Maternal dietary glycemic index and glycemic load in pregnancy and offspring neonatal DNA methylation

Supplemental File

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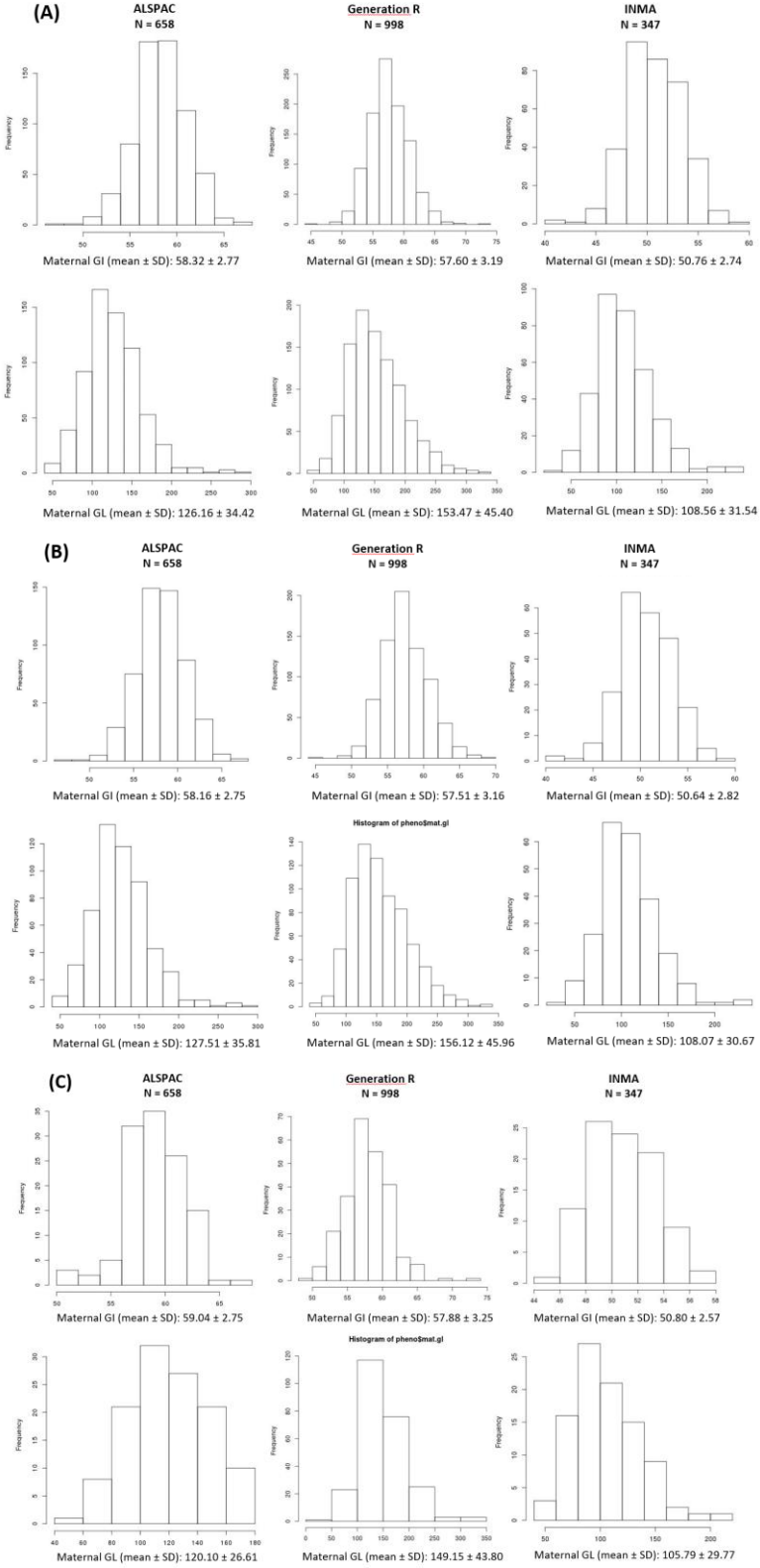
Contents

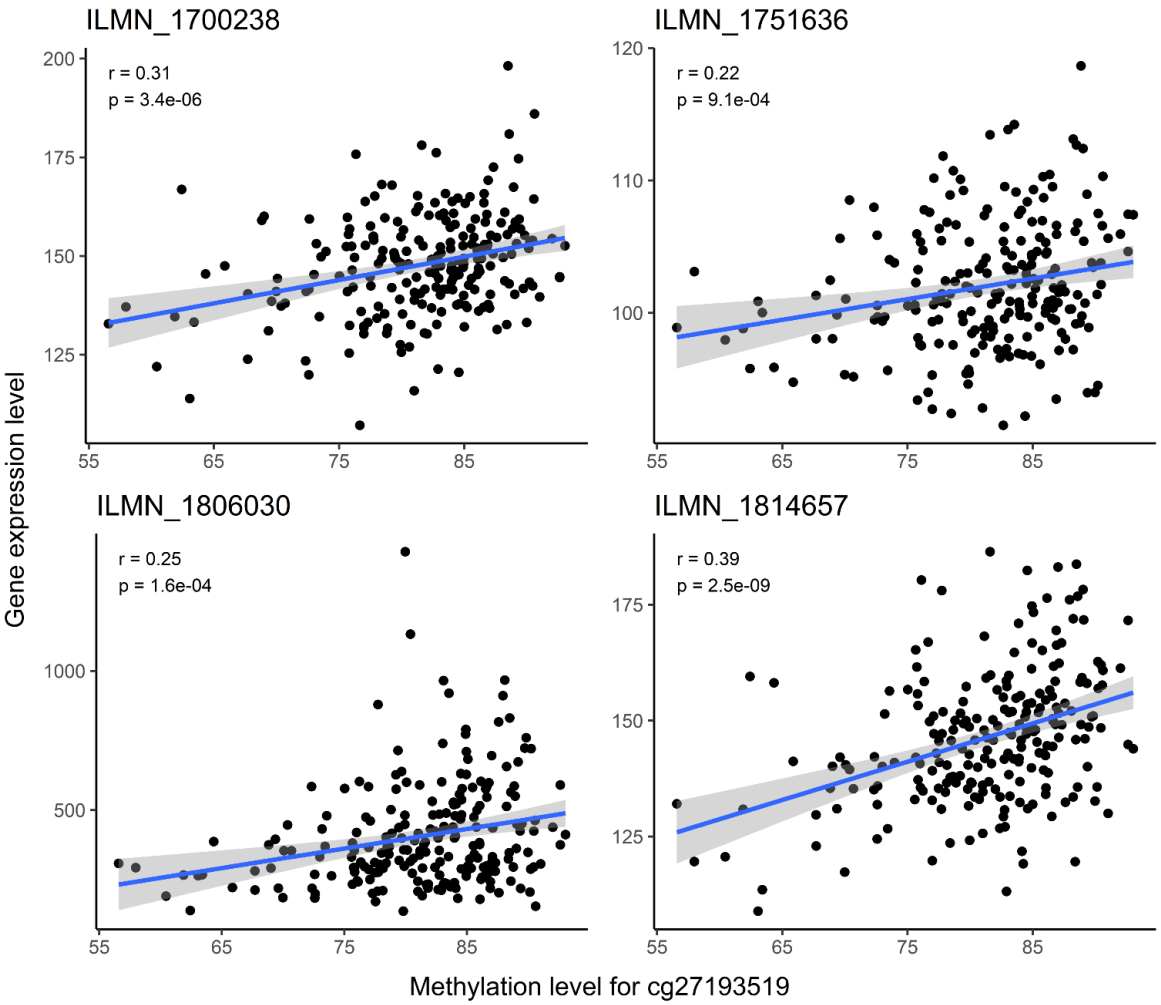
SUPPLEMENTAL TABLES

Supplemental tables are included in a separate Excel file.

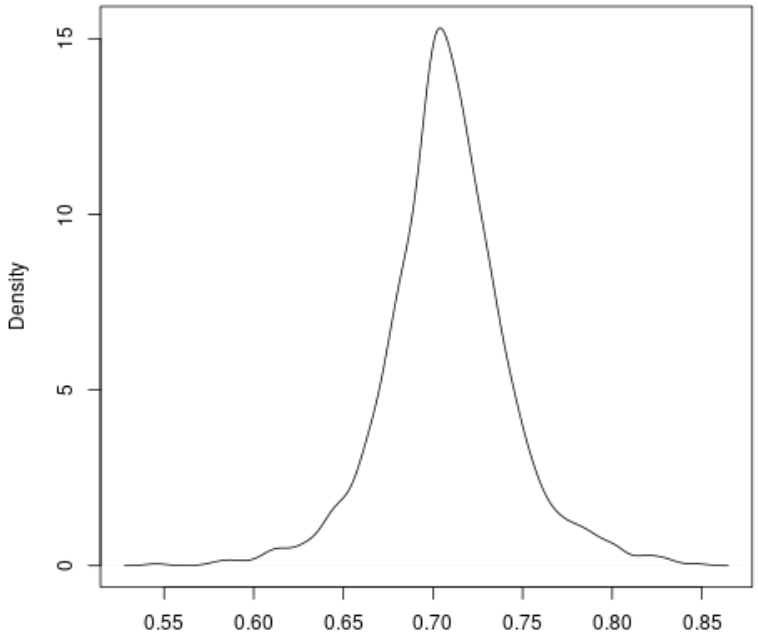
SUPPLEMENTAL FIGURES



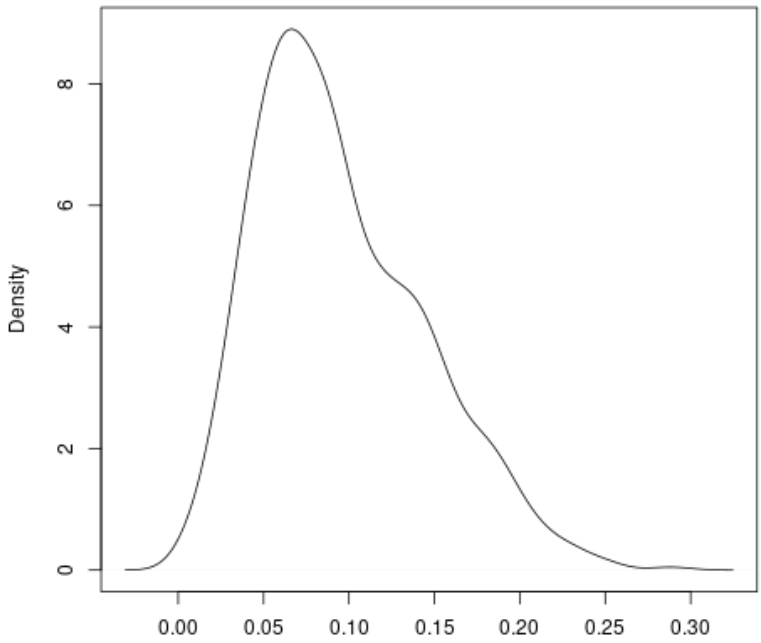
Supplemental Figure 1. Cohort-specific distribution of maternal glycemic index (GI) and maternal glycemic load (GL) in all mothers (A), mothers with normal weight (B) and mothers with overweight/obesity (C).



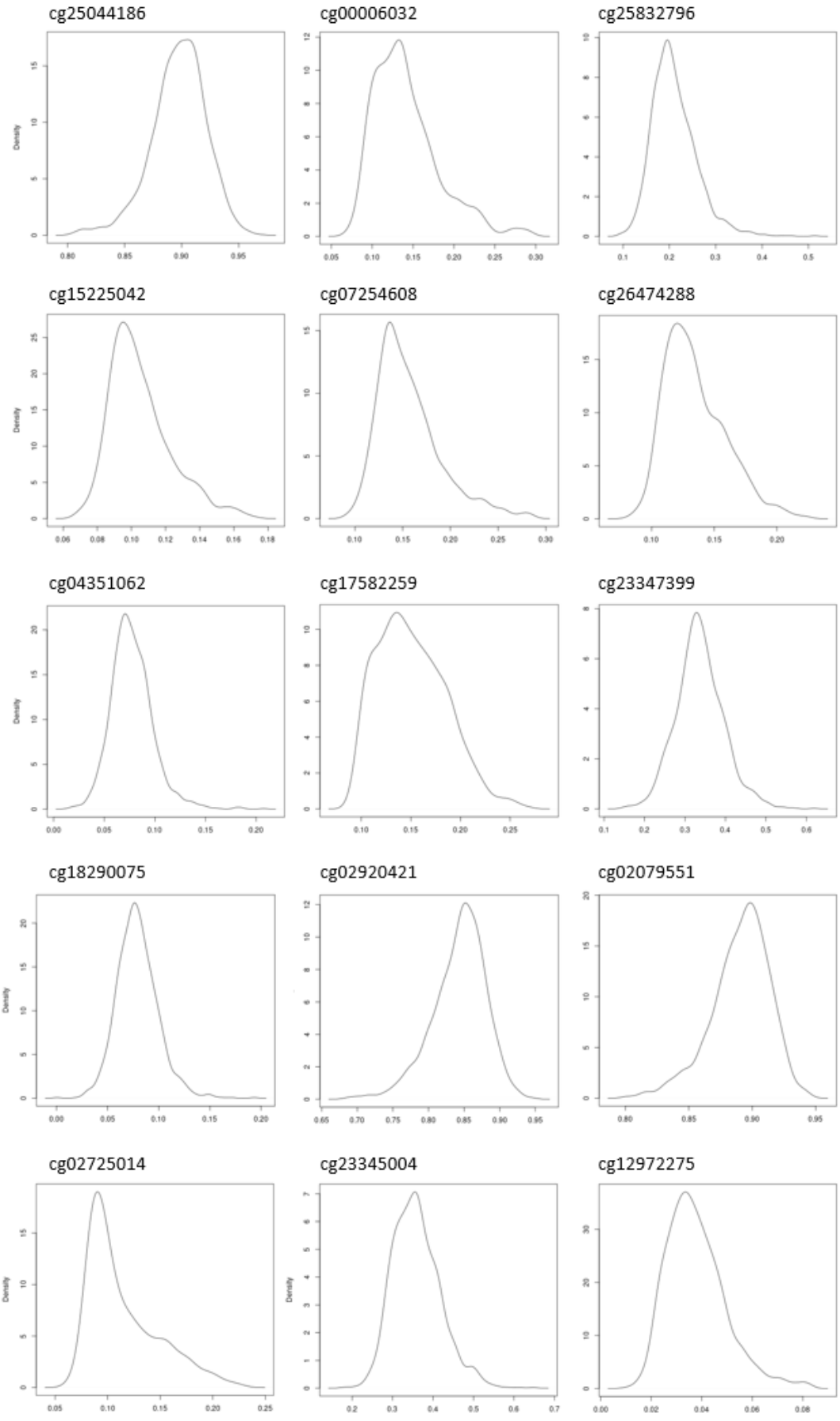
Supplemental Figure 2. Correlation plots for the four significant CpG-transcript pairs in adipose tissue in the Leipzig Childhood AT Cohort. DNA methylation level is measured in whole blood sample and gene expression level is measured in adipose tissue of the same individuals.

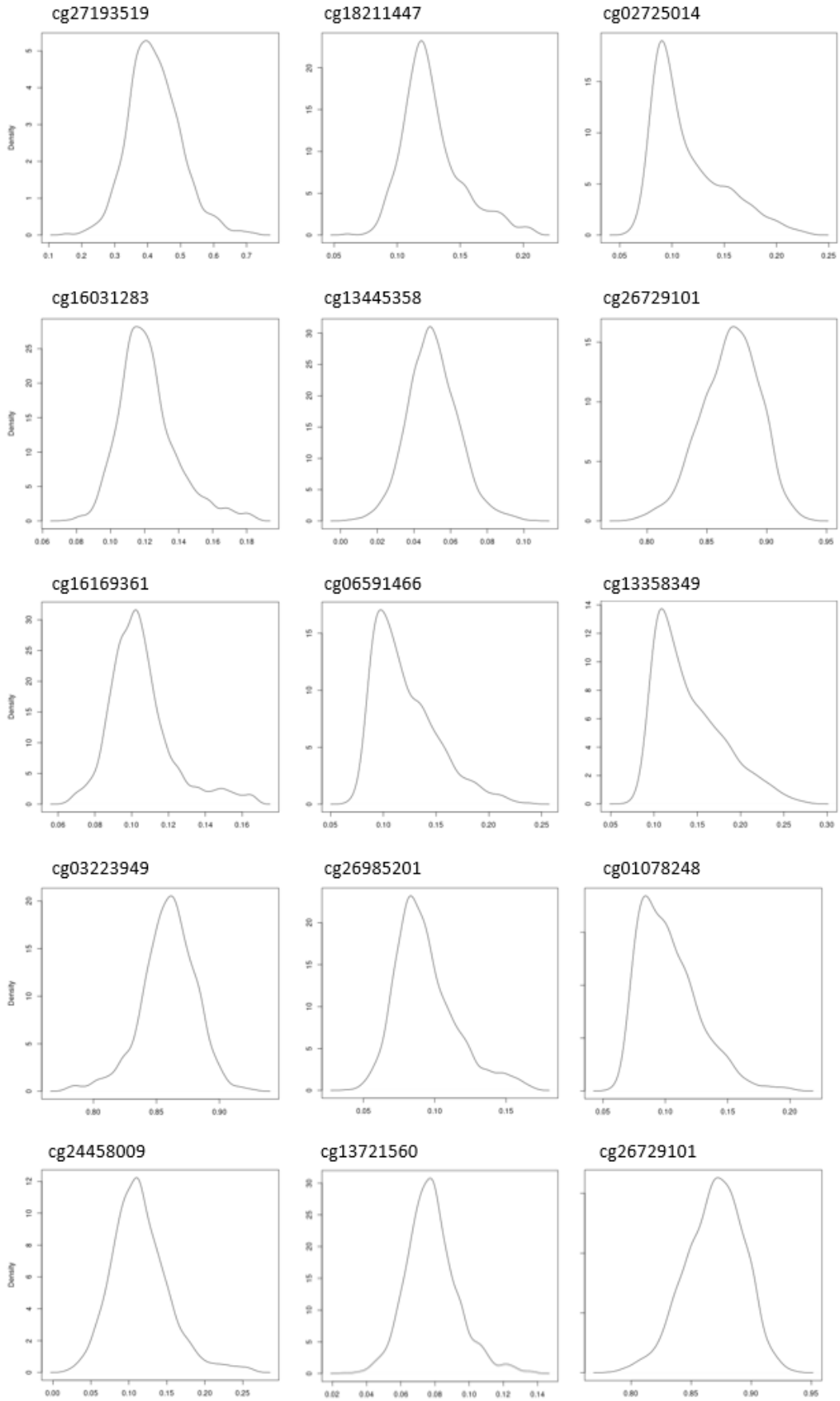


Supplemental Figure 3. Distribution plot for cg21301148 in Generation R.

