

**Supplementary Table 1: Top EWAS hits from ALSPAC data in girls selected at the  $P=1.10^{-4}$  level.**

| CpG site       | Gene                  | Chr | Pos.    | Group           | <i>GWAS</i><br><i>SNP</i>            | <i>P</i> | <i>P</i> <sub>adj</sub> <sup>†</sup> | EBF effect on DNAm<br>(≥3 months vs. 0) <sup>#</sup> |            |            |             | EBF direct effect on BMI<br>(≥3 months vs. 0) <sup>§</sup> |            |            |             | EBF effect on BMI mediated<br>by DNAm<br>(≥3 months vs. 0) <sup>&amp;</sup> |            |            |             |
|----------------|-----------------------|-----|---------|-----------------|--------------------------------------|----------|--------------------------------------|--|------------|------------|-------------|--|------------|------------|-------------|---|------------|------------|-------------|
|                |                       |     |         |                 |                                      |          |                                      | 1<br>year  | 2<br>years | 7<br>years | 15<br>years | 1<br>year  | 2<br>years | 7<br>years | 15<br>years | 1<br>year   | 2<br>years | 7<br>years | 15<br>years |
| cg06471491     | miR-21                | 17  | 57,918  | TSS1500         | N                                    | <E-16    | <E-16                                | 0.02   | -0.08      | -0.07      | -0.07       | -1.13  | -0.51      | -0.17      | -0.37       | 0.36  | 0.11       | 0.00       | 0.01        |
| cg16645539     | SNAPC3                | 9   | 15,423  | TSS200          | rs62571018<br>BMI                    | <E-16    | <E-16                                | -0.05  | -0.03      | 0.00       | -0.01       | -0.28  | -0.73      | -0.21      | -0.29       | -0.38   | 0.00       | 0.02       | 0.00        |
| cg07408552     | ATP6V0A1              | 17  | 40,612  | 5'UTR           | rs11079041<br>Waist-hip ratio        | 3.E-08   | 2.E-08                               | -0.19  | -0.18      | 0.06       | 0.00        | -1.84  | -0.44      | -0.16      | -0.32       | -0.34   | -0.08      | 0.03       | -0.01       |
| cg08224066     | DHX15/<br>PPARGC1A    | 4   | 24,578  | Body            | N                                    | 4.E-08   | 2.E-08                               | -0.04  | 0.03       | 0.05       | 0.05        | -0.30  | -0.44      | -0.20      | -0.30       | 0.00  | 0.03       | 0.00       | 0.02        |
| cg14822546     | LINC00398/<br>ALOX5AP | 13  | 31,381  |                 | N                                    | 7.E-08   | 8.E-08                               | -0.01  | 0.01       | 0.01       | -0.01       | -0.76  | -0.53      | -0.22      | -0.40       | 0.09  | -0.04      | 0.01       | 0.00        |
| cg14776321     | ANKRD26               | 10  | 27,220  | Body            | rs7081476<br>BMI                     | 7.E-08   | 2.E-07                               | -0.05  | -0.01      | 0.04       | 0.04        | -0.10  | -0.43      | -0.12      | -0.30       | -0.30   | 0.03       | 0.06       | 0.02        |
| ch.8.18261148F | NATP/NAT2             | 8   | 18,217  |                 | rs4921913<br>Metabolic<br>syndrome   | 7.E-08   | 1.E-07                               | -0.11  | -0.06      | -0.03      | -0.04       | -0.66  | -0.67      | -0.19      | -0.26       | 0.05  | 0.01       | 0.00       | 0.01        |
| cg00313685     | CUX1                  | 7   | 101,469 | Body            | rs367026<br>Waist-hip ratio          | 2.E-07   | 2.E-07                               | 0.19   | 0.06       | -0.01      | 0.05        | -0.39  | -0.14      | -0.22      | -0.30       | -0.10   | 0.00       | -0.02      | -0.04       |
| cg17476951     | TRAPPC9               | 8   | 141,054 | Body            | rs71514664<br>Hip circum<br>ference  | 2.E-07   | 6.E-07                               | -0.12  | -0.06      | 0.02       | 0.01        | -0.67  | -0.53      | -0.25      | -0.30       | 0.13  | 0.20       | 0.01       | 0.00        |
| cg26398656     | OSBPL1A               | 18  | 21,852  | Body;<br>TSS200 | rs275856<br>Type 2<br>diabetes       | 3.E-07   | 5.E-07                               | -0.11  | -0.06      | 0.00       | 0.04        | -0.36  | -0.60      | -0.23      | -0.25       | -0.27   | -0.11      | 0.03       | -0.01       |
| cg26872564     | ZNF185                | X   | 152,087 | Body            | N                                    | 3.E-07   | 2.E-06                               | -0.06  | -0.01      | 0.06       | 0.07        | -0.27  | -0.19      | -0.23      | -0.38       | 0.04  | 0.01       | 0.00       | -0.01       |
| cg18176842     | NSE1                  | 2   | 14,776  | 3'UTR           | rs7602441<br>BMI                     | 3.E-07   | 4.E-07                               | -0.11  | -0.09      | -0.02      | -0.06       | -0.17  | -0.03      | -0.27      | -0.41       | 0.10  | 0.08       | 0.00       | -0.03       |
| cg04354689     | PDPK1                 | 16  | 2,661   | Body            | N                                    | 5.E-07   | 6.E-07                               | 0.19   | 0.06       | -0.01      | 0.05        | -0.39  | -0.14      | -0.22      | -0.30       | 0.14  | 0.02       | -0.02      | 0.00        |
| cg03664802     | EPC2                  | 2   | 149,402 | TSS200          | rs1234423<br>Body height             | 5.E-07   | 5.E-07                               | 0.05   | 0.00       | -0.01      | -0.04       | -0.71  | -0.37      | -0.24      | -0.34       | -0.01   | 0.04       | 0.01       | 0.00        |
| cg04781580     | TRAV14DV4             | 14  | 22,393  |                 | N                                    | 6.E-07   | 3.E-07                               | -0.01  | 0.03       | -0.02      | -0.02       | -0.31  | -0.42      | -0.22      | -0.38       | 0.11  | -0.01      | 0.03       | 0.06        |
| cg11746359     | MAML3                 | 4   | 141,012 | Body            | rs2667360<br>BMI                     | 6.E-07   | 4.E-07                               | -0.21  | -0.11      | 0.01       | -0.03       | -0.52  | -0.33      | -0.22      | -0.40       | -0.09   | 0.02       | 0.01       | 0.01        |
| cg27215185     | GMDS                  | 6   | 2,198   | Body            | rs143303199<br>Body height           | 1.E-06   | 2.E-06                               | -0.11  | -0.06      | 0.00       | 0.04        | -0.36  | -0.60      | -0.23      | -0.25       | -0.21   | 0.13       | -0.01      | 0.00        |
| cg23057721     | LINC02594             | 17  | 41,791  |                 | N                                    | 1.E-06   | 2.E-06                               | -0.10  | -0.04      | 0.04       | -0.01       | -0.61  | -0.05      | -0.31      | -0.47       | -0.09   | 0.07       | 0.02       | 0.02        |
| cg04738270     | ACTR1A                | 10  | 104,262 | Body            | rs3862030<br>Waist cir<br>cumference | 2.E-06   | 3.E-06                               | 0.05   | 0.04       | 0.01       | 0.07        | -0.71  | -0.37      | -0.27      | -0.46       | -0.53   | -0.14      | 0.02       | -0.01       |
| cg09029192     | TNRC6C                | 17  | 76,015  | 5'UTR           | rs1656794<br>Body height             | 2.E-06   | 3.E-06                               | -0.05  | -0.01      | 0.04       | 0.04        | -0.10  | -0.43      | -0.12      | -0.30       | -0.05   | 0.00       | 0.00       | -0.01       |
| cg11566521     | RAPGEF2               | 4   | 160,128 |                 | rs563875<br>Body height              | 2.E-06   | 7.E-07                               | -0.04  | 0.03       | 0.05       | 0.05        | -0.30  | -0.44      | -0.20      | -0.30       | 0.02  | 0.06       | -0.01      | -0.04       |
| cg00524694     | PROP1                 | 5   | 177,388 |                 | rs6601211<br>Body height             | 3.E-06   | 3.E-06                               | -0.19  | -0.18      | 0.06       | 0.00        | -1.84  | -0.44      | -0.16      | -0.32       | -0.02   | 0.00       | 0.01       | 0.00        |
| cg00070899     | GRM4                  | 6   | 34,024  | Body            | rs1759645<br>Body height             | 3.E-06   | 3.E-06                               | -0.21  | -0.11      | 0.01       | -0.03       | -0.52  | -0.33      | -0.22      | -0.40       | 0.17  | 0.06       | 0.00       | -0.02       |
| cg23027583     | HLX                   | 1   | 221,053 | TSS200          | rs10218741                           | 3.E-06   | 5.E-06                               | 0.05   | 0.04       | 0.01       | 0.07        | -0.71  | -0.37      | -0.27      | -0.46       | 0.01  | -0.02      | 0.01       | 0.00        |

