Associations between body size, nutrition and socioeconomic position in early life and the epigenome: A systematic review

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Abstract

Background

Body size, nutrition and socioeconomic position (SEP) in early life have been associated with a wide range of long-term health effects. Epigenetics is one possible mechanism through which these early life exposures can impact later life health. We conducted a systematic review examining the observational evidence for the impact of body size, nutrition and SEP in early life on the epigenome in humans.

Methods

This systematic review is registered with the PROSPERO database (registration number: CRD42016050193). Three datasets were simultaneously searched using Ovid and the resulting studies were evaluated by at least two independent reviewers. Studies measuring epigenetic markers either at the same time as, or after, the early life exposure and have a measure of body size, nutrition or SEP in early life (up to 12 years), written in English and from a community-dwelling participants were included.

Results

We identified 90 eligible studies. Seventeen of these papers examined more than one early life exposure of interest. Fifty six papers examined body size, 37 nutrition and 17 SEP. All of the included papers examined DNA methylation (DNAm) as the epigenetic marker. Overall there was no strong evidence for a consistent association between these early life variables in DNAm which may be due to the heterogeneous study designs, data collection methods and statistical analyses.
Conclusions
Despite these inconclusive results, the hypothesis that the early life environment can impact DNAm, potentially persisting into adult life, was supported by some studies and warrants further investigation. We provide recommendations for future studies.

Introduction
Substantial evidence from the field of life course epidemiology has supported a relationship between physical and social exposures across the entire life course and later life health [1]. Rapid growth and development that occurs in early life marks a sensitive period during which external factors can influence an individual’s later life health [2–4] Evidence has accumulated for the importance of nutrition and growth in utero and early postnatal life on a wide range of health and ageing outcomes such as cardiometabolic and bone health [5]. Childhood socioeconomic position (SEP) has also been found to be associated with a wide range of later life health outcomes [6, 7].

Exposures in early life must impact the organism in order for their effects to manifest after a long latency period. The biological, behavioural and psychosocial mechanisms linking these earlier life exposures with later life health are complex [1, 3]. Epigenetics is one possible mechanism [3, 8–10]. Epigenetics refers to processes that regulate gene expression but do not change the underlying DNA sequence. These tissue and cell-specific processes include DNA methylation (DNAm), histone modification, other changes to chromatin structure, and post-transcriptional control [3]. Genetic variation, stochastic events as well as the environment have been shown to influence the epigenome [11]. Since these epigenetic processes can persist during mitosis, it is feasible that early life exposures influencing the epigenome may have a phenotypic manifestation in later life [9].

A number of early life exposures have been investigated in relation to epigenetics. Animal studies have made a convincing case for the role of nutrition during fetal and early neonatal growth on epigenetics [12, 13]. DNA or histone methylation in offspring in these studies has been shown to be particularly susceptible to maternal dietary intake of folate, vitamin B6 (pyridoxine), vitamin B12 (cobalamin), vitamin B2 (riboflavin), choline and methionine. These nutrients are involved in one-carbon metabolism, influencing the amount of available S-adenosylmethionine and co-enzymes which are required for methylation [14]. In human studies, participants who were affected by the Dutch Famine provide evidence for the lasting impact of severe caloric restriction during particular periods of gestation [12, 15]. The role of nutrition on epigenetics beyond this fetal and early neonatal period is less studied [12]. Growth and body size in early life are related to nutrition, and indeed there is also evidence for predominantly cross-sectional associations between birth weight, childhood and adolescence BMI/obesity, body composition and DNA methylation from human studies [15]. The small number of human studies also suggest a role for early life SEP on DNA methylation [15].

Since this is a relatively new and rapidly developing area of research, most evidence examining the epigenetic effect of these key early life factors have come from animal and exploratory studies incorporating a variety of early life exposures and applying different analytical methods. In 2015 Demetriou et al. conducted a non-systematic review of the evidence for early-life nutrition, SEP and overweight/obesity on DNA methylation [15]. In 2017, Hartwig et al. systematically reviewed the literature of the effects of breastfeeding on DNA methylation [16]. To the best of our knowledge, there has been no comprehensive systematic review of the potential

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effects of the key early life exposures of nutrition, body size and SEP on epigenetic processes. Therefore, the aim of this study was to systematically review the literature on the association between 1) body size and growth in early life 2) nutrition during pregnancy and early life 3) markers of SEP in early life on epigenetic processes in human studies. This will provide information on the potential for epigenetics to mediate the association between these early life exposures and later life health.

Methods

This systematic review is registered with the PROSPERO database (registration number: CRD42016050193) and the protocol has been published in a peer-review journal [17].

Eligibility criteria

We included studies that tested the association between any measure of (i) body size or growth in early life, (ii) nutrition during pregnancy or early life, or (iii) SEP in early life on epigenetics in human samples. We defined early life as 12 years and under to capture exposures during the pre-adolescent period including prenatal, infancy, early and middle childhood. We considered any indicator of DNAm or histone modification measured in any tissue as an outcome. Early life factors could be prospectively measured or recorded, or retrospectively recalled at later data collections. Eligible measures of body size were weight, height, BMI, and head circumference at birth or any stage in early life or change in any of these measurements. Nutrition included any measure of maternal nutrition, supplement use and/or diet during pregnancy, breastfeeding/formula, weaning practices and nutrition/diet of the child in early life measured using dietary questionnaires and/or objectively by nutritional biomarkers. Eligible measures of SEP included any recognised indicator of SEP within society, including occupation, education, income, occupational or social class, poverty, and household overcrowding, as defined by Krieger et al. [18].

Reviews, clinical trials, animal studies, studies assessing the effect of adulthood exposures on epigenetic markers and those assessing the epigenetic marker before the early life measure were excluded. Studies in samples with a specific clinical condition were excluded. Studies were only included if they were published in the English language in peer-reviewed journals.

Search strategy

We performed a systematic review of the literature in March 2017. Using OvidSP as the database interface, a joint electronic search on MEDLINE and Embase was conducted. We searched BIOSIS database using ISI Web of Science. The search used free-text search terms (S1 Table) with truncations to allow for different spellings, proximity operators ('adj' in OvidSP, 'NEAR' in ISI Web of Science) and joined using Boolean logic (“AND”, “OR”). The reference lists’ of relevant reviews, all included papers and their ISI citation index (via Web of Science) was searched for studies meeting inclusion criteria. Given the extensive number of studies identified using these databases; we did not search grey literature. Eligible studies identified were combined with the electronic search results.

Study selection and data extraction

All abstracts were screened independently for eligibility by two researchers (from JM, WW and RH). The full text of all potentially eligible papers was also double screened by JM, RH, WW and JCF and reasons for their exclusion were documented. Disagreements about the paper’s eligibility were resolved through discussion and if necessary, a third reviewer.
The following information was extracted from selected papers: citation details, study details (including type, country/region and sample size), participant details (including age and sex), and exposure and outcome details (including details on methods used). A free-text box for recording main findings was used because of the expected heterogeneous methods that will have been used.

The following aspects of the paper which may relate to the quality of each study were extracted: study type, methods used to measure epigenetics, statistical analysis (including adjustment of relevant confounders), recall bias such as prospective or retrospective measures of early life factors, and generalisability [19].

Due to the diversity in eligible studies in terms of methods used, a meta-analysis was not conducted [19]. Therefore, a narrative synthesis was undertaken [20].

Results

Overall we identified 90 eligible papers (Fig 1 and Tables 1–3). Seventeen of these papers examined more than one early life exposure of interest. All of the included papers examined DNAm as the epigenetic marker with none examining histone modifications. Results of each of these papers will be outlined below according to the main exposure of interest.

Body size and growth in early life

Of the included papers, n = 56 examined the role of body size and growth in early life on DNAm (Table 1). There were 14 prospective (3 of which compared extreme groups), 33 cross-sectional (6 of which compared extreme groups), and 9 twin studies.

Prospective studies of body size and growth in early life and DNA methylation. Thirteen prospective papers examined size at birth [53, 55, 56, 58–62, 64–66, 77, 78], one paper body size in childhood [58], and two growth [59, 67].

Body size at birth: Three papers examined body size at birth in relation to childhood and adolescent genome-wide methylation using the Illumina Human-Methylation450 or Human-Methylation27 BeadChip array [55, 58, 77]. Agha et al. demonstrated that birth weight-for-gestation age (GA) was associated with methylation at 34 CpGs of which 4 of these CpGs remained at age 7–10 years in 235 children. Three of these CpGs were located on PBX1 (embryonic development regulator) and one was on NOS1AP (neuronal nitric oxidase synthase) [55]. In the Accessible Resource for Integrated Epigenomic Studies cohort (ARIES, a sub sample of The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort), birth weight was not associated with genome-wide DNA methylation in blood when the children were aged 7 and 17 years old [77]. However, analyses in the ARIES cohort did find that birth weight was associated with age acceleration based on Horvath’s clock (i.e. residuals from regression of epigenetic age on actual age) at birth, 7 and 17 years; a finding that was replicated in an independent cohort [58].

Two studies examined associations between body size at birth and global DNA methylation in adulthood [59, 60]. Rerkasem et al. found no associations between birth weight or birth length and blood methylation at LINE-1 or Alu in 249 20 year old adults [59]. In the other paper, global methylation measured in blood at age 38–48 years using a [3H]-methyl acceptance assay, was associated with birth length, but not birth weight [60].

Five papers examined body size at birth and subsequent DNAm in candidate genes [53, 61, 62, 64, 65]. Three of these papers examined methylation in imprinted genes. In the Motherwell Cohort, there was an association between birth length, but not birth weight, and methylation at IGF2/H19 differentially methylated region (DMR) measured in blood at 40 years [61]. Birth weight was associated with H19 DMR measured in childhood (~8 years) in girls, but not boys [53] and with methylation at the IGF2 DMR measured in blood samples of infants aged 17
Fig 1. PRISMA Flow diagram of study selection. *Other includes: reviews, not peer reviewed, publication not found, randomised control trials, animal studies **N's including overlapping studies (n = 17).

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### Table 1. Body size in early life and epigenetics. *(Organised by study design, exposure, DNA methylation (epigenome wide, global methylation, imprinted genes, other genes)).