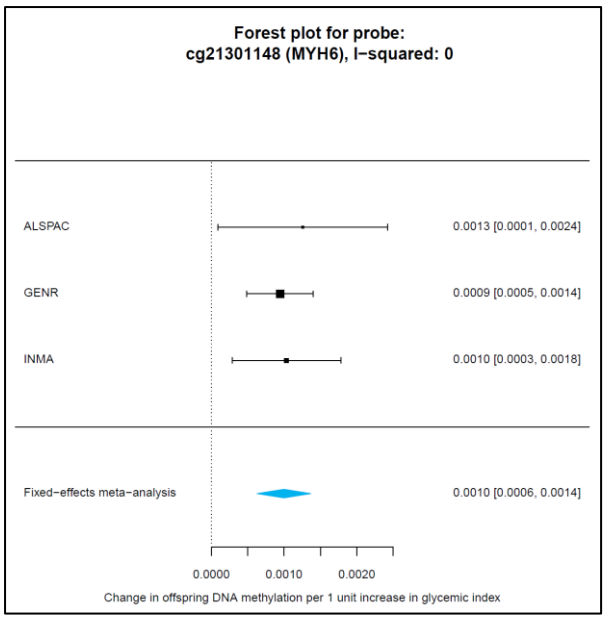


Supplemental Figure 4. Distribution plot for cg27528695 in Generation R.

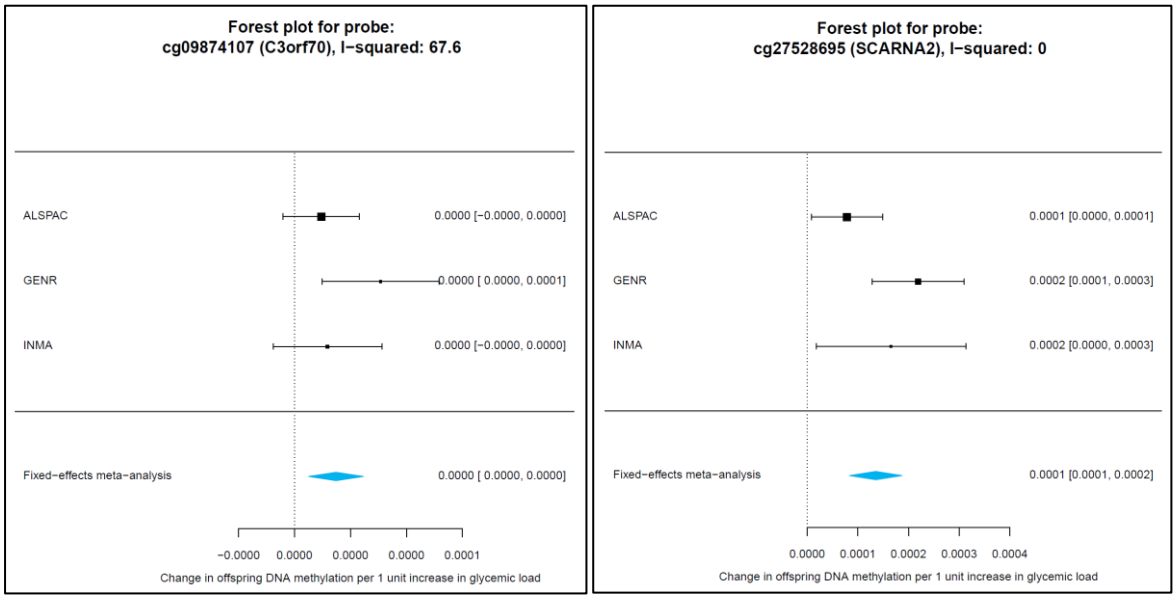

cg25044186
cg00006032
cg25832796
cg15225042
cg07254608
cg26474288
cg04351062
cg17582259
cg23347399
cg18290075
cg02920421
cg02079551
cg02725014
cg23345004
cg12972275
Density



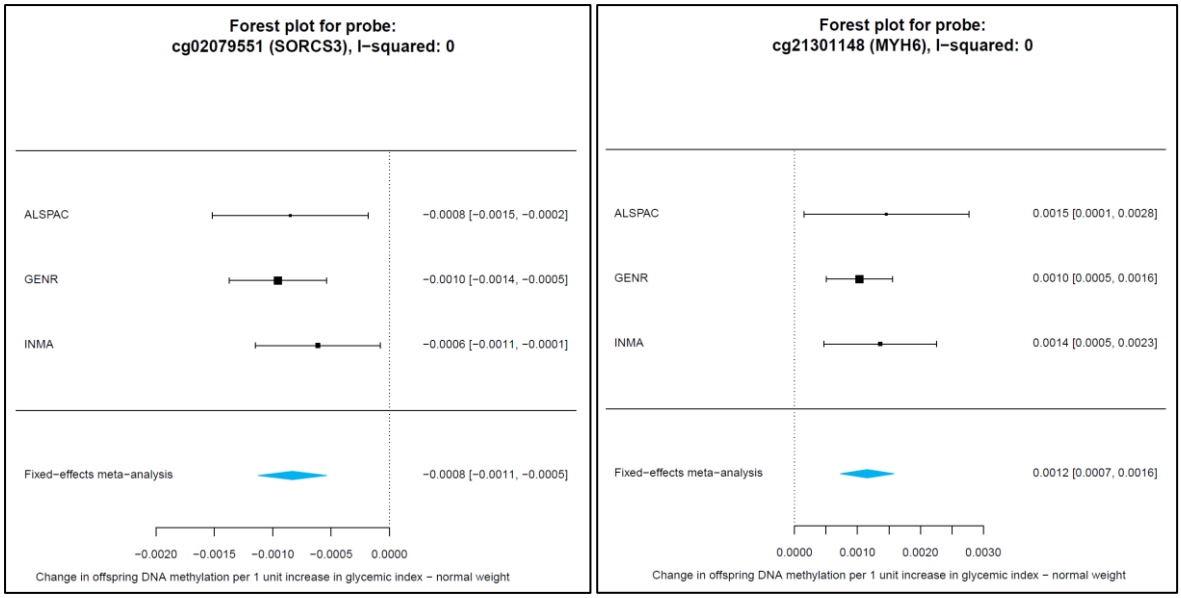
Supplemental Figure 5. Distribution plots for all top hits from the stratified analyses that were flagged as either mQTL or polymorphic.



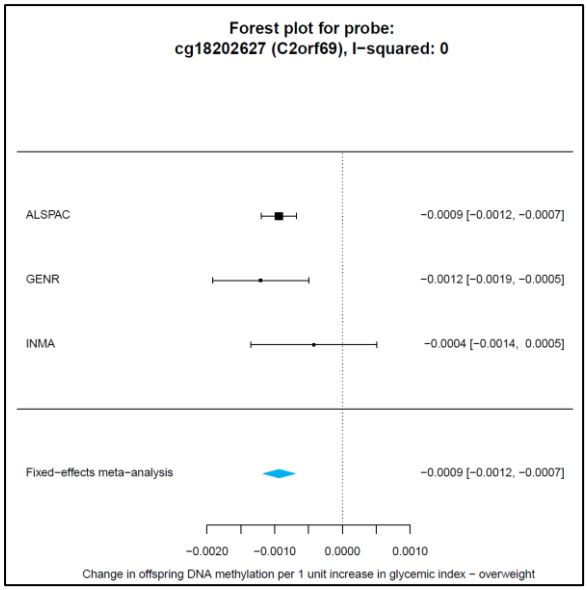
Supplemental Figure 6. Forest plot for the CpG associated with glycemic index in the full group.

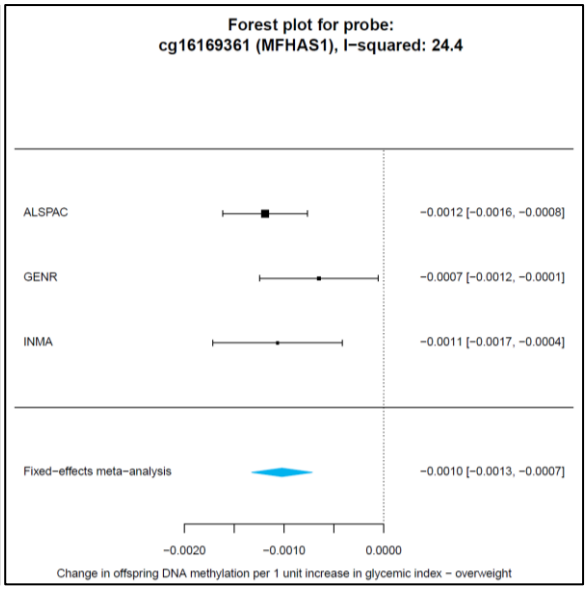


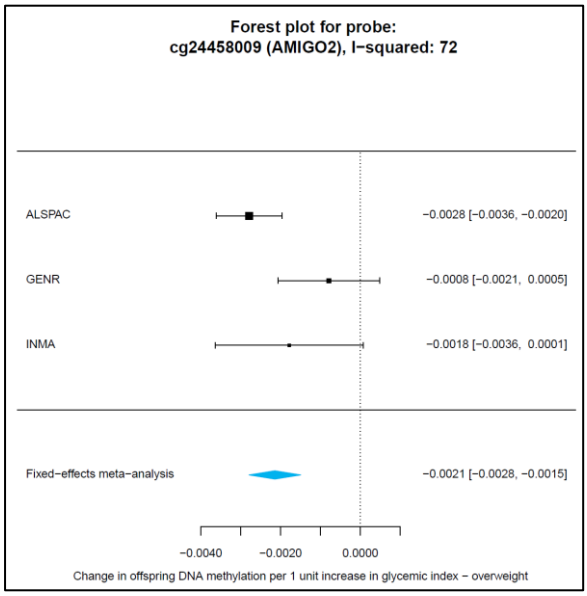
Supplemental Figure 7. Forest plot for the CpGs associated with glycemic load in the full group.

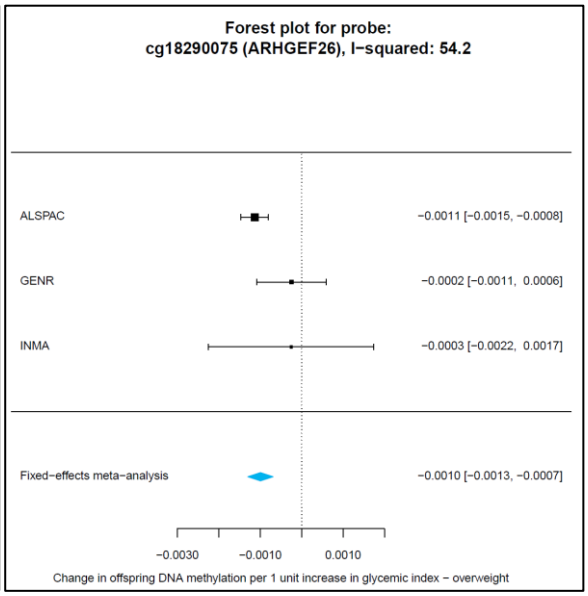


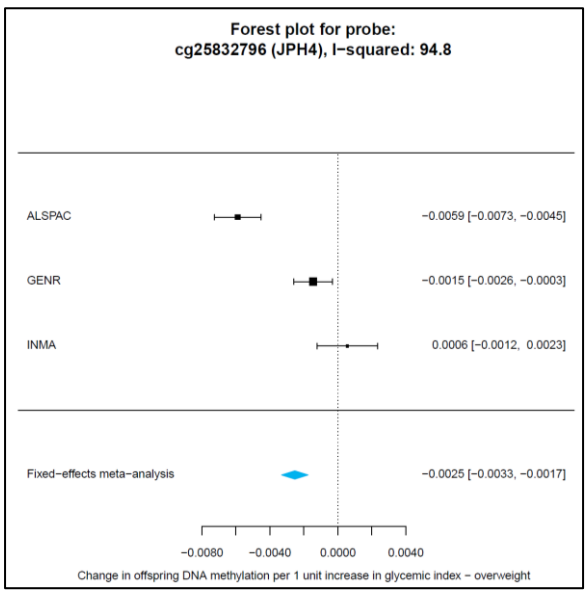
Supplemental Figure 8. Forest plot for the CpGs associated with glycemic index in mothers with normal weight.

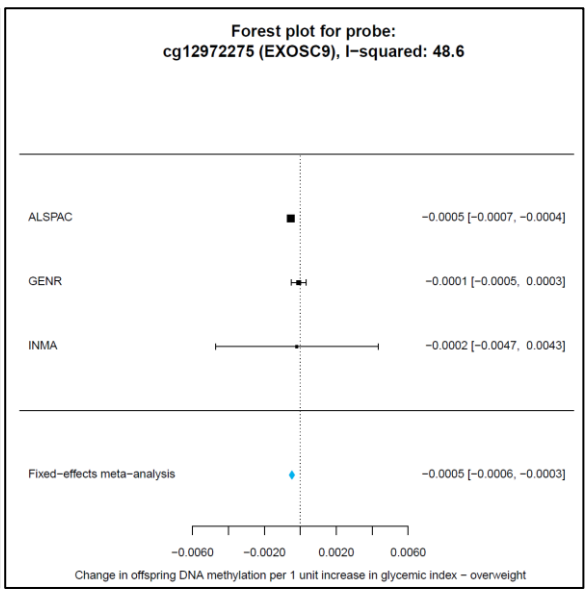

Forest plot for probe:
cg18202627 (C2orf69), I−squared: 0
ALSPAC
GENR
INMA
Fixed−effects meta−analysis
−0.0009 [−0.0012, −0.0007]
−0.0012 [−0.0019, −0.0005]
−0.0004 [−0.0014, 0.0005]
−0.0009 [−0.0012, −0.0007]
−0.0020
−0.0010
0.0000
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

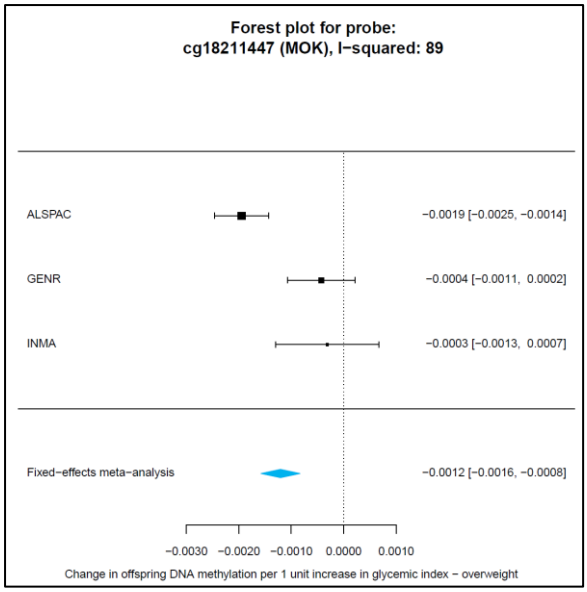

Forest plot for probe:
cg16169361 (MFHAS1), I−squared: 24.4
ALSPAC
GENR
INMA
Fixed−effects meta−analysis
−0.0012 [−0.0016, −0.0008]
−0.0007 [−0.0012, −0.0001]
−0.0011 [−0.0017, −0.0004]
−0.0010 [−0.0013, −0.0007]
−0.0020
−0.0010
0.0000
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

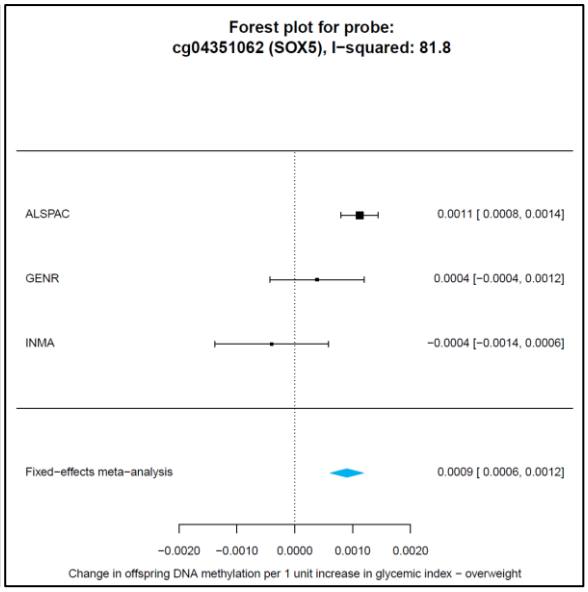

Forest plot for probe:
cg24458009 (AMIGO2), I−squared: 72
ALSPAC
GENR
INMA
Fixed−effects meta−analysis
−0.0028 [−0.0036, −0.0020]
−0.0008 [−0.0021, 0.0005]
−0.0018 [−0.0036, 0.0001]
−0.0021 [−0.0028, −0.0015]
−0.0040
−0.0020
0.0000
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