|            |                   |    |         |                  |  |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
|------------|-------------------|----|---------|------------------|--|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| cg05241732 | MYH6/<br>miR-208A | 14 | 23,859  | Body;<br>TSS1500 | Body height<br>rs2231301               | 3.E-06 | 1.E-05 | -0.20 | -0.12 | 0.03  | 0.00  | -0.28 | -0.22 | -0.26 | -0.39 | -0.04 | -0.02 | -0.01 | 0.01  |
| cg26992566 | EMC8              | 16 | 85,814  | Body             | N                                      | 5.E-06 | 5.E-05 | -0.12 | -0.06 | 0.02  | 0.01  | -0.67 | -0.53 | -0.25 | -0.30 | -0.06 | -0.04 | 0.01  | 0.01  |
| cg23543615 | MEF2B             | 19 | 19,281  | Body;<br>5'UTR   | rs11670016<br>waist-hip ratio          | 5.E-06 | 9.E-06 | -0.02 | -0.02 | 0.01  | -0.02 | -0.40 | -0.59 | -0.20 | -0.30 | -0.15 | -0.04 | 0.01  | 0.00  |
| cg01505676 | TGM7              | 15 | 43,595  | TSS1500          | N                                      | 6.E-06 | 8.E-06 | -0.07 | -0.03 | 0.00  | 0.02  | -0.29 | -0.45 | -0.16 | -0.30 | -0.23 | -0.06 | 0.02  | 0.00  |
| cg17862404 | TSC22D1           | 13 | 45,009  | Body             | rs10507524<br>waist-hip ratio          | 7.E-06 | 9.E-06 | 0.07  | 0.07  | 0.05  | 0.00  | -0.35 | -0.27 | -0.20 | -0.27 | -0.59 | -0.12 | 0.05  | 0.01  |
| cg06683602 | CXCR1             | 2  | 219,032 | TSS1500          | N                                      | 7.E-06 | 2.E-05 | -0.20 | -0.12 | 0.03  | 0.00  | -0.28 | -0.22 | -0.26 | -0.39 | -0.88 | -0.51 | -0.05 | 0.00  |
| cg23662178 | ZNF518A           | 10 | 97,884  |                  | rs1172955<br>Body height               | 7.E-06 | 7.E-06 | -0.03 | -0.01 | 0.02  | 0.02  | -0.46 | -0.16 | -0.25 | -0.47 | 0.15  | 0.12  | -0.01 | 0.01  |
| cg21966975 | PADI3             | 1  | 17,575  | TSS200           | rs2284746<br>Body height               | 8.E-06 | 6.E-06 | -0.01 | 0.03  | -0.02 | -0.02 | -0.31 | -0.42 | -0.22 | -0.38 | -0.20 | -0.05 | 0.03  | -0.14 |
| cg22851175 | DDX11             | 12 | 31,274  |                  | rs3214606<br>Type 2 diabetes           | 9.E-06 | 2.E-05 | 0.15  | 0.05  | -0.09 | -0.06 | -0.52 | 0.12  | -0.24 | -0.35 | -0.49 | -0.19 | -0.01 | 0.08  |
| cg14531663 | PRRT1             | 6  | 32,117  | 3'UTR            | rs2857693<br>Body height               | 1.E-05 | 6.E-06 | -0.19 | -0.18 | 0.06  | 0.00  | -1.84 | -0.44 | -0.16 | -0.32 | -0.29 | 0.24  | 0.03  | 0.00  |
| cg10053073 | RECQL5            | 17 | 73,623  | 3'UTR            | rs2385263<br>Waist-hip ratio           | 1.E-05 | 3.E-05 | 0.07  | 0.07  | 0.05  | 0.00  | -0.35 | -0.27 | -0.20 | -0.27 | -0.02 | -0.01 | 0.00  | -0.04 |
| cg07548512 | SDF4              | 1  | 1,155   | Body             | rs1240697<br>Body height               | 1.E-05 | 1.E-05 | -0.15 | -0.07 | 0.03  | 0.02  | -0.29 | -0.41 | -0.17 | -0.32 | 0.22  | 0.01  | -0.01 | -0.01 |
| cg17401282 | GABRG2            | 5  | 161,494 | TSS1500          | N                                      | 1.E-05 | 4.E-05 | -0.05 | -0.03 | 0.00  | -0.01 | -0.28 | -0.73 | -0.21 | -0.29 | 0.18  | 0.21  | -0.01 | -0.04 |
| cg12510087 | GALNT9            | 12 | 132,887 | Body             | rs11247009<br>BMI                      | 1.E-05 | 8.E-05 | -0.06 | -0.01 | 0.06  | 0.07  | -0.27 | -0.19 | -0.23 | -0.38 | -0.10 | -0.10 | -0.02 | 0.16  |
| cg10082165 | CTSG              | 14 | 25,044  | Body             | N                                      | 2.E-05 | 2.E-05 | -0.11 | -0.04 | 0.04  | -0.05 | -0.28 | 0.05  | -0.16 | -0.33 | -0.01 | 0.00  | 0.01  | -0.03 |
| cg06340161 | GPT2              | 16 | 46,963  | 3'UTR            | N                                      | 2.E-05 | 5.E-05 | 0.00  | 0.05  | 0.05  | -0.01 | 0.40  | -0.07 | -0.24 | -0.57 | -0.06 | 0.02  | 0.01  | -0.03 |
| cg12251803 | LRRFIP1           | 2  | 238,640 | Body             | rs11680012<br>obesity                  | 2.E-05 | 3.E-05 | -0.34 | -0.23 | -0.04 | -0.12 | -0.27 | -0.27 | -0.21 | -0.40 | -0.18 | -0.26 | -0.03 | 0.00  |
| cg22334632 | TMEM160           | 19 | 47,553  | TSS1500          | rs112551143<br>BMI                     | 2.E-05 | 3.E-04 | 0.00  | 0.05  | 0.05  | -0.01 | 0.40  | -0.07 | -0.24 | -0.57 | 0.00  | 0.05  | 0.04  | 0.01  |
| cg09560549 | SPG7              | 16 | 89,573  | TSS1500          | rs4785574<br>Body height               | 2.E-05 | 6.E-05 | -0.01 | 0.00  | -0.01 | -0.01 | -0.79 | -0.72 | -0.21 | -0.35 | 0.03  | -0.18 | 0.00  | -0.01 |
| cg04516203 | N/A               | 16 | 51,443  |                  | N                                      | 2.E-05 | 2.E-05 | 0.14  | 0.00  | -0.07 | -0.07 | -0.97 | -0.36 | -0.19 | -0.37 | -0.12 | -0.18 | 0.00  | 0.00  |
| cg03553386 | IGF2;INS-IGF2     | 11 | 2,171   | TSS200;<br>Body  | rs217227<br>Body height                | 2.E-05 | 8.E-05 | -0.10 | -0.04 | 0.04  | -0.01 | -0.61 | -0.05 | -0.31 | -0.47 | -0.65 | -0.21 | -0.02 | 0.02  |
| cg14086922 | MICAL3            | 22 | 18,268  |                  | rs10854521<br>Body height              | 2.E-05 | 3.E-05 | -0.04 | -0.02 | -0.01 | 0.01  | -0.78 | -0.89 | -0.21 | -0.28 | -0.09 | -0.18 | -0.04 | 0.09  |
| cg19497523 | TMPRSS9           | 19 | 2,425   | Body             | N                                      | 3.E-05 | 8.E-06 | -0.04 | -0.02 | -0.01 | 0.01  | -0.78 | -0.89 | -0.21 | -0.28 | 0.13  | 0.10  | 0.00  | 0.04  |
| cg03409272 | CCL14-CCL15       | 17 | 34,330  | TSS1500          | N                                      | 3.E-05 | 3.E-05 | -0.21 | -0.11 | 0.01  | -0.03 | -0.52 | -0.33 | -0.22 | -0.40 | -1.49 | -0.52 | 0.02  | 0.04  |
| cg02822745 | DKK2              | 4  | 108,271 |                  | N                                      | 3.E-05 | 3.E-05 | -0.01 | 0.00  | -0.01 | -0.01 | -0.79 | -0.72 | -0.21 | -0.35 | 0.75  | 0.37  | 0.00  | -0.06 |
| cg16004911 | FRYL              | 4  | 48,783  | TSS1500          | rs10031777<br>Body height              | 3.E-05 | 5.E-05 | 0.02  | -0.08 | -0.07 | -0.07 | -1.13 | -0.51 | -0.17 | -0.37 | 0.08  | 0.00  | 0.00  | 0.03  |
| cg07988060 | UTP6              | 17 | 30,235  |                  | rs7209766<br>Body height               | 3.E-05 | 2.E-05 | -0.05 | -0.03 | 0.00  | -0.01 | -0.28 | -0.73 | -0.21 | -0.29 | -0.01 | 0.06  | 0.01  | -0.01 |
| cg23000550 | P2RX6             | 22 | 21,369  | TSS1500          | N                                      | 3.E-05 | 9.E-05 | -0.16 | -0.06 | 0.05  | -0.12 | -0.46 | 0.07  | -0.40 | -0.54 | -0.44 | -0.30 | 0.01  | 0.00  |
| cg15921911 | RAD51B            | 14 | 69,156  |                  | rs11158743<br>Body height              | 3.E-05 | 7.E-05 | -0.34 | -0.23 | -0.04 | -0.12 | -0.27 | -0.27 | -0.21 | -0.40 | -0.62 | -0.64 | 0.01  | -0.06 |
| cg15243597 | WDPCP             | 2  | 63,553  | Body             | rs775417095<br>Waist cir<br>cumference | 3.E-05 | 4.E-05 | -0.07 | -0.03 | 0.00  | 0.02  | -0.29 | -0.45 | -0.16 | -0.30 | 0.11  | 0.17  | 0.01  | 0.00  |
| cg07364240 | NRROS             | 3  | 196,389 | 3'UTR            | N                                      | 4.E-05 | 2.E-05 | -0.15 | -0.07 | 0.03  | 0.02  | -0.29 | -0.41 | -0.17 | -0.32 | -0.12 | -0.03 | 0.01  | -0.08 |
| cg07012178 | PRKAG2            | 7  | 151,305 | Body             | N                                      | 4.E-05 | 5.E-05 | 0.00  | 0.05  | 0.05  | -0.01 | 0.40  | -0.07 | -0.24 | -0.57 | -0.07 | -0.13 | 0.01  | -0.08 |
| cg10883421 | RMND1/            | 6  | 151,773 | TSS200           | rs9397403                              | 4.E-05 | 2.E-05 | 0.02  | -0.08 | -0.07 | -0.07 | -1.13 | -0.51 | -0.17 | -0.37 | -0.55 | 0.14  | 0.06  | -0.04 |