| First author (year), country | Cohort, N (% female) | Early life variable (mean age ± SD (age range)) | DNA methylation | Tissue | Mean age at epigenetic measure (SD (age range)) | Main result | Conclusion |
|-----------------------------|----------------------|-----------------------------------------------|----------------|--------|-----------------------------------------------|------------|------------|
| Engdahl (2014), Norway [21] | MoBo, 1,046 (66) | Birth weight, Birth, GAD 94.6% 37–42w | Infinium Human Methylation 60 BeadChip | Cord Blood | Birth (GAD 90% 37–42w) | Adjusted mean difference (SD) in birth weight per log unit increase in DNA methylation fraction of CpG sites Significant 4.8% p = 1.52 × 10⁻³ | Child sex, maternal plasma cortisone, parity, maternal age, dietary factors (not including supplements), asthma, GAD, GAD², pre-eclampsia, season of birth, haemocytic cell-type composition |
| Haworth (2014), UK [13]    | Discovery cohort: 12 (NR) | Investigation cohort: 11 (NR) | EWHP (Both, median GAD 38.4 (IQR: 38.7–40.3w)) | Discovery cohort: Infinium Methylation 60 Bead Chip Investigation cohort: PMID251, MiR, ATAF1, FGFR2, UHRF1 | Growth, proliferation or embryonic development) | 27 of these 314 candidate genes with CpG sites associated with BWP. 23 of these genes had ≥2 CpGs associated with BWP. Authors focused on genes with a difference in methylation if P value: ≥2.5 between low and high BWP groups. Four loci with ≥2 CpGs were identified; MiR26, PMID251, ATAF1, FGFR2. UHRF1 was not validated using pyrosequencing and therefore not brought forward. Investigation cohort: No associations between PMID251 or MiR26 and BWP. Moderate methylation % of FGFR2 across BWP groups p = 0.001. A single CpG site in ATAF1 with low methylation in birth weight groups with a 3.8-fold ratio of 0.0081 p = 0.027. High BWP group: 33.7% vs all other BWP groups: 20.2% (This suggests that low methylation in FGFR2 is associated with reduced risk of high birth weight) |
| Turan (2012), US [23]      | 70 (44.2) | Birth weight (Both) | GoldenGate methylation array (1356 CpGs in 700 genes that were selected for their function in cell growth, proliferation or embryonic development) | Infinium Methylation 60 Bead Chip | Correlation (β) between methylation of mechanism-based candidate genes and birth weight in GoldenGate CpGs (n = 21) & Infinium Methylation 60 Bead Chip | GA | Correlation (β) between methylation of mechanism-based candidate genes and birth weight in GoldenGate CpGs (n = 21) & Infinium Methylation 60 Bead Chip |
| First author (year, country) | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure (age range) | Main result | Confounders |
|-----------------------------|----------------------|-----------------------------------------------|-----------------|--------|-------------------------------------------|------------|------------|
| Adkins (2012), US (25)      | CANDLE, 201(45.3)    | Birth weight, Birth, GAD 39.1±1 (36-41w)       | Infinium Human Methylation27 ReadChip | Cord Blood | Birth (GAD 39.1 ±1)                       | No genome-wide-significance for change in birth weight per increase in % methylation was reached for any CpG site in Bonferroni-corrected p = 1.96×10^-6 | Newborn sex, maternal BMI, race, GA |
| Fryer (2011), UK (25)       | 1.202                | Birth weight, (Birth)                         | Infinium Human Methylation27 ReadChip | Cord Blood | Birth                                      | Two clusters were identified following unsupervised hierarchical clustering to identify subgroups. BWP was higher (p = 0.019) in cluster B. 369 CpGs associated with BWP (p < 0.05, false discovery) | Surrogate variables estimated via SVA |
| Lee (2012), US (25)         | THREE, 141 (47)      | Birth weight, (Birth, BMI7-GAD 2≥37w)          | Genome-wide DMRs identified using microarray technique, CHARM 2.0 | Cord Blood | Birth                                      | Among sex-matched DNA methylation across top three DMRs associated with birth weight | Surrogative variables estimated via SVA |
| Herbstman (2013), US (25)  | COCEH, 279 (53.6)    | Birth weight, Birth length, Pre-Birth Index, Head Circumference (Birth) | Global methylation using Methylation Global DNA Methylation Quantification Kit | Cord Blood | Birth                                      | Change in birth outcomes in univariate logistic transformed DNA methylation (95% CI) | GA, placent, maternal height, pre-pregnancy BMI, maternal age at delivery, ethnicity, sex, public assistance, total polycyclic aromatic hydrocarbons and tobacco smoke, delivery mode (for head circumference) |
| First author | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|--------------|---------------------|-----------------------------------------------|----------------|-------|-----------------------------------------------|-------------|-------------|
| Nomura (2014), US [28] | 502 (41) | Birth weight, Head circumference, Birth length, (Both) | Global methylation using LUMA | Cord blood | Early life variable (mean age ± SD) | Association between global methylation (%) and birth outcomes in multivariate general linear model (SES), β | Newborn sex, mother’s education, welfare status, maternal status, ethnicity, GA |
| Hagerty (2013), UK [29] | 1,073 (NR) | Birth weight, Head circumference, Birth length, (Both) | LINE-1 (4 CpGs), IC2 (4 CpGs), IG2 (7 CpGs), SNRPN (4 CpGs) using pyrosequencing | Cord blood | Birth (GAD 39 ± 2w) | Change in early life variable per % increase methylation (average methylation) (95% CI) | Newborn sex, GA |
| Haggarty (2013) | 1,073 (NR) | Birth weight, Head circumference, Birth length, (Both) | LINE-1 (4 CpGs), IC2 (4 CpGs), IG2 (7 CpGs), SNRPN (4 CpGs) using pyrosequencing | Cord blood | Birth (GAD 39 ± 2w) | Change in early life variable per % increase methylation (average methylation) (95% CI) | Newborn sex, GA |
| Michels (20122) | Nomura (2014), US [28] | Birth weight, Head circumference, Birth length, (Both) | LINE-1 (4 CpGs), IC2 (4 CpGs), IG2 (7 CpGs), SNRPN (4 CpGs) using pyrosequencing | Cord blood | Birth (GAD 39 ± 2w) | Change in early life variable per % increase methylation (average methylation) (95% CI) | Newborn sex, mother’s education, welfare status, maternal status, ethnicity, GA |
| Michels (20122) | Nomura (2014), US [28] | Birth weight, Head circumference, Birth length, (Both) | LINE-1 (4 CpGs), IC2 (4 CpGs), IG2 (7 CpGs), SNRPN (4 CpGs) using pyrosequencing | Cord blood | Birth (GAD 39 ± 2w) | Change in early life variable per % increase methylation (average methylation) (95% CI) | Newborn sex, mother’s education, welfare status, maternal status, ethnicity, GA |
| Naess (2009), UK | 2461 (NR) | Birth weight (Both) | LINE-1 using pyrosequencing | Cord blood | Birth | LINE-1 methylation associated with BWP, p = 0.014, adjusted β = 0.011 |
| Battie (2013), Mexico | 2,149 (77.2) | Birth weight (Birth, GAD 39 ± 1.1w) | KCI (14 CpGs), IC2 (6 CpGs), H19 (2 CpGs), LINE-1 (4 CpGs), Abh (3 CpGs), ABEK (13 CpGs), GCR (1 CpG) using pyrosequencing | Cord blood | Birth (GAD39 ± 1.1w) | Mean birth weight (g): difference in % change of DNA methylation (95% CI) | Maternal age at delivery, maternal ethnicity, maternal smoking prior to or during pregnancy, newborn sex, preterm birth |
| Bouwland-Both (2013), The Netherlands [33] | Generation R, SGA: 69 (43) AGA (control): 471 (43) | Birth weight, (G.A 40-36w) | KCI2 (20 CpGs), BEF (25 CpGs), MTHFR using mass-spectrometry based method | Cord blood | Birth (G.A 40-36w) | Adjusted difference (95% CI) in % methylation for SGA vs. control | GA, maternal age, second trimester maternal weight, parity, education, infant sex |
| Qian (2016), China | SGA:39 (41.0) AGA:49 (52.7) | Birth weight (Both) | H19 (12 CpGs), 1b MEST (11 CpGs) using mass spectrometry based method | Cord blood | Birth | Higher methylation level in H19p SGA vs. AGA | Correlations between CpG site, birth/length, sex of child, maternal BMI, fetal sex, parity, smoking, smoking, preeclampsia |
| Hoyte (2014), US | NEST, 496 (49.7) | Birth weight, (Birth 450-500G >37w) | DMRT in MEG3N/1/NST1/P3 (3 GSE/MEG3-3G), PLAGE, LPGAP1, MEST, H19, K22 using pyrosequencing | Cord blood | Birth (85% GAD >37w) | J (0.05) association between DMR and birth weight (g): Results are similar with methylation levels in the fourth quartile | Maternal age, sex, cigarette smoking, GAD, A of blood type, physical activity, pre-pregnancy BMI and delivery route |
| Hoyte (2012), US | NEST, 300 (54.3) | Birth weight, (Birth 450-500G >37w) | DMRT in JGF2, H19 using pyrosequencing | Cord blood | Birth (85% GAD >37w) | DMRT methylation fraction % (SD) | Maternal age, sex, cigarette smoking, GAD, A of blood type, physical activity, pre-pregnancy BMI and delivery route |
Table 1. (Continued)

| First author (year), country | Cohort, N (% female) | Early life variables/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|-----------------------------------------------|-----------------|--------|--------------------------------------------|-------------|-------------|
| Liu (2012), UK [27]         | NEST, 406 (48)     | Birth weight/Birth, GAD ≥ 37w                 | DMRs in IGF2, PEG10, PLAGL1 using pyrosequencing | Cord blood | Birth (GAD > 37w) | % methylation difference in DMRs between LBW (≤ 2500g), NBW (2500-4500g), HBW (≥ 4500g) | IGF2 (DMRs): 1.6% lower methylation among LBW vs. NBW, p = 0.06 (female infants 2.3%, p = 0.01, black mothers 2.8%, p = 0.08); PEG10 (DMR): 5.9% higher methylation among LBW vs. NBW, p = 0.02; PLAGL1 (DMR): 3.4% higher methylation among HBW compared with NBW, p = 0.06 |
| Sorkney (2011), US [30]    | NEST, 436 (47.5)   | Birth weight (Birth)                         | IGF2 (5 CpGs) and H19 (4 CpGs) using pyrosequencing | Cord blood | Birth (GAD 39.5) | Birth weight (Birth) | % methylation difference in DMRs between NBW (2500-4500g), LBW (< 2500g), & HBW (≥ 4500g) | HBW (mean% methylation n = 411) (female infants 2.3%, p = 0.08) |
| Su (2016), China [39]      | 115 (NR)           | Birth weight (Birth, all full term)          | IGF2 (5 CpGs) using mass spectrometry based method | Cord blood | Birth, all full term | Linear mixed model of IGF2 methylation on birth weight accounting for correlations between CpG sites; Coef (p): CpG1: 0.06 (0.65), CpG2: -0.20 (0.07), CpG10: -0.22 (0.05), p < 0.05, CpG12: -0.22 (0.04), p < 0.05, CpG13: 0.006 (0.90), p < 0.05 |
| Vidal (2013), US [41]     | NEST, 397 (51)     | Birth weight (Birth)                         | MEG3 & PLAGL1 DMR, using pyrosequencing | Cord blood | Birth (GAD 39.5) | Birth weight (Birth) | Pearson’s rank partial correlation coefficients for early life variables and ZAC1 DMR methylation: site 1: 0.18 GSTM5 (2 CpGs), site 1: 0.55 ALOX12 (5 CpGs), site 2: 0.90 ALOX12 (2 CpGs), site 3: 0.93 ALOX12 (5 CpGs), site 4: 0.11 AMN (1 CpG), site 5: 0.56 AMN (1 CpG) using pyrosequencing | Correlations between CpG sites; Coef (p): CpG4: 0.04 (0.73), CpG14: -0.09 (0.41), CpG15: 0.89 (0.03), CpG14-16: 0.27 (0.07) |
| Zhang (2015), China [40]  | SAGA: 400 (48.7)   | Birth weight (Birth)                         | IGF2 and NGF2 DMR using pyrosequencing | Blood | Birth | The methylation level of IGF2 DMR was significantly higher in the AGA (p = 0.00) and LGA (p = 0.04) compared to AGA group |
| Ghosh (2015), US [42]     | LB: 475 (37.2) HKW: 57 (NR) | Birth weight (Birth)                         | H19 and IGF2 DMR using pyrosequencing | Blood | Birth | LBW infants had greater number (mean = 14) of disrupted CpGs/outliers than HBW children (mean = 5) (fisher’s exact test, p = 0.05) |
| Arlot (2014), France [43] | EDEN: 254 (NR)     | Birth weight, Birth length, (Birth, GAD 39.5±1.5w) | ZAC1 DMR methylation using allele-specific methylation multiplex real-time quantitative PCR | Cord blood | Birth (GAD 39.5±1.5w) | Spearman’s rank partial correlation coefficients for early life variables and ZAC1 DMR methylation: birth weight z-score: 0.08 (p = 0.51) | Centre, child’s sex, GA |
| Burris (2015), Mexico [44] | PROGRESS, 531 (45) | Birth weight (Birth, GAD 39.5±1.8w) | AHRR gene promoter (3 CpGs) using pyrosequencing | Blood | Birth (GAD 39.5±1.8w) | Average difference (95% CI) in AHRR DNA methylation, across 3 CpG sites, Bonferroni adjustment, p = 0.008; Birth weight (GAD 39.5±1.8w) | Maternal age, maternal BMI, maternal education, parity, smoking, folic acid intake, GA at delivery |
| Haworth (2013), UK [45]   | 129 (5) | Birth weight (Median GAD 39.4±1.8w) | Selector of MMR based on [23]: GSTM3 (2 CpGs), HMOX2 (1 CpG), ALOX12 (5 CpGs), APOB (7 CpGs), AQP3 (5 CpGs), AQP1 (2 CpGs), AMN (1 CpG) using pyrosequencing | Cord blood | Birth (Median GAD 39.4±1.8w) | Association between methylation % and BW Pp | GSTM3 site 1: 0.18 GSTM3 site 2: 0.25 HMOX2 site 1: 0.095 ALOX12 site 1: 0.55 ALOX12 site 2: 0.91 ALOX12 site 3: 0.93 APOB site 1: 0.11 APOB site 2: 0.96 APOB site 3: 0.88 APOB site 4: 0.39 |
| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|-----------------------------------------------|----------------|--------|-----------------------------------------------|-------------|-------------|
| Mulligan (2012), Democratic Republic of Congo [46] | 25 (NR) Birth weight (17% full term) | NR3CI (9 CpGs) using PCR Cord blood Birth (17% full term) | APOB site 3: 0.99 | Cord blood | Birth (37% full term) | First PC of % methylation of 39 CpG sites explained 16.15% of variance & correlated with birth weight \( r = -0.45 \), \( p = 0.02 \) | Child sex, ethnicity, cell type proportions and interactions between ethnicity and cell type proportions |
| Pan (2015), Singapore [47] | GUSTO, 991 (41) Birth weight, Birth length, Body composition (Birth, GAD 38.9 ± 1w) | HIF3A (3CpGs) using Infinium Human Methylation450 BeadChip Cord blood Birth (GAD 38.9 ± 1w) | Association between % methylation and proportion with low BWP (< 50% vs. > 50%) OR (95%CI) | GSTM5: 0.33 (0.14–0.77), \( p = 0.01 \); MAP2K3: 0.24 (0.01–0.83), \( p = 0.02 \); APOB: 2.56 (1.14–5.76), \( p = 0.02 \); No significant associations for methylation in other genes (data not shown) |
| Lessoeur (2013), US [48] | Rhode Island Child Health Study, 58 (~49) Birth weight (Birth, GAD 39 ± 1.1w) | LEF promoter using pyrosequencing Cord blood Birth (GAD 39 ± 1.1w) | \( \beta \) coef (SE), \( p \) of LEF as dependent variable: AGA (reference) vs. LGA: 0.47 (0.53), \( p = 0.31 \); AGA (reference) vs. SGA: 1.78 (0.60), \( p = 4.6 \times 10^{-3} \) | Maternal blood LEF, pre-pregnancy BMI, race, tobacco use during pregnancy, hypertension during pregnancy, delivery method, maternal age, rs2167270 genotype, infant sex |
| Almeida (2012), Greece [49] | Greek Healthy Growth Study, Normal weight: 24 (100) Obese: 23 (100) Body size (normal weight: 10.6±0.5y & 10.5±0.5y for FTO A/T respectively) Obese: 11.1±0.5y & 10.7±0.5y for FTO A/T respectively | Infinium Human Methylation27 BeadChip Blood | | | Differentially methylated genes between obese and normal weight children. Average methylation (beta), % methylation change in obese relative to average methylation, \( p \) adjusted for multiple comparisons |
Table 1. (Continued)