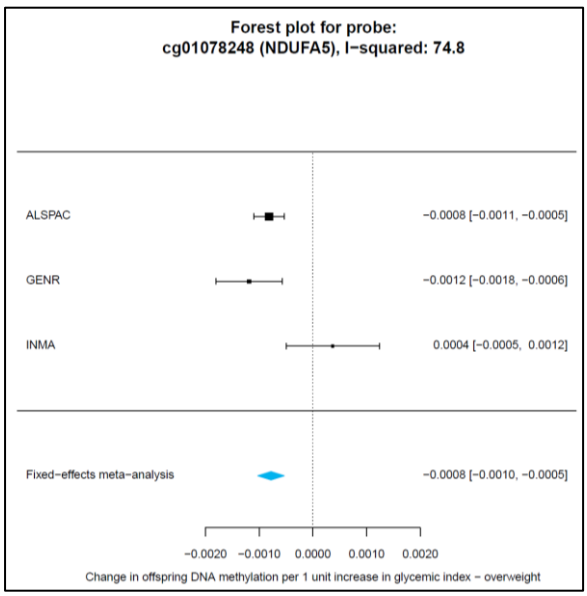

Forest plot for probe:
cg18290075 (ARHGEF26), I−squared: 54.2
ALSPAC
GENR
INMA
Fixed−effects meta−analysis
−0.0011 [−0.0015, −0.0008]
−0.0002 [−0.0011, 0.0006]
−0.0003 [−0.0022, 0.0017]
−0.0010 [−0.0013, −0.0007]
−0.0030
−0.0010
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

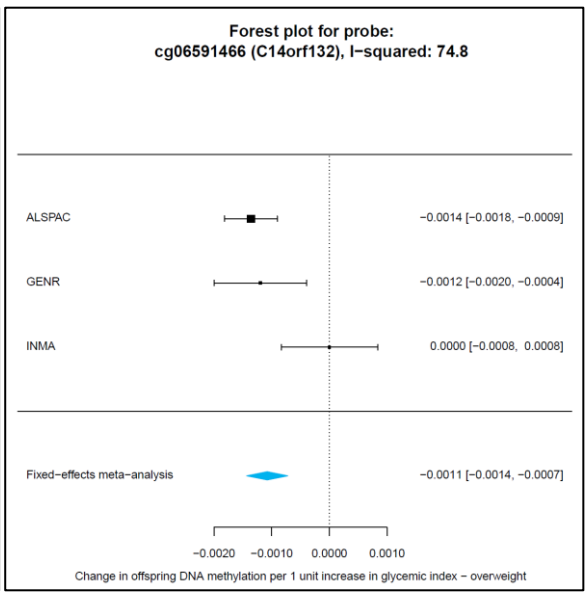

Forest plot for probe:
cg25832796 (JPH4), I−squared: 94.8
ALSPAC
GENR
INMA
Fixed−effects meta−analysis
−0.0059 [−0.0073, −0.0045]
−0.0015 [−0.0026, −0.0003]
0.0006 [−0.0012, 0.0023]
−0.0025 [−0.0033, −0.0017]
−0.0080
−0.0040
0.0000
0.0040
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

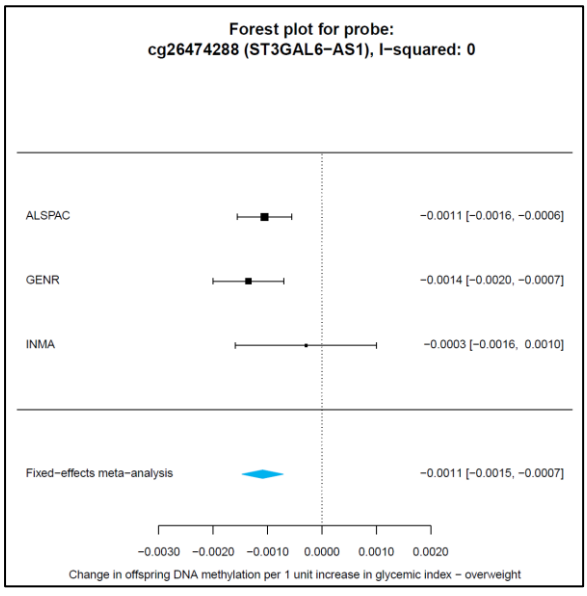

Forest plot for probe:
cg12972275 (EXOSC9), I−squared: 48.6
ALSPAC
GENR
INMA
Fixed−effects meta−analysis
−0.0005 [−0.0007, −0.0004]
−0.0001 [−0.0005, 0.0003]
−0.0002 [−0.0047, 0.0043]
−0.0005 [−0.0006, −0.0003]
−0.0060
−0.0020
0.0020
0.0060
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

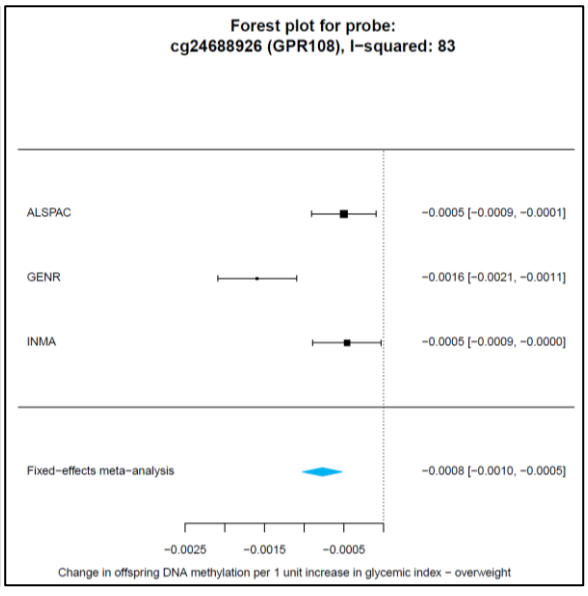

Forest plot for probe:
cg18211447 (MOK), I−squared: 89
ALSPAC
−0.0019 [−0.0025, −0.0014]
GENR
−0.0004 [−0.0011, 0.0002]
INMA
−0.0003 [−0.0013, 0.0007]
Fixed−effects meta−analysis
−0.0012 [−0.0016, −0.0008]
−0.0030 −0.0020 −0.0010 0.0000 0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

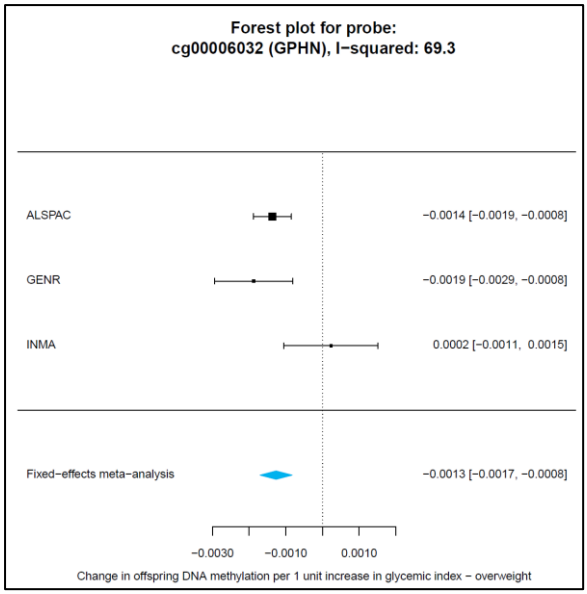

Forest plot for probe:
cg04351062 (SOX5), I−squared: 81.8
ALSPAC
0.0011 [0.0008, 0.0014]
GENR
0.0004 [−0.0004, 0.0012]
INMA
−0.0004 [−0.0014, 0.0006]
Fixed−effects meta−analysis
0.0009 [0.0006, 0.0012]
−0.0020 −0.0010 0.0000 0.0010 0.0020
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

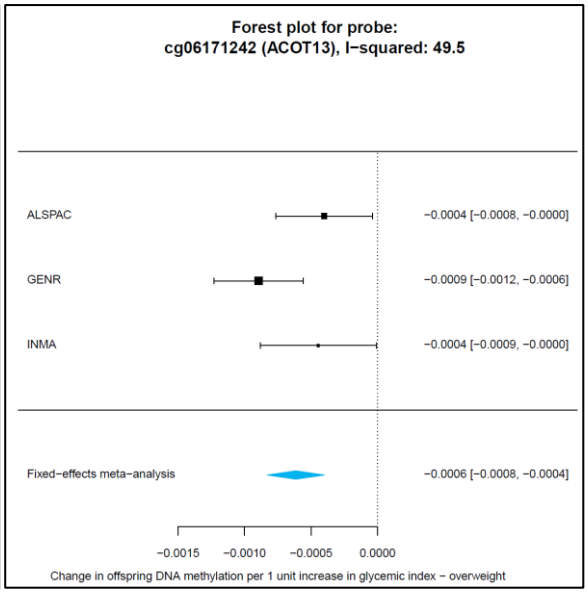

Forest plot for probe:
cg01078248 (NDUFA5), I−squared: 74.8
ALSPAC
−0.0008 [−0.0011, −0.0005]
GENR
−0.0012 [−0.0018, −0.0006]
INMA
0.0004 [−0.0005, 0.0012]
Fixed−effects meta−analysis
−0.0008 [−0.0010, −0.0005]
−0.0020 −0.0010 0.0000 0.0010 0.0020
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

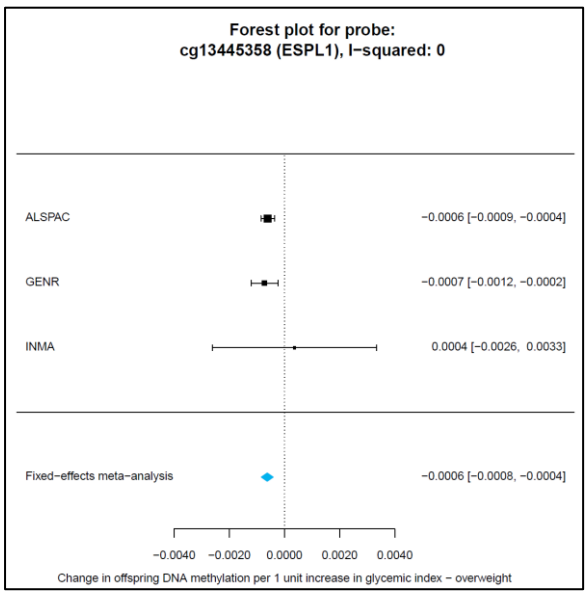

Forest plot for probe:
cg06591466 (C14orf132), I−squared: 74.8
ALSPAC
−0.0014 [−0.0018, −0.0009]
GENR
−0.0012 [−0.0020, −0.0004]
INMA
0.0000 [−0.0008, 0.0008]
Fixed−effects meta−analysis
−0.0011 [−0.0014, −0.0007]
−0.0020 −0.0010 0.0000 0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

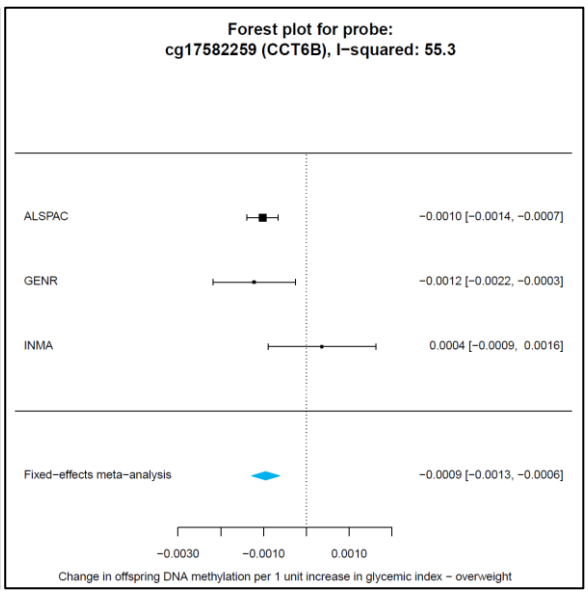

Forest plot for probe:
cg26474288 (ST3GAL6−AS1), I−squared: 0
ALSPAC
−0.0011 [−0.0016, −0.0006]
GENR
−0.0014 [−0.0020, −0.0007]
INMA
−0.0003 [−0.0016, 0.0010]
Fixed−effects meta−analysis
−0.0011 [−0.0015, −0.0007]
−0.0030 −0.0020 −0.0010 0.0000 0.0010 0.0020
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

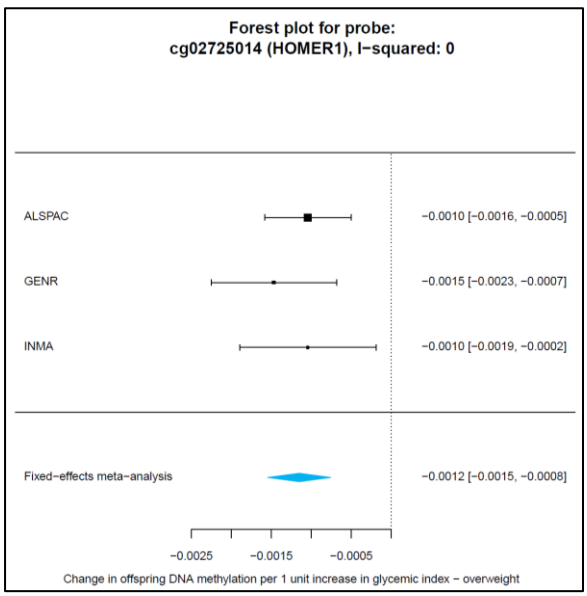

Forest plot for probe:
cg24688926 (GPR108), I−squared: 83
ALSPAC
−0.0005 [−0.0009, −0.0001]
GENR
−0.0016 [−0.0021, −0.0011]
INMA
−0.0005 [−0.0009, −0.0000]
Fixed−effects meta−analysis
−0.0008 [−0.0010, −0.0005]
−0.0025 −0.0015 −0.0005
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

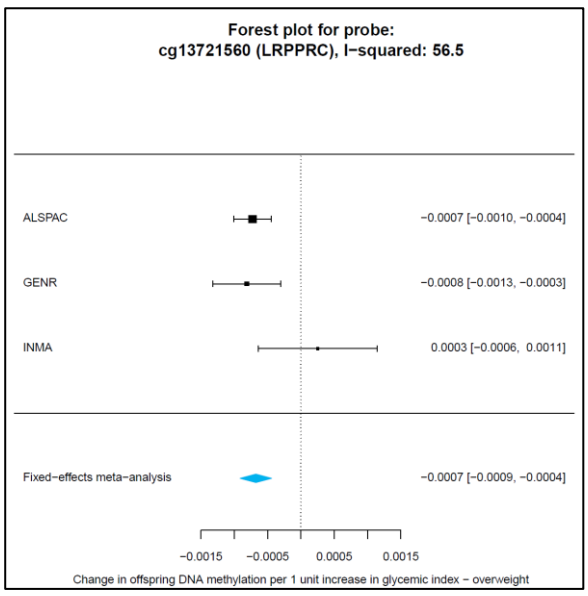

Forest plot for probe:
cg00006032 (GPHN), I−squared: 69.3
ALSPAC
−0.0014 [−0.0019, −0.0008]
GENR
−0.0019 [−0.0029, −0.0008]
INMA
0.0002 [−0.0011, 0.0015]
Fixed−effects meta−analysis
−0.0013 [−0.0017, −0.0008]
−0.0030
−0.0010
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

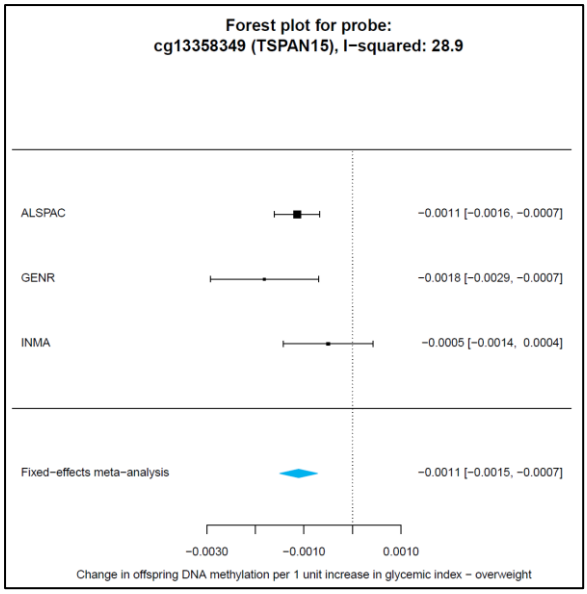

Forest plot for probe:
cg06171242 (ACOT13), I−squared: 49.5
ALSPAC
−0.0004 [−0.0008, −0.0000]
GENR
−0.0009 [−0.0012, −0.0006]
INMA
−0.0004 [−0.0009, −0.0000]
Fixed−effects meta−analysis
−0.0006 [−0.0008, −0.0004]
−0.0015
−0.0010
−0.0005
0.0000
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