|            |                    |    |         |                   |                                       |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
|------------|--------------------|----|---------|-------------------|---------------------------------------|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|            | ARMT1              |    |         |                   | Body height                           |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
| cg06527213 | KLHL25/<br>MIR1276 | 15 | 86,315  | 5'UTR;<br>TSS1500 | rs10520587<br>Body height             | 4.E-05 | 7.E-05 | -0.04 | -0.03 | -0.05 | -0.05 | -0.92 | -1.03 | -0.22 | -0.31 | -0.13 | -0.03 | -0.02 | -0.09 |
| cg02754470 | RNF111             | 15 | 59,158  |                   | N                                     | 4.E-05 | 9.E-05 | -0.11 | -0.09 | -0.02 | -0.06 | -0.17 | -0.03 | -0.27 | -0.41 | -0.05 | -0.04 | 0.01  | -0.03 |
| cg26144456 | NXT2               | X  | 108,779 | TSS200            | N                                     | 4.E-05 | 2.E-05 | -0.04 | -0.03 | -0.05 | -0.05 | -0.92 | -1.03 | -0.22 | -0.31 | 0.15  | 0.07  | 0.01  | 0.02  |
| cg09699373 | USP10              | 16 | 84,823  |                   | rs2326458<br>Body height              | 4.E-05 | 5.E-05 | -0.04 | 0.03  | 0.05  | 0.05  | -0.30 | -0.44 | -0.20 | -0.30 | -0.10 | -0.01 | 0.04  | 0.03  |
| cg00469800 | TOR1A              | 9  | 132,585 | Body              | N                                     | 5.E-05 | 9.E-05 | -0.04 | -0.02 | -0.01 | 0.01  | -0.78 | -0.89 | -0.21 | -0.28 | -0.33 | -0.19 | -0.01 | 0.01  |
| cg17901584 | DHCR24             | 1  | 55,354  | TSS1500           | rs597021<br>Body height               | 5.E-05 | 1.E-04 | -0.31 | -0.20 | -0.02 | -0.05 | -0.74 | -0.30 | -0.30 | -0.47 | 0.07  | 0.03  | -0.01 | 0.01  |
| cg04126095 | MASP1              | 3  | 186,954 | Body              | rs3864095<br>Type 2 diabetes          | 5.E-05 | 9.E-05 | -0.01 | 0.00  | -0.01 | -0.01 | -0.79 | -0.72 | -0.21 | -0.35 | -0.52 | -0.31 | 0.01  | 0.00  |
| cg02612228 | MYOM2              | 8  | 1,983   |                   | N                                     | 5.E-05 | 3.E-04 | -0.01 | 0.01  | 0.01  | -0.01 | -0.76 | -0.53 | -0.22 | -0.40 | 0.41  | 0.06  | -0.02 | 0.03  |
| cg16824319 | LYPD8              | 1  | 248,904 | TSS1500           | N                                     | 5.E-05 | 8.E-05 | 0.02  | 0.02  | 0.00  | 0.01  | -0.64 | -0.41 | -0.29 | -0.49 | -0.02 | 0.03  | 0.00  | -0.05 |
| cg18000306 | DUSP22             | 6  | 289     |                   | N                                     | 5.E-05 | 3.E-05 | -0.11 | -0.04 | 0.04  | -0.05 | -0.28 | 0.05  | -0.16 | -0.33 | 0.29  | 0.25  | 0.00  | 0.11  |
| cg01875529 | ANKRD11            | 16 | 89,355  | Body              | rs57258486<br>Body height             | 5.E-05 | 7.E-05 | -0.15 | -0.07 | 0.03  | 0.02  | -0.29 | -0.41 | -0.17 | -0.32 | -0.41 | -0.14 | 0.06  | 0.06  |
| cg12489353 | EHD2               | 19 | 48,231  | Body              | rs12973221<br>BMI                     | 5.E-05 | 7.E-05 | 0.19  | 0.06  | -0.01 | 0.05  | -0.39 | -0.14 | -0.22 | -0.30 | 0.18  | 0.16  | 0.00  | 0.02  |
| cg02593766 | MYCBPAP/EP<br>N3   | 17 | 48,609  | Body;<br>TSS1500  | N                                     | 5.E-05 | 2.E-04 | -0.34 | -0.23 | -0.04 | -0.12 | -0.27 | -0.27 | -0.21 | -0.40 | 0.08  | 0.02  | -0.03 | 0.00  |
| cg07873325 | KRCC1              | 2  | 88,356  | TSS1500           | N                                     | 5.E-05 | 5.E-04 | -0.02 | -0.02 | 0.01  | -0.02 | -0.40 | -0.59 | -0.20 | -0.30 | -1.19 | -0.55 | 0.00  | -0.04 |
| cg10975863 | RAD51B             | 14 | 68,831  | Body              | rs11158743<br>Body height             | 6.E-05 | 3.E-05 | 0.05  | 0.05  | 0.05  | 0.05  | -0.43 | -0.32 | -0.24 | -0.40 | -0.07 | -0.06 | -0.02 | -0.03 |
| cg21324211 | FSD2               | 15 | 83,419  |                   | N                                     | 6.E-05 | 8.E-05 | -0.11 | -0.06 | 0.00  | 0.04  | -0.36 | -0.60 | -0.23 | -0.25 | -0.36 | 0.03  | 0.03  | -0.01 |
| cg21575634 | STX2               | 12 | 131,310 | Body              | N                                     | 6.E-05 | 2.E-04 | 0.05  | 0.05  | 0.05  | 0.05  | -0.43 | -0.32 | -0.24 | -0.40 | -0.12 | -0.05 | 0.00  | 0.01  |
| cg20817228 | LOC728855          | 1  | 149,615 | Body              | N                                     | 6.E-05 | 6.E-05 | -0.01 | 0.01  | 0.01  | -0.01 | -0.76 | -0.53 | -0.22 | -0.40 | -0.04 | 0.10  | 0.00  | 0.00  |
| cg03112433 | CDK14              | 7  | 90,339  | TSS200            | N                                     | 7.E-05 | 3.E-04 | -0.31 | -0.20 | -0.02 | -0.05 | -0.74 | -0.30 | -0.30 | -0.47 | 0.04  | 0.16  | 0.01  | -0.02 |
| cg03103888 | TMCO3              | 13 | 114,148 | 5'UTR             | N                                     | 7.E-05 | 1.E-04 | -0.31 | -0.20 | -0.02 | -0.05 | -0.74 | -0.30 | -0.30 | -0.47 | -0.09 | 0.00  | 0.02  | -0.05 |
| cg16756527 | RCAN1              | 21 | 35,891  | Body              | N                                     | 7.E-05 | 7.E-05 | -0.11 | -0.06 | -0.03 | -0.04 | -0.66 | -0.67 | -0.19 | -0.26 | 0.06  | -0.06 | -0.01 | 0.02  |
| cg19755813 | GEMIN4             | 17 | 650     | Body              | N                                     | 7.E-05 | 9.E-05 | -0.11 | -0.06 | -0.03 | -0.04 | -0.66 | -0.67 | -0.19 | -0.26 | 0.52  | 0.20  | -0.01 | 0.02  |
| cg02386599 | DAAM2              | 6  | 39,770  | 5'UTR             | rs1928191<br>Body height              | 7.E-05 | 2.E-04 | -0.05 | -0.01 | 0.04  | 0.04  | -0.10 | -0.43 | -0.12 | -0.30 | 0.00  | -0.07 | 0.02  | 0.01  |
| cg14363249 | TMC1               | 9  | 75,214  | 5'UTR             | N                                     | 7.E-05 | 1.E-04 | -0.01 | 0.03  | -0.02 | -0.02 | -0.31 | -0.42 | -0.22 | -0.38 | -0.03 | -0.05 | 0.00  | -0.02 |
| cg03217337 | CHMP4B             | 20 | 32,447  |                   | Rs12625495<br>Body height             | 7.E-05 | 1.E-04 | 0.05  | 0.00  | -0.01 | -0.04 | -0.71 | -0.37 | -0.24 | -0.34 | 0.06  | 0.05  | 0.00  | 0.12  |
| cg10107890 | -                  | 2  | 44,314  |                   | rs4953076<br>Body height              | 7.E-05 | 1.E-04 | 0.14  | 0.00  | -0.07 | -0.07 | -0.97 | -0.36 | -0.19 | -0.37 | -0.04 | -0.04 | -0.02 | -0.03 |
| cg07414571 | ZNF322             | 6  | 26,690  |                   | rs198853<br>Body height               | 7.E-05 | 8.E-05 | 0.07  | 0.07  | 0.05  | 0.00  | -0.35 | -0.27 | -0.20 | -0.27 | -0.16 | 0.23  | 0.10  | -0.10 |
| cg27457201 | RPTOR              | 17 | 78,854  | Body              | rs11150745<br>BMI                     | 8.E-05 | 4.E-04 | 0.05  | 0.04  | 0.01  | 0.07  | -0.71 | -0.37 | -0.27 | -0.46 | 0.02  | -0.07 | 0.01  | -0.01 |
| cg04580750 | LINC02774          | 1  | 244,200 |                   | rs12027747<br>Body height             | 8.E-05 | 1.E-04 | -0.10 | -0.04 | 0.04  | -0.01 | -0.61 | -0.05 | -0.31 | -0.47 | -0.24 | -0.10 | 0.01  | 0.00  |
| cg16678522 | CBFA2T2            | 20 | 32,150  | Body;<br>TSS1500  | rs12625495<br>Body height             | 8.E-05 | 2.E-04 | -0.12 | -0.06 | 0.02  | 0.01  | -0.67 | -0.53 | -0.25 | -0.30 | -0.13 | 0.02  | 0.01  | -0.11 |
| cg25527325 | PLIN5              | 19 | 4,524   | Body              | rs56356382<br>BMI                     | 8.E-05 | 4.E-04 | -0.03 | -0.01 | 0.02  | 0.02  | -0.46 | -0.16 | -0.25 | -0.47 | -0.58 | -0.36 | -0.05 | 0.00  |
| cg08104594 | DRAXIN             | 1  | 11,786  |                   | rs2336030<br>BMI                      | 8.E-05 | 9.E-05 | 0.15  | 0.05  | -0.09 | -0.06 | -0.52 | 0.12  | -0.24 | -0.35 | 0.07  | 0.01  | 0.00  | 0.01  |
| cg24134056 | FLJ12825           | 12 | 54,495  | Body;<br>TSS1500  | Rs12822416<br>Waist cir<br>cumference | 8.E-05 | 7.E-05 | 0.02  | 0.02  | 0.00  | 0.01  | -0.64 | -0.41 | -0.29 | -0.49 | 0.07  | 0.04  | 0.00  | 0.00  |
| cg07658646 | PRR4               | 12 | 11,002  | TSS200;           | N                                     | 8.E-05 | 7.E-05 | -0.16 | -0.06 | 0.05  | -0.12 | -0.46 | 0.07  | -0.40 | -0.54 | 0.06  | 0.06  | 0.00  | 0.06  |

|                   |                      |    |         |                 |                              |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
|-------------------|----------------------|----|---------|-----------------|------------------------------|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| <b>cg14009440</b> | TMEM53               | 1  | 45,139  | Body<br>Body    | Rs781771<br>IL6              | 8.E-05 | 2.E-04 | -0.16 | -0.06 | 0.05  | -0.12 | -0.46 | 0.07  | -0.40 | -0.54 | 0.05  | 0.02  | 0.00  | 0.03  |
| <b>cg04515702</b> | AKR1B10P1            | 10 | 69,510  |                 | rs573819939<br>Body weight   | 8.E-05 | 1.E-04 | -0.02 | -0.02 | 0.01  | -0.02 | -0.40 | -0.59 | -0.20 | -0.30 | 0.06  | 0.11  | 0.00  | -0.04 |
| <b>cg09010699</b> | ACAP2                | 3  | 195,172 |                 | rs149877182<br>Body height   | 8.E-05 | 2.E-04 | 0.14  | 0.00  | -0.07 | -0.07 | -0.97 | -0.36 | -0.19 | -0.37 | 0.10  | 0.13  | -0.04 | -0.01 |
| <b>cg13081568</b> | NKAIN2               | 6  | 125,145 | 3'UTR           | rs1871329<br>BMI             | 9.E-05 | 2.E-04 | 0.02  | 0.02  | 0.00  | 0.01  | -0.64 | -0.41 | -0.29 | -0.49 | 0.00  | -0.02 | -0.01 | -0.06 |
| <b>cg26543333</b> | NFIC                 | 19 | 3,398   | Body            | rs56356382<br>BMI            | 9.E-05 | 2.E-04 | -0.07 | -0.03 | 0.00  | 0.02  | -0.29 | -0.45 | -0.16 | -0.30 | 0.20  | -0.01 | 0.00  | 0.00  |
| <b>cg20946054</b> | DRAXIN               | 1  | 11,762  | 5'UTR           | rs2336030<br>BMI             | 9.E-05 | 7.E-05 | -0.06 | -0.01 | 0.06  | 0.07  | -0.27 | -0.19 | -0.23 | -0.38 | 0.31  | 0.16  | 0.01  | 0.04  |
| <b>cg13931599</b> | CUBNP3/<br>ANKRD54P1 | 10 | 45,650  | TSS200          | N                            | 9.E-05 | 1.E-04 | 0.05  | 0.00  | -0.01 | -0.04 | -0.71 | -0.37 | -0.24 | -0.34 | 0.40  | 0.17  | 0.00  | -0.09 |
| <b>cg22941668</b> | miR-145              | 5  | 148,810 | TSS200;<br>Body | rs783779<br>Body height      | 9.E-05 | 9.E-05 | -0.03 | -0.01 | 0.02  | 0.02  | -0.46 | -0.16 | -0.25 | -0.47 | 0.02  | 0.08  | 0.02  | -0.20 |
| <b>cg20814202</b> | AATK                 | 17 | 79,129  | Body            | rs62073017<br>Body height    | 9.E-05 | 7.E-05 | -0.11 | -0.04 | 0.04  | -0.05 | -0.28 | 0.05  | -0.16 | -0.33 | -0.49 | -0.33 | 0.01  | -0.01 |
| <b>cg24465329</b> | -                    | 2  | 172,453 |                 | rs56228832<br>Lean body mass | 9.E-05 | 6.E-05 | -0.04 | -0.03 | -0.05 | -0.05 | -0.92 | -1.03 | -0.22 | -0.31 | 0.10  | 0.08  | -0.01 | 0.05  |
| <b>cg11211384</b> | -                    | 6  | 142,360 |                 | rs6930558<br>Birth weight    | 9.E-05 | 1.E-04 | 0.15  | 0.05  | -0.09 | -0.06 | -0.52 | 0.12  | -0.24 | -0.35 | 0.06  | 0.01  | 0.04  | 0.03  |
| <b>cg07603794</b> | CLASP1               | 2  | 122,355 | Body            | N                            | 1.E-04 | 8.E-05 | 0.05  | 0.05  | 0.05  | 0.05  | -0.43 | -0.32 | -0.24 | -0.40 | 0.10  | 0.05  | 0.04  | -0.01 |

<sup>†</sup>*P* values adjusted for obesity-related polygenic risk score

<sup>#</sup>Corresponds to estimate of  $\beta_M(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

<sup>§</sup>Corresponds to estimate of  $\beta_{DIR}(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

<sup>&</sup>Corresponds to estimate of  $\beta_{IND}(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