| First author (year) | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|---------------------|----------------------|-----------------------------------------------|-----------------|--------|-----------------------------------------------|-------------|-------------|
| Perng (2012), Columbia [50] | BSCC60033.7 | Birth weight, Body size (5-12y) | LINE-1 using pyrosequencing | Blood (5-12y) | LINE-1 methylation mean(SD): Birth weight (g). | | |
| | | | | | | **AP**(p-trend) | | |
| | | | | | **<2000 n = 44, 80.71(0.77)** | | |
| | | | | | 2,000–2,999 n = 11, 80.28(0.67) | | |
| | | | | | 3,000–3,999 n = 12, 80.28(0.66) | | |
| | | | | | >3,500 n = 147, 80.22(0.62) | | |
| | | | | | **Main result** | | |
| | | | | | **TSC22D2**: 6.4, 7.4% **t** = 0.008 | | |
| | | | | | **CBX6**: 3.1, -16.7% **t** = 0.008 | | |
| | | | | | **FOXF1**: 4.7, -13.3% **t** = 0.008 | | |
| | | | | | **PSMD7**: 7.5, -7.7% **t** = 0.012 | | |
| | | | | | **COL4A1**: 9.9, 10.2% **t** = 0.02 | | |
| | | | | | **H1FX**: 4.1, 10.2% **t** = 0.02 | | |
| | | | | | **PRRC2C**: 4.1, -8.4% **t** = 0.02 | | |
| | | | | | **MSI1**: 23.8, -3.8% **t** = 0.02 | | |
| | | | | | **NBPF3**: 5.8, -8.4% **t** = 0.02 | | |
| | | | | | **USP5**: 4.4, -10.4% **t** = 0.03 | | |
| | | | | | **TLE3**: 5.5, -6.9% **t** = 0.03 | | |
| | | | | | **RPS24**: 5.8, -10.0% **t** = 0.04 | | |
| | | | | | **DVL3**: 4.4, 8.5% **t** = 0.05 | | |
| | | | | | **POLD3**: 6.1, -8.8% **t** = 0.05 | | |
| | | | | | **PLOD2**: 30.8, -5.4% **t** = 0.03 | | |
| | | | | | **TLE3**: 5.5, -6.9% **t** = 0.03 | | |
Cohort, N (% female) Early life variable/mean ± SD (age range) DNA methylation Time point Mean age at epigenetic measure (± SD age range) Main result

Ouni (2015), NR [51] Discovery cohort 106 (41) Body size, nutrition and socioeconomic position in early life and the epigenome Correlation between % methylation and child height

Hernandez Valero (2013), US [52] 75 (40) Body size (0.2–1.5y) IGFBP1 promoter P1 (9 CpGs) & P2 (7 CpGs) using pyrosequencing Blood 9.7y boys; 9.6y girls Correlation between % methylation and child height

Gardner (2015), US [54] 64 (39.37) Body size at 5-6y) Promoter region of FTO, MAGA, ADIPOQ, LEPR, DNMT3B, BNDF and CGA Rating methylation-sensitive restriction enzyme digestion and qRT-PCR Saliva (5-6y) Mean BMI percentiles according to DNMT738 methylation (based on pyrosequencing) Lower tertile: 0.82 (p = 0.05) Upper tertile: 0.72 (p = 0.05) (data from other genes not presented)

Prospective

Body size at birth

(Continued)
| First author | Cohort | Early life variables/case age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenomic measure (SD age range) | Main result |
|--------------|--------|---------------------------------------------|-----------------|-------|---------------------------------------------|-------------|
| Agha (2016), US | Project Viva, 406 (birth), 235 (7-10y) (40) | Birth weight/Birth, all GA/D >36w | Infinium Human Methylation450 BeadChip | Cord blood/Adipose | Birth (7-10y) | Adjusted difference (95% CI) in % cord blood methylation for 1 unit increase in birth weight for GA/D adjustment: cg00325458 (gene: TFAP2B): 1.93 (1.22, 2.64), p = 1.15 x 10^-47 |
| Broholm (2016), Denmark | LBW: 13(0) Controls:13(0) | Birth weight (Birth) | Illumina HumanMethylation450 BeadChip | Adipose derived stem cells | LBW: 22.6 ± 7.1y Control: 23.2 ± 6.6y | No significant difference in methylation between LBW and control for individual CpG sites at TFBq q = 0.05. Top 20 CpG sites (gene: SNPS): cg06610403 (gene: NGN1): 3.85 x 10^-5 |

Table 1. (Continued)

| Confounders | Body size, nutrition, smoking, parity, delivery mode, pre-pregnancy BMI, gestational diabetes, newborn sex, cord blood composition, childhood age and adult illness composition for prospective analyses. |
| First author | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|--------------|----------------------|---------------------------------------------|-----------------|--------|-----------------------------------------|-------------|-------------|
| *Simpkin (2015), UK* [57] | ARIES (1,018 (~51)) | Birth weight, (Birth) | ARIES & MoBa Infinium Human Methylation 450 BeadChip | Cord blood & blood | Birth, 7.5y, 17.1y | Cord blood methylation 25 probes in 14 genes (30 positive associations) Blood at 7y/17y: No strong evidence for birth weight and methylation 
Replication: Probes (gene), p with negative association between birth weight and methylation in ARIES and MoBa: cg07804426 (ARIES): 3.4x10^-9 
cg11435954 (RARB): 2.3x10^-9 
Probes (gene), p with negative association between birth weight and methylation in ARIES only: cg24642591 (ARID5B): 1.1x10^-7 
cg12409567 (CHD5): 3.3x10^-7 
cg00654448 (NA): 9.4x10^-8 
cg00442282 (RARA): 2.8x10^-8 
cg13696490 (LOC201651): 6.2x10^-8 
Longitudinal analysis at identified probes: Results suggest faster rates of change in methylation during childhood in children with low birth weight. No strong evidence for ages 7 to 17y | GA, parity, maternal age, maternal smoking, child sex, delivery method, cell type composition |
| *Rerkasem (2015), Thailand* [59] | GOYA (249 (NR)) | Birth weight, birth length (Birth & 7y) | COBRA LINE-1 & Alu | Blood | 20y | Birth weight (kg) was positively associated with newborn AA in GOYA (0.04y per kg, 95% CI 0.02, 0.07, p = 0.002) | Cell-type composition |
| First author (year), country      | Cohort, N (% female) | Early life variables/mean age ± SD (age range) | DNA methylation | Time | Mean age at epigenetic measure ± SD (age range) | Main result                                                                 | Confounders                                                                 |
|----------------------------------|----------------------|-----------------------------------------------|----------------|-----|-----------------------------------------------|----------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Terry (2000), US [69]             | 85 (100)             | Birth weight, Birth length (Birth)            | Global DNA methylation using [3H] methyl acceptor assay  | Blood | 38 (28-48)                                    | Unadjusted differences log DPM/μg(95% CI) for association between DNA methylation by variables (higher values indicated less DNA methylation) | Smoke exposure, adult BMI, SEP, parity                                    |
| Drake (2012), UK [61]             | The Motherwell Cohort, 58 (64) | Birth weight, Birth length, Fused oral index (Birth, GAD 27-55, 5-54) | Promoter region of HSD2, exon 1 (C) and 1 (F) of GR, IGF2 DMRs using pyrosequencing | Blood | 40±12y                                      | Pearson correlation coefficients of mean methylation with birth weight      | GAD, parity, sex, maternal anastomized BMI                                 |
| Hernandes Valero (2013), Spain [53] | 75 (40)             | Birth weight (Birth)                         | H19 DMR (CpG4, SNP n = 10732516)                          | Blood | 8±1.5y                                      | Association of CpG4 methylation status of H19 DMR (yes vs. no) with birth weight (95% CI) | Maternal BMI, residence (urban vs. rural), sex                               |
| Steegers–Thomeevis (2009), Netherland [62] | HAVEN study control 120 (~56) | Birth weight (Birth, GAD 39–96) | IGF2 DMR (5 CpG) using mass spectrometry based method | Blood | 17m                                         | IGF2 DMR %S of mean change in relative methylation                          | Periconceptional folic acid use, G.A                                       |
| Welshalamps (2013), Finland [63]  | The Helsinki Study of VLBW Adults, VLBW:1983 (57) | Controls 161 (40)                          | IGF2 (GF2A0 & IGF2D0) DMR using Sequenom technology (Fam 180) | Blood | 38 (27-58)                                   | Mean (95% methylation % at IGF2 VLBW (~57,500) vs. control)                | Plac-o sex, age, height, BMI, mother’s smoking during pregnancy, mother’s age, father’s age, mother’s BMI before pregnancy, highest education of either parent |
Table 1. (Continued)

| First author | Cohort, N (% female) | Early life variable | mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure | Model result (Continued) | Confounders |
|--------------|----------------------|---------------------|--------------------------|-----------------|--------|-------------------------------|--------------------------|-------------|
| Obermann-Borst (2013), the Netherlands [64] | 120 (42) | Birth weight (Birth) | 17± 2.5m | % Absolute methylation change (SE) | Blood | Model 1—each variable in model separately | % relative methylation change (SE) | Birth weight: -1.2 (0.4); -5.0 (1.7), p = 0.005 |
| | | | | | | | | Growth rate (SD): 0.0 (0.4); 0.0 (0.3), p = 0.99 |
| | | | | | | | Model 2—adjusted for all variables | Birth weight: -0.6 (0.5); -2.5 (2.1), p = 0.16 |
| Tao (2013), US [65] | 639 (100) | breast cancer cases | 57.5± 11.3y | OR (95%CI) for methylation | Breast tumor | Premenopausal group | Birth weight | Birth weight 2.5kg: 2.79 (1.15, 6.82) |
| | | | | | | | | 2.6–3.9kg: ref |
| | | | | | | | | >3.9kg: 1.69 (0.70, 4.05) |
| | | | | | | | | Postmenopausal group | Birth weight | Birth weight 2.5kg: 0.77 (0.38, 1.54) |
| | | | | | | | | 2.6–3.9kg: ref |
| | | | | | | | | >3.9kg: 0.86 (0.42, 1.73) |
| Rangel (2014), Brazil [66] | 115 (47) | Birth weight (Birth) | 17± 2.5m | % Absolute methylation change (SE) | Blood | Model 1 Correlation between individual CpG dinucleotides, bisulfite batch, GA | % relative methylation change (SE) | LBW (2.5kg): 5.4± 0.28% |
| | | | | | | | | NBW (3kg): 6.8± 0.19% |
| | | | | | | | | LBW children had lower methylation at CpG1 (p = 0.001) and CpG3 (p = 0.009). No significant difference at CpG2 (p = 0.14) |
| Childhood body size and growth | | | | | | | | Adjusted model, p < 0.001 |
| Sapienza (2015), UK & Denmark [58] | 1018 (51) | GOYA 981 (NR) | 7± 3.5m | Correlations between early life variable and age acceleration | Blood | Birth, 7.5y, 17.1y | r = 0.06, p = 0.06 | Height at 7y & AA 7 years r = 0.06, p = 0.06 |
| | | | | | | | | Height at 7y & AA 7.7 years r = 0.07, p = 0.007 |
| | | | | | | | | BMI at 7y & AA 7 years r = 0.005, p = 0.25 |
| | | | | | | | | BMI at 7y AA at 17 years r = 0.006, p = 0.88 |
| Beckmann (2015), Thailand [59] | 249 (NR) | Growth (birth, 3, 6, 12 months) | 20y | Correlations between early life variable and age acceleration | Blood | Birth, 7.5y, 17.1y | r = 0.06, p = 0.06 | Height at 7y & AA 7 years r = 0.06, p = 0.06 |
| | | | | | | | | Height at 7y & AA 7.7 years r = 0.07, p = 0.007 |
| | | | | | | | | BMI at 7y & AA 7 years r = 0.005, p = 0.25 |
| | | | | | | | | BMI at 7y AA at 17 years r = 0.006, p = 0.88 |
| | | | | | | | | Age, education, race, oestrogen receptor status |
| | | | | | | | | Cell-type composition |
Table 1. (Continued)

| First author | Year, country | Cohort, N (% female) | Early life variable (mean age ± SD (age range)) | Tissue | Mean age at epigenetic measure (± SD (age range)) | Main result | Confounders |
|--------------|---------------|----------------------|-----------------------------------------------|--------|-----------------------------------------------|-------------|-------------|
| Groom (2012), UK [67] | Cohort 1: Newcastle Twin Birth Growth Study, Cohort 2: AllSPAC (see results for N) | Postnatal growth (cohort 1: 10-16 wk; cohort 2: birth to 8 weeks) | DNA methylation | Tissue | Mean age at epigenetic measure (± SD (age range)) | Main result | Confounders |
| Chen (2016), Denmark [69] | DTR, 150 MZ twin pairs (80) | Birth weight (Birth) | Infinium Human Methylation450 BeadChip | Blood | Medium 57y (30-74) | No genome-wide significant DMRs at FDR < 0.2 for qualitative (large or small) or quantitative (linear) birth weight discordance. All twins for discovery at 5% FDR. | Age, sex, batch effects |
| Tsai (2015), UK [70] | Twin UK (discovery): 37 MZ pairs (108) | Birth weight (Birth) | Infinium Human Methylation450 BeadChip | Blood | Medium 57y (30-74) | No genome-wide significant CpGs associated with qualitative (large or small) or quantitative (linear) birth weight discordance. All twins for discovery at 5% FDR. | WBC counts, age, sex, batch effects |
| Casey (2017), Canada [71] | Quebec Newborn Twin Study, 52 pairs of MZ twins (58) | Birth weight (Birth) | Infinium Human Methylation450 BeadChip | Blood | Medium 15·7 ± 16·3 | No one gene was significantly differentially methylated in birth weight discordant MZ twin pairs after correcting for multiple testing. | Cell type composition, sex, family |
| Baird (2011), NR [72] | 10 MZ twin pairs | Birth weight (Birth) | Infinium Human Methylation450 BeadChip | Peripheral blood mononuclear cells | Adult (NR) | No one gene was significantly differentially methylated in all birth weight discordant MZ twin pairs. | (Continued) |
| First author (year), country | Cohort, N (% female) | Early life variables mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measurement ± SD (age range) | Main result | Conclusions |
|---|---|---|---|---|---|---|---|
| Gordon (2012), Australia [73] | 22 MZ and 12 DZ twin pairs (50) | Birth weight, (GAD 36.2±1.8wk (32–38)) | Epigenetic measure: Human Methylation450 BeadChip: Cord Blood, umbilical cord blood, placenta | Cord Blood, umbilical cord blood, placenta | GAD 36.2±1.8wk (32–38) | Geneic linear model with twin pair as a factor and birth weight as covariate. | Batch effects |