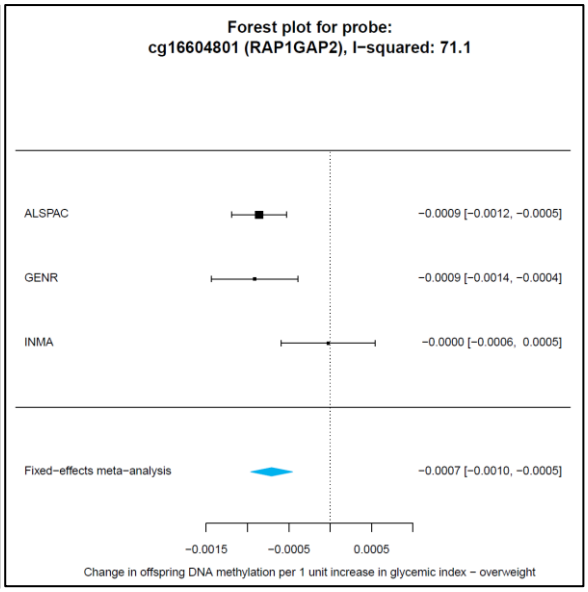

Forest plot for probe:
cg13445358 (ESPL1), I−squared: 0
ALSPAC
−0.0006 [−0.0009, −0.0004]
GENR
−0.0007 [−0.0012, −0.0002]
INMA
0.0004 [−0.0026, 0.0033]
Fixed−effects meta−analysis
−0.0006 [−0.0008, −0.0004]
−0.0040
−0.0020
0.0000
0.0020
0.0040
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

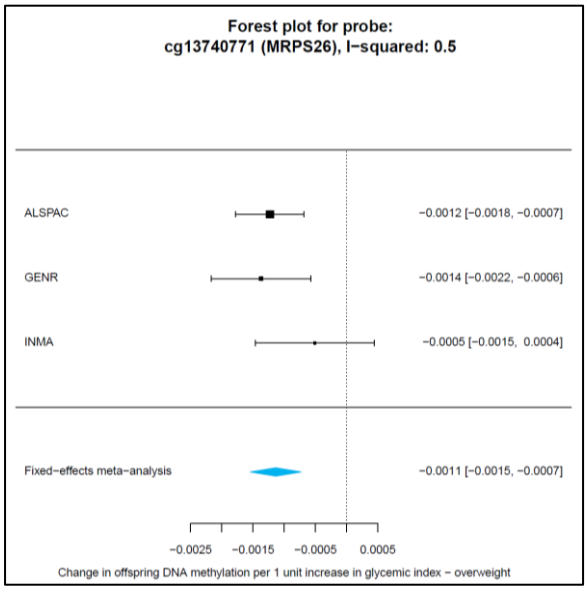

Forest plot for probe:
cg17582259 (CCT6B), I−squared: 55.3
ALSPAC
−0.0010 [−0.0014, −0.0007]
GENR
−0.0012 [−0.0022, −0.0003]
INMA
0.0004 [−0.0009, 0.0016]
Fixed−effects meta−analysis
−0.0009 [−0.0013, −0.0006]
−0.0030
−0.0010
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

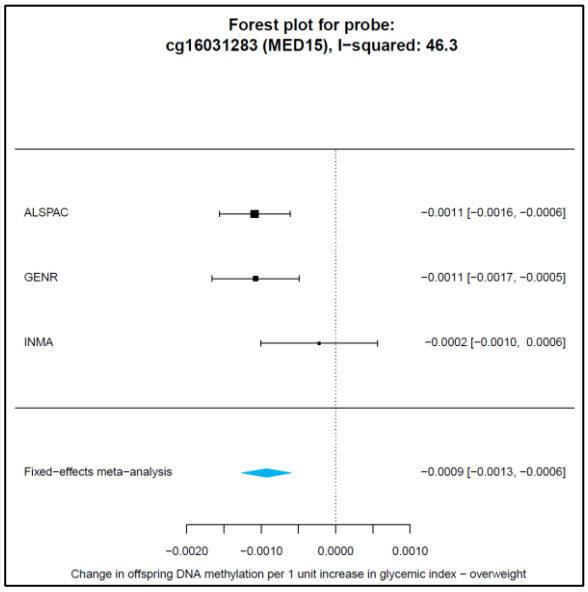

Forest plot for probe:
cg02725014 (HOMER1), I−squared: 0
ALSPAC
−0.0010 [−0.0016, −0.0005]
GENR
−0.0015 [−0.0023, −0.0007]
INMA
−0.0010 [−0.0019, −0.0002]
Fixed−effects meta−analysis
−0.0012 [−0.0015, −0.0008]
−0.0025
−0.0015
−0.0005
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

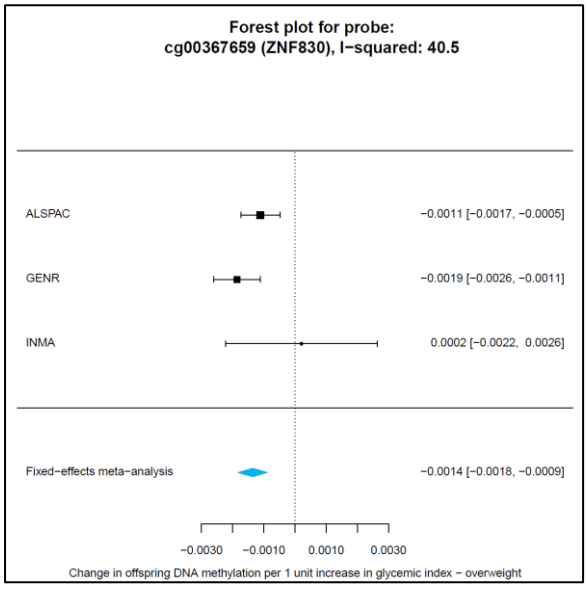

Forest plot for probe:
cg13721560 (LRPPRC), I−squared: 56.5
ALSPAC
−0.0007 [−0.0010, −0.0004]
GENR
−0.0008 [−0.0013, −0.0003]
INMA
0.0003 [−0.0006, 0.0011]
Fixed−effects meta−analysis
−0.0007 [−0.0009, −0.0004]
−0.0015
−0.0005
0.0005
0.0015
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

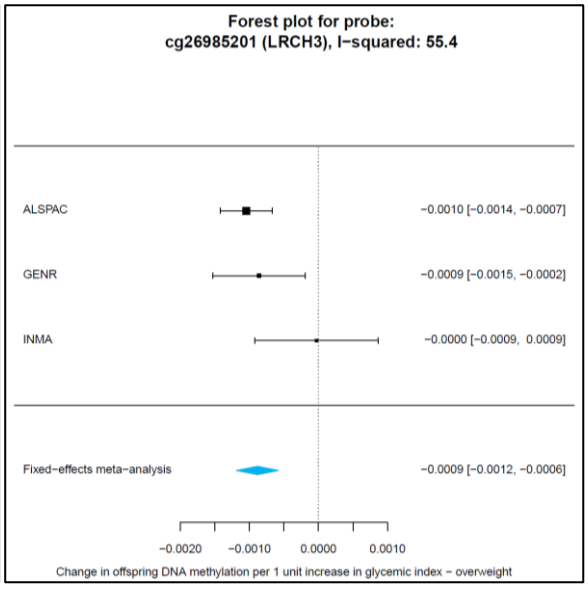

Forest plot for probe:
cg13358349 (TSPAN15), I−squared: 28.9
ALSPAC
−0.0011 [−0.0016, −0.0007]
GENR
−0.0018 [−0.0029, −0.0007]
INMA
−0.0005 [−0.0014, 0.0004]
Fixed−effects meta−analysis
−0.0011 [−0.0015, −0.0007]
−0.0030
−0.0010
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

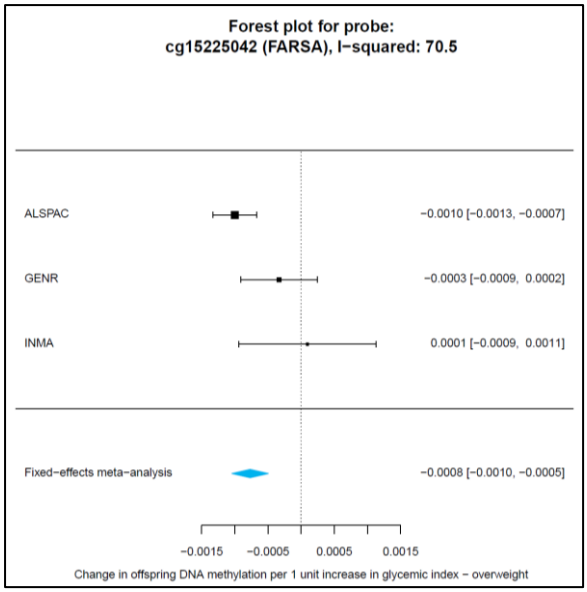

Forest plot for probe:
cg16604801 (RAP1GAP2), I−squared: 71.1
ALSPAC
−0.0009 [−0.0012, −0.0005]
GENR
−0.0009 [−0.0014, −0.0004]
INMA
−0.0000 [−0.0006, 0.0005]
Fixed−effects meta−analysis
−0.0007 [−0.0010, −0.0005]
−0.0015
−0.0005
0.0005
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

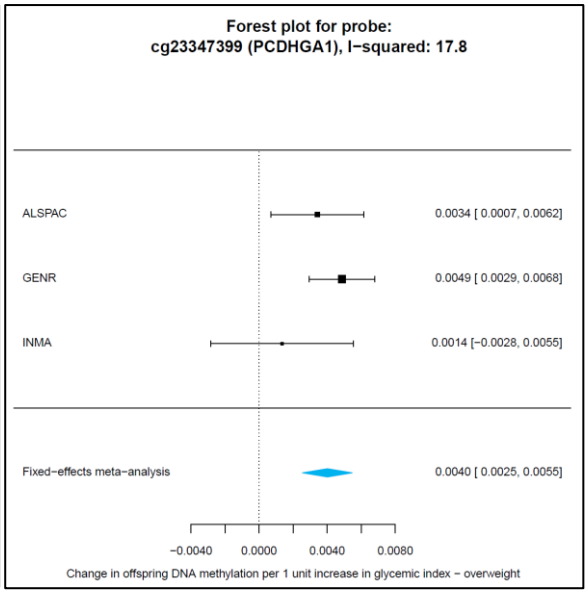

Forest plot for probe:
cg13740771 (MRPS26), I−squared: 0.5
ALSPAC
−0.0012 [−0.0018, −0.0007]
GENR
−0.0014 [−0.0022, −0.0006]
INMA
−0.0005 [−0.0015, 0.0004]
Fixed−effects meta−analysis
−0.0011 [−0.0015, −0.0007]
−0.0025
−0.0015
−0.0005
0.0005
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

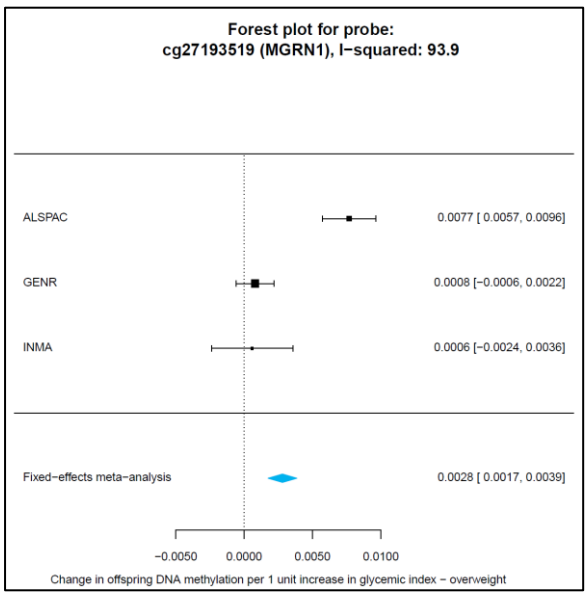

Forest plot for probe:
cg16031283 (MED15), I−squared: 46.3
ALSPAC
−0.0011 [−0.0016, −0.0006]
GENR
−0.0011 [−0.0017, −0.0005]
INMA
−0.0002 [−0.0010, 0.0006]
Fixed−effects meta−analysis
−0.0009 [−0.0013, −0.0006]
−0.0020
−0.0010
0.0000
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

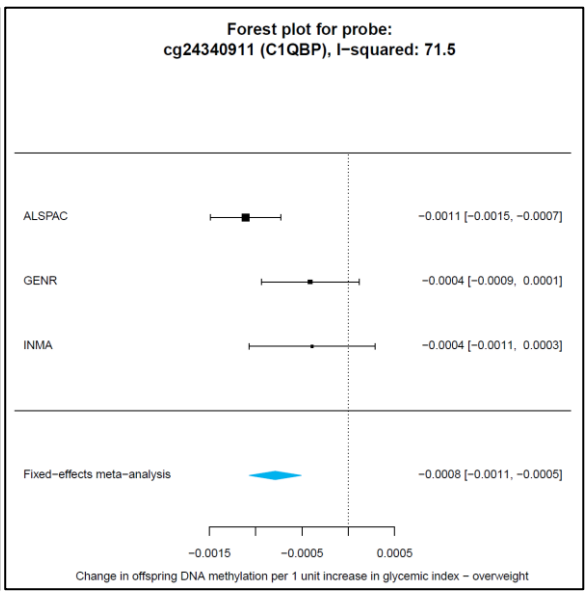

Forest plot for probe:
cg00367659 (ZNF830), I−squared: 40.5
ALSPAC
−0.0011 [−0.0017, −0.0005]
GENR
−0.0019 [−0.0026, −0.0011]
INMA
0.0002 [−0.0022, 0.0026]
Fixed−effects meta−analysis
−0.0014 [−0.0018, −0.0009]
−0.0030
−0.0010
0.0010
0.0030
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

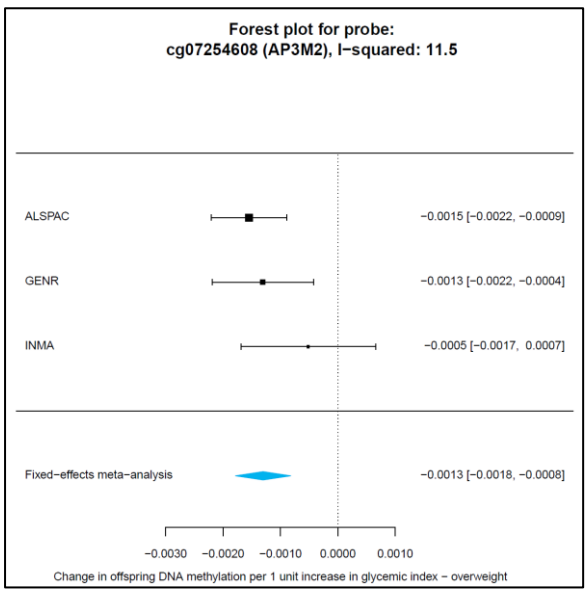

Forest plot for probe:
cg26985201 (LRCH3), I−squared: 55.4
ALSPAC
−0.0010 [−0.0014, −0.0007]
GENR
−0.0009 [−0.0015, −0.0002]
INMA
−0.0000 [−0.0009, 0.0009]
Fixed−effects meta−analysis
−0.0009 [−0.0012, −0.0006]
−0.0020
−0.0010
0.0000
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

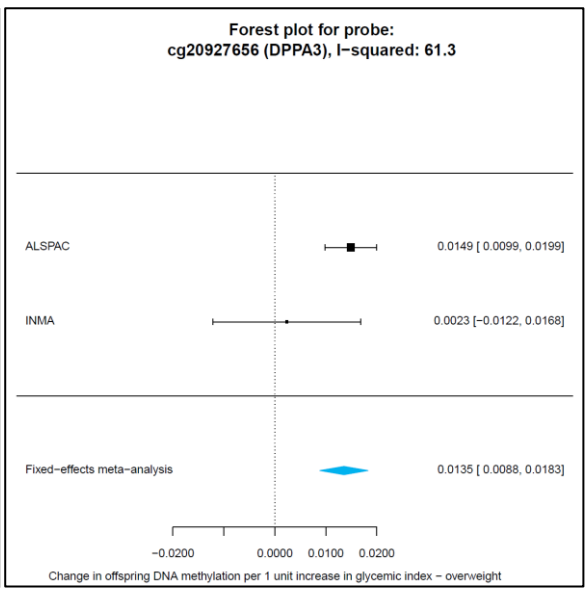

Forest plot for probe:
cg15225042 (FARSA), I−squared: 70.5
ALSPAC
−0.0010 [−0.0013, −0.0007]
GENR
−0.0003 [−0.0009, 0.0002]
INMA
0.0001 [−0.0009, 0.0011]
Fixed−effects meta−analysis
−0.0008 [−0.0010, −0.0005]
−0.0015
−0.0005
0.0005
0.0015
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

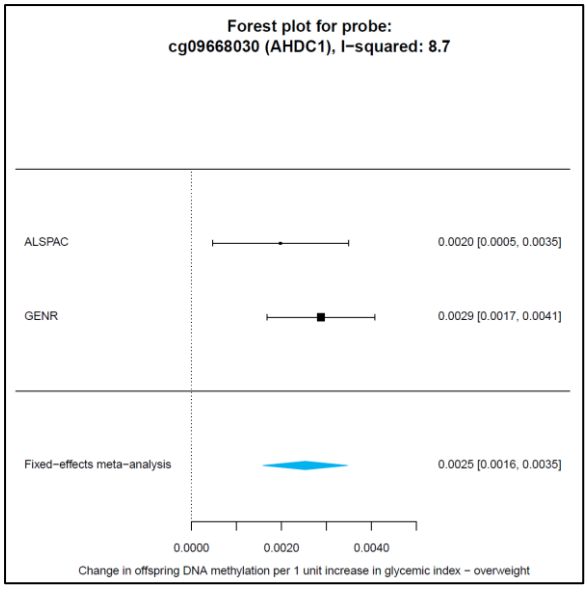

Forest plot for probe:
cg23347399 (PCDHGA1), I−squared: 17.8
ALSPAC
0.0034 [0.0007, 0.0062]
GENR
0.0049 [0.0029, 0.0068]
INMA
0.0014 [−0.0028, 0.0055]
Fixed−effects meta−analysis
0.0040 [0.0025, 0.0055]
−0.0040
0.0000
0.0040
0.0080
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight


Forest plot for probe:
cg27193519 (MGRN1), I−squared: 93.9
ALSPAC
0.0077 [0.0057, 0.0096]
GENR
0.0008 [−0.0006, 0.0022]
INMA
0.0006 [−0.0024, 0.0036]
Fixed−effects meta−analysis
0.0028 [0.0017, 0.0039]
−0.0050
0.0000
0.0050
0.0100
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

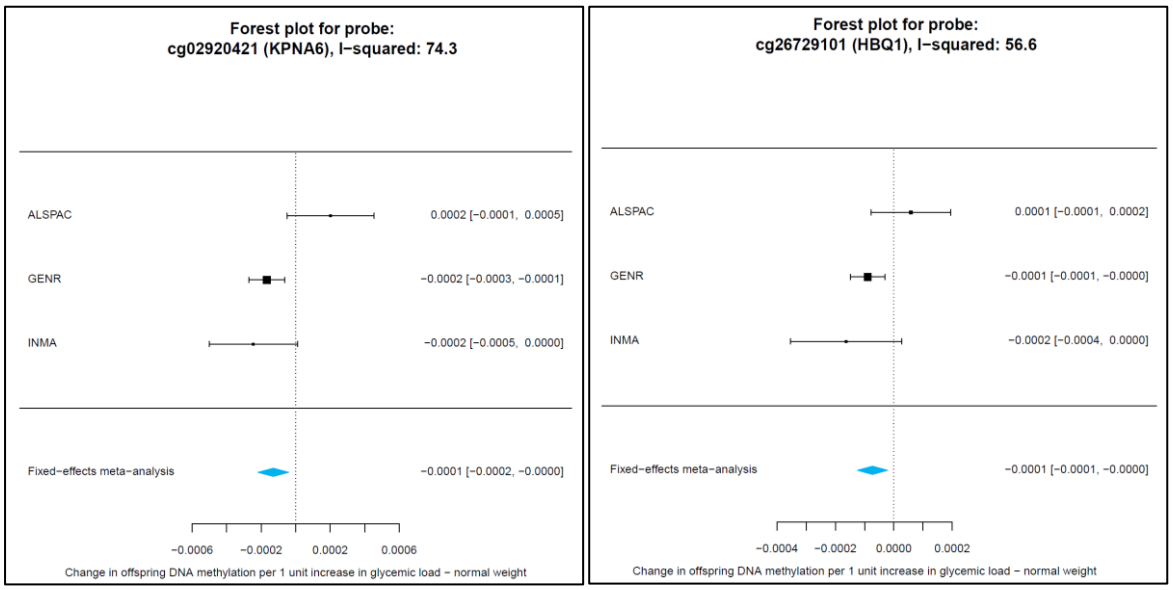

Forest plot for probe:
cg24340911 (C1QBP), I−squared: 71.5
ALSPAC
−0.0011 [−0.0015, −0.0007]
GENR
−0.0004 [−0.0009, 0.0001]
INMA
−0.0004 [−0.0011, 0.0003]
Fixed−effects meta−analysis
−0.0008 [−0.0011, −0.0005]
−0.0015
−0.0005
0.0005
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight


Forest plot for probe:
cg07254608 (AP3M2), I−squared: 11.5
ALSPAC
−0.0015 [−0.0022, −0.0009]
GENR
−0.0013 [−0.0022, −0.0004]
INMA
−0.0005 [−0.0017, 0.0007]
Fixed−effects meta−analysis
−0.0013 [−0.0018, −0.0008]
−0.0030
−0.0020
−0.0010
0.0000
0.0010
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight

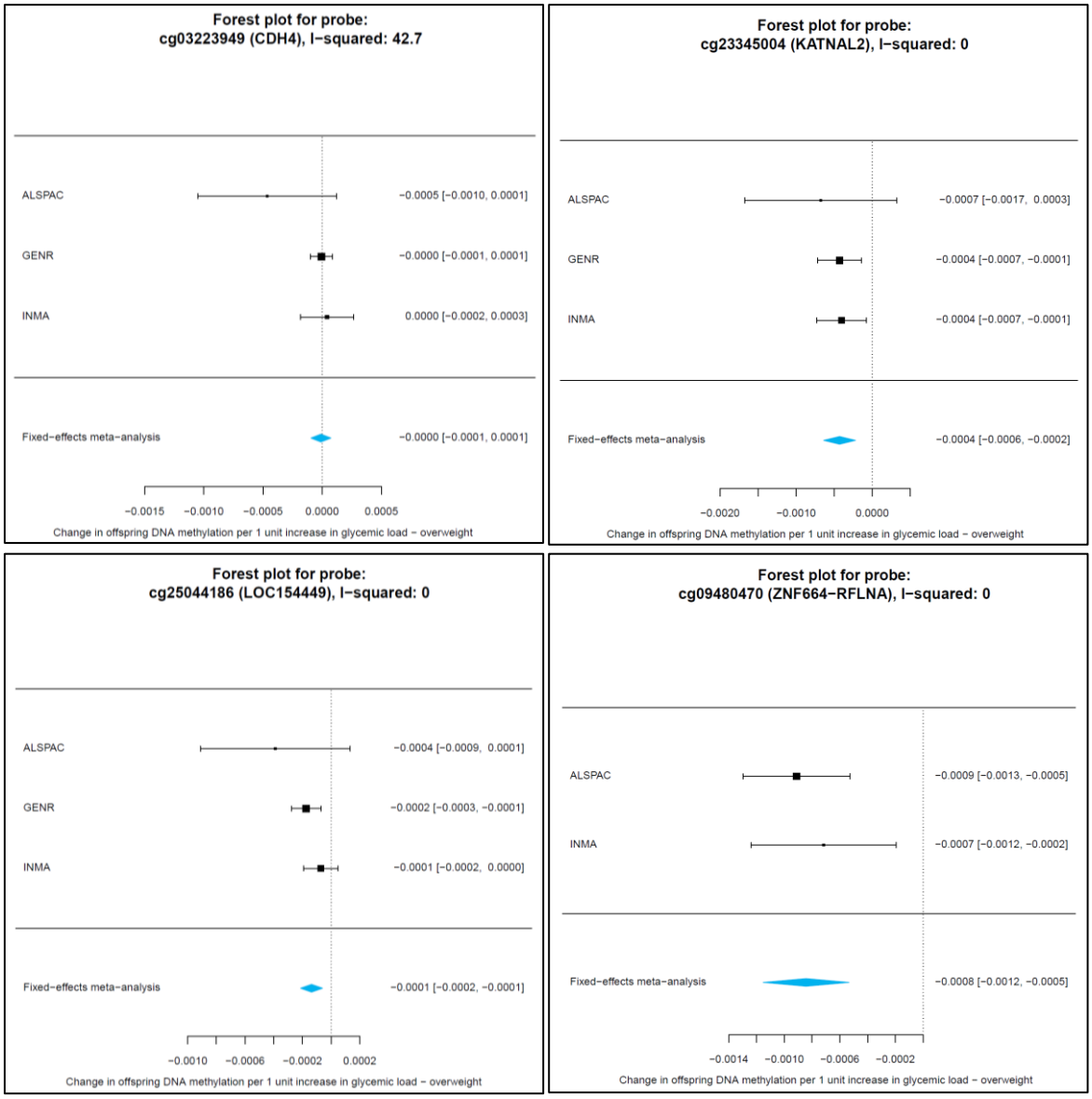

Forest plot for probe:
cg20927656 (DPPA3), I−squared: 61.3
ALSPAC
0.0149 [0.0099, 0.0199]
INMA
0.0023 [−0.0122, 0.0168]
Fixed−effects meta−analysis
0.0135 [0.0088, 0.0183]
−0.0200
0.0000
0.0100
0.0200
Change in offspring DNA methylation per 1 unit increase in glycemic index − overweight



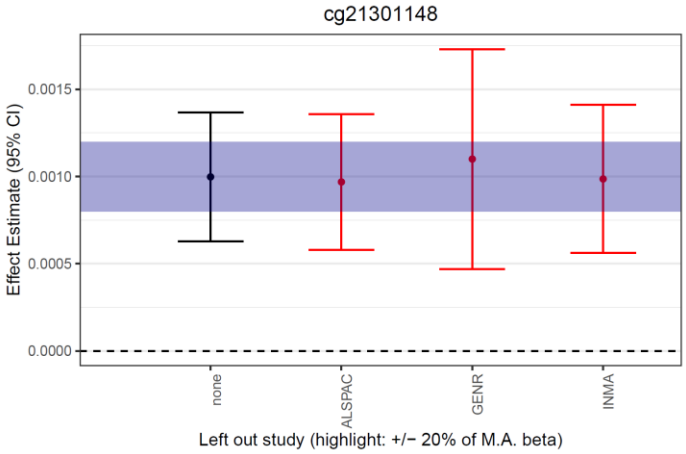
Supplemental Figure 9. Forest plot for the CpGs associated with glycemic index in mothers with overweight.



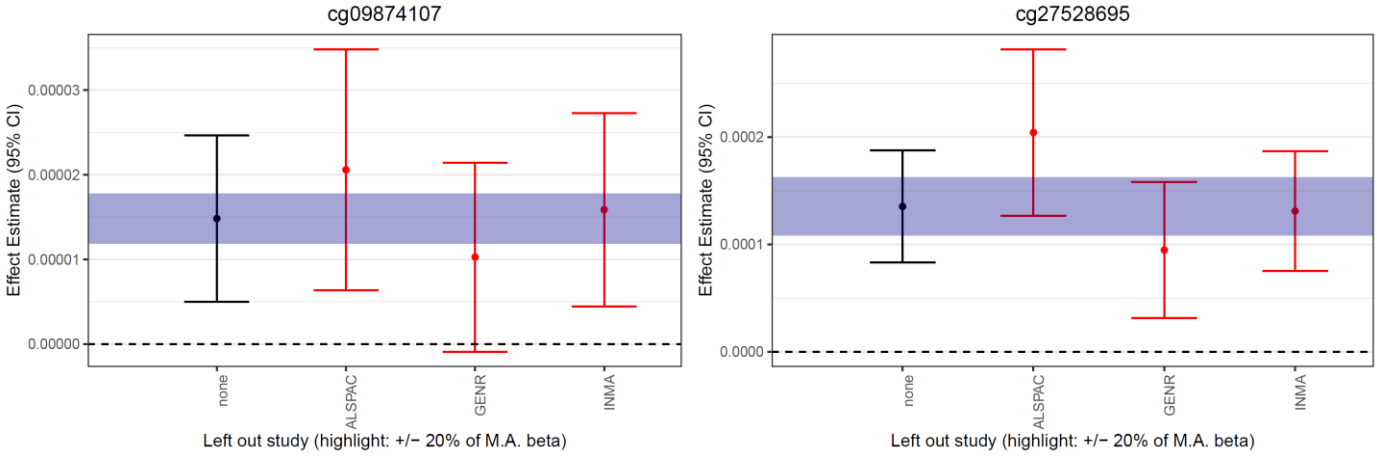
Supplemental Figure 10. Forest plot for the CpGs associated with glycemic load in mothers with normal weight.



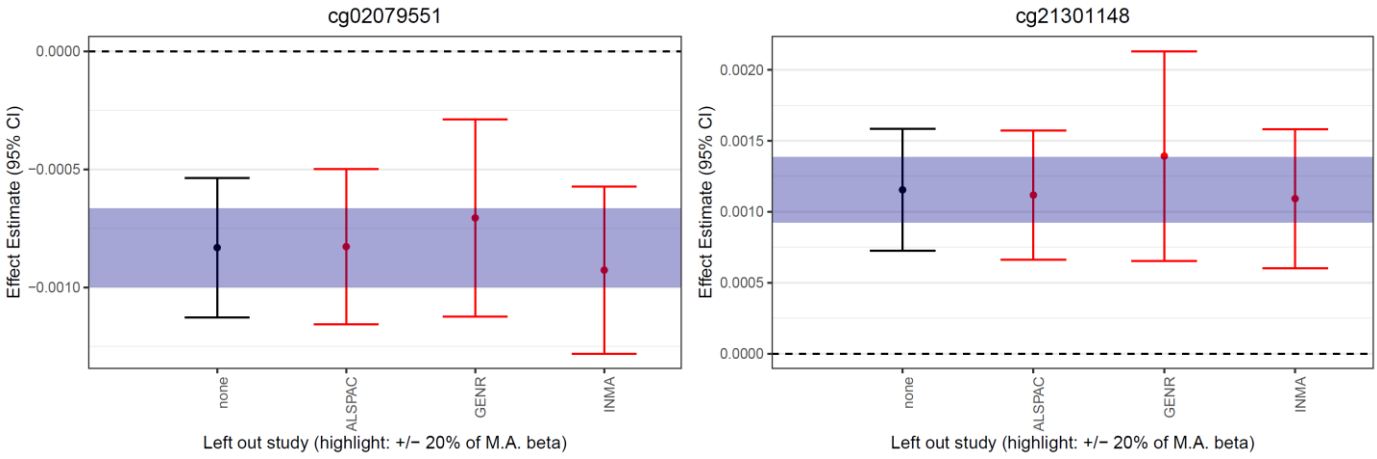
Supplemental Figure 11. Forest plot for the CpGs associated with glycemic load in mothers with overweight.



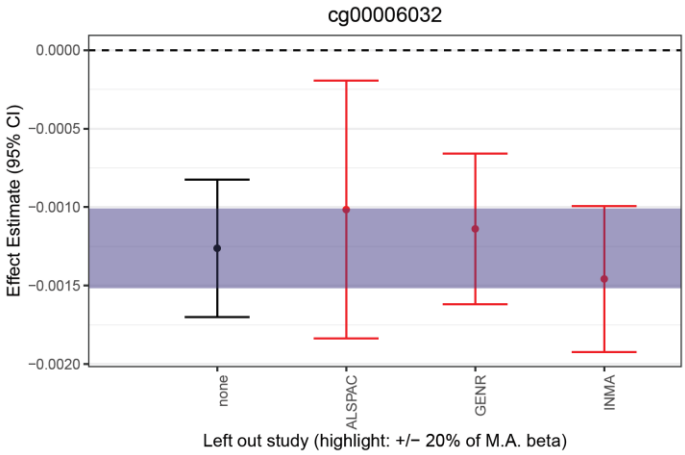
Supplemental Figure 12. Leave-one-out plot for the CpG associated with glycemic index in the full group.

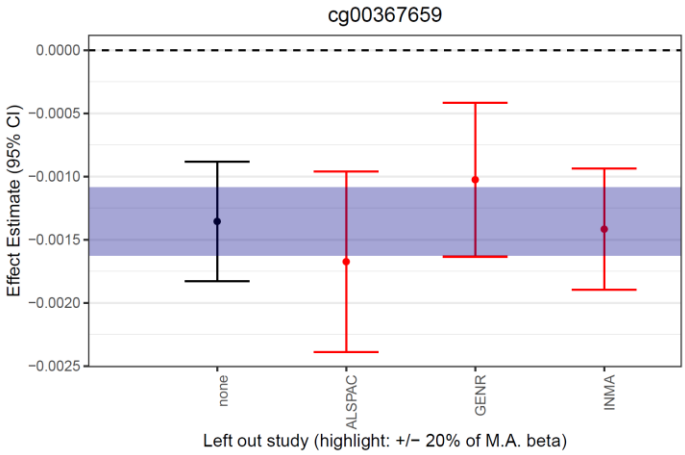


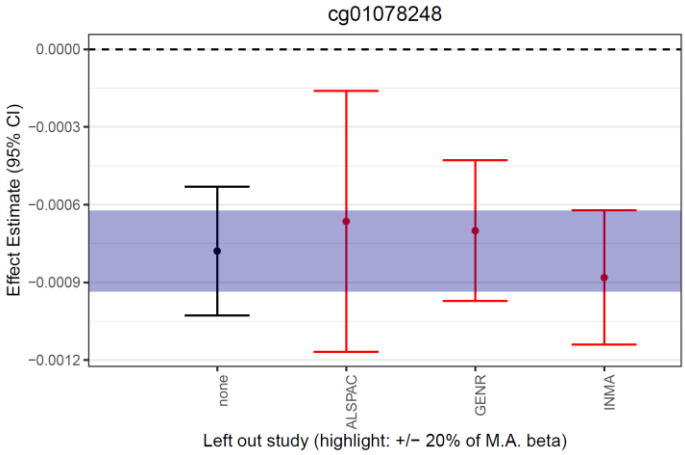
Supplemental Figure 13. Leave-one-out plots for the CpGs associated with glycemic load in the full group.

