood obesity and obesity (https://www.ebi.ac.uk/gwas/efotraits/EFO_0001073; 295 associations), cardiovascular disease (https://www.ebi.ac.uk/gwas/efotraits/EFO_0000319; 10,141 associations) and type 2 diabetes (https://www.ebi.ac.uk/gwas/efotraits/MONDO_0005148; 5,443 associations) and evaluated the overlap between genetic risk variants of these traits and the identified mQTLs. We performed mendelian randomization analysis (two-sample) using the Wald-estimate as implemented in the *TwoSampleMR* R package. The ARIES mQTL data were used as exposure set and the overlapping genetic variants as instrumental variables.

Material and methods – eQTM analyses Leipzig Childhood Adipose Tissue Cohort

We analysed 223 participants from the Leipzig Childhood AT Cohort, for which subcutaneous adipose tissue samples had been obtained as previously described (28).

Methylome profiling was obtained with the Illumina Infinium MethylationEPIC BeadChip Kit (Illumina, California, USA). The Illumina intensity data (IDAT) files were processed using the ChAMP pipeline (21) implemented in the corresponding in R package, filtering out probes with detection p-value > 0.1 and low bead counts, non-CpG probes, SNP-related probes, and probes on sex chromosomes. Intra-array between-sample bias was corrected using beta-mixture quantile normalization (BMIQ), and batch effects and unknown confounders were removed using Combat (17). Methylation levels at each CpG site were expressed as a β -value representing the approximate proportion of methylation at the site (0–100%).

RNA transcript levels were quantified via Illumina HumanHT-12 v4.0 Expression BeadChip (Illumina, California, USA). 48,106 probes, corresponding to 47,230 gene-expression probes and 876 control probes, could be successfully imputed. Mapping of genes corresponding to expression probes and assignment of gene names was done using a remapping approach (29) which resulted in 23,593 valid gene-expression probes

corresponding to 17,726 unique genes with good or perfect annotation quality grade. Transcription start and end sites according to Ensembl version 106 (April 2022) were retrieved via the Bioconductor package biomaRt (<https://bioconductor.org/packages/release/bioc/html/biomaRt.html>). Prior to the analysis, expressions were quantile-normalised and log2 transformed.

We looked up the association of the 537 prioritized CpGs with the gene transcripts. 35 of the 537 prioritized CpGs were not available as they were discarded during the pre-processing phase, while a further 22 did not fall within a 500kb region of the transcription start site of valid gene transcripts. For each of the remaining 480 CpGs, we regressed the log2 expression signals for the transcripts on methylation β -values for the CpG, using linear regression models adjusted for age and sex. We declared statistical significance of each CpG-transcript pair according to a Bonferroni-corrected p-value, with denominator corresponding to the number of tests evaluated for each pair. The number of tests for each pair was determined as the total number of CpGs tested (480, since 57 CpGs were discarded prior to the statistical analysis) plus the number of tests per each unique CpG-transcript pair.

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