**Table 1.** (Continued)
| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|-----------------------------------------------|------------------|--------|-----------------------------------------------|------------|------------|
| Souren (2013), Belgium [75] | EFPTS, 17 MZ monochorionic twin pairs (100) | Birth weight (GAD 37.9 ± 2.4w (34–42)) | Infinium Human Methylation450 BeadChip & LINE-1 & HERVK using methylation-dependent primer extension assays (SIRPH) | Saliva | 34.4 ± 7.4y (22–45) | 3,153 CpGs differentially methylated between heavy and light co-twins (p < 0.01), of which 45 show sensible absolute mean methylation differences (β-value difference > 0.05). Validation analysis of 8 selected BW-MVPs mean difference (SD) in heavy vs. light twins: cg14123607 (APBA1): 0.07 (0.05), p = 0.0008 cg12170649 (APPL2): -0.06 (0.05), p = 0.001 cg15049370 (PPARGC1B): -0.07 (0.07), p = 0.002 cg22768222 (RUNX2): 0.06 (0.07), p = 0.008 Differences remain in the range of technical variation, arguing against a reproducible biological effect. Analysis of methylation in repetitive elements showed no significant intra-pair differences. | Cell composition |
| Mill (2006), UK [76] | TEDS, 12 MZ twin pairs (98) | Birth weight, (Birth) | COMT using pyrosequencing | Buccal | 5y | Average methylation difference (%) between birth weight discordant pairs: CpG1: 10.3 CpG2: 16.1 Average: 13.19 | |

* Studies spanning more than one exposure may appear twice in the table; ** Abstract; 

AA: Age acceleration; Δbw%: Percentage of Birth Weight Difference; AGA: Average for Gestational Age; ALSPAC: Avon Longitudinal Study of Parents and Children; ARIES: Accessible Resource for Integrated Epigenomic Studies; BMI: Body Mass Index; BSCC: Bogota School Children Cohort; BW: Birth Weight Percentile; BW-MVP: Birth Weight Associated Methylation Variable Positions; CANDLE: Conditions Affecting Neurocognitive Development and Learning in Early Childhood Study; CCCEH: The Northern Manhattan Mothers and Newborns Study of the Columbia Center for Children’s Environmental Health; CI: Confidence Interval; COBRA: Combined Bisulfite Restriction Analysis; CVD: Cardiovascular Disease; DMR: Differentially Methylated Regions; DPM: Disintegrations Per Minute; DTR: Danish Twin Registry; DZ: Dizygotic twins; EFPTS: East Flanders Prospective Twins Survey; EWAS: Epigenome Wide Association Study; FDR: False Discovery Rate; FT: Full Term; GAD: Gestational age at delivery; GUSTO: Growing up in Singapore towards Healthy Outcomes; HBW: High Birth Weight; IQR: Interquartile Range; ISS: Idiopathic Short Stature; LBW: Low birth weight; LGA: Large for gestational age; LUMA: Luminometric Methylation Assay; M: Months; MoBa: Norwegian Mother and Child Cohort; MZ: Monozygotic twin; NBW: Normal Birth Weight; NEST: Newborn Epigenetics Study; NGT: Normal Glucose Tolerance; NR: Not Reported; NTR: Netherlands Twin Register; OR: Odds Ratio; PAH: Princess Anne Hospital Study; PC: Principle Component; PROGRESS: Programming Research in Obesity, Growth Environment and Social Stress; qRT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SD: Standard Deviation; SE: Standard Error; SGA: Small for Gestational Age; SEP: Socioeconomic Position; SVA: Surrogate Variable Analysis; SWS: Southampton Women’s Study; TEDS: Twins Early Development Study; THREE: Baltimore Tracking Health Related to Environmental Exposures Study; VLBW: Very Low Birth Weight; VPT: Very Preterm; W: Week; WMHP: Women’s Mental Health Program; Y: Years.

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### Table 2. Nutrition in early life and epigenetics.

(Organised by, exposure, DNA methylation (epigene wide, global methylation, imprinted genes, other genes).

| Maternal dietary intake / nutritional biomarker | Cohort, N (% female) | Early life variable/measure ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------------------------|----------------------|---------------------------------------------|------------------|--------|-----------------------------------------------|-------------|-------------|
| Johansson (2016), Norway & The Netherlands [8] | MoRa: 1275 (NR) Gen 7, 733 (NR) | Plasma folate | Infinium Human Methylation450 Read Chip Cord blood Birth 443 FDR-significant CpGs were differentially methylated in cord blood in relation to maternal folate. 48 CpGs met Bonferroni threshold (p < 1.19x10^-7). Selected loci from meta-analysis, Coef(SE), p:
|                                      | Maternal age, education, smoking during pregnancy, parity, b-allele effects |
|Boeke (2012), US [36] | Project Viva, Periconceptional intake 51.6 Second trimester intake 49.4 (67.7) | FFQ for B-vitamins (32 ± 5.1) | LINE-1 using pyrosequencing Cord blood Birth 0-4 weeks gestation β = %5MC difference in LINE-1 methylation for increment of 1 SD in nutrient
|                                      | Maternal age, maternal BMI, maternal smoking before and during each trimester of pregnancy, gestational weight gain, education, cotinine level |
|Poland (2017), Belgium [67] | MANOSE, 115(47.8) | FFQ for methyl donor intake & folate and vitamin B supplementation (30 ± 3.6) | Global DNA methylation using mass-spectrometry method & DNMT1, LEP, RXRA, KRAS, MGMT using PCR Cord blood Birth (GAD 39.6 ± 5.1) | Other methyl donors, child's sex, mother's age, sex, smoking, pregnancy, weight gain, education, cotinine level |

(Continued)
| First author | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|--------------|----------------------|---------------------------------------------|----------------|--------|---------------------------------------------|-------------|-------------|
| Fryer (2009), UK (21) | 24(363) | Folic acid supplementation during pregnancy (29/45/7) | LINE-1 methylation using pyrosequencing | Cord blood | Both | Correlation with LINE-1 methylation | Sex, GA maternal age, parity, and BMI and cord serum folate, plasma homocysteine |
| Huggett (2013), UK (11) | 913 (46) | FFQ for folate intake, folic acid supplementation, RBC folate (305 095%CI: 302 – 303) | XGP2/4 CpGs, PEG2/7 CpGs, SNRPN (134 L Cpgs) LINE-1 (4 CpGs) using pyrosequencing | Cord blood | Both | Correlation with LINE-1 methylation | Maternal folic acid intake (periconception): β = 0.31, p = 0.15 |
| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|-----------------------------------------------|----------------|--------|-----------------------------------------------|------------|-------------|
| McKay (2012), UK [89]       | The North Cumbria Community Genetics Project, Infants: 294/46 Maternal: 121 | Serum B12 (median 28y) | Global DNA methylation using LUMA & IGF2, IGFBP3, ZNT5 using pyrosequencing | Cord blood | Birth | Global DNA methylation correlated inversely with maternal vitamin B12 concentrations \( \beta = 0.0002(0.0001), p = 0.06 \). After adjustment: \( \beta = 0.00017(0.00007), p = 0.029 \) | Sex, GA, infant MTHFR genotype |
| Hoyo (2011), US [90]        | NEST 428 (50) | Folic acid supplement before \( (n = 428) \) and during pregnancy \( (n = 223) \) (29 ± 6.2y) | IGF2 & IGF1 DMR using pyrosequencing | Cord blood | Birth | Methylation % difference for folic acid supplement before pregnancy: IGF2 methylation: Moderate vs. non-users: 0.28, \( p = 0.76 \); High (i.e. prescribed & over the counter) vs. non-users: -1.15, \( p = 0.39 \); H19 methylation: Moderate vs. non-users: -1.96, \( p = 0.04 \); High vs. non-users: -2.76, \( p = 0.04 \); Methylation % difference for folic acid supplement during pregnancy: IGF2 methylation: Moderate vs. non-users: 0.75, \( p = 0.59 \); High vs. non-users: 0.25, \( p = 0.93 \); H19 methylation: Moderate vs. non-users: -2.87, \( p = 0.02 \); High vs. non-users: -4.90, \( p = 0.05 \) | Maternal education, race, mode of delivery, cigarette smoking |
| Steegers-Theunissen (2009), The Netherlands [62] | HAVEN study controls 120 (~58) | Folic acid supplementation during pregnancy 400 μg/day vs. no supplement | IGF2/G CPGs using mass-spectrometry based method | Blood | 17 months | Mean (SE) of IGF2 methylation in childhood without maternal exposure to folic acid n = 34 vs. exposed n = 86: 0.474(0.007) vs. 0.495(0.004), \( p = 0.014 \). Adjusted analysis: mean difference in IGF2 methylation 4.5% (1.8) with maternal exposure to folic acid vs unexposed, \( p = 0.014 \) | Maternal education |
| Loke (2013), Australia [91] | PETS 95 twin pairs (55 MZ & 40 DZ) (~50%) | Folate and macronutrient intake | IGF2 and IGF1 DMRs using mass-spectrometry based method | HUVECs, (CBMCs and granulocytes); ectoderm (buccal epithelium) and extra embryonic ectoderm (placenta) | Birth (GAD median 37.0 ± 1.94w) | Differences in coefficients between cell types | Had folate: HUVECs vs buccal -4.5%; \( p = 0.026 \); Vitamin B12 z-score: Granulocytes vs buccal (2.1%; \( p = 0.004 \)). No other differences found |
| First author | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|--------------|---------------------|---------------------------------------------|-----------------|--------|---------------------------------------------|-------------|-------------|
| Azzi (2014), France [49] | EDEN 256 (NR) | FPQ for B-vitamins & supplementation (during pregnancy) (29.8±4.4y) | ZACI DMR using methylation-specific PCR | Cord blood | Birth (GA at birth 39.5±1.5) | Spearman’s rank partial correlation coefficients | No association with folic acid supplementation and/or the use of a combination of micronutrients either prior to or during pregnancy (estimates not provided) |
| Obermann-Bors (2013), The Netherlands [64] | 120 (50) | Folic acid supplementation | LFP using mass-spectrometry based method | Blood | 17± 2.5m | No folic acid: 0.09 (0.10), p = 0.91 | No association with folic acid supplementation and/or the use of a combination of micronutrients either prior to or during pregnancy (estimates not provided) |
| Adkins (2010), NK [65] | 30 (NR) | Biomarkers on one-carbon pathway | -15,000 loci (Details not specified) | NR | Birth | Phosphatidyl choline was significantly correlated with newborn DNA methylation at a subset of loci |
| Raj (2011), China [65] | 99 (48) | B-vitamin biomarkers (27.8 ±5.3y) | IGF2-promoter using methylation-specific PCR | Cord blood | Birth (96% GA 37-41w) | Vitamin B2: 0.14, p = 0.04, Vitamin B9: 0.02, p = 0.74, Vitamin B12: 0.02, p = 0.79 | No association with folic acid supplementation and/or the use of a combination of micronutrients either prior to or during pregnancy (estimates not provided) |
| Hay (2014), US [39] | NEST 406 (407) | Erythrocyte folate (first trimester) | IGF2, IGF3, JSK1, MBG, PCG, MET, IGF3, SGCE, NNN, using pyrosequencing | Cord blood | Birth | No association with folic acid supplementation and/or the use of a combination of micronutrients either prior to or during pregnancy (estimates not provided) |
| McCullough (2016), US [66] | NEST 429 (50) | B-vitamin biomarkers (0.5% between 20-29y) | IGF2-PLAG1 using methylation-specific PCR | Cord blood | Birth | No association with folic acid supplementation and/or the use of a combination of micronutrients either prior to or during pregnancy (estimates not provided) |