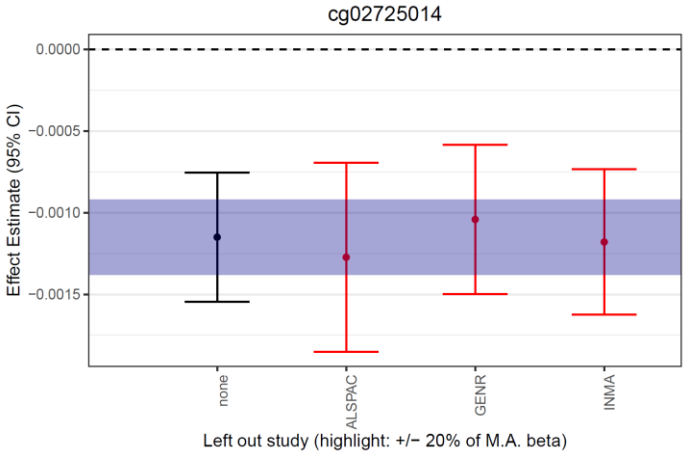


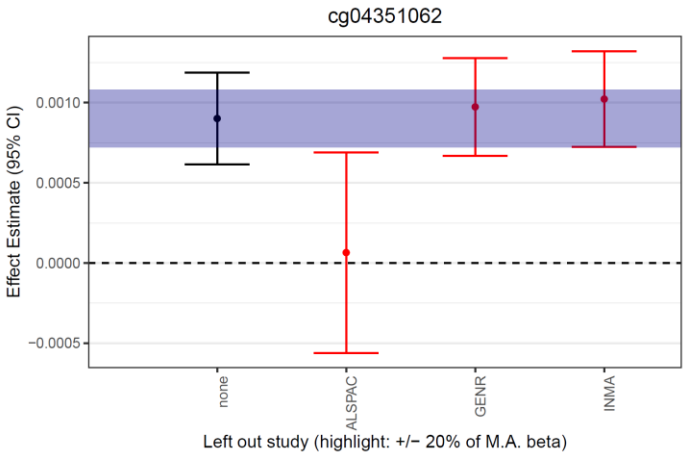
Supplemental Figure 14. Leave-one-out plots for the CpGs associated with glycemic index in mothers with normal weight.

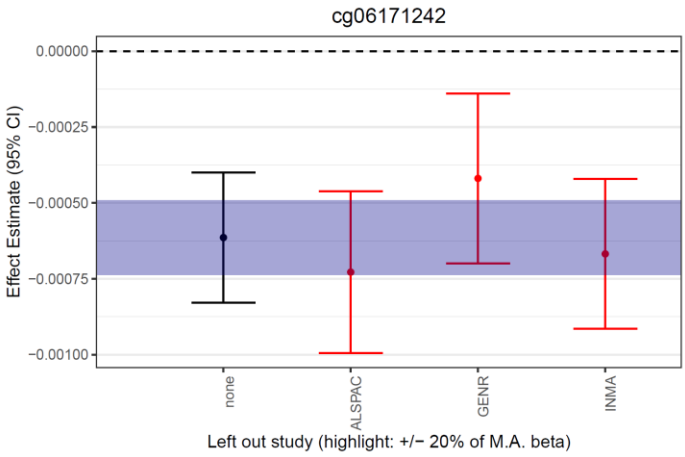

cg00006032
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
−0.0020
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

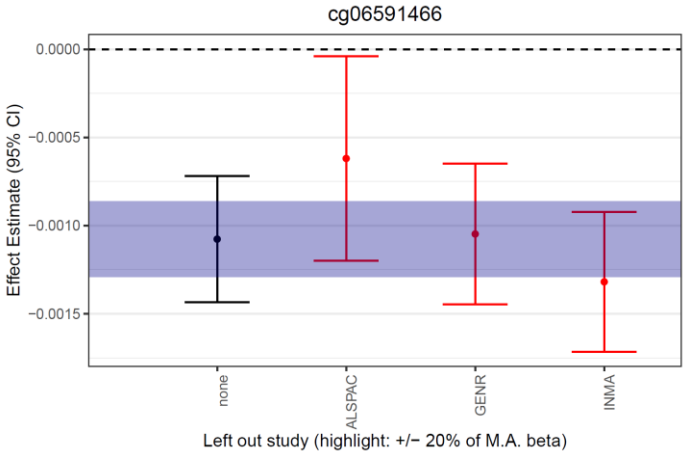

cg00367659
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
−0.0020
−0.0025
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

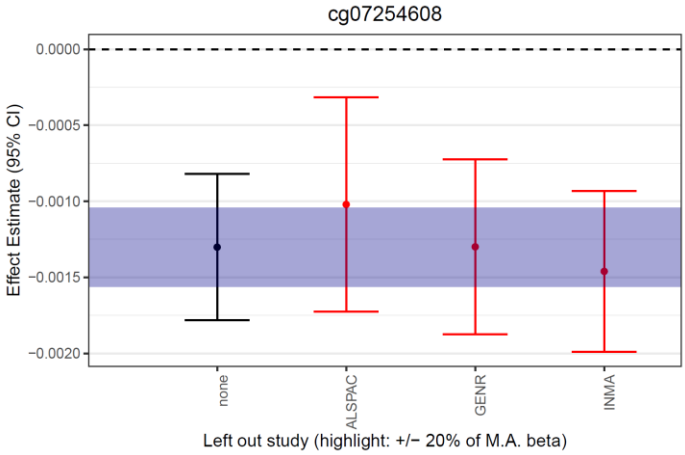

cg01078248
Effect Estimate (95% CI)
0.0000
−0.0003
−0.0006
−0.0009
−0.0012
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

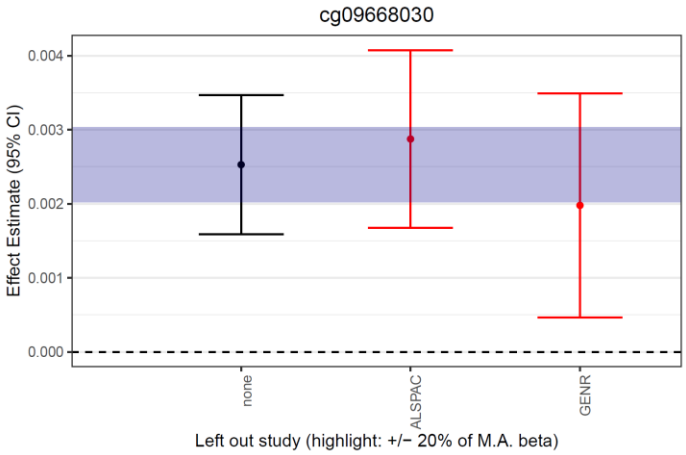

cg02725014
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

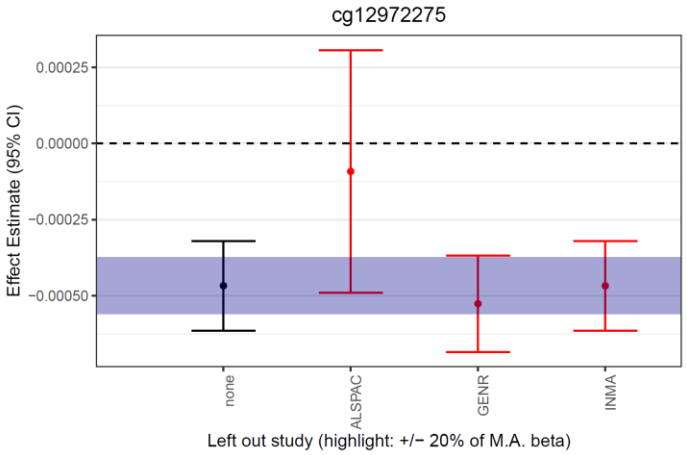

cg04351062
Effect Estimate (95% CI)
0.0010
0.0005
0.0000
−0.0005
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

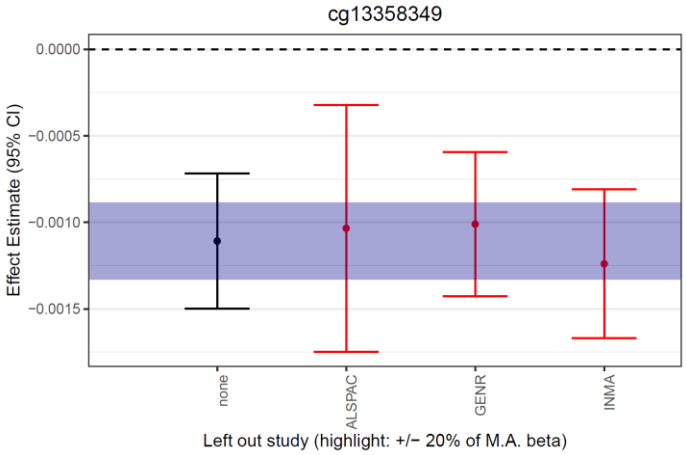

cg06171242
Effect Estimate (95% CI)
0.00000
−0.00025
−0.00050
−0.00075
−0.00100
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

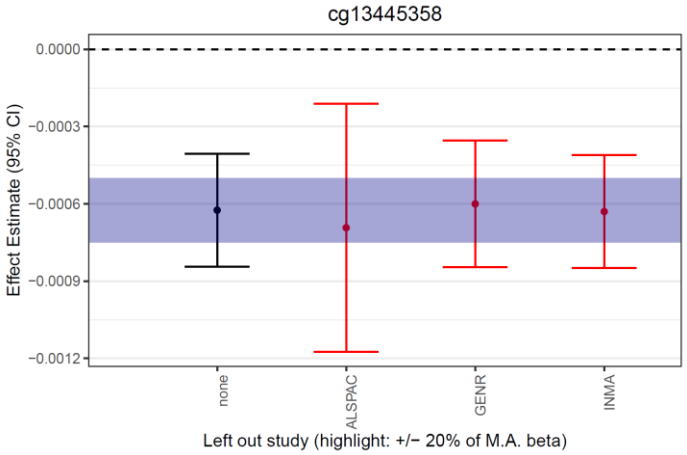

cg06591466
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

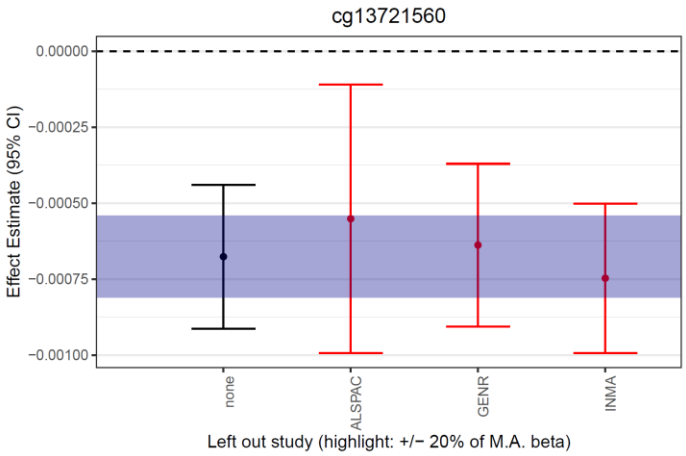

cg07254608
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
−0.0020
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

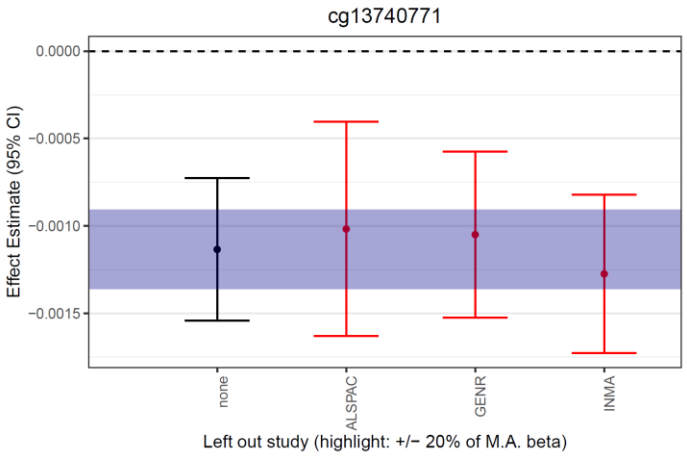

cg09668030
Effect Estimate (95% CI)
0.004
0.003
0.002
0.001
0.000
none
ALSPAC
GENR
Left out study (highlight: +/− 20% of M.A. beta)

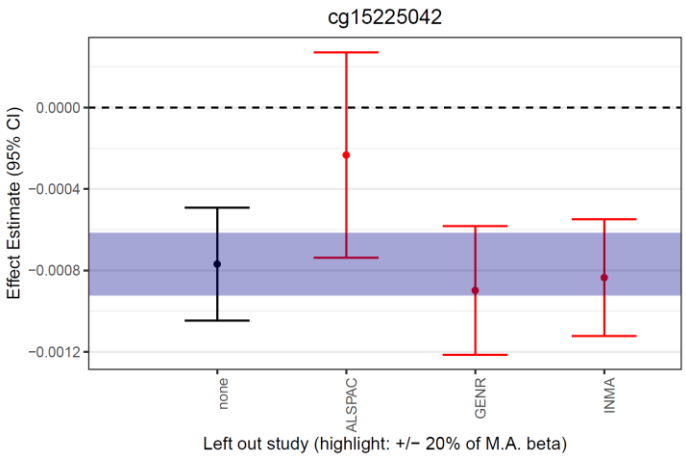

cg12972275
Effect Estimate (95% CI)
0.00025
0.00000
−0.00025
−0.00050
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

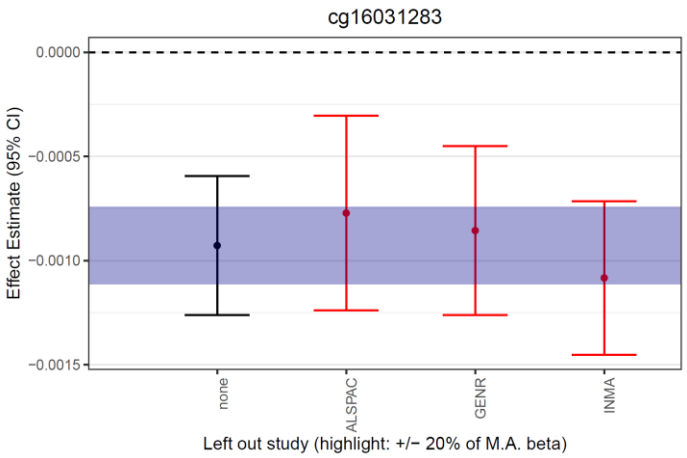

cg13358349
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

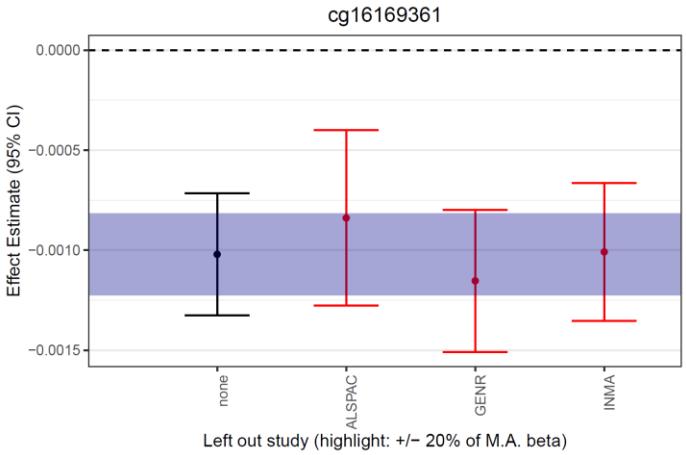

cg13445358
Effect Estimate (95% CI)
0.0000
−0.0003
−0.0006
−0.0009
−0.0012
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

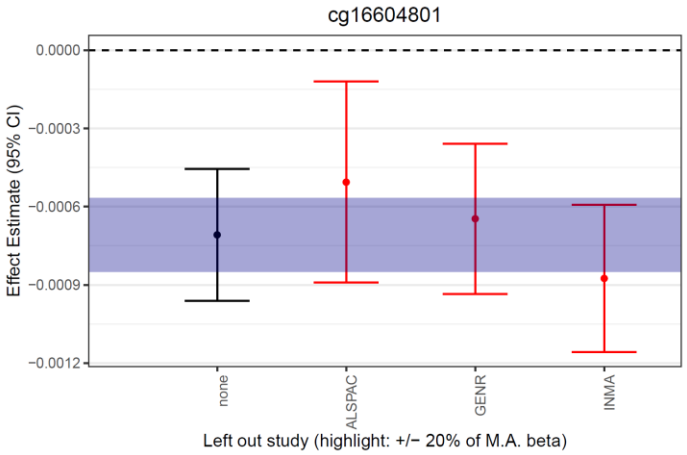

cg13721560
Effect Estimate (95% CI)
0.00000
−0.00025
−0.00050
−0.00075
−0.00100
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

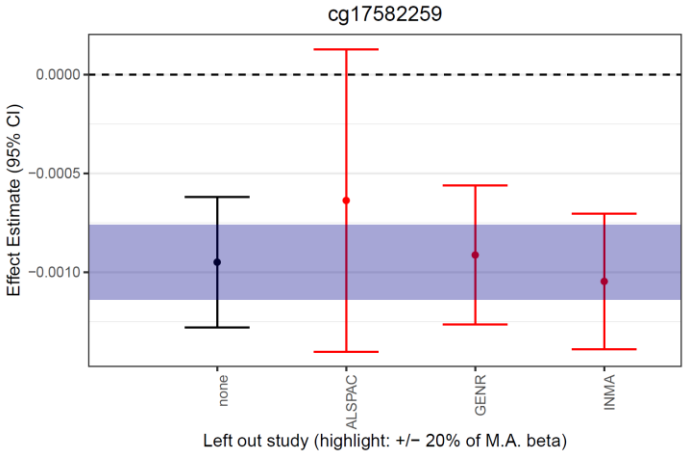

cg13740771
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

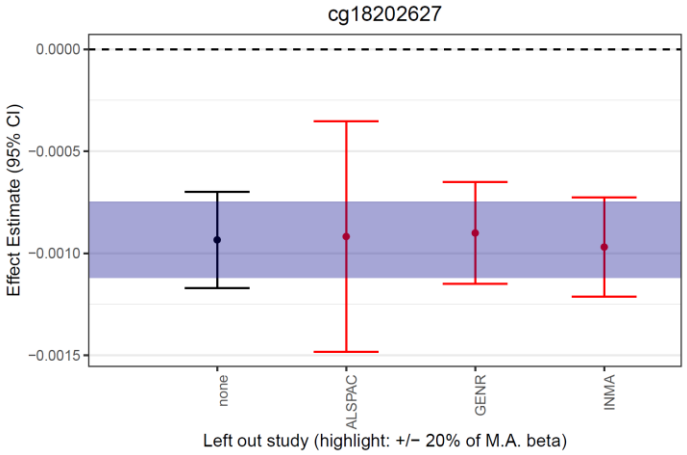

cg15225042
Effect Estimate (95% CI)
0.0000
−0.0004
−0.0008
−0.0012
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