**Supplementary Table 2: Top EWAS hits from ALSPAC data in boys selected at the  $P=1.10^{-4}$  level.**

| CpG site   | Gene                | Chr | Pos.    | Group           | GWAS<br>SNP                      | P      | P <sub>adj</sub> <sup>†</sup> | EBF effect on DNAm<br>(≥3 months vs. 0) <sup>#</sup> |            |            |             | EBF direct effect on BMI<br>(≥3 months vs. 0) <sup>§</sup> |            |            |             | EBF effect on BMI mediated<br>by DNAm<br>(≥3 months vs. 0) <sup>&amp;</sup> |            |            |             |
|------------|---------------------|-----|---------|-----------------|----------------------------------|--------|-------------------------------|--|------------|------------|-------------|--|------------|------------|-------------|---|------------|------------|-------------|
|            |                     |     |         |                 |                                  |        |                               | 1<br>year  | 2<br>years | 7<br>years | 15<br>years | 1<br>year  | 2<br>years | 7<br>years | 15<br>years | 1<br>year   | 2<br>years | 7<br>years | 15<br>years |
| cg26657240 | IL16                | 15  | 81,475  |                 | rs11325<br>Body height           | 3.E-07 | 5.E-06                        | -0.02  | -0.02      | -0.03      | -0.03       | -1.43  | -0.39      | -0.01      | -0.06       | -0.01   | 0.00       | 0.05       | 0.23        |
| cg08651538 | NREP                | 5   | 111,070 | Body            | rs26543<br>BMI                   | 4.E-07 | 7.E-06                        | -0.06  | -0.05      | -0.03      | 0.02        | -1.32  | -0.42      | 0.02       | -0.07       | 0.03  | 0.02       | 0.00       | 0.09        |
| cg26227569 | CPZ/GPR78           | 4   | 8,687   |                 | N                                | 2.E-06 | 8.E-07                        | -0.04  | -0.03      | -0.02      | -0.01       | -0.92  | -0.62      | 0.02       | -0.10       | 0.69  | 0.52       | 0.01       | 0.01        |
| cg10658438 | GP5                 | 3   | 194,117 | 3'UTR           | N                                | 4.E-06 | 4.E-05                        | 0.03   | 0.03       | 0.11       | 0.04        | -0.55  | -0.45      | -0.16      | -0.31       | 0.18  | 0.13       | 0.02       | 0.04        |
| cg22230229 | BAHCC1              | 17  | 79,372  | TSS1500         | rs68007459<br>Body height        | 5.E-06 | 2.E-05                        | -0.02  | -0.02      | 0.00       | 0.02        | -1.36  | -0.43      | -0.08      | -0.09       | 0.07  | 0.02       | -0.02      | 0.05        |
| cg20559217 | DCPS                | 11  | 126,174 | TSS200          | rs7115672<br>Body height         | 6.E-06 | 3.E-05                        | -0.01  | 0.00       | 0.02       | 0.00        | -1.31  | -0.73      | 0.00       | -0.09       | 0.69  | 0.45       | 0.05       | -0.01       |
| cg18436737 | CTBP1               | 4   | 1,234   | Body            | rs72501962<br>Type 2<br>diabetes | 7.E-06 | 1.E-04                        | 0.19   | 0.12       | -0.05      | 0.01        | -1.51  | -0.71      | 0.08       | -0.17       | -0.04   | 0.00       | 0.02       | 0.09        |
| cg27149179 | ME3/ PRSS23         | 11  | 86,452  |                 | rs4944571<br>obesity             | 8.E-06 | 2.E-05                        | -0.35  | -0.26      | -0.04      | -0.04       | -0.79  | -0.70      | 0.09       | -0.34       | 0.83  | 0.23       | -0.01      | 0.05        |
| cg01972418 | PAX9                | 14  | 37,125  | TSS1500         | rs10131337<br>Body height        | 9.E-06 | 2.E-05                        | 0.01   | -0.01      | -0.06      | -0.03       | -1.01  | -0.66      | 0.05       | -0.14       | 0.16  | 0.05       | -0.02      | 0.09        |
| cg15185570 | BARX2               | 11  | 129,488 |                 | N                                | 1.E-05 | 5.E-06                        | -0.02  | -0.02      | -0.01      | 0.01        | -0.88  | -0.67      | 0.01       | -0.20       | -0.08   | -0.02      | 0.03       | -0.01       |
| cg05145608 | FO XK1              | 7   | 4,758   | Body            | N                                | 1.E-05 | 8.E-05                        | -0.06  | -0.04      | -0.02      | -0.08       | -0.73  | -0.65      | 0.04       | -0.09       | -0.04   | -0.08      | -0.01      | -0.03       |
| cg09552166 | MSL2                | 3   | 135,913 | TSS200;<br>Body | rs372030255<br>Body height       | 1.E-05 | 3.E-05                        | 0.08   | 0.08       | 0.08       | 0.01        | -1.01  | -0.53      | 0.02       | -0.05       | -0.77   | -0.05      | -0.01      | 0.05        |
| cg08079596 | ATOH8               | 2   | 86,000  | Body            | N                                | 1.E-05 | 1.E-04                        | -0.01  | -0.03      | -0.04      | -0.02       | -1.31  | -0.78      | 0.14       | 0.01        | -0.01   | 0.00       | 0.00       | 0.03        |
| cg02640147 | KCNIP1              | 5   | 170,025 | Body            | N                                | 1.E-05 | 3.E-04                        | 0.02   | 0.01       | -0.05      | -0.01       | -1.15  | -0.67      | 0.05       | -0.02       | -0.04   | -0.02      | 0.00       | 0.07        |
| cg09188763 | LMO1                | 11  | 8,286   | TSS1500         | rs110419<br>Body height          | 1.E-05 | 5.E-05                        | 0.01   | -0.02      | -0.03      | -0.06       | -1.21  | -0.75      | 0.04       | 0.02        | 0.45  | 0.24       | -0.01      | 0.04        |
| cg07143733 | miR155HG-<br>miR155 | 21  | 26,939  | Body            | N                                | 2.E-05 | 4.E-05                        | -0.20  | -0.19      | -0.01      | -0.08       | -1.96  | -0.38      | -0.11      | -0.15       | -0.44   | -0.18      | -0.05      | 0.05        |
| cg22792674 | VPS72               | 1   | 151,164 | TSS1500         | rs4512652<br>BMI                 | 2.E-05 | 24.E-05                       | 0.00   | 0.00       | 0.00       | 0.00        | -1.39  | -0.82      | 0.03       | -0.10       | 0.01  | -0.02      | -0.01      | -0.10       |
| cg17765387 | FBXW8               | 12  | 117,355 | Body            | rs12823620<br>Body height        | 2.E-05 | 2.E-05                        | -0.26  | -0.19      | -0.03      | -0.07       | -0.34  | -0.17      | 0.02       | -0.25       | -0.15   | 0.11       | 0.00       | -0.07       |
| cg19865725 | RTN4                | 2   | 55,321  |                 | rs7582359<br>BMI                 | 2.E-05 | 1.E-04                        | -0.07  | -0.04      | 0.04       | -0.04       | -0.95  | -0.68      | 0.01       | -0.15       | -0.14   | -0.04      | -0.02      | -0.17       |
| cg03389890 | ABCD1P4             | 22  | 16,868  |                 | N                                | 2.E-05 | 4.E-05                        | -0.10  | -0.04      | 0.04       | 0.03        | -2.19  | -0.99      | 0.06       | -0.03       | 0.11  | 0.23       | 0.02       | -0.09       |
| cg13915886 | KCNT1               | 9   | 138,637 | Body            | N                                | 2.E-05 | 1.E-04                        | -0.03  | -0.03      | -0.01      | -0.04       | -1.27  | 0.09       | -0.13      | -0.08       | 0.40  | 0.32       | -0.03      | 0.02        |
| cg17945323 | SLC22A8             | 11  | 62,767  | Body            | rs11231299<br>Adipose<br>tissue  | 2.E-05 | 1.E-04                        | 0.03   | 0.02       | -0.04      | 0.01        | -2.35  | -0.40      | -0.10      | -0.19       | 0.33  | 0.13       | 0.00       | -0.02       |
| cg23864514 | TOMM7/<br>IL6       | 7   | 22,883  |                 | rs112330055<br>Body height       | 2.E-05 | 6.E-05                        | -0.02  | -0.03      | -0.02      | -0.02       | -1.04  | -0.38      | -0.07      | -0.10       | 0.11  | 0.01       | -0.06      | 0.06        |
| cg09187933 | AC079949.3          | 12  | 127,631 |                 | N                                | 2.E-05 | 5.E-05                        | 0.02   | 0.04       | 0.10       | -0.03       | -0.81  | -0.15      | -0.03      | -0.02       | -0.03   | -0.07      | -0.07      | 0.01        |

|                       |                       |    |         |                  |  |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
|-----------------------|-----------------------|----|---------|------------------|--|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| <b>cg21692620</b>     | CCR10/<br>CNTNAP1     | 17 | 42,683  | Body             | rs4792953<br>Body height               | 2.E-05 | 2.E-04 | -0.03 | 0.00  | 0.01  | 0.06  | -1.11 | -0.78 | 0.05  | 0.03  | 4.71  | 1.01  | 0.00  | 0.10  |
| <b>cg23847109</b>     | COL9A2                | 1  | 40,783  | TSS200           | rs1846158<br>Body height               | 2.E-05 | 4.E-04 | 0.25  | 0.14  | -0.05 | -0.05 | -2.25 | -0.72 | -0.24 | -0.33 | -0.88 | -0.46 | 0.00  | 0.02  |
| <b>cg21550785</b>     | ALK                   | 2  | 29,439  | Body             | rs1406230<br>Type 2<br>diabetes        | 2.E-05 | 3.E-04 | 0.41  | 0.30  | -0.01 | -0.02 | -1.12 | -0.40 | 0.00  | -0.09 | -0.01 | 0.00  | -0.01 | -0.03 |
| <b>cg03253268</b>     | CRYAA2                | 21 | 44,593  | 3'UTR            | Rs574083674<br>Waist cir<br>cumference | 2.E-05 | 1.E-05 | 0.05  | 0.02  | -0.05 | 0.03  | -1.22 | -0.47 | 0.01  | -0.02 | -0.83 | -0.54 | -0.01 | -0.26 |
| <b>cg17431280</b>     | ARHGAP35              | 19 | 47,507  | 3'UTR            | N                                      | 2.E-05 | 2.E-04 | -0.12 | -0.10 | -0.08 | 0.06  | -0.92 | -0.36 | 0.04  | -0.18 | -0.02 | -0.01 | 0.00  | 0.01  |
| <b>cg17868723</b>     | FGF14                 | 13 | 102,926 | Body             | rs2607653<br>Type 2<br>diabetes        | 2.E-05 | 7.E-05 | -0.03 | -0.03 | -0.01 | -0.07 | -0.86 | -0.29 | -0.10 | -0.28 | -0.46 | -0.19 | -0.01 | 0.22  |
| <b>cg04781638</b>     | CPEB1                 | 15 | 83,241  | TSS1500;<br>Body | rs150684763<br>Body height             | 2.E-05 | 1.E-06 | 0.00  | -0.01 | -0.01 | -0.01 | -1.21 | -0.36 | -0.04 | -0.01 | -0.30 | -0.11 | 0.03  | 0.17  |
| <b>cg22897141</b>     | MEN1                  | 11 | 64,810  | Body             | rs3782089<br>Body height               | 3.E-05 | 2.E-04 | -0.49 | -0.35 | 0.05  | 0.00  | -0.58 | -0.11 | -0.13 | -0.24 | -0.11 | -0.08 | 0.00  | 0.01  |
| <b>cg04709822</b>     | RPS14                 | 5  | 149,824 | Body             | Rs113681861<br>Waist-hip<br>ratio      | 3.E-05 | 1.E-04 | -0.38 | -0.25 | 0.04  | 0.00  | -0.07 | -0.32 | -0.03 | -0.12 | -1.42 | -0.40 | 0.01  | 0.00  |
| <b>cg25225655</b>     | MSI2                  | 17 | 55,469  | Body             | rs703862<br>Body height                | 3.E-05 | 4.E-04 | 0.14  | 0.09  | -0.02 | -0.03 | -1.04 | -0.40 | -0.02 | -0.22 | -0.35 | -0.11 | -0.04 | 0.07  |
| <b>cg25494075</b>     | NCAM1                 | 11 | 112,752 |                  | rs1816537<br>BMI                       | 3.E-05 | 2.E-04 | -0.31 | -0.22 | -0.02 | 0.00  | -1.06 | -0.51 | 0.10  | -0.05 | -0.09 | -0.23 | -0.04 | 0.16  |
| <b>cg12765567</b>     | miR-7159/<br>miR-1275 | 6  | 33,919  |                  | N                                      | 3.E-05 | 6.E-05 | -0.01 | -0.01 | -0.03 | 0.01  | -1.61 | -0.47 | -0.05 | -0.13 | -0.57 | -0.20 | -0.05 | 0.01  |
| <b>cg27122431</b>     | CDH18                 | 5  | 19,989  | TSS1500          | rs80240198<br>Type 2<br>diabetes       | 3.E-05 | 2.E-04 | -0.09 | -0.07 | 0.06  | 0.13  | -1.46 | -0.38 | -0.18 | -0.33 | 0.11  | 0.09  | -0.03 | 0.03  |
| <b>cg15689991</b>     | RASSF3                | 12 | 65,019  | Body             | N                                      | 3.E-05 | 3.E-04 | 0.03  | 0.02  | -0.03 | -0.05 | -1.64 | -0.73 | -0.03 | 0.06  | -0.01 | 0.02  | -0.02 | -0.01 |
| <b>cg13585930</b>     | NPFFR1                | 10 | 72,027  | TSS1500          | rs4747011<br>Body height               | 4.E-05 | 5.E-05 | -0.06 | 0.00  | 0.03  | 0.00  | -0.92 | -0.58 | 0.04  | -0.23 | -0.41 | -0.16 | 0.02  | 0.07  |
| <b>cg19822851</b>     | NR2C2AP               | 19 | 19,315  | TSS1500          | rs11670016<br>Waist-hip<br>ratio       | 4.E-05 | 2.E-04 | -0.17 | -0.11 | 0.03  | -0.04 | -0.45 | -0.89 | -0.04 | -0.28 | 0.09  | 0.02  | -0.03 | 0.00  |
| <b>cg24924449</b>     | IPO5/RAP2A            | 13 | 98,508  |                  | N                                      | 4.E-05 | 4.E-05 | -0.10 | -0.09 | -0.04 | 0.01  | -0.81 | -0.46 | -0.05 | -0.09 | -0.96 | -0.42 | -0.01 | -0.02 |
| <b>cg17434643</b>     | MIR124-3              | 20 | 61,805  |                  | N                                      | 4.E-05 | 1.E-04 | 0.09  | 0.05  | -0.01 | 0.10  | -1.27 | -0.61 | 0.02  | -0.24 | 0.05  | 0.01  | 0.03  | 0.10  |
| <b>cg19509778</b>     | FOXI2                 | 10 | 129,537 | 3'UTR            | N                                      | 4.E-05 | 9.E-05 | 0.09  | 0.08  | 0.05  | 0.06  | -1.30 | -0.66 | 0.05  | -0.04 | -5.63 | -2.77 | -0.03 | 0.08  |
| <b>cg05694290</b>     | HIP1R                 | 12 | 123,335 | Body             | rs11060344<br>Waist-hip<br>ratio       | 4.E-05 | 4.E-05 | -0.01 | -0.02 | -0.08 | 0.06  | -2.07 | -0.38 | -0.22 | -0.33 | 0.32  | 0.19  | 0.00  | 0.25  |
| <b>cg26938334</b>     | SERPINA1              | 14 | 94,850  | 5'UTR            | rs28929474<br>Body height              | 4.E-05 | 6.E-05 | -0.03 | -0.03 | 0.07  | 0.21  | -1.42 | -0.39 | -0.01 | 0.15  | 0.08  | 0.03  | -0.01 | 0.08  |
| <b>cg22284030</b>     | ARFGAP2               | 11 | 47,186  | 3'UTR            | rs10501320<br>Insulin<br>measurement   | 4.E-05 | 6.E-05 | 0.29  | 0.22  | -0.04 | -0.06 | -1.63 | -1.01 | 0.04  | -0.06 | -0.02 | -0.03 | -0.02 | 0.07  |
| <b>cg13748564</b>     | COL27A1               | 9  | 116,917 | TSS1500          | rs10817582<br>Body height              | 4.E-05 | 4.E-04 | 0.20  | 0.10  | -0.05 | -0.02 | -1.59 | -0.28 | -0.09 | -0.13 | 0.03  | 0.02  | -0.01 | -0.05 |
| <b>ch.15.1141100F</b> | PKM                   | 15 | 72,509  | Body             | Rs181706692<br>Hip circum              | 4.E-05 | 7.E-05 | -0.05 | -0.04 | 0.01  | 0.03  | -0.76 | -0.63 | 0.10  | -0.01 | 0.08  | 0.08  | -0.05 | 0.12  |