(Continued)
| First author (year), country | Cohort, N (% female) | Early life variables/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-------------------------------|----------------------|-----------------------------------------------|-----------------|--------|-----------------------------------------------|-------------|-------------|
| Dominguez-Salas (2014), The Gambia [95] | Keneba Cohort 126 (43) | Metabolite epilogue: BGLA3, LOC654633, SP2D3, ZNF284 using methylation specific amplification microarray and pyrosequencing. | Blood lymphocytes (n = 126), Hair follicle (n = 87) | 3.6 ± 0.9m | Effect sizes are 1) standardised β coefficient for change in mean DNA methylation (combined MEs) per 1 SD of the predictor and 2) odds ratio per change in predictor: | | |
| First author | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|--------------|----------------------|-----------------------------------------------|-----------------|--------|-----------------------------------------------|------------|-------------|
| Rerkasem (2015), Thailand [59] | 249(NR) | 24-hour food recall & FFQ in each trimester | LINE-1 and Alu using COBRA | Blood | 20y | % Total methylation, c (pFDR) | Maternal Protein intake | LINE-1: 0.09, p = 0.06<br>2nd trimester: Alu: 0.18, p = 0.46<br>LINe-1: -0.11, p = 0.75 | Sex, BMI, birth weight. |
| Drake (2012), UK [61] | The Motherwell Cohort, 34(NR) | FFQ (early <20w & late pregnancy >20w) | HSD2 (promoter region), exon 1(C) and 1(F) using pyrosequencing | Blood | 40 (1.2y) | Correlations of mean GR exon 1F methylation during late pregnancy | Mean/w: r = 0.48, p = 0.009<br>Fish/w: r = 0.38, p = 0.048<br>Veg/w: r = 0.67, p < 0.001<br>Bread/w: r = -0.49, p = 0.009<br>Potato/w: r = -0.39, p = 0.04 | Sex, BMI, birth weight. |
| Godfrey (2011), UK [56] | PAH 70 (NR) | FFQ (GA 15w) | eNOS, SOD1, IL8, P13KCD, RXRA using pyrosequencing | Cord blood | Birth | Higher methylation of RXRA but not of aNOS was associated with lower maternal CHO intake. Maternal fat and protein intake were not associated with RXRA methylation. No estimates for other nutrients/genes | Maternal selenium & AA at birth: -0.103, p = 0.06<br>Maternal selenium & AA 7 years: -0.137, p = 0.009<br>Maternal vitamin D & AA at birth: -0.05, p = 0.20<br>Maternal vitamin D & AA at 17 years: -0.009, p = 0.82 | Sex, BMI, birth weight. |
| Simpkin (2015), UK [58] | AIRES 1018 (51) | Serum selenium & vitamin D | Infinium Human Methylation450 BeadChip to estimate Horvath epigenetic age | Cord blood & blood | Birth, 7.5y, 17.1y | Correlations between early life dietary intake/nutritional biomarker and age acceleration | Maternal selenium & AA at birth: r = 0.035, p = 0.30<br>Maternal selenium & AA at 7 years: r = -0.010, p = 0.76<br>Maternal selenium & AA at 17 years: r = 0.026, p = 0.43 | Cell-type composition |

**Early life dietary intake/nutritional biomarker**

| Early life dietary intake/nutritional biomarker | Simpkin (2015), UK [58] | AIRES 1018 (51) | Breastfeeding | Infinium Human Methylation450 BeadChip to estimate Horvath epigenetic age | Cord blood & blood | Birth, 7.5y, 17.1y | Correlations between early life dietary intake/nutritional biomarker and age acceleration | Breastfeeding & AA at birth: r = 0.035, p = 0.30<br>Breastfeeding & AA at 7 years: r = -0.010, p = 0.76<br>Breastfeeding & AA at 17 years: r = 0.026, p = 0.43 | Cell-type composition |

| Obermann-Borst (2013), The Netherlands [56] | Asthmatics:100 (45)<br>Controls:100(45) | Breastfeeding | Infinium Human Methylation450 BeadChip to estimate Horvath epigenetic age | Cord blood | 11.6±2y | Breastfeeding was associated with overall DNA methylation, but no statistical test performed | Methylation was increased at a specific CpG sites in HSD2 with increased meat (r = 0.42, p = 0.03) and fish (r = 0.40, p = 0.04) intake in late pregnancy. Other nutrients not measured. | Sex, BMI, birth weight. |
| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|---------------------------------------------|-----------------|--------|---------------------------------------------|------------|-------------|
| Tao (2013), US [65]         | 639 (100) breast cancer cases | Breastfeeding | Early life variable(mean age ± SD (age range) | Breast tumour tissue | 57.5y ±11.3 | OR (95%CI) for methylation breastfed yes(ref) vs no | Age, education, race, oestrogen receptor status |
| Wijnands (2015), UK [98]    | 120 (41.7) Breastfeeding & lipid biomarkers | LEP & TNFα using mass-spectrometry-based method | Blood | 17±2.5m %Absolute methylation change (i.e. methylation change per SD change in biomarker (SE)) | TNFα methylation was not associated with duration of breastfeeding. LEP methylation was significantly associated with duration of breastfeeding: -0.6 (95%CI -1.19, -0.01) per increment in breastfeeding duration category | | |
| Fryer (2011), UK [27]       | 12 (92) Plasma homocysteine (birth) | Infinium Human Methylation27 BeadChip Cord blood Birth | Correlation with LINE-1 methylation: Cord plasma homocysteine: $\beta$ = -0.69, $p = 0.001$ (p = 0.004 following adjustment) | Gerd Blood | Birth | Two clusters were identified in low-energy-unsaturated hierarchical clustering to identify carbohydrate methylation -value across samples. Plasma homocysteine was lower ($p = 0.038$) in cluster B. There was no difference in serum folate (estimates not presented). 298 CpGs associated with plasma homocysteine ($p < 0.05$) | Sex, GA, maternal age, parity, BMI, serum folate and maternal folic acid intake |
| Fryer (2009), UK [39]       | 24 (58.3) Plasma homocysteine & serum folate (birth) | LINE-1 methylation using pyrosequencing | Gerd Blood | Birth | Correlation with LINE-1 methylation: Great placental cone shape: $\beta$ = -0.28, $p = 0.014$ (following adjustment) Cord serum folate: $\beta = 0.34$ | Sea, GA, maternal age, parity, BMI, serum folate and maternal folic acid intake |
| M-S-Kar (2012), UK [9]      | The North Cumbria Community Genetics Project 294 (40) | RRS folate & serum B12 (GA 39.5 ± 1.4w) | Global DNA methylation using UMA1 & IGF2, IGFBP3, ZNT5 using pyrosequencing | Gerd Blood | Birth | Methylation of the IGF2 locus inversely correlated with infant vitamin B12 concentration ($r = -0.16, p = 0.007$) | Sea, GA, infant MTHFR genotype |
| Natile (2009), UK* [81]     | 24 (NR) Homocysteine (birth) | LINE-1 | Gerd Blood | Birth | LINE-1 methylation levels were inversely correlated with cord blood homocysteine ($p = 0.01$), $r = -0.698$ | | |
| Pemg (2010), Columbia [59]  | BGC 506033.7 | Erythrocyte folate, plasma vitamin B12, vitamin A (as an indicator of iron status), serum zinc concentrations (5-12y) | LINE-1 using pyrosequencing | Blood | (5-12y) | LINE-1 methylation (90%CI) & Erythrocyte Foliate (nmol/L), $AD_{P<0.05} = 0.51$, $AD_{P<0.05} = 0.30$, $AD_{P<0.05} = 0.45$, $AD_{P<0.05} = 0.30$ | Sex, vitamin A, CRP, maternal BMI, breastfed socio-economic position |
| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|----------------------------|----------------------|-----------------------------------------------|-----------------|-------|-----------------------------------------------|-------------|-------------|
| Ba (2011), China [93]      | 99 (48)              | B-vitamin biomarkers (96% GAD 37-41w)          | JGF2/2 promoters using methylation-specific PCR | Cord blood | Birth (96% GAD 37-41w) | LINE-1 methylation |  β (95%CI) & serum zinc (umol/L), All p trend = 0.60: |  |
|                           |                      |                                               |                 |       |                                               | Q1: n = 140, ref | Q2: n = 142, 0.014 (-0.14, 0.16) |  |
|                           |                      |                                               |                 |       |                                               | Q3: n = 141, 0.07 (-0.08, 0.23) | Q4: n = 141, 0.02 (-0.14, 0.18) |  |
|                           |                      |                                               |                 |       |                                               | Adjusted: LINE-1 methylation |  β (95%CI) & plasma ferritin (ug/L), All p trend = 0.22: |  |
|                           |                      |                                               |                 |       |                                               | Q1: n = 141, ref | Q2: n = 139, -0.16 (-0.31, -0.01) |  |
|                           |                      |                                               |                 |       |                                               | Q3: n = 143, -0.08 (-0.24, 0.07) | Q4: n = 141, -0.13 (-0.28, 0.03) |  |
|                           |                      |                                               |                 |       |                                               | LINE-1 methylation |  β (95%CI) & plasma vitamin A (umol/L), All p trend = 0.006: |  |
|                           |                      |                                               |                 |       |                                               | Q1: n = 141, ref | Q2: n = 140, 0.014 (-0.14, 0.16) |  |
|                           |                      |                                               |                 |       |                                               | Q3: n = 141, 0.07 (-0.08, 0.23) | Q4: n = 141, 0.02 (-0.14, 0.18) |  |
| Haggarty (2013), UK [81]  | 913 (46)             | RBS folate (GAD: 39.3 (95%CI: 39.4, 39.6w))   | JGF2/4 CpG, PEG3 (7 CpGs), SNRPN (15q11, 4 CpGs) LINE-1 (4 CpGs) using pyrosequencing | Cord blood | Birth | LINE-1 methylation: |  β (95%CI) & cord RBC folate 100 nmol/L: |  |
|                           |                      |                                               |                 |       |                                               | cord blood serum folate: 0.18 (0.07) | cord blood serum vitamin B12: -0.03 (-0.24, 0.10) |  |
|                           |                      |                                               |                 |       |                                               | Adjusted: LINE-1 methylation |  β (95%CI) & blood serum folate 100 nmol/L: |  |
|                           |                      |                                               |                 |       |                                               | cord blood serum folate: -0.03 (0.77) | cord blood serum vitamin B12: -0.04 (0.60) |  |
| Voisin (2015), Greece [99] | Greek Healthy Growth Study, Obese: 35 (68) | 24-hour recall for % energy from fat, cholesterol intake, MUFA/SFA, PUFA/SFA & MUFA/PUF A (10y) | Infinium Human Methylation27 BeadChip | Blood | ~ 10y | The methylation levels of one CpG island shore and four sites were significantly correlated with total fat intake. No significance was found for cholesterol intake. The methylation levels of 2 island shores and 15 island shores were significantly correlated with PUFA/SFA of 9 islands, 26 island shores and 158 sites with MUFA/SFA; 4 island shores and 140 sites with (MUFA+PUFA)/SFA | Top 10 most significant CpG sites/shores (Gene, Coefficient, adjusted p): |  |
|                           | Normal weight: 34 (66) |                                               |                 |       |                                               | GSE1: 0.0135, p = 0.006 | TAMM41: 0.0097, p = 0.006 |  |
|                           |                      |                                               |                 |       |                                               | TSSR11: -0.0118, p = 0.012 | MRR1: 0.0145, p = 0.023 |  |
|                           |                      |                                               |                 |       |                                               | TXNAP: 0.0044, p = 0.0045 | MUFA/SFA |  |
|                           |                      |                                               |                 |       |                                               | ALDH3A2: -0.330, p = 0.0007 | MTLK: -0.259, p = 0.00003 |  |
|                           |                      |                                               |                 |       |                                               | DGCG258625: -0.317, p = 0.00004 | 2H4E2: -3.309, p = 0.00004 |  |
|                           |                      |                                               |                 |       |                                               | KFIFP2: -0.263, p = 0.00004 | DMRMB: -0.205, p = 0.00004 |  |
|                           |                      |                                               |                 |       |                                               | ZMAPN: -0.263, p = 0.00004 | VCAM1: -0.259, p = 0.00008 |  |
|                           |                      |                                               |                 |       |                                               | KRT73: -0.243, p = 0.00004 | KRTCA2: -0.205, p = 0.00004 |  |
| (Continued)                |                      |                                               |                 |       |                                               |                         |                         |  |
Table 2. (Continued)