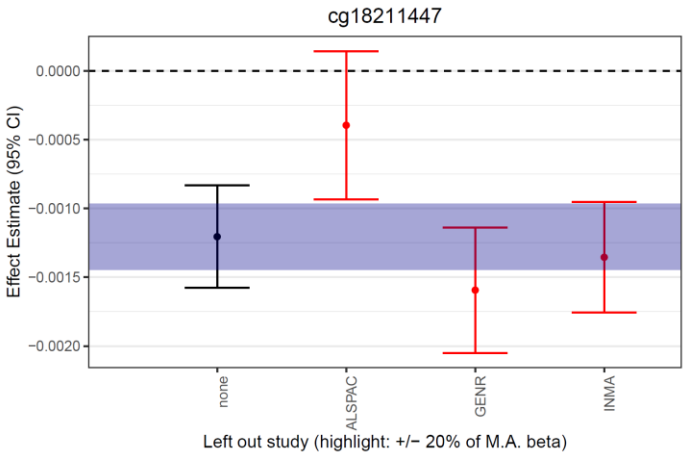

cg16031283
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

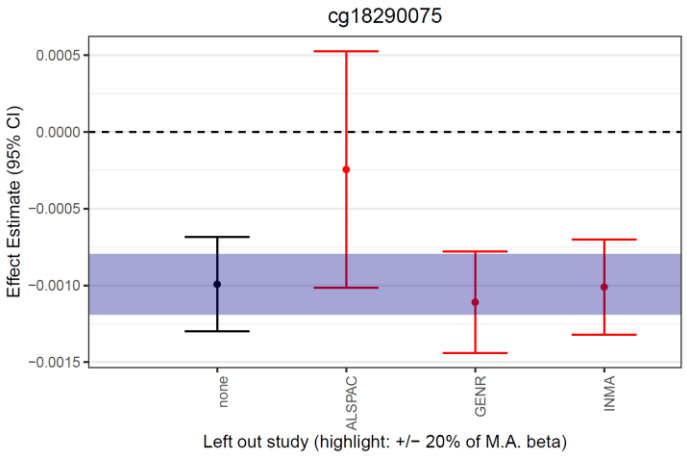

cg16169361
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

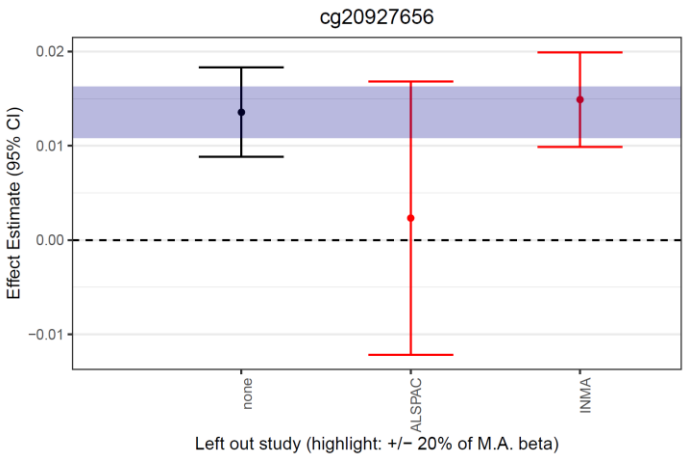

cg16604801
Effect Estimate (95% CI)
0.0000
−0.0003
−0.0006
−0.0009
−0.0012
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

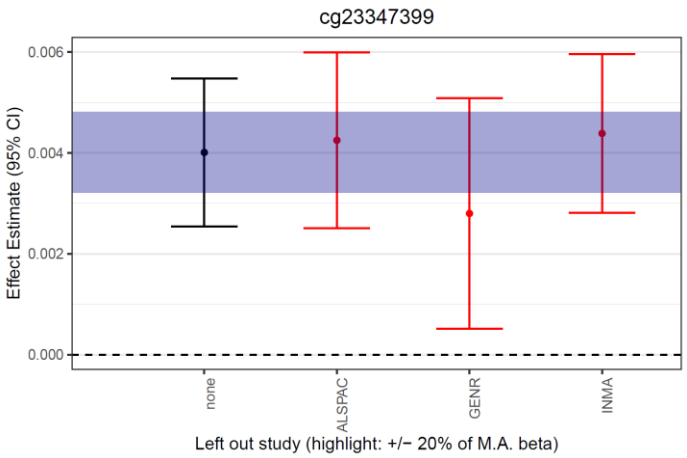

cg17582259
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

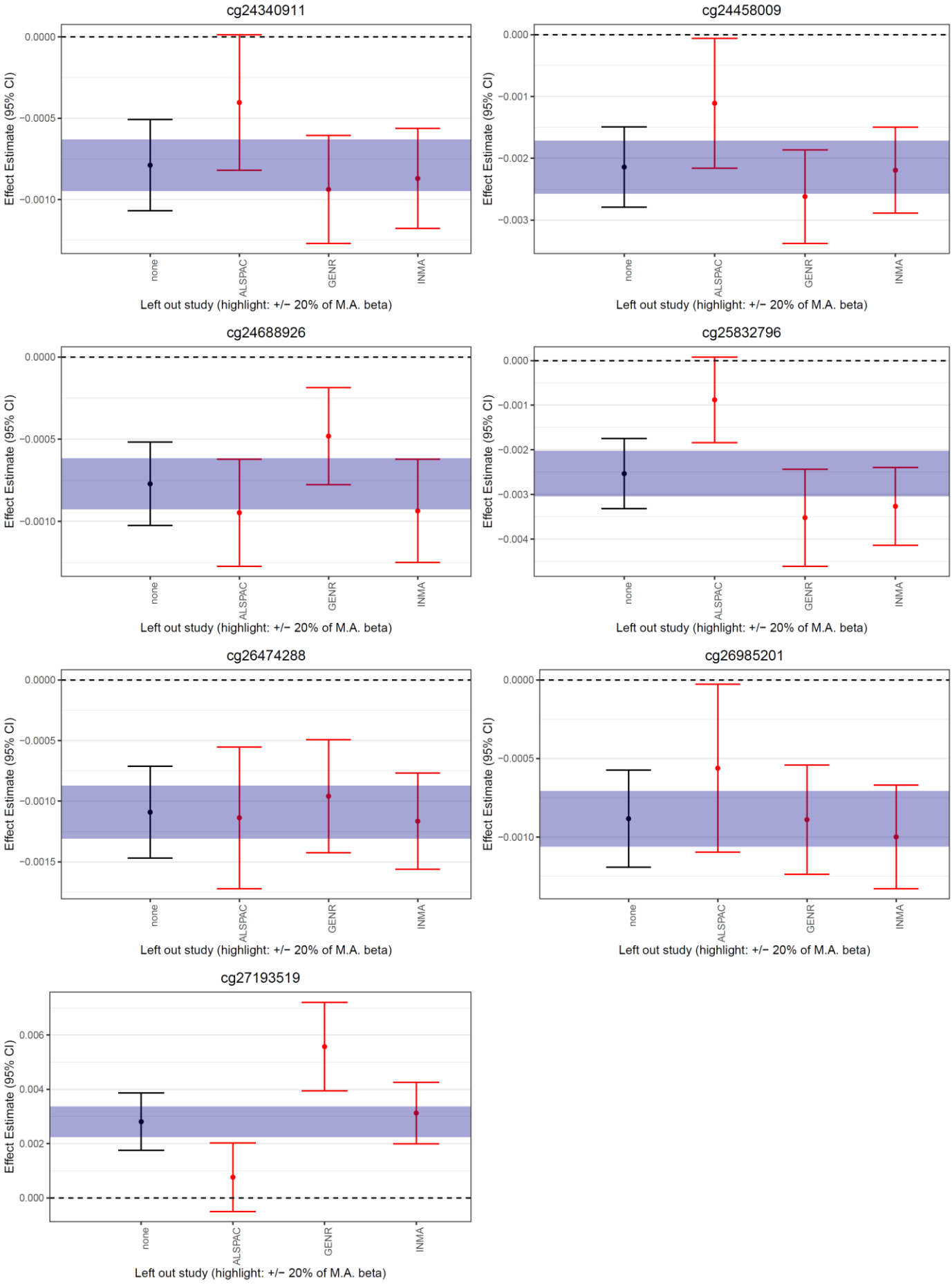

cg18202627
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)


cg18211447
Effect Estimate (95% CI)
0.0000
−0.0005
−0.0010
−0.0015
−0.0020
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)

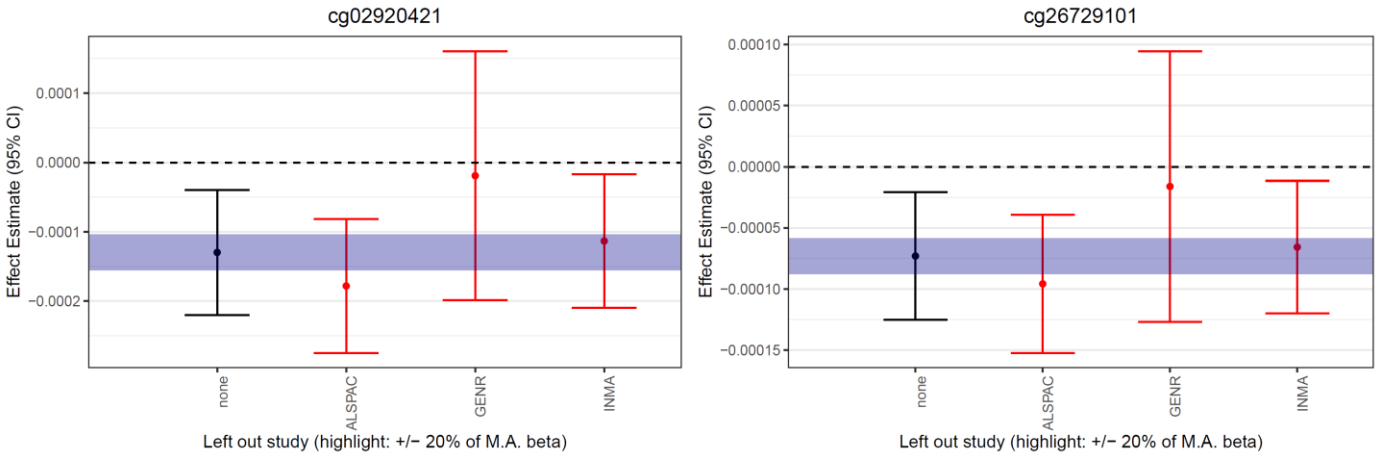

cg18290075
Effect Estimate (95% CI)
0.0005
0.0000
−0.0005
−0.0010
−0.0015
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)


cg20927656
Effect Estimate (95% CI)
0.02
0.01
0.00
−0.01
none
ALSPAC
INMA
Left out study (highlight: +/− 20% of M.A. beta)

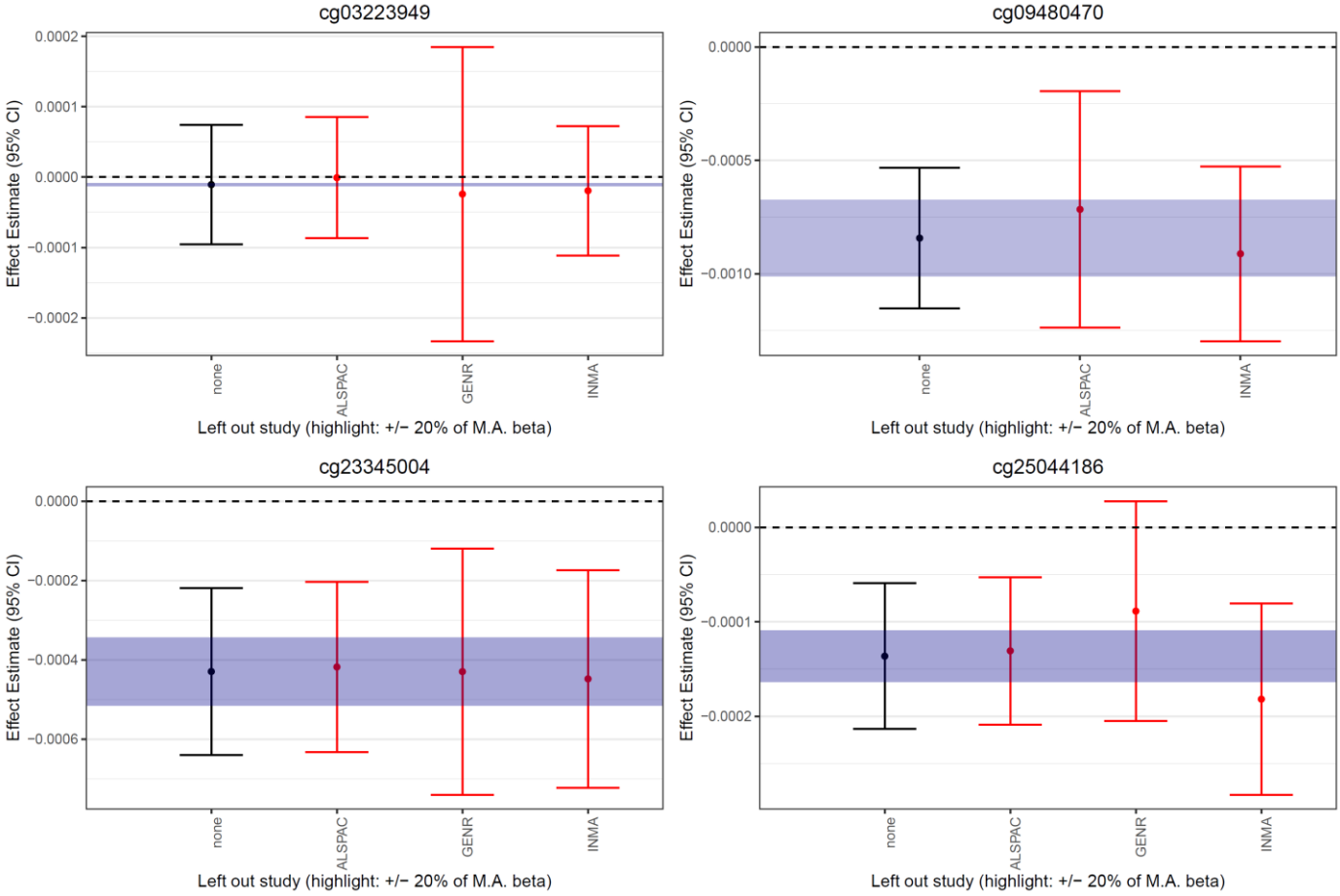

cg23347399
Effect Estimate (95% CI)
0.006
0.004
0.002
0.000
none
ALSPAC
GENR
INMA
Left out study (highlight: +/− 20% of M.A. beta)



Supplemental Figure 15. Leave-one-out plots for the CpGs associated with glycemic index in mother with overweight.



Supplemental Figure 16. Leave-one-out plots for the CpGs associated with glycemic load in mothers with normal weight.



Supplemental Figure 17. Leave-one-out plots for the CpGs associated with glycemic load in mothers with overweight.

SUPPLEMENTAL COHORT-SPECIFIC METHODS

The Avon Longitudinal Study of Parents and Children (ALSPAC)

Description of cohort:

Pregnant women resident in Avon, UK with expected dates of delivery 1st April 1991 to 31st December 1992 were invited to take part in the study (1,2). The initial number of pregnancies enrolled is 14,541 (for these at least one questionnaire has been returned or a "C_h_i_l_d_r_e_n_ _i_n_ _F_o_c_u_s_" _c_l_i_n_i_c_ _had been attended by 19/07/99). Of these initial pregnancies, there was a total of 14,676 foetuses, resulting in 14,062 live births and 13,988 children who were alive at 1 year of age.

When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had failed to join the study originally. As a result, when considering variables collected from the age of seven onwards (and potentially abstracted from obstetric notes) there are data available for more than the 14,541 pregnancies mentioned above. The number of new pregnancies not in the initial sample (known as Phase I enrolment) that are currently represented on the built files and reflecting enrolment status at the age of 24 is 913 (456, 262 and 195 recruited during Phases II, III and IV respectively), resulting in an additional 913 children being enrolled. The phases of enrolment are described in more detail in the cohort profile paper and its update. The total sample size for analyses using any data collected after the age of seven is therefore 15,454 pregnancies, resulting in 15,589 foetuses. Of these 14,901 were alive at 1 year of age.

A 10% sample of the ALSPAC cohort, known as the Children in Focus (CiF) group, attended clinics at the University of Bristol at various time intervals between 4 to 61 months of age. The CiF group were chosen at random from the last 6 months of ALSPAC births (1432 families attended at least one clinic). Excluded were those mothers who had moved out of the area or were lost to follow-up, and those partaking in another study of infant development in Avon. As part of the Accessible Resources for Integrated Epigenomic Studies (ARIES (3)) project, DNA methylation was generated for 1018 mother-offspring pairs from the ALSPAC cohort, using the Infinium HumanMethylation450 BeadChip array (Illumina Inc., San Diego, United States). ARIES participants were selected based on availability of DNA samples at two time points for

the mother (antenatal and at follow-up when the offspring were adolescents) and at three time points for the offspring (neonatal, childhood (age 7), and adolescence (age 15/17)).