|            |                               |    |         |         |                                       |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
|------------|-------------------------------|----|---------|---------|---------------------------------------|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| cg25477843 | PARP10                        | 8  | 145,061 | Body    | ference<br>rs11783655<br>Body height  | 4.E-05 | 2.E-04 | -0.13 | -0.10 | -0.01 | 0.05  | -0.74 | -0.60 | -0.01 | 0.03  | 0.02  | 0.01  | 0.00  | -0.02 |
| cg17395800 | CACNA1F                       | X  | 49,088  | Body    | N                                     | 4.E-05 | 8.E-05 | -0.03 | -0.04 | -0.06 | 0.05  | -0.92 | 0.03  | -0.06 | -0.12 | -0.94 | -0.66 | 0.00  | 0.10  |
| cg15797834 | STAP2                         | 19 | 4,339   | TSS200  | N                                     | 4.E-05 | 1.E-04 | 0.18  | 0.13  | 0.02  | 0.10  | -1.71 | -0.77 | 0.05  | 0.00  | -0.01 | 0.00  | -0.02 | -0.01 |
| cg08443605 | RARB                          | 3  | 24,872  |         | N                                     | 5.E-05 | 2.E-04 | 0.07  | 0.04  | -0.01 | -0.01 | -1.49 | -0.55 | -0.08 | -0.09 | 2.46  | 0.71  | 0.01  | 0.00  |
| cg05475524 | ACTN3                         | 11 | 66,327  | Body    | rs679228<br>Body height               | 5.E-05 | 4.E-04 | 0.04  | 0.02  | 0.03  | -0.03 | -0.47 | -0.34 | -0.16 | -0.21 | 0.60  | 0.18  | 0.00  | 0.04  |
| cg22464447 | IQGAP1/CRTC3                  | 15 | 91,054  |         | rs11609<br>Body height                | 5.E-05 | 4.E-04 | 0.00  | 0.00  | -0.02 | -0.03 | -1.16 | -0.55 | -0.02 | -0.20 | 0.18  | 0.12  | 0.00  | -0.13 |
| cg03569876 | CSNK1A1/<br>miR143-<br>miR145 | 5  | 148,908 | Body    | rs368510<br>Body height               | 5.E-05 | 2.E-04 | -0.32 | -0.22 | 0.04  | -0.03 | 0.41  | 0.17  | 0.04  | -0.17 | -0.02 | 0.06  | 0.00  | -0.04 |
| cg19842091 | RASGEF1C                      | 5  | 179,567 | 5'UTR   | rs4290977<br>Body height              | 5.E-05 | 5.E-05 | 0.03  | 0.03  | 0.07  | 0.02  | -1.13 | -0.59 | -0.11 | -0.12 | 0.35  | 0.05  | 0.00  | 0.01  |
| cg06483432 | KIT                           | 4  | 55,523  | TSS1500 | rs11727273<br>BMI                     | 5.E-05 | 2.E-04 | -0.33 | -0.24 | -0.01 | 0.09  | -0.79 | -0.40 | -0.03 | -0.16 | -0.17 | 0.00  | -0.03 | 0.00  |
| cg25507226 | DNAJB6                        | 7  | 157,191 | Body    | rs1182436<br>Type 2<br>diabetes       | 5.E-05 | 3.E-04 | -0.10 | -0.07 | -0.01 | 0.02  | -1.09 | -0.64 | -0.01 | -0.01 | -0.45 | -0.22 | 0.00  | 0.16  |
| cg17141902 | NINJ1                         | 9  | 95,897  | TSS1500 | rs13810828<br>Body height             | 6.E-05 | 2.E-05 | 0.03  | 0.02  | -0.02 | -0.05 | -2.50 | -0.60 | -0.27 | -0.30 | -0.09 | -0.04 | 0.01  | -0.02 |
| cg10222361 | USP31                         | 16 | 23,071  |         | N                                     | 6.E-05 | 5.E-04 | -0.10 | -0.06 | 0.03  | -0.06 | -1.08 | -0.72 | 0.01  | 0.03  | -0.04 | -0.02 | -0.05 | 0.03  |
| cg26479868 | TMTC1                         | 12 | 29,916  | Body    | rs188945888<br>Hip circum<br>ference  | 6.E-05 | 2.E-04 | -0.12 | -0.10 | -0.05 | -0.06 | -0.78 | -1.11 | 0.04  | -0.15 | -0.02 | 0.01  | -0.05 | -0.20 |
| cg05738687 | RFLNB                         | 17 | 290     | 3'UTR   | rs77612020<br>Waist circum<br>ference | 6.E-05 | 9.E-05 | -0.07 | -0.05 | 0.02  | 0.17  | -1.73 | -0.63 | -0.08 | -0.18 | 0.00  | 0.02  | 0.00  | 0.03  |
| cg25591451 | TRIM4                         | 7  | 99,518  | TSS1500 | rs11973801<br>BMI                     | 6.E-05 | 1.E-04 | 0.05  | 0.06  | 0.18  | -0.05 | -1.16 | -0.78 | -0.06 | -0.17 | -0.14 | 0.02  | 0.00  | 0.05  |
| cg25104430 | ALKBH1                        | 14 | 78,128  |         | N                                     | 6.E-05 | 1.E-04 | -0.15 | -0.12 | -0.04 | -0.09 | -0.92 | -0.51 | 0.14  | 0.02  | -0.02 | -0.02 | 0.00  | 0.05  |
| cg05895666 | SLC25A43                      | X  | 118,533 | TSS1500 | rs3848873<br>Body height              | 6.E-05 | 2.E-04 | -0.07 | -0.04 | 0.04  | 0.01  | -1.01 | -0.63 | -0.08 | -0.06 | 0.27  | 0.45  | -0.04 | 0.00  |
| cg26507353 | MAP3K8/LYZL2                  | 10 | 30,843  |         | N                                     | 7.E-05 | 4.E-04 | 0.04  | 0.03  | 0.02  | 0.05  | -1.46 | -0.08 | -0.06 | -0.12 | -0.33 | -0.18 | 0.03  | 0.16  |
| cg03048432 | NIN                           | 14 | 51,291  | 5'UTR   | N                                     | 7.E-05 | 2.E-04 | 0.30  | 0.21  | -0.01 | 0.00  | -0.80 | -0.58 | 0.03  | -0.06 | -0.95 | -0.31 | 0.02  | 0.12  |
| cg12394014 | MORF4L1                       | 15 | 79,172  | Body    | N                                     | 7.E-05 | 7.E-04 | 0.04  | 0.02  | 0.00  | -0.02 | -0.73 | -0.67 | 0.10  | 0.03  | 0.13  | 0.10  | -0.02 | -0.02 |
| cg13478737 | FIBCD1                        | 9  | 133,807 | Body    | rs3739514<br>BMI                      | 8.E-05 | 2.E-04 | 0.88  | 0.64  | 0.02  | -0.13 | -0.56 | 0.11  | -0.01 | -0.33 | 0.05  | 0.02  | -0.04 | 0.01  |
| cg07798347 | RAP1GAP                       | 1  | 21,918  |         | Rs55722102<br>Body height             | 8.E-05 | 6.E-05 | 0.22  | 0.14  | -0.02 | 0.10  | -1.30 | -0.51 | -0.06 | -0.29 | -1.20 | -0.36 | 0.00  | 0.05  |
| cg17929273 | LGALS2                        | 22 | 37,968  | Body    | N                                     | 8.E-05 | 3.E-04 | -0.12 | -0.09 | 0.03  | -0.05 | -1.65 | -0.53 | -0.12 | -0.18 | 0.10  | 0.00  | 0.02  | 0.17  |
| cg09469566 | SOX1                          | 13 | 112,717 |         | N                                     | 8.E-05 | 7.E-04 | 0.02  | 0.01  | -0.02 | -0.01 | -1.13 | -0.85 | 0.05  | -0.03 | -0.02 | -0.01 | 0.00  | -0.07 |
| cg15661389 | GAS7                          | 17 | 10,019  | Body    | rs2320549<br>Body height              | 8.E-05 | 2.E-04 | -0.23 | -0.17 | 0.02  | -0.02 | 0.03  | -0.46 | -0.12 | -0.38 | -0.16 | -0.06 | -0.02 | 0.12  |
| cg01381374 | GNGT1                         | 7  | 93,474  |         | rs2528531<br>BMI                      | 8.E-05 | 1.E-04 | -0.05 | -0.03 | 0.04  | -0.07 | -1.18 | -0.47 | -0.14 | -0.16 | 1.01  | 0.30  | 0.00  | 0.01  |
| cg10614809 | COBL                          | 7  | 51,539  |         | rs11765748<br>BMI                     | 8.E-05 | 3.E-04 | -0.17 | -0.16 | -0.02 | -0.03 | -1.08 | -0.70 | 0.08  | 0.10  | 0.15  | 0.05  | 0.00  | 0.00  |
| cg07951931 | GALNT9                        | 12 | 132,886 | Body    | rs11247009                            | 8.E-05 | 8.E-05 | -0.40 | -0.30 | -0.02 | -0.01 | -1.42 | -0.99 | 0.06  | -0.05 | -0.29 | -0.25 | 0.00  | 0.02  |