| First author    | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------|----------------------|----------------------------------------------|-----------------|--------|-----------------------------------------------|------------|-------------|
| De La Rocha     | 49 (52)              | Serum fatty acids                            | Global DNA methylation using total 5-methylcytosine content | Blood | Lactating infant (0.09 ± 0.2d) | Change in N6methyladenosine per one % increase in FA serum C20:4 (arachidonic acid); β = 0.08, p = 0.04 | Age, birth weight, normalised weight gain |
| Lee (2012), US  | 141 (67)             | Serum copper (0.8% G.A.D ± 1.97)             | NFIK, TAF4, MRPL13 using pyrosequencing | Gland blood | Both | Association (95% CI) with serum copper in g/dl in cord blood: NFIK β = 0.13 (0.00,0.26) TAF4 β = -0.10 (-0.22,0.02) MRPL13 β = 0.15 (-0.21,0.50) | Batch effects |
| Famine / Seasonality |                   |                                               |                 |        |                                               |            |             |
| ThoB (2012), The Netherlands [100] |                   | Famine                                       | Infinium Human Methylation 450 BeadChip | Blood | 58.9 ± 5.9 | Famine vs. time-matched controls: METHylation (95%CI) Famine in 1-40 weeks gestation (n = 270) q26928920 (SAMAP98/MEMER (19); 2.34; 5.91; 1.1; 3.3; 1.0; 3.4) p = 0.047 269343980 (XLRGN, ZPINT, BRLA (11); 2.71; 3.73; 1.7; 3.4; 1.8; 3.4) p = 0.0046 277370375 (JLFPC); 2.70; 3.73; 1.7; 3.4; 1.8; 3.4) p = 0.0046 249269706 (SFRG1, BRLA (12); 1.8; 2.8; 1.5; 2.1; 1.5; 2.1) p = 0.0046 218690838 (XLRGN, BRLA (12); 2.1; 3.1; 1.5; 2.1; 1.5; 2.1) p = 0.0046 227780592 (KLF6, BRLA (12); 2.1; 3.1; 1.5; 2.1; 1.5; 2.1) p = 0.0046 222721032 (ZMUG, BRLA (12); 2.1; 3.1; 1.5; 2.1; 1.5; 2.1) p = 0.0046 | Age, sex, batch effects, cell homogeneity, smoking status, current macro nutrient and micro nutrient intake and SEP |
| Fizer (2016), Bangladesh [102] | 143 (60)     | Famine (postnatal exposure 1-2y or exposure during gestation or unexposed) | Infinium Human Methylation 450 BeadChip | Blood | Postnatal exposed: 31 (64) | Comparison of gestational exposure vs non-exposed n = 85 vs unexposed n = 54 16 Meas: 50% FDR Targeted DNA methylation | No differences between groups at 5% FDR Large scale DNA methylation. Methylation differences between groups in 615 ME at p<0.05, driven by gestational exposure group: VTRNA2L-1, PAXA, PRDM4, ZFPM3, ZPINT, A-KAP1L, JXP5, LORAT, PRIPL1, DUSP28, EXT3, PARDEG, ZNF678, ZF3V53 | Cell composition |

(Continued)
Table 2. (Continued)

| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Main age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|-----------------------------------------------|-----------------|--------|-----------------------------------------------|------------|-------------|
| Lumey (2012), The Netherlands [103] | Dutch Hunger Winter 947 (54) (Prenatal:338, Unexposed time controls:296, Unexposed same-sex siblings:97) | Famine | LINE-1 & Sat-2 using pyrosequencing | Blood | Prenatal exposure group: 58.9 ± 0.5y Unexposed time controls: 58.5 ± 0.5y, Unexposed same-sex siblings: 57.3 ± 0.6y | Changes in DNA methylation (Spearman's r in exposed vs. all non-exposed). Global methylation: Mean % (SD): 75.2% (4.7) 95% CI: -0.15 (-0.49, 0.81), p = 0.63 LINE-1 methylation % (SD): Mean % (SD): 77.1% (2.5) B (95% CI): -0.05 (-0.33, 0.22), p = 0.70 Sat2 methylation % (SD): Mean % (SD): 122.2% (56.2) B (95% CI): -0.51 (-7.38, 6.36), p = 0.88 | Age, within family clustering |
| Heijmans (2008), The Netherlands [104] | Dutch Hunger Winter 244 (~54) (periconceptional:60, late gestation: 62, Unexposed same-sex sibling:122) | Famine | JGB2 DMR (5 CpGs) using mass spectrometry-based method | Blood | Periconceptional group: 58.1 ± 0.35y Late gestation group: 58.8 ± 0.4y Controls: 57.1 ± 5.5y | Mean (SD) methylation in those periconceptionally exposed to famine vs. non-exposed siblings: Average: 0.488 (0.047) vs. 0.515 (0.055), p = 5.9x10^-5. CpG1: 0.436 (0.037) vs. 0.470 (0.041), p = 1.5x10^-4, CpG2 and 3: 0.451 (0.033) vs. 0.473 (0.055), p = 8.1x10^-3, CpG4: 0.577 (0.114) vs. 0.591 (0.112), p = 0.41, CpG5: 0.491 (0.061) vs. 0.529 (0.068), p = 1.4x10^-5. No difference in methylation of IGF2 DMR between a subset exposed in late gestation and unexposed siblings | Age and family relations |
| Tobi (2014), The Netherlands [105] | Dutch Hunger Winter 48 (50) Famine (early gestation) | Famine (early gestation) | 1.2M CpGs using RRBS | Blood | Genomic annotation-centred analysis of differential methylation after famine (vs. unexposed siblings), p< FDR. Non-CGI, ‘bona fide’ promoters: 0.026 Enhancers: 0.026 DNaseI/FAIRE-seq regions: 0.036 Middle exons: 0.036 Developmental enhancer type I: 0.036 ‘Bonafide’ CGI shores: 0.053 Non-coding RNA: 0.053 Conserved regions: 0.053 CGI shores: 0.053 3’UTR: 0.085 Non genic CGI: 0.085 ‘Bonafide’ CGI border: 0.085 Developmental enhancer type II: 0.15 CGI: 0.15 Intromer 0.15 MESC bound chromatin domain: 0.28 ‘Bonafide’ CGI: 0.32 CGI type specific gene promoters: 0.32 First exons: 0.36 Promoters: 0.36 H3K27me3 bound chromatin domain: 0.36 Imprinted promoter 0.36 ‘Bonafide’ CGI promoter: 0.37 CTCF insulations from MCM4+ cells: 0.37 Imprinted DHS: 0.37 Positive methylatable epialleles: 0.47 Vastly methylated regions: 0.57 Promoters cancer genes: 0.63 Within the 5 annotations found to be significant, 181 DMRs were associated with prenatal famine (p< FDR, < 0.05). | Family relatedness, bisulfite batch, age |
| Tobi (2009), the Netherlands [106] | Dutch Hunger Winter 244 (~54) (periconceptional:60, late gestation: 62, Unexposed same-sex siblings:97) | Famine | GNASAS, GNAS A/B, MEG3, KCNQ1OT1, INSIGF and GAB1-10, IKG2R, IL10, TNF, ARCA1, AP027340, LEP, ARCC1 and GSTF using mass spectrometry-based method | Blood | Periconceptional group: 58.1 ± 0.35y Late gestation group: 58.8 ± 0.4y Controls: 57.1 ± 5.5y | Within-pair differences divided vs sibling controls, p< FDR. Genomic annotation control analysis of differential methylation after famine (vs. unexposed siblings). p< FDR. GNASAS: 0.24, 3.1x10^-6. MEG3: 0.21, 8.4x10^-3 (non-significant after Bonferroni correction) IKG2R: 0.37, 1.8x10^-4 ARCA1: 0.21, 8.4x10^-4 LEP: 0.24, 2.9x10^-3 INSIGF: 0.64, 2.3x10^-3 No significant for all other loci Late gestation exposure No associations except for reduction in GNASAS: 0.26, 1.1x10^-5 | Family relatedness, bisulfite batch, age |
| First author (year), country | Cohort, N (% female) | Early life variable/mean age ± SD (age range) | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|-----------------------------|----------------------|---------------------------------------------|-----------------|---------|---------------------------------------------|------------|------------|
| Veenendaal (2012), The Netherlands [107] | Dutch Hunger Winter 759 (54%) | Periconceptional death, late gestation 62, unexposed same-sex sibling 122 | Fetal | Blood | 58.1 ± 1y | Methylation differences % (95%CI) for exposed vs. unexposed; Late gestation: | |  |
| | | | | | | GR: 0.60 (-16.39, 21.05) | | |  |
| | | | | | | LPL: 11.01 (-5.55, 30.54) | | |  |
| | | | | | | FSH: 0.13 (42.25, 95.03) | | |  |
| | | | | | | PPARγ: -0.37 (-14.53, 12.32) | | |  |
| | | | | | | LPL: 0.14 (42.25, 95.03) | | |  |
| | | | | | | | Mid-gestation: | |  |
| | | | | | | GR: 0.14 (42.25, 95.03) | | |  |
| | | | | | | LPL: 0.14 (42.25, 95.03) | | |  |
| | | | | | | | FSH: 0.13 (42.25, 95.03) | | |  |
| | | | | | | | PPARγ: -0.37 (-14.53, 12.32) | | |  |
| | | | | | | | Late gestation: | |  |
| | | | | | | GR: 0.14 (42.25, 95.03) | | |  |
| | | | | | | LPL: 0.14 (42.25, 95.03) | | |  |
| | | | | | | | FSH: 0.13 (42.25, 95.03) | | |  |
| | | | | | | | PPARγ: -0.37 (-14.53, 12.32) | | |  |
| | | | | | | | No significant associations were found | | |
| Waterland (2010), The Gambia [108] | The Keneba cohort 50 (50%) | Conceived in rainy season 25, conceived in dry season 25 | Fetal | Blood | Conceived in rainy season: 6.61 ± 2.73y | DNA methylation was significantly higher among individuals conceived during the rainy season (i.e., hungry season): | |  |
| | | | | | | BOLA3: p = 0.03 | |  |
| | | | | | | FLJ20433: p = 0.03 | |  |
| | | | | | | PAX8: p = 0.02 | |  |
| | | | | | | SLOTRK1: p = 0.006 | |  |
| | | | | | | ZFYVE28: p = 0.002 | |  |
| | | | | | | Overall p = 0.0001 | |  |
| | | | | | | All 5 MEs DNA methylation was significantly higher among individuals conceived during the rainy season (i.e., hungry season): | | |
| | | | | | | BOLA3 | p = 0.03 |  |
| | | | | | | FLJ20433 | p = 0.03 |  |
| | | | | | | PAX8 | p = 0.02 |  |
| | | | | | | SLOTRK1 | p = 0.006 |  |
| | | | | | | ZFYVE28 | p = 0.002 |  |
| | | | | | | Overall p = 0.0001 | |  |

*Studies spanning more than one exposure may appear twice in the table;*

**Abstract**

A: Age acceleration; ARIES: Accessible Resource for Integrated Epigenomic Study; BMI: Body Mass Index; BSCC: Bogotá School Children Cohort; CHO: Carbohydrate; CI: Confidence Interval; CBMCs: Cord Blood Mononuclear Cells; COBRA: Combined Bisulfite Restriction Analysis; D: Days; DMR: Differentially Methylated Region; DA: Dizygotic; FDR: False discovery rate; FFQ: Food frequency Questionnaire; GAD: Gestational Age at Delivery; HUVEC: Human Umbilical Vein Endothelial Cells; LUMA: Luminometric methylat ion assay); M: Months; MANO: Maternal Nutrition and Offspring’s Epigenome Study; MoBA: Norwegian Moher and Child Cohort Study; MUFA: Monounsaturated fatty acid; MZ: Monozygotic; NEST: Newborn Epigenetics Study; NR: Not Reported; OR: Odds Ratio; PAH: Princess Anne Hospital Study; PETS: Peri/postnatal Epigenetic Twins Study; PUFA: Polyunsaturated fatty acid; RBC: Red Blood Cell; SD: Standard Deviation; SE: Standard Error; SEP: Socioeconomic Position; SFA: Saturated Fatty Acid; THREE: Tracking Health Related to Environmental Exposures Study; W: Weeks; Y: Year

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Table 3. Socioeconomic position in early life and epigenetics. (Organised by exposure, DNA methylation (epigenome wide, global methylation, imprinted genes, other genes).