Ethical approval:

Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Informed consent for the use of data collected via questionnaires and clinics was obtained from the participants following the recommendations of the ALSPAC Ethics and Law Committee at the time.

EWAS analyst:

Giulia Mancano

Description of FFQ and glycemic index and load calculation:

We used a 47-item (of which 42 items were used for this study) semi-quantitative food frequency questionnaire (FFQ) with questions worded as "How many times nowadays do you eat [*food item*]?" (4). Maternal nutritional intake was registered around 32 weeks of gestation with the reference period being "nowadays". Intakes from nutrient supplements or alcoholic drinks were not included in the calculations. The FFQ was used to calculate an approximate daily nutrient intake for every woman. Each food item question was assigned a composition, based on consideration of how commonly various foods included in that food item are consumed, and using an amount equivalent to one portion of that food. If responses to the FFQ resulted in unrealistically high or low figures, those individuals were removed from the final data set. The nutrient content for each food was obtained from the 5th edition of the McCance and Widdowson's the composition of foods and its supplements (5–8). The FFQ was validated for measuring oily fish intake (5) and standard portion sizes were assumed based on typical consumption patterns in Britain. To calculate glycemic index and load, we used the Diogenes-UK reference database (9), using glucose as a reference (glycemic index for glucose equal to 100). Values for each individual food were found in the database and we summed them to calculate glycemic index and load based on each of the 42-item. All foods were found except for Eccles cake and low calorie Cola, for which GI and GL values from mince pie and Diet Lilt in the same database were used instead.

Methylation normalization and QC steps taken in your cohort:

Cord blood samples:

Methods for methylation measurements in ALSPAC have been described previously (3). Briefly, cord blood was collected according to standard procedures. DNA methylation assays and data pre-processing were performed at the University of Bristol as part of the ARIES project. DNA was extracted using standard protocol and was bisulfite-converted using the Zymo EZ DNA MethylationTM kit (Zymo, Irvine, CA). DNA methylation was then measured using the Infinium HM450 BeadChip assay (Illumina Inc, San Diego, CA), according to the standard protocol. Arrays were scanned using an Illumina iScan. An initial review of data quality was assessed using GenomeStudio (version 2011.1). A semi-random approach (sampling criteria were in place to ensure that all time points were represented on each array) was used to distribute ARIES samples across slides to minimize the possibility of potential confounding by batch. Data were normalised using the meffil R package (10) using the functional normalisation approach.

In this study, methylation outliers were removed using the IQR*3 (Tukey) method and probes with high detection p-values were removed.

Childhood blood samples:

For the look-ups in childhood, we used DNA extracted from blood samples taken at the 7-year and 17-year follow-up visits. The procedure for measuring and normalization of methylation data, and QC steps were similar to that for the cord blood samples.

Covariates:

Maternal education was defined based on the UK highest qualification achieved by the mothers. The covariate is binary and CSE/none, Vocational and O-level qualifications were grouped to describe lower educational level and A-level and university degree to describe higher educational level. **Maternal smoking** during pregnancy was determined by questionnaire at the time of recruitment and defined here as “no smoker” if mother was a never smoker or quit before second trimester, or as a “smoker” if mother smoked and did not quit before second trimester. **Maternal total energy intake** was estimated from the total diet as kJ/day using self-reported FFQs at 32 weeks gestation. For the current study energy intake was converted to kcal/day. **Newborn sex** was obtained from obstetric records. **Maternal age** was derived from the mother’s date of birth at the time of delivery. **Maternal BMI** was calculated from self-reported height and pre-pregnancy weight, which were collected by questionnaire

during the first trimester of pregnancy. **Child ethnic group** was derived from mother reports of her own and partners ethnic group during pregnancy. Participants with non-white European ancestry were excluded from all analyses. **Cord blood cell type composition** was estimated using the "Salas" reference set (11) in the ''FlowSorted.CordBlood.Combined.450K'' Bioconductor package for cell type correction and normalised using meffil R package (10). We attempted to control for technical **batch effects** by generating 20 surrogate variables using the SVA R package (12) and including these directly in the EWAS models.

For the **look-ups in childhood** (mean age 7.5y and 17.1y), we additionally adjusted for **childhood age** at DNA methylation measurement. Further, for this look-up in childhood, **cell type correction** was applied using estimates calculated using the Houseman method (13) .

Acknowledgements:

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The Generation R Study

Description of cohort:

The Generation R Study is a prospective population-based cohort in Rotterdam, the Netherlands (14,15). All pregnant women residing in Rotterdam with a delivery date between April 2002 and January 2006 were invited to participate. The Medical Ethical Committee of Erasmus MC, University Medical Center Rotterdam, approved the study and an informed consent was obtained for all participating children. In total, 9,778 mothers were enrolled in the Generation R study. The present analyses were limited to mothers of Dutch national origin, since nutrition generally differs between ethnic groups and the FFQ was validated for the assessment of dietary intake in a Dutch population.

Ethical approval:

The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and was approved by the Medical Ethics Committee at Erasmus Medical Center, University Medical Center Rotterdam, The Netherlands. Written consent was obtained from all participants.

EWAS analyst:

Leanne Küpers

Description of FFQ and glycemic index and load calculation:

We used a modified version of a validated semi-quantitative 293-item food frequency questionnaire (FFQ) (16). The FFQ was validated against three 24-h recalls and blood biomarkers in 80 pregnant women with Dutch ethnicity living in Rotterdam, the Netherlands. Energy-adjusted intra-class correlation coefficients for macronutrient intakes ranged from 0.41 to 0.88 and was 0.60 for carbohydrate intake (17). Maternal nutritional intake was registered around median 13.5 weeks of gestation, 95% range 10.1-21.8 weeks, with the past three months as the reference period. Portion sizes were estimated using standard household measures and using photographs showing different portion sizes. We aimed to exclude mothers with implausibly low or high energy intake (<500kcal/d or >5000kcal/d), but none of the mothers in our selection reported such low or high energy intakes. Nutrient intake, including total energy intake and carbohydrate content, was calculated using the 2006 Dutch Food

Composition Table (NEVO) (18). To calculate glycemic index and load we used the Dutch Diogenes reference database(9), using glucose as a reference (glycemic index for glucose equal to 100). We found 84.3% of the food items in this database, for the food items that could not be found, glycemic index values for similar food items were obtained from proxies (87.8%) or from Diogenes databases for other countries (9.8%). If no equivalent food item was available for a food item, a value of 70 was assigned according to the Diogenes procedure (2.4%)

Methylation normalization and QC steps taken in your cohort:

Cord blood samples:

DNA extracted (using the salting-out method) from blood samples taken at birth (cord blood) was used for this analysis. 500 ng DNA per sample underwent bisulfite conversion using the EZ-96 DNA Methylation kit (Shallow) (Zymo Research Corporation, Irvine, USA). Samples were plated onto 96-well plates in no specific order. Samples were processed with the Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA). Preparation and normalization of the HumanMethylation450 BeadChip array data was performed according to the CPACOR workflow (19) using the software package R (20). In detail, the idat files were read using the minfi package. Probes that had a detection p-value above background (based on sum of methylated and unmethylated intensity values) ≥ 1E-16 were set to missing per array. Next, the intensity values were stratified by autosomal and non-autosomal probes and quantile normalized for each of the six probe type categories separately: type II red/green, type I methylated red/green and type I unmethylated red/green. Beta values were calculated as proportion of methylated intensity value on the sum of methylated+unmethylated+100 intensities. Arrays with observed technical problems such as failed bisulfite conversion, hybridization or extension, as well as arrays with a mismatch between sex of the proband and sex determined by the chr X and Y probe intensities were removed from subsequent analyses. Additionally, only arrays with a call rate > 95% per sample were processed further. Probes on the X and Y chromosomes were excluded from the dataset. The final dataset contained information on 458,563 CpGs.

Childhood blood samples:

For the look-up in childhood, we used DNA extracted (using the salting-out method) from blood samples taken at the 5-year follow-up visit. The procedure for processing with the

Illumina Infinium HumanMethylation450 BeadChip (Illumina Inc., San Diego, USA) and for the normalization and QC steps was similar to that for the cord blood samples.

Covariates:

Maternal education was self-reported and defined based on the highest level of education finished by the mothers. The covariate is binary with higher education describing the higher educational level. **Maternal smoking** during pregnancy was self-reported as "no smoking during pregnancy", "smoked but quit before second trimester", or "smoked throughout pregnancy". **Newborn sex** was obtained from midwife and hospital registries. **Maternal age** was reported by the mother in the questionnaire. **Maternal BMI** was calculated based on self-reported height and weight. If available, pre-pregnancy BMI was used, otherwise BMI in early pregnancy was used. **Maternal total energy intake** was calculated in kcal/day from the total diet by means of the self-reported FFQ and the Dutch food composition table. **Cell type composition** was estimated using the reference-based Houseman method (13) in the minfi Package (21) in R (20). This method estimates the relative proportions of white blood cell subtypes CD8T, CD4T, NK, Bcells, Monocytes, Granulocytes, nucleated red blood cells in cord blood (11). Plate number was included as **batch variable**.

For the **look-ups in childhood** (mean age 6.1y and 9.8y), we additionally adjusted for **childhood age** at DNA methylation measurement. Further, for this look-up in childhood, **cell type correction** was applied using the reference-based Houseman method (13) in the minfi package (21) in R (20), using the adult Reinius reference panel (22). This method estimates the relative proportions of six white blood cell subtypes (CD4+ T-lymphocytes, CD8+ T-lymphocytes, NK (natural killer) cells, B-lymphocytes, monocytes and granulocytes), based on a standard reference population (as published by Reinius *et al*.) (22).

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Rotterdam. Written informed consent was obtained for all participants. The generation and management of the Illumina 450K methylation array data (EWAS data) for the Generation R Study was executed by the Human Genotyping Facility of the Genetic Laboratory of the Department of Internal Medicine, Erasmus MC, the Netherlands. We thank Mr. Michael Verbiest, Ms. Mila Jhamai, Ms. Sarah Higgins, Mr. Marijn Verkerk and Dr. Lisette Stolk for their help in creating the EWAS database. We thank Dr. A.Teumer for his work on the quality control and normalization scripts.

The INMA—INfancia y Medio Ambiente—(Environment and Childhood) Project

Description of cohort:

The present study used data from participants recruited between 2003 and 2008 in the de novo cohort sited in Sabadell of the INfancia y Medio Ambiente (INMA) Project, a population-based mother–child cohort study in Spain (23). Current project uses data from European ancestry children from the Sabadell subcohort. Study website: http://www.proyectoinma.org/

Ethical approval:

The study was approved by the Ethics Committee of the reference hospital, and all participants gave their written informed consent.

EWAS analyst:

Sílvia Fernández-Barrés

Description of FFQ and glycemic index and load calculation:

We used a biomarker-validated 101-item FFQ and standard units and serving sizes were specified for each food item (24). In the validation study of the FFQ, no women were found with implausible low or high energy intake ((<500kcal/d or >5000kcal/d) or missing data. Information on usual dietary intake was collected around 12 weeks of gestation, using as the reference the period between the last menstruation and the first prenatal visit that occurred between the 10–13 weeks of pregnancy. Portion sizes were estimated using standard household measures. The FFQ had nine possible responses, ranging from 'never or less than once per month' to 'six or more per day'. Nutrient intake, including total energy intake and carbohydrate content were estimated using the available information in the US Department of Agriculture food composition tables and other published sources for Spanish foods and portion sizes (25–27). To calculate glycemic index and load for foods with >1g total carbohydrate per 100g, we used the Atkinson reference database (28), using glucose sugar as a reference food (glycemic index for glucose sugar equal to 100). All relevant food items for GI and load were found in the Atkinson database.

Methylation normalization and QC steps taken in your cohort:

Cord blood and childhood blood samples:

INMA 450k data was produced within the MEDALL, BREATHE and HELIX projects. Cord or peripheral blood 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 3 different laboratories: in the Genome Analysis Facility of the University Medical Center Groningen (UMCG) in the Netherlands (MEDALL 0y and 4y), and in the Bellvitge Biomedical Research Institute (IDIBELL, Barcelona) (BREATHE 0y), and in the Spanish National Genotyping Center (CEGEN, Madrid) (HELIX 9y). All 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. The quality control of the methylation data obtained at birth and at 4y was done together, while the quality control of the methylation data at age 9y was done together with other samples from the HELIX project.

Cord and 4y DNA methylation data (MEDALL and BREATHE) were quality controlled and preprocessed using the minfi package. (21) 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 were removed. (29) Then, we removed 3 samples whose sex was wrongly predicted using shinyMethyl. (30) Following guidelines of Lehne work, 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%. (19) The next step was normalizing data with the functional normalization method with Noob background subtraction and dye-bias correction. (31) Correlation between SNPs in replicates was checked and probes not measuring SNPs were discarded. Probes with a call rate lower than 95% were also removed. Probes in the sexual chromosomes, cross-hybridizing or containing SNPs were flagged but not removed at this point. ComBat was applied to remove laboratory batch effect. (32) Finally, duplicated samples were removed, prioritizing MeDALL samples over BREATHE samples. The final DNA methylation dataset contained information on 476,946 probes.

DNA methylation data at the age of 9 years (HELIX) was pre-processed using minfi R package. (21) Probes not reaching a 98% call rate based on a detection p-value threshold <1E-

16 were excluded. (19) Samples with a call rate <98% were removed from the study. Then, data was normalized with the functional normalization method with Noob background subtraction and dye-bias correction. (31) Then, we checked sex consistency using the shinyMethyl R package, and genetic consistency was checked making use of the genotype probes included in the Infinium HumanMethylation450K BeadChip and the genome-wide genotyping data when available. Batch effect (slide) was corrected using the ComBat R package. (30,32) Control probes, probes in sexual chromosomes, probes designed to detect Single Nucleotide Polymorphisms (SNPs) and probes to measure methylation levels at non-CpG sites were excluded, giving a final number of 476,946 probes.

Covariates:

Maternal education was assessed in week 12 of gestation and coded as an ordinal variable: 1 = primary or without education, 2= secondary, and 3 = University. **Maternal smoking** was assessed as an ordinal variable representing 1 = No smoking during pregnancy, 2 = Smoked, stopped before 2nd trimester, 3 = Smoked throughout pregnancy. **Newborn sex** was taken from obstetric records. **Maternal age** was a continuous numeric variable in years assessed at enrolment. **Maternal pre-pregnancy BMI** was calculated from measured height and self-reported pre-pregnancy weight collected using a questionnaire at enrolment (week 12 of pregnancy). Reported pre-pregnancy weight was highly correlated with measured weight at 12 weeks of pregnancy in INMA ($r= 0.96$; $P < 0.0001$). **Maternal total energy intake** from the total diet was assessed in the first trimester of pregnancy using a 101-item FFQ. Total energy intake was obtained from the US Department of Agriculture food composition tables and other published sources (26,33). **Cord blood cell proportions** were estimated using the Gervin and Salas reference panel (11), the IDOL algorithm for selection of 517 CpGs (for 450K and EPIC arrays) (34), and the constrained projection-quadratic programming algorithm by Houseman (13) for deconvolution of 7 main blood cell types. Combat was used as laboratory **batch variable**.

For the two **look-ups in childhood** (mean age 4.5y and 8.8y), we additionally adjusted for **childhood age** at DNA methylation measurement. Further, for this look-up in childhood, **cell type correction** was applied using the Reinius reference panel (22) with the pickCompProbes method (minfi (21)) for CpG selection, and the Houseman algorithm (13) for deconvolution of 6 main blood cell types.

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Leipzig Childhood AT Cohort: RNA transcript – CpG association look-up

Materials and methods:

We analysed 223 participants from the Leipzig Childhood AT Cohort, for which subcutaneous adipose tissue samples had been obtained as previously described (35).

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. Expressions were quantile-normalised and log2 transformed. Mapping of genes corresponding to expression probes and assignment of gene names was done using information of a remapping approach (36). This remapping approach 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 the Hg38 build) were retrieved via the Bioconductor package biomaRt (https://bioconductor.org/packages/release/bioc/html/biomaRt.html)

Methylome profiling was obtained with the Illumina Infinium MethylationEPIC BeadChip Kit (Illumina, California, USA). Tthe Illumina intensity data (IDAT) files were processed using the ChAMP pipeline (37) implemented in the corresponding in R package (https://bioconductor.org/packages/release/bioc/html/ChAMP.html), 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. Methylation levels at each CpG site expressed as a β-value representing the approximate proportion of methylation at the site (0%–100%), were transformed to M-values using the logit transformation ($log2(\frac{\beta}{1-\beta})$) prior to performing the analysis. Probe positions were lifted to the Hg38 build using the UCSC liftOver command-line tool.

We tested the association of the 41 prioritized CpGs with the gene transcripts for which the CpG position was within 500Kb of the transcription start site of the transcript in the main analysis on cord blood. Seven of the 41 prioritized CpGs were discarded during the pre-

processing phase (cg02920421, cg16169361, cg24458009, cg26729101, cg12972275, cg17582259, cg16031283) and 1 CpG (cg02079551) did not fall in a 500kb region of the transcription start site of the valid gene transcripts analyzed. We regressed the log2 expression signals for the transcripts on methylation M-values for a single CpG, using linear regression models adjusted for age and sex. We applied Bonferroni correction using the total number of CpGs tested (33, since 8 CpGs were discarded prior to the statistical analysis) and the number of tests per each unique CpG-transcript pair (reported in column *N tests CpG*). We focused on CpGs ≤500kb of the transcription start site of the transcript.

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Leipzig Childhood AT Cohort:

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