|                   |                 |    |         |                   |                                  |        |        |       |       |       |       |       |       |       |       |       |       |       |       |
|-------------------|-----------------|----|---------|-------------------|----------------------------------|--------|--------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
| <b>cg01919939</b> | DPH6            | 15 | 35,990  |                   | BMI<br>rs7181610<br>BMI          | 8.E-05 | 2.E-04 | -0.27 | -0.19 | -0.01 | -0.08 | -0.63 | -1.03 | 0.01  | -0.09 | 3.06  | 1.29  | 0.01  | 0.00  |
| <b>cg13882795</b> | NRARP           | 9  | 140,195 | 1stExon;<br>3'UTR | N                                | 8.E-05 | 9.E-05 | 0.18  | 0.14  | 0.11  | 0.09  | -0.68 | -0.59 | 0.07  | -0.02 | -0.01 | 0.07  | -0.01 | 0.07  |
| <b>cg15661753</b> | TUBA1C          | 12 | 49,627  |                   | N                                | 8.E-05 | 4.E-04 | -0.17 | -0.13 | 0.00  | -0.02 | -1.02 | -0.31 | -0.07 | -0.09 | -1.38 | -0.54 | 0.01  | 0.00  |
| <b>cg20276677</b> | NPSR1           | 7  | 34,698  | TSS200            | rs73310815<br>Obesity            | 9.E-05 | 2.E-04 | -0.29 | -0.18 | 0.05  | 0.02  | -0.61 | -0.81 | -0.02 | -0.19 | -0.29 | -0.16 | 0.01  | 0.01  |
| <b>cg18335290</b> | LIMS2           | 2  | 128,439 | 1stExon;<br>5'UTR | rs73954691<br>Type 2<br>diabetes | 9.E-05 | 4.E-04 | 0.05  | 0.03  | 0.03  | -0.04 | -0.87 | -0.12 | -0.02 | -0.13 | 0.14  | 0.05  | 0.00  | 0.05  |
| <b>cg17566334</b> | PACRG           | 6  | 163,515 | Body              | N                                | 9.E-05 | 9.E-05 | 0.00  | 0.00  | -0.01 | 0.03  | -1.36 | -0.54 | 0.09  | -0.09 | 0.00  | -0.01 | -0.03 | -0.14 |
| <b>cg11704631</b> | RUNX1           | 21 | 36,396  | Body              | Rs4507181<br>Waist-hip<br>ratio  | 9.E-05 | 4.E-04 | -0.19 | -0.14 | 0.07  | 0.03  | -1.03 | -0.63 | 0.00  | -0.13 | -0.13 | 0.00  | -0.05 | 0.06  |
| <b>cg07341022</b> | FOXD4L1         | 2  | 114,269 |                   | N                                | 9.E-05 | 4.E-04 | -0.01 | -0.01 | -0.05 | -0.13 | -1.01 | -0.74 | 0.06  | -0.02 | -0.34 | -0.23 | 0.01  | -0.07 |
| <b>cg02129885</b> | ID1/<br>miR3193 | 20 | 30,218  |                   | N                                | 1.E-04 | 2.E-04 | 0.23  | 0.15  | -0.06 | 0.06  | -2.13 | -0.90 | 0.00  | -0.15 | -0.13 | -0.10 | -0.01 | 0.03  |
| <b>cg02324580</b> | SRCAP           | 16 | 30,751  | Body              | rs4402589<br>BMI                 | 1.E-04 | 2.E-03 | 0.08  | 0.07  | 0.09  | -0.12 | -1.08 | -0.50 | -0.05 | -0.13 | -0.17 | -0.09 | 0.00  | 0.12  |
| <b>cg01260615</b> | ZNF184          | 6  | 27,485  |                   | N                                | 1.E-04 | 2.E-04 | -0.13 | -0.11 | -0.02 | -0.05 | -1.25 | -0.57 | 0.07  | -0.02 | 0.18  | 0.11  | 0.01  | -0.09 |
| <b>cg01877937</b> | L3MBTL          | 20 | 42,143  | TSS1500           | N                                | 1.E-04 | 3.E-04 | 0.18  | 0.11  | 0.02  | -0.02 | -1.19 | -0.64 | 0.02  | 0.00  | 0.11  | -0.03 | 0.00  | 0.01  |

<sup>†</sup>*P* values adjusted for obesity-related polygenic risk score

<sup>#</sup>Corresponds to estimate of  $\beta_M(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

<sup>§</sup>Corresponds to estimate of  $\beta_{DIR}(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

<sup>&</sup>Corresponds to estimate of  $\beta_{IND}(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.



**Supplementary Table 3.** CpG sites selected in multi-mediator analyses based on forward selection. The P-value to enter the model is  $10^{-4}$  and to stay in the model  $10^{-3}$ .

| Girls      |        |                       | Boys       |                     |                       |
|------------|--------|-----------------------|------------|---------------------|-----------------------|
| CpG site   | Gene   | P-value <sup>#</sup>  | CpG site   | Gene                | P-value <sup>#</sup>  |
| cg06471491 | miR-21 | $<10^{-16}$           | cg26657240 | IL16                | $<10^{-16}$           |
| cg16645539 | SNAPC3 | $5.6 \times 10^{-16}$ | cg08651538 | NREP                | $6.1 \times 10^{-10}$ |
| cg04126095 | MASP1  | $2.5 \times 10^{-14}$ | cg20559217 | DCPS                | $1.3 \times 10^{-9}$  |
| cg10082165 | CTSG   | $6.6 \times 10^{-10}$ | cg07951931 | GALNT9              | $1.7 \times 10^{-9}$  |
| cg26872564 | ZNF185 | $1.2 \times 10^{-8}$  | cg26227569 | CPZ/GPR78           | $9.4 \times 10^{-8}$  |
| cg00524694 | PROP1  | $2.3 \times 10^{-7}$  | cg01972418 | PAX9                | $1.7 \times 10^{-7}$  |
| cg26992566 | EMC8   | $3.1 \times 10^{-7}$  | cg07143733 | miR155HG-<br>miR155 | $9.0 \times 10^{-7}$  |
| cg17401282 | GABRG2 | $5.0 \times 10^{-7}$  | cg19509778 | FOXI2               | $1.4 \times 10^{-6}$  |
| cg07603794 | CLASP1 | $1.6 \times 10^{-4}$  | cg22230229 | BAHCC1              | $8.0 \times 10^{-6}$  |
| cg17901584 | DHCR24 | $2.7 \times 10^{-4}$  | cg23847109 | COL9A2              | $3.2 \times 10^{-5}$  |
| cg11746359 | MAML3  | $6.4 \times 10^{-4}$  | cg19822851 | NR2C2AP             | $1.5 \times 10^{-4}$  |
| cg07012178 | PRKAG2 | $9.2 \times 10^{-4}$  |            |                     |                       |
| cg03103888 | TMCO3  | $9.7 \times 10^{-4}$  |            |                     |                       |

<sup>#</sup>P-value in the final model.

**Supplementary Table 4.** Functional annotation clustering with DAVID, significant terms at the 5% level

| Category     | Term   | Number of Genes | P-value            |
|--------------|--|-----------------|--------------------|
| <b>Girls</b> |  |                 |                    |
| KEGG_PATHWAY | AMPK signaling pathway   | 4               | 0.034              |
| KEGG_PATHWAY | Insulin signaling pathway  | 4               | 0.046              |
| KEGG_PATHWAY | Endocytosis  | 5               | 0.050              |
| GOTERM       | ATP binding  | 14              | 0.019              |
| GOTERM       | Multicellular organism development                                   | 7               | 0.049              |
| <b>Boys</b>  |  |                 |                    |
| KEGG_PATHWAY | Pathways in cancer   | 7               | 0.025              |
| GOTERM       | Negative regulation of transcription, DNA-templated                  | 10              | 1E10 <sup>-4</sup> |
| GOTERM       | Positive regulation of tyrosine phosphorylation of Stat3 protein     | 3               | 0.020              |
| GOTERM       | Negative regulation of transcription from RNA polymerase II promoter | 9               | 0.031              |
| GOTERM       | Regulation of cell shape   | 4               | 0.035              |
| GOTERM       | Hemopoiesis  | 3               | 0.036              |

**Supplementary Table 5:** Top miRNAs associated with child longitudinal BMI from ALSPAC data in boys and girls selected at the  $P=1.10^{-4}$  level.

| CpG site     | miRNA                 | Chr | Pos.<br>(kb) | Breast<br>Milk <sup>†</sup> | P      | EBF effect on DNAm<br>(≥3 months vs. 0) <sup>#</sup> |            |            |             | EBF direct effect on BMI<br>(≥3 months vs. 0) <sup>§</sup> |            |            |             | EBF effect on BMI<br>mediated by DNAm<br>(≥3 months vs. 0) <sup>&amp;</sup> |            |            |             |
|--------------|-----------------------|-----|--------------|-----------------------------|--------|--|------------|------------|-------------|--|------------|------------|-------------|---|------------|------------|-------------|
|              |                       |     |              |                             |        | 1<br>year  | 2<br>years | 7<br>years | 15<br>years | 1<br>year  | 2<br>years | 7<br>years | 15<br>years | 1<br>year   | 2<br>years | 7<br>years | 15<br>years |
| <b>Girls</b> |                       |     |              |                             |        |  |            |            |             |  |            |            |             |   |            |            |             |
| cg06471491   | miR-21                | 17  | 57,918       | Yes                         | <E-16  | 0.02   | -0.08      | -0.07      | -0.07       | -1.13  | -0.51      | -0.17      | -0.37       | 0.36  | 0.11       | 0.00       | 0.01        |
| cg05241732   | 1Kb from<br>miR-208a  | 14  | 23,859       | No                          | 3.E-06 | -0.20  | -0.12      | 0.03       | 0.00        | -0.28  | -0.22      | -0.26      | -0.39       | -0.04   | -0.02      | -0.01      | 0.01        |
| cg06527213   | 1Kb from<br>miR-1276  | 15  | 86,315       | Yes                         | 4.E-05 | -0.04  | -0.03      | -0.05      | -0.05       | -0.92  | -1.03      | -0.22      | -0.31       | -0.13   | -0.03      | -0.02      | -0.09       |
| cg22941668   | miR-145               | 5   | 148,810      | Yes                         | 9.E-05 | -0.03  | -0.01      | 0.02       | 0.02        | -0.46  | -0.16      | -0.25      | -0.47       | 0.02  | 0.08       | 0.02       | -0.20       |
| <b>Boys</b>  |                       |     |              |                             |        |  |            |            |             |  |            |            |             |   |            |            |             |
| cg07143733   | miR-155HG             | 21  | 26,939       | Yes                         | 2.E-05 | -0.20  | -0.19      | -0.01      | -0.08       | -1.96  | -0.38      | -0.11      | -0.15       | -0.44   | -0.18      | -0.05      | 0.05        |
| cg12765567   | 2Kb from<br>miR-7159  | 6   | 33,919       | No                          | 3.E-05 | -0.01  | -0.01      | -0.03      | 0.01        | -1.61  | -0.47      | -0.05      | -0.13       | -0.57   | -0.20      | -0.05      | 0.01        |
| cg17434643   | 4Kb from<br>miR-124-3 | 20  | 61,805       | Yes                         | 4.E-05 | 0.09   | 0.05       | -0.01      | 0.10        | -1.27  | -0.61      | 0.02       | -0.24       | 0.05  | 0.01       | 0.03       | 0.10        |
| cg22941668   | miR-145               | 5   | 148,810      | Yes                         | 5.E-05 | -0.32  | -0.22      | 0.04       | -0.03       | 0.41   | 0.17       | 0.04       | -0.17       | -0.02   | 0.06       | 0.00       | -0.04       |

<sup>†</sup>Expressed in breast milk according to database liqDB

<sup>#</sup>Corresponds to estimate of  $\beta_M(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

<sup>§</sup>Corresponds to estimate of  $\beta_{DIR}(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

<sup>&</sup>Corresponds to estimate of  $\beta_{IND}(t)$  in Figure 1. We estimated the average effect of 3 to 5 months of EBF vs. 0 month.