| Cohort, N (% female) | Early life variable | DNA methylation | Time | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|----------------------|---------------------|------------------|------|-----------------------------------------------|-------------|-------------|
| Simpkin (2015), UK [58] | ARIES 1018 (51) | Maternal education | Infinium Human Methylation 450 BeadChip to estimate Horvath epigenetic age | Cord blood & blood | Both, 7y, 17y | ANOVA F-statistic & p for early life variable and age acceleration: Maternal education & AA at birth: 0.55, p = 0.70 Maternal education & AA at 7 years: 0.37, p = 0.83 Maternal education & AA at 17 years: 1.40, p = 0.23 Longitudinal analysis of maternal education & AA: Average AA during childhood: CSE: ref Voc: -0.30 (-1.84, 1.23) O-level: -0.24 (-1.56, 1.08) A-level: -0.38 (-1.69, 0.93) Degree: -0.51 (-1.87, 0.85) p = 0.76 Longitudinal analysis of maternal education & AA changes: A:A during childhood: CSE: ref Voc: 0 (0.0, 0.0) O-level: 0.00 (0.07, 0.15) A-level: 0.30 (0.05, 0.17) Degree: 0.10 (0.01, 0.22) p = 0.18 | Cell-type proportions |
| Herbstman (2015), US [27] | CCCEH 279 (53.6) | Maternal education & maternal hardship (last trimester of pregnancy) | Global methylation using Methylamp Global DNA Methylation Quantification Kit | Cord blood & blood | Birth & ~3y | Maternal education & cord blood global methylation: high school vs no high school: β = 0.10 (-0.29, 0.50) Higher education vs no high school: β = 0.09 (-0.33, 0.51) Maternal hardship (yes vs no) & cord blood global methylation: β = 0.09 (-0.23, 0.42) Maternal education & 3y blood global methylation: high school vs no high school: β = 0.03 (-0.41, 0.48) Higher education vs no high school: β = -0.28 (-0.80, 0.23) Material hardship (yes vs no) & 3y global methylation: β = -0.19 (-0.58, 0.42) | GA, ploidy, maternal height, pre-pregnancy BMI, maternal age at delivery, ethnicity, race, public assistance, total polycyclic aromatic hydrocarbons and environmental tobacco smoke |
| Perng (2012), Columbia [50] | BSCC 568 (53.7) | Maternal education, household socioeconomic stratum | LINE-1 using pyrosequencing | Blood | (5-12y) | Maternal education (university): All: 80.39 (0.70), p_trend = 0.34 Males: 80.71 (0.56), p_trend = 0.06 Females: 80.13 (0.72), p_trend = 0.78 Household socioeconomic stratum: All: 1(lowest): 80.35 (0.49) 2: 80.20 (0.67) 3: 80.21 (0.64) 4(highest): 80.62 (0.71) p_trend = 0.15 Males: 1(lowest): 80.40 (0.55) 2: 80.35 (0.68) 3: 80.32 (0.64) 4(highest): 80.62 (0.61) p_trend = 0.30 Females: 1(lowest): 80.29 (0.38) 2: 80.10 (0.63) 3: 80.13 (0.64) 4(highest): 80.62 (0.89) p_trend = 0.27 | | (Continued) |
Table 3. (Continued)

| Cohort, N (% female) | Early life variable | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|----------------------|---------------------|-----------------|--------|-----------------------------------------------|-------------|-------------|
| Tehranifar (2013), US [113] | New York Women’s birth cohort, 90 (100) | Mother’s education, family income at birth | Sat2, Alu, LINE-1 using MethyLight | Blood | 3.8-46y | Univariate analysis, methylation mean (95% CI) |
|                |                    |                  |        |                                               |                           | Age, prenatal smoking, birth order, adult education, adult occupation |
| Tehanifar (2013), US [113] | New York Women’s birth cohort, 90 (100) | Mother’s education, family income at birth | Sat2, Alu, LINE-1 using MethyLight | Blood | 3.8-46y | Univariate analysis, methylation mean (95% CI) |
|                |                    |                  |        |                                               |                           | Age, prenatal smoking, birth order, adult education, adult occupation |
| King (2015), US [114] | NEST, 619 (NR) | Maternal education & income | DMR in IGF2, H19, MEG3, NNAT using pyrosequencing | Cord blood | β | Maternal education, unstandardized β, p = 16y |
|                |                    |                  |        |                                               |                           | IGF2: 1-12y: -1.58, p < 0.05 |
|                |                    |                  |        |                                               |                           | 13-15y: -2.10, p < 0.05 |
|                |                    |                  |        |                                               |                           | 17+y: -1.74, p < 0.05 |
|                |                    |                  |        |                                               |                           | H19: 1-12y: -1.46, NS |
|                |                    |                  |        |                                               |                           | 13-15y: -0.45, NS |
|                |                    |                  |        |                                               |                           | 17+y: -0.57, NS |
|                |                    |                  |        |                                               |                           | MEG: 1-12y: 0.53, NS |
|                |                    |                  |        |                                               |                           | 13-15y: -0.05, NS |
|                |                    |                  |        |                                               |                           | 17+y: -0.70, NS |
|                |                    |                  |        |                                               |                           | NNAT: 1-12y: -1.27, NS |
|                |                    |                  |        |                                               |                           | 13-15y: -1.13, NS |
|                |                    |                  |        |                                               |                           | 17+y: -0.28, NS |
|                |                    |                  |        |                                               |                           | Household income, unstandardized β, p = 16y |
|                |                    |                  |        |                                               |                           | IGF2: $25k: -1.19, NS |
|                |                    |                  |        |                                               |                           | $25-$50k: -1.87, p < 0.05 |
|                |                    |                  |        |                                               |                           | $50-$100k: -0.89, NS |
|                |                    |                  |        |                                               |                           | H19: $25k: -1.07, NS |
|                |                    |                  |        |                                               |                           | $25-$50k: -1.10, NS |
|                |                    |                  |        |                                               |                           | $50-$100k: -0.69, NS |
|                |                    |                  |        |                                               |                           | MEG: $25k: -0.94, NS |
|                |                    |                  |        |                                               |                           | $25-$50k: -0.85, NS |
|                |                    |                  |        |                                               |                           | $50-$100k: -0.48, NS |
|                |                    |                  |        |                                               |                           | NNAT: $25k: 0.37, NS |
|                |                    |                  |        |                                               |                           | $25-$50k: 0.69, NS |
|                |                    |                  |        |                                               |                           | $50-$100k: 1.78, NS |

Obermaier-Borst (2012), The Netherlands [115] | HAVEN 120 (42) | Maternal education | JGP2, JMR, JG2R, INSRG using PCR | Blood | 17±2.5m | JSE1Unchange in methylation in multiple mixed model |

|                |                    |                  |        |                                               |                           | JG22 DMR: -0.030/0.59, p = 0.71 |
|                |                    |                  |        |                                               |                           | JG2R: 2.15, p = 0.11 |
|                |                    |                  |        |                                               |                           | INSRG: 1.40/9.1, p = 0.02 |

Correlation between individual CpG dinucleotides, bisulfite bands, smoking.
Table 3. (Continued)

| Study                  | Cohort, N (% female) | Early life variable | DNA methylation | Tissue | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|------------------------|----------------------|---------------------|-----------------|--------|-------------------------------------------------|-------------|-------------|
| Soubry (2011), US [38] | NEST, 436 (47.5)     | Maternal education  | IGF2 DMR (3 CpGs) and H19 DMR (4 CpGs) using pyrosequencing | Cord blood | Both | Mean methylation %SD, difference (p) | IGFBP2, College yes: 46.99 (6.61), College no: 47.72 (7.04), Δ: -0.73 (0.34) |
|                       |                      |                     |                 |        |                                                 |             | IGFBP2, College no: 58.00 (7.49) |
| Obermann-Borst (2013), The Netherlands [64] | 120 (62) | Maternal education | LEP using mass-spectrometry based method | Blood | Both | % Absolute change (SE) & % Relative methylation change (SE) from linear mixed model | Model 1: Low education: 2.10 (0.8); 7.15 (3.5), p = 0.008; Model 2: Low education: 1.01 (0.8); 6.42 (3.4), p = 0.23 |
|                       |                      |                     |                 |        |                                                 |             | Correlation between individual CpG dinucleotides, bisulfite batch, GA |
| Wijnands (2015), UK [9] | 120 (42) | Mother’s education | LEP & TNFα using mass-spectrometry based method | Blood | Both | Percentage change | Race, smoking, mother’s smoking during pregnancy |
| Mulligan (2012), Democratic Republic of Congo [98] | 25 (NR) | Maternal deprivation | NR3CI (39 CpGs) using PCR | Cord blood | Birth | First PC of % methylation of 39 CpG sites explained 16.15% of variance & correlated with maternal deprivation r = 0.44, p = 0.03 |
| Agha (2014), US [116] | New England Family Study birth cohort, 106 (64) | Parental SEI | Infinium Human Methylation 450 BeadChip | Subcutaneous adipose tissue & peripheral blood leukocytes | 44-50y | Adipose tissue | Parental SEI was associated with DNA methylation in women (p < 0.001), but not men or the pooled sample. |
| Terry (2008), US [60] | Family SES (measured by parental education and income at birth and 7y) | Global DNA methylation using (3H)-methyl acceptance assay | Blood | Both | Multivariate linear regression DPM/μg (95% CI) for association between DNA methylation by variables | Family SES: -0.01 (-0.01,0.002) |
| Beach (2016), US [117] | Preadolescent cumulative SEP risk (11.7y) | Infinium Human Methylation 450 BeadChip | Blood | Both | 28,640 loci were associated at the p < 0.01 level of significance, with 2,032 loci associated at FDR < 0.05. No specific loci presented | Sex, age |
| Lam (2012), Canada [118] | Early Life SES | Infinium Human Methylation 27 BeadChip | Blood | Both | 3 differentially methylated CpG sites (<1% change were found among low SES n = 46) with high SES (n = 46). 134 loci exhibited 0% variance explained by SES. |
| Borghol (2011), UK [119] | 1958 British Birth cohort: 40(0) | Cumulative SEP Index | Genome-wide methylation (MeDIP) | Blood | 45y | 1252 gene promoters associated with childhood SEP were identified |
| Subramanyam (2013), US [120] | MESA 988 (52) | Childhood SES | LINE-1 and Alu using pyrosequencing | Blood | 44 y | Mean difference (SD) in DNA methylation percentage change in exposure low, medium, high | LINE-1: 0.004 (0.00); p = 0.05; Alu: 0.012 (0.02), p = 0.05 |

(Continued)
| Cohort, N (% female) | Early life variable | DNA methylation | Time | Mean age at epigenetic measure ± SD (age range) | Main result | Confounders |
|----------------------|---------------------|-----------------|------|-----------------------------------------------|-------------|-------------|
| Beach (2014), US [121] 388 (55) | Preadolescent cumulative SEP risk | SLAGA 4 (1.6CpGs) measured using Infinium Human Methylation 450 BeadChip | Blood | 19.3y | From two-way ANOVA, as indicated significant after multiple testing: cg12074493 p = 0.588 cg03618106 p = 0.198 cg17024495 p = 0.494 cg27563022 p = 0.816 cg10941969 p = 0.243 cg26731280 p = 0.138 cg26729866 p = 0.500 cg09016953 p = 0.922 cg18925774 p = 0.001 ** cg10363743 p = 0.22 cg21094318 p = 0.502 cg05914817 p = 0.555 cg26731280 p = 0.138 cg03618106 p = 0.032 cg18925774 p = 0.001 ** cg09016953 p = 0.608 |

** * Abstract; AA: Age acceleration; ARIES: Accessible Resource for Integrated Epigenomic Study; BSCC: Bogotá School Children Cohort; CCCEH: The Northern Manhattan Mothers and Newborns Study of the Columbia Center for Children's Environmental Health; DMR: Differentially Methylated Region; DPM: Disintegrations Per Minute; M: Months; MeDIP: Methylated DNA Immunoprecipitation; MESA: The Multi-Ethnic Study of Atherosclerosis; NEST: Newborn Epigenetics Study; NR: Not reported; PC: Principle Component; SEI: Socioeconomic Index; SEP: Socioeconomic Position; SES: Socioeconomic Status; Y: Years

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In relation to non-imprinted genes, birth weight was found to be associated with methylation at HSD2, but not GR (both related to glucocorticoid) in blood samples of 34 participants aged 40 years [61] while another study found it not to be associated with methylation at the LEP gene in blood among infants aged ~17 months once confounders were taken into account [64].

Among the papers comparing extreme groups, one found no genome-wide differences in DNA methylation in adipose derived stem cells between 13 low birth weight (LBW) babies and controls [56]. Another found some evidence for a difference in methylation in specific CpG sites of IGF2 in blood between 158 very LBW (≤1500g) with controls [63]. The third paper found that methylation at two out of three CpG sites in ACE (angiotensin-converting enzyme, a gene related to cardiovascular disease) was lower among LBW children (6-12y) compared with normal birth weight children [79].

Childhood body size and growth: Using data from the ARIES cohort weak, associations between taller height at 7 years and epigenetic age acceleration at 7 and 17 years (p = 0.06, p = 0.07) were observed. However, no associations were seen with BMI [58].

Two papers examined growth in early life in relation to DNA methylation [59, 67]. In one, catch up growth during the first year of life was associated with Alu but not LINE-1 methylation measured in blood at 20 years [59]. In the other, those defined as rapid growers between term and 12 weeks had higher methylation at TACSTD2 (associated with adiposity) at 12 years compared with slow growers. This was not replicated in ALSPAC where methylation was measured at 7 years [67].

Cross-sectional studies of body size and growth in early life and DNA methylation.

Most (n = 28) of the cross-sectional papers investigated the association between birth weight and cord blood DNA methylation (Table 1). Five included birth length/head circumference/crown heel length [27, 43, 80–82], one body composition at birth [82], and six childhood height/weight [49, 50, 52–54, 83].

Birth weight: Five papers examined birth weight and cord blood genome-wide methylation measured using the Illumina Human-Methylation450 or Human-Methylation27 BeadChip array [21, 22, 24, 25, 55]. In a Norwegian study, birth weight was associated with methylation at 19 CpG sites including CpGs on the ARID5B and XRCC3 genes which are related to adipogenesis and DNA repair respectively [21]. Birth weight percentile also related to methylation in three genes of which one, FGFR2 (involved in metabolic regulation) replicated in a cohort of 110 participants [22]. Fryer et al. observed 304 CpG sites to be associated with birth weight percentile in 12 newborns [25]. However no genome-wide significance between birth weight and cord blood methylation was found among 201 participants of another study [24]. Using a different microarray technique, Lee et al. found birth weight to be associated with differentially methylated regions (DMRs) near three genes involved in early development (NFIX, RAPGEF2, MSRB3) [26].

Six papers examined markers of global methylation in cord blood [27–30, 32, 84]. There was no evidence for an association between birth weight and cord blood global methylation measured using Methylamp, LUMA, LINE-1 or Alu in most papers [27, 28, 32, 84]. One paper observed an association (p = 0.05) between lower birth weight and higher cord blood LINE-1 methylation [29] while others found that LINE-1 methylation was slightly lower among newborns with high birth weight compared with normal weight [30].