**Supplementary Table 6: mQTL analysis for the top EWAS hits based on the mQTLdb database<sup>37</sup>**

| CpG site       | Gene                  | Chr | Pos.<br>(kb) | mQTL       | SNP<br>Chr | SNP<br>position | Cis/Trans | Epoch                       |
|----------------|-----------------------|-----|--------------|------------|------------|-----------------|-----------|-----------------------------|
| <b>Girls</b>   |                       |     |              |            |            |                 |           |                             |
| cg06471491     | miR-21                | 17  | 57,918       | rs4742392  | 9          | 789             | Trans     | Childhood                   |
| cg16645539     | SNAPC3                | 9   | 15,423       | -          | -          | -               | -         | -                           |
| cg07408552     | ATP6V0A1              | 17  | 40,612       | Multiple   | 6          | 29,918-31,457   | Trans     | Birth/Childhood/Adolescence |
| cg08224066     | DHX15/<br>PPARGC1A    | 4   | 24,578       | -          | -          | -               | -         | -                           |
| cg14822546     | LINC00398/<br>ALOX5AP | 13  | 31,381       | -          | -          | -               | -         | -                           |
| cg14776321     | FAM238C               | 10  | 27,220       | -          | -          | -               | -         | -                           |
| ch.8.18261148F | NATP/NAT2             | 8   | 18,217       | -          | -          | -               | -         | -                           |
| cg00313685     | CUX1                  | 7   | 101,469      | Multiple   | 7          | 101,460-101,498 | Cis       | Childhood/Adolescence       |
| cg17476951     | TRAPPC9               | 8   | 141,054      | Multiple   | 8          | 141,047         | Cis       | Birth                       |
| -              | -                     | -   | -            | Multiple   | 11         | 38,646-38,984   | Trans     | Adolescence                 |
| -              | -                     | -   | -            | Multiple   | 1          | 47,129-47,178   | Trans     | Adolescence                 |
| -              | -                     | -   | -            | Multiple   | 8          | 141046- 141047  | Cis       | Birth                       |
| cg26398656     | OSBPL1A               | 18  | 21,852       | Multiple   | 16         | 79563- 79568    | Trans     | Childhood                   |
| -              | -                     | -   | -            | rs34918972 | 18         | 21896           | Cis       | Adolescence                 |
| -              | -                     | -   | -            | Multiple   | 8          | 76716- 77199    | Trans     | Birth                       |
| -              | -                     | -   | -            | Multiple   | 15         | 97556- 79569    | Trans     | Birth                       |
| cg26872564     | ZNF185                | X   | 152,087      | Multiple   | X          | 152059-152105   | Cis       | Birth/Childhood/Adolescence |
| cg18176842     | FAM84A                | 2   | 14,776       | Multiple   | 9          | 131985- 131982  | Trans     | Birth                       |
| cg04354689     | PDPK1                 | 16  | 2,660        | -          | -          | -               | -         | -                           |
| <b>Boys</b>    |                       |     |              |            |            |                 |           |                             |
| cg26657240     | IL16                  | 15  | 81,475       | Multiple   | 15         | 81465- 81667    | Cis       | Childhood/Adolescence       |
| cg08651538     | NREP                  | 5   | 111,070      | -          | -          | -               | -         | -                           |

**Supplementary Table 7: Distribution of the main epidemiological variables in Gen3G**

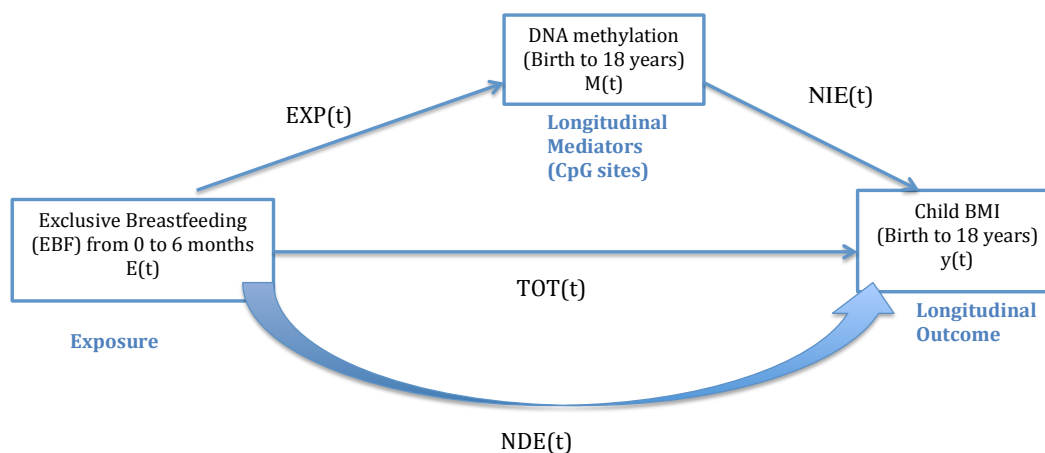
|  | <b>Boys</b> | <b>Girls</b> |
|--|-------------|--------------|
|  | N=104       | N=89         |
| <b>Duration of exclusive breastfeeding (EXBF) (in months)</b>                    |             |              |
| 0  | 22 (21.2%)  | 22 (24.7%)   |
| 1  | 15 (14.4%)  | 3 (3.4%)     |
| 2  | 11 (10.6%)  | 7 (7.9%)     |
| 3  | 6 (5.8%)    | 6 (6.7%)     |
| 4  | 15 (14.4%)  | 12 (13.5%)   |
| ≥5   | 35 (33.7%)  | 39 (43.8%)   |
| <b>Mother's Education</b>  |             |              |
| Lower than college   | 24 (24.1%)  | 25 (28.1%)   |
| College or higher  | 80 (76.9%)  | 64 (71.9%)   |
| <b>Mother's ever smoking status</b>  |             |              |
| No   | 97 (93.3%)  | 83 (93.3%)   |
| Yes  | 7 (6.7%)    | 6 (6.7%)     |
| <b>Child BMI at birth (in kg/m<sup>2</sup>)</b>                                  |             |              |
| Mean (±SD)   | 13.0 (±1.1) | 13.1 (±1.1)  |
| <b>Mother's BMI (1<sup>st</sup> semester of pregnancy) (in kg/m<sup>2</sup>)</b> |             |              |
| Mean (±SD)   | 26.1 (±6.6) | 24.9 (±4.9)  |
| <b>Gestational age (in weeks)</b>  |             |              |
| Mean (±SD)   | 39.6 (1.1)  | 39.5 (1.1)   |
| <b>Ethnic group</b>  |             |              |
| Caucasians   | 101 (97.1%) | 85 (95.5%)   |
| Non-Caucasians   | 3 (2.9%)    | 4 (4.5%)     |

**Supplementary Table 8:** Replication of top EWAS hits associated with child longitudinal BMI in Gen3G data at 5 years of age (at the  $P=2.9 \times 10^{-4}$  level)

| CpG site          | Gene      | Chr | Pos.<br>(kb) | <i>P</i> -value      | EBF effect on<br>DNAm<br>( $\geq 3$ months vs. 0) | EBF direct effect<br>on BMI<br>( $\geq 3$ months vs. 0) | EBF effect on BMI<br>mediated by DNAm<br>( $\geq 3$ months vs. 0) |
|-------------------|-----------|-----|--------------|----------------------|---|---|---|
| <b>Girls</b>      |           |     |              |                      |   |   |   |
| <b>cg22879191</b> | CUX1      | 7   | 101,469      | <8E-05               | -0.033  | -0.57   | 0.03  |
| <b>cg19769982</b> | miR-155HG | 21  | 26,934       | $1.7 \times 10^{-4}$ | -0.003  | 0.24  | -0.001  |

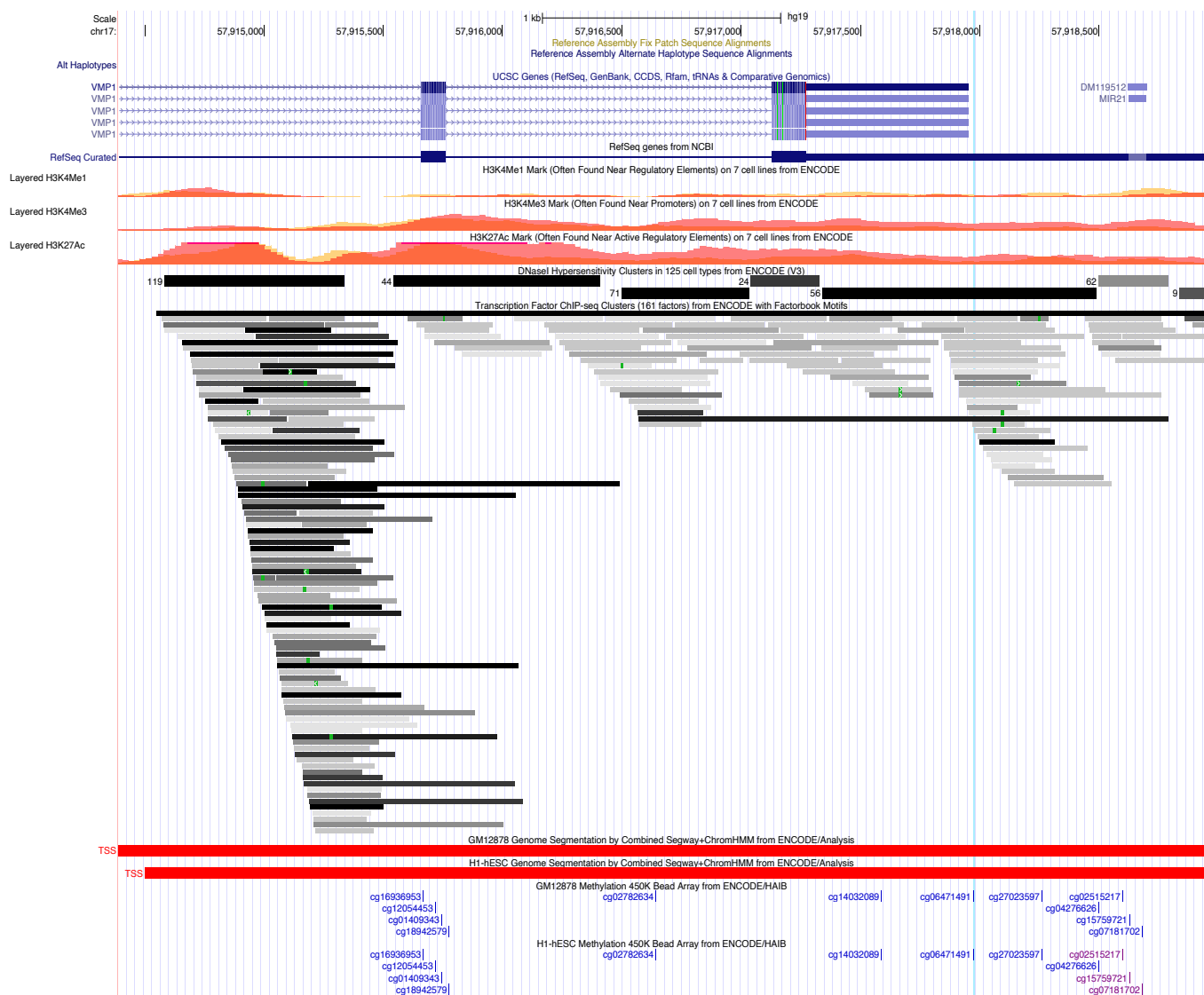
## Extended data figures

**Extended data Fig.1. Mediation model for the association between exclusive breastfeeding (EBF) and child BMI from birth to 18 years of age.**  $EXP(t)$  represents the estimate of EBF duration on DNAm at age  $t$ .  $NIE(t)$  represents the indirect effect of EBF duration on child BMI at age  $t$  mediated by DNAm (see Methods section).  $NDE(t)$  represents the direct effect of EBF on child BMI at age  $t$  not mediated by DNAm.  $TOT(t)$  represents the total effect of EBF on child BMI at age  $t$  (i.e., direct + indirect effects). The top CpG sites were selected based on the  $M(t)*E(t)$  interaction effect on  $y(t)$ , that is the overall interaction effect on child BMI from birth to 18 years.



**Extended data Fig.2. Genomic landscape of the EWAS-significant CpG site cg06471491 in *miR-21* discovered in ALSPAC.**

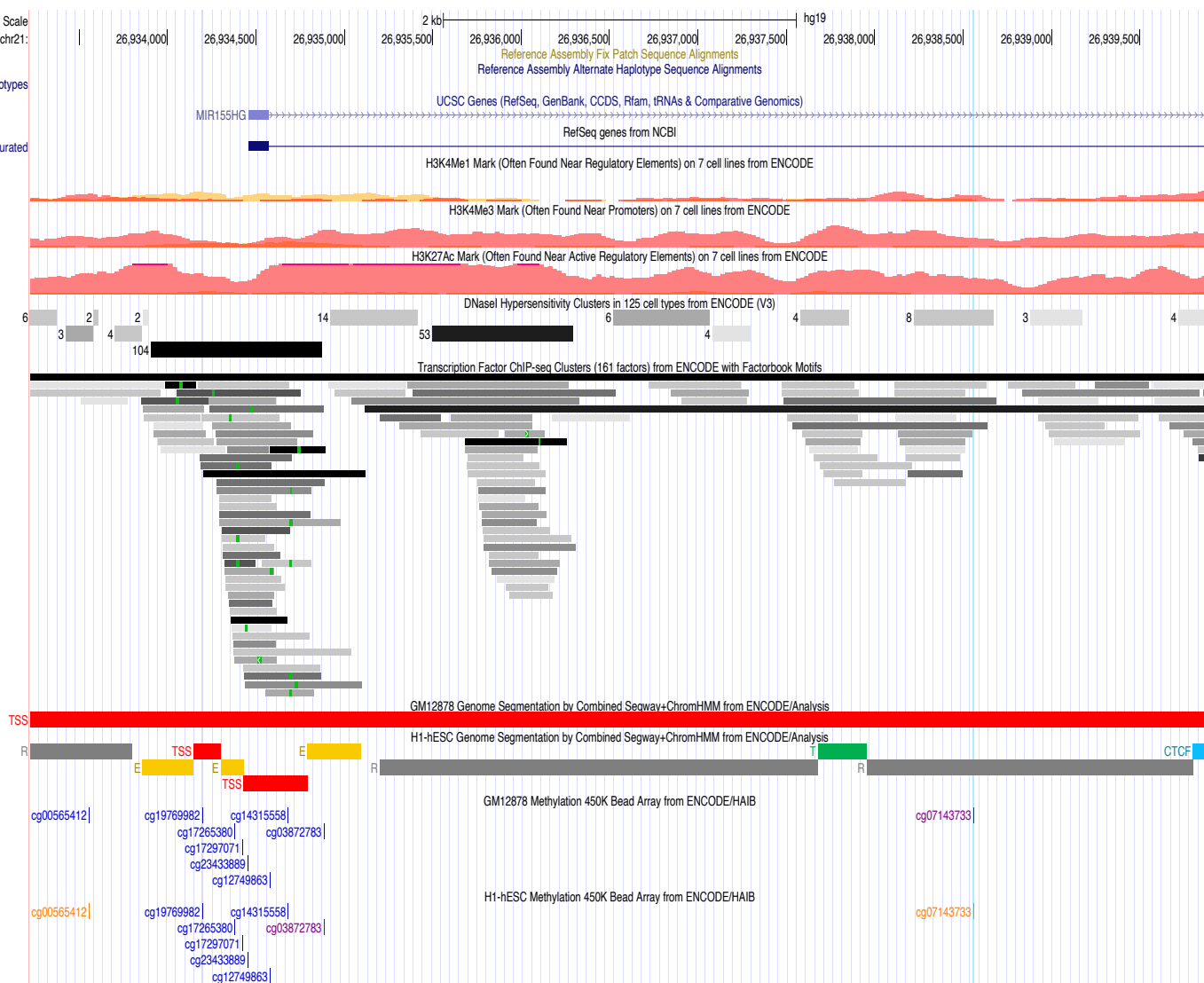
The *H3K4Me1*, *H3K27Ac* and *H3K4Me3* tracks show histone modifications, suggestive of regulatory activities. The DNase hypersensitivity track shows regions hypersensitive to cutting by the DNase enzyme. Regulatory regions are generally DNase sensitive. Transcription factor (TF) binding track displays regions of TF (proteins responsible for modulating gene transcription) binding. The DNA regulatory elements track displays the chromatin states, where different colors represent different annotations. Bright red predicted promoter region including TSS; The CpG tracks display the methylation status of specific CpGs in blood cell line and embryonic stem cell line, respectively, where the methylation status is color coded. Orange is methylated; purple is partially methylated; blue is unmethylated.



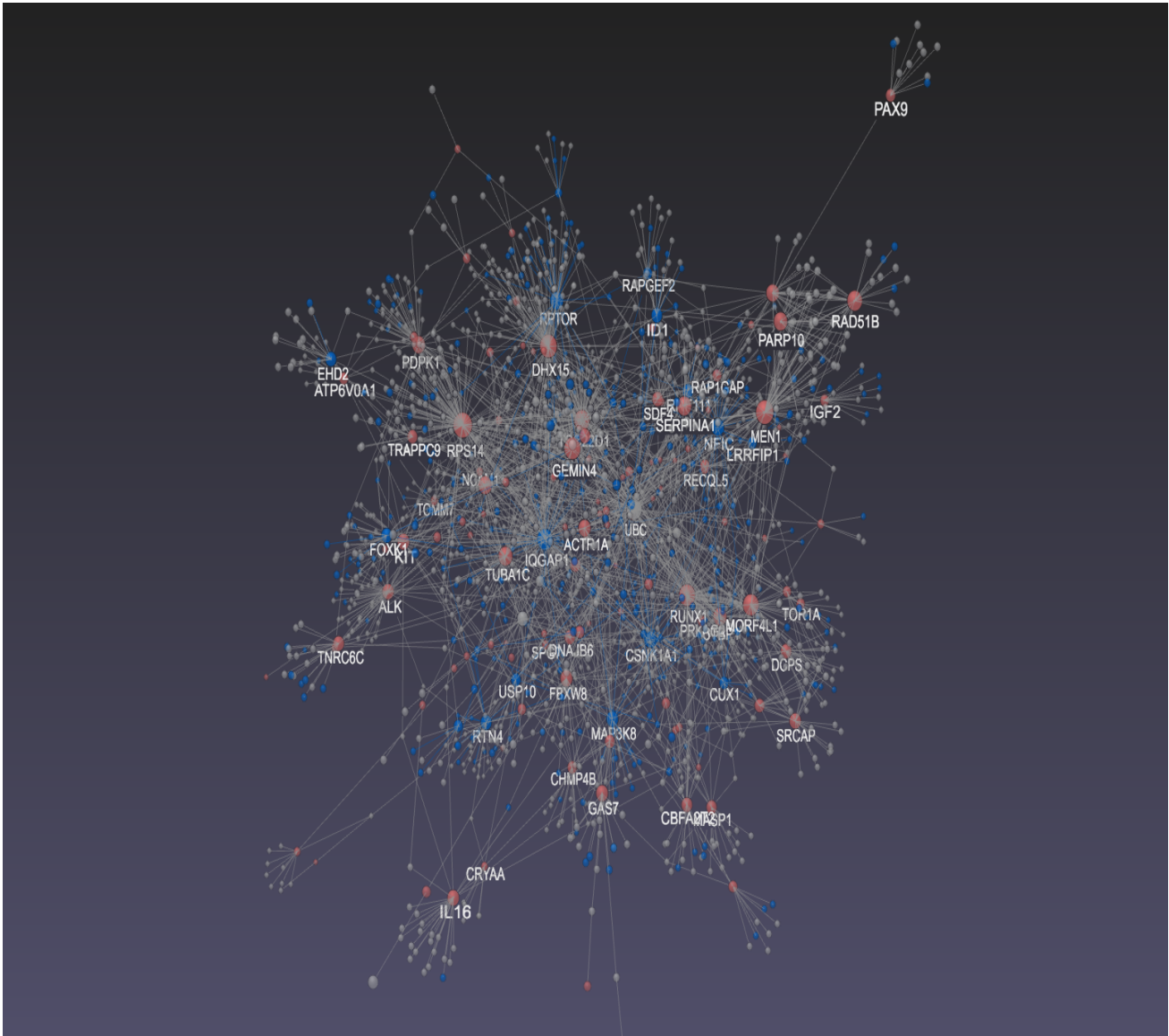


**Extended data Fig.3. Genomic landscape of the EWAS-significant CpG site cg07143733 discovered in ALSPAC and cg19769982 found in GEN3G in *miR-155HG*.**

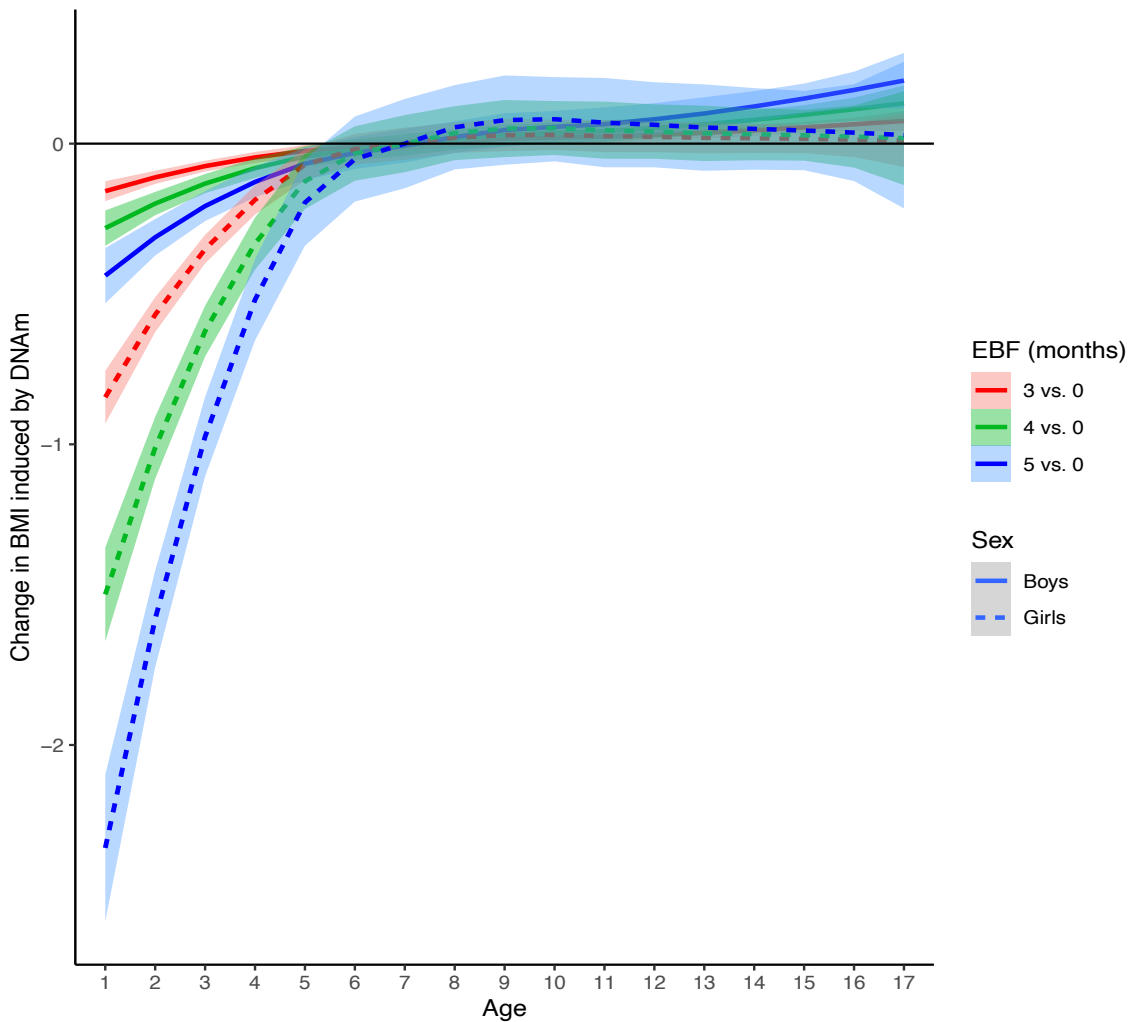
The *H3K4Me1*, *H3K27Ac* and *H3K4Me3* tracks show histone modifications, suggestive of regulatory activities. The DNase hypersensitivity track shows regions hypersensitive to cutting by the DNase enzyme. Regulatory regions are generally DNase sensitive. Transcription factor (TF) binding track displays regions of TF (proteins responsible for modulating gene transcription) binding. The DNA regulatory elements track displays the chromatin states, where different colors represent different annotations. Bright red predicted promoter region including TSS; Orange predicted enhancer; blue predicted CTCF (CCCTC-binding factor) enriched element; gray predicted repressed or low activity region; Green predicted a transcribed region. The two CpG tracks display the methylation status of specific CpG in blood cell line and embryonic stem cell line, respectively, where the methylation status is color coded. Orange is methylated; purple is partially methylated; blue is unmethylated.



**Extended data Fig.4. Gene-gene and gene-miRNA networks built from CpG sites mediating the association between EBF and child BMI.** (The red nodes correspond to genes and blue nodes to miRNAs discovered in our analysis. The grey nodes correspond to other known miRNAs not discovered in our analysis).



**Extended data Fig.5. Change in BMI mediated by DNA methylation from the combined effect of multiple CpG sites where DNA methylation is induced by different durations (3,4 and 5 months vs. no breastfeeding) of exclusive breastfeeding (EBF) in ALSPAC girls and boys, at different ages from birth to 17 years, and after adjustment for BMI-related polygenic risk score. The CpG sites in the final multi-mediator model were selected by forward selection (see Methods). Each curve represents a smooth estimate function (loess estimate) of BMI changes over time and the confidence bands are the 95% confidence intervals of the smoothed curve.**



**Extended data Fig.6. QQ plots of our test statistic to detect significant CpG sites after adjustment for genomic controls in ALSPAC girls (a) and boys (b).** Each plot displays the sample quantiles (y-axis) vs. the theoretical quantiles of a  $\chi^2(4)$  distribution (x-axis).