The remaining papers examined cord blood methylation in candidate genes with the majority focused on imprinted genes. Five reported associations with cord blood methylation at imprinted genes in the Newborn Epigenetics Study (NEST) [35–38, 40]. Most did not demonstrate an association between birth weight and IGF2 methylation [35, 36, 38]. However, one observed a lower methylation at IGF2 DMRs among low birth weight compared with normal
weight newborns (p = 0.06) [37]. There was a significant relationship between birth weight and methylation at PEG10 and/or PLAGL1 in three NEST papers [35, 37, 40]. Findings for H19 methylation were inconsistent [35, 36, 38]. In another study, methylation at IGF2 was lower in high birth weight newborns compared with normal birth weight groups [39]. There was no correlation between birth weight and methylation at the ZAC1 DMR [43] or with methylation of IGF2, H19, PEG3, SNRPN [29, 32].

In the papers investigating non-imprinted genes, birth weight was not associated with methylation in genes related to the glucocorticoid receptor [32, 46]. A follow on study from the paper by Fryer et al. [25], found that increased cord blood methylation at GSTM5 and MAP2K3 was associated with a reduced risk of a lower birth weight percentile while higher methylation levels in APOB were associated with an increased risk [45]. Birth weight was also associated with AHRR (involved in cell growth and differentiation), HIF3A (obesity-associated gene) and LEP (appetite-related) methylation [44, 47, 48].

Among the papers comparing extreme groups, Qian et al. did see differences in the methylation of H19, but not MEST, in cord blood between 39 small–for-GA (SGA) versus average-for-GA (AGA) babies [34]. Similarly, Zhang et al. found methylation at H19 DMR in blood to be different between AGA, SGA and large-for-GA infants [41].

Other body size measures at birth: There was no evidence for an association between birth length, ponderal index, head circumference, crown heel length and global cord blood methylation [27–29, 43, 47] at imprinted genes [29, 43] or HIF3A [47].

Among 991 participants of Chinese, Malay or Indian ethnicity, subscapular skinfold thickness and subscapular:triceps skinfold thickness increased with increasing methylation at 2 CpG sites in HIF3A [47].

Childhood height/weight: In school age children (5-12y) in Columbia (n = 568), there was no association between global blood DNA methylation and height-for-age z-score [50]. Methylation in 4 out of 8 CpG sites at the P2 promoter region of IGF1 was inversely correlated with height in both a discovery and replication cohort [52]. There was no difference in the methylation of H19 DMR comparing overweight versus lean boys or girls aged ~8 years [53]. Among 64 African-American children (5-6y), there was a weak association between lower BMI percentiles and higher saliva methylation in DNMT3B, but no relationships with other obesity-related genes (FTO, MAOA, SH2B1, LEPR, BDNF or CCKAR) [54]. Ouni et al. identified differentially methylated CpG sites in IGF promoters between 94 children (~10y) with idiopathic short structure compared to children of normal height [51].

TWIN-studies of body size and growth in early life and DNA methylation. All twin studies examined birth-weight discordance [68–76]. There were no genome-wide DNAm differences between birth weight-discordant monozygotic (MZ) twins in blood from adults in two papers [68, 69], or using saliva samples from 15 year olds in another [71]. In twin participants aged 22–45 years, although 45 differentially methylated CpGs were identified using saliva samples, there was no difference in the methylation of repetitive elements [75]. In TwinsUK, one CpG of IGF1 was associated with birth weight discordance [70] while there was a 13% average difference in methylation of COMT (implicated in psychiatric disorders) between MZ twins at 5 years [76].

**Nutrition in early life**

Thirty seven papers included in this systematic review examined the role of nutrition in early life (Table 2). The majority of these studies (37%, n = 14) investigated maternal nutrition during pregnancy as a proxy for fetal nutrition. Nine studies examined nutrition in early life and six studies looked at both maternal pregnancy and early life nutrition. We also included eight
studies that examined the impact of gestational exposure to famine or periods of restricted dietary intake.

**Maternal nutrition during pregnancy and offspring DNA methylation.** Most papers focused on the nutrients involved in one-carbon metabolism i.e. folate, vitamin B6, vitamin B12, methionine, choline, and betaine given their role as methyl donors [14].

Nutrition-related methyl donor intake and/or supplementation: Joubert et al. identified 443 CpG sites, measured on the Illumina Human-Methylation450 BeadChip, that were differentially methylated in cord blood in relation to maternal plasma folate [85]. No association was observed in three of the four papers which examined maternal nutrition-related methyl donor intake/folic acid supplementation in relation with infant cord blood global DNA methylation [81, 86–88]. The forth paper found an inverse association between folic acid supplementation after 12 weeks gestation and LINE-1 methylation [81].

Six papers examined imprinted genes. Hoyo et al. found no differences in cord blood IGF2 methylation among infants born to women taking moderate to high (≥400 μg/d) folic acid supplements before or during pregnancy compared to non-users, however H19 methylation was reduced [90]. While Loke et al. also observed a reduction in infant’s H19 methylation, they found an increase in one IGF2 DMR (DMR2) across different tissues for mothers taking folic acid [91]. Another paper found that methylation at ZAC1 was positively correlated with maternal intakes of vitamin B2 prior to pregnancy, however no association was observed for any other B-vitamin intake or folic acid supplement [64].

Two papers considered the effect at other candidate genes. In one, a difference in cord blood methylation at LEP, RXRA and/or DNMT1 was observed for the intake of certain methyl donors [87]. However there was no association between maternal folic acid supplementation and blood LEP methylation among 17 month old infants in the other [64].

Nutrition-related methyl donor biomarker: In the paper by Haggarty et al., maternal red blood cell (RBC) folate was inversely associated with LINE-1 methylation [81]. Similarly, another paper observed that maternal serum markers of vitamin B12 were correlated with cord blood global DNA methylation [89]. Results from four papers examining maternal methyl donor biomarkers in relation to offspring’s cord blood methylation at imprinted genes were inconsistent [35, 93, 94]. In the Gambian Keneba cohort, serum vitamin B2, vitamin B6, homocysteine, and cysteine were associated with methylation at the combined metastable epialleles (MEs i.e. alleles that are variably expressed in genetically identical individuals due to epigenetic modifications [109])) [95].

Other nutrient intake/biomarker: Four papers investigated the effect of maternal intake of other nutrients. One found no association of maternal intake of protein, fat or carbohydrate with LINE-1 or Alu methylation [59]. Findings from the Motherwell cohort suggest that higher maternal intake of meat/fish and vegetable and lower intake of bread/potato in late pregnancy is associated with methylation at HSD2 and GR in adult offspring blood [61], while another observed that lower maternal carbohydrate intake, but not fat or protein, was associated with higher cord blood methylation of RXRA but not of eNOS [96]. Finally, Simpkin et al. observed an association with maternal serum selenium, but not vitamin D, in children ages 7 and 17 years [58].

**Early life nutrition and offspring DNA methylation.** Breastfeeding: Five papers examined the impact of breastfeeding on DNA methylation. In Simpkin et al’s epigenetic age paper there was no correlation with breastfeeding duration [58]. In secondary analyses in another paper there was an implied association between breastfeeding and DNA methylation at approximately 11 years as measured on the Illumina Human-Methylation27 BeadChip, however no statistical test was performed [97]. In two papers using the same sample of 17 month
old infants, there was a reduction in blood methylation of LEP with increasing duration of breastfeeding [64, 98]. A correlation between breastfeeding and methylation of a cancer-related gene, CDKN2A, in tumour tissues among premenopausal but not postmenopausal women was observed in the final paper [65].

Nutrition-related methyl donor biomarker: Seven papers examined the role of early life nutrition-related methyl donor biomarkers [25, 31, 50, 81, 88, 89, 93]. Across three cross-sectional papers, plasma homocysteine concentrations were negatively correlated with cord blood LINE-1 methylation or were different between two clusters defined by unsupervised hierarchical clustering using data from the Illumina Human-Methylation27 BeadChip [25, 31, 88]. In the Haggarty et al. paper described above, authors also observed that RBC folate in cord blood was associated with cord blood LINE-1, and methylation in IGF2, PEG-3 but not SNRPN [81]. However, serum folate/plasma B12 was not cross-sectionally associated with cord blood LINE-1 methylation or blood samples of 5–12 year olds in two studies [50, 88]. While a negative cross-sectional correlation between serum B12 and IGF2 cord blood methylation was observed in one study [89], this was not replicated by Ba et al, who also found no correlation with folate [93].

Other nutrient intake/biomarker: One paper found that fatty acid intake was associated with methylation levels in children’s blood as measured by from Illumina Human-Methylation27 BeadChip [99]. Another observed an association between HDL-cholesterol, but not LDL-cholesterol, and blood methylation at LEP and TNFα among young children. However this was attenuated after Bonferroni correction [98].

Two cross-sectional studies examined the effect of other early life nutrient biomarkers. One observed an association with arachidonic acid and eicosapentaenoic acid, but not other fatty acids in lactating infants global blood methylation [100]. The other paper reported an association between serum copper and NFIX but not FAPGE or MSRB3 cord blood methylation [26].

Famine/rainy season exposure and offspring DNA methylation. The Dutch Hunger Winter, which lasted from September 1944 to May 1945, was the setting for 75% of the famine papers [104, 106, 107, 110–112]. In these papers DNA methylation was measured in blood samples of adults with mean age of 59 (0.5 SD) years who were exposed to famine at some point during gestation and compared with time and/or family matched controls. Using the Illumina Human-Methylation450 BeadChip, famine exposure during gestational weeks 1–10, but not later, was associated with differences in DNA methylation [105]. This time-sensitive association was also seen for IGF2 methylation [104], and in an investigation of 15 candidate genes that are involved in metabolism, CVD and growth [106]. However, one study did not find an association between famine exposure at any point in gestation and DNA methylation at genes involved in stress response, developmental process and lipid metabolism [107].

Two papers were from other settings. In a sample of children in rural Gambia, methylation at MEs was higher among children conceived during the rainy season (i.e. “hungry” period) compared with those conceived in the dry season [108]. In Bangladeshi young adults no genome-wide differences in methylation was observed between those postnatally exposed to famine, exposed during gestation or unexposed [102]. However, a difference in methylation at MEs between those exposed to famine during gestation compared to the other groups was found [102].

Socioeconomic position in early life

17 papers investigated the association between markers of SEP and DNA methylation (Table 3).
Maternal education: There was no association between maternal education and epigenetic age acceleration in the Simpkin et al paper [58] and no association with global methylation in two other papers [27, 50]. Tehranifar et al. found no association with LINE-1 or Alu methylation, but did observe higher blood Sat2 methylation among adults who’s mother’s had lower education compared with those whose mothers had at least a high school education [113]. Although one study found that maternal education was associated with cord blood IGF2 methylation, but not with other imprinted genes [114], two other papers did not observe an association with IGF2 methylation [38, 115]. However, in one of these papers an increase in H19 methylation in cord blood of those with mothers who did not have a college education was reported [38].

In three papers using the same sample of 120 children aged 17 months, maternal education was correlated with INSDGF but not with LEP or TNFα blood methylation [64, 115, 122].

Other markers of SEP: No association was observed between family SEP measured by parental education and income at birth and 7 years, and blood measures of global DNA methylation in adults [60]. In a Columbian cohort of children aged 5–12 years, household socioeconomic stratum was not associated with blood LINE-1 methylation [50]. King et al. found that household income was associated with methylation at MEG3 in cord blood, but not with other imprinted genes [114]. Results from a peer-reviewed abstract suggested that parental SEP was associated with DNA methylation in adipose tissue, but not blood of adult women as measured by Illumina Human-Methylation450 BeadChip [116].

Two papers using the same sample found preadolescent cumulative SEP risk (measured by family poverty, primary caregiver education, primary caregiver unemployment, single-parent family, receipt of assistance, and income) to be related to 2,032 loci at false discovery rate (FDR) <0.05 using data from the Illumina Human-Methylation450 BeadChip [117] and to specific CpG sites in SLC6A4 [121].

Lam et al. used the Illumina Human-Methylation27 BeadChip to find three differentially methylated CpGs between adults with low early life SEP as defined by their parents occupation compared with high SEP [118]. Similarly, using a genome-wide approach, Borghol et al. found that childhood SEP as measured by father’s occupation and access to household amenities, was associated with methylation at 1,252 gene promoters in blood measures of 45 year old adults [123]. In the multi-ethnic study of atherosclerosis study, there was no evidence for an association between childhood SEP and LINE-1 and Alu blood methylation in adulthood [120].

Discussion

This systematic review identified 90 papers that examined the relationship between body size, nutrition and/or SEP in early life with epigenetic markers measured at the same time or after the exposure. DNAm was the epigenetic marker used in all of the included studies. There was no strong evidence for a consistent association between these early life variables and DNAm. This may be due to the heterogeneous study designs, data collection methods and statistical analyses. Despite these inconclusive results, the hypothesis that the early life environment can impact DNAm, potentially persisting into adult life, was supported by some studies and war- rants further investigation.

There has been one previous non-systematic review examining the impact of body size, and/or nutrition and SEP on DNAm [15] and one systematic review examining the effect of breastfeeding [16]. Our search strategy was designed to be sensitive; therefore we captured a large number of initial papers and included substantially more papers than the previous reviews. We limited results to articles published in English which may have excluded relevant non-English language papers There were slight differences in the papers included in our
systematic review compared with previous reviews. For instance, Demetriou et al. included RCTs and studies where DNAm was the exposure. Hartwig et al. included animal studies and studies of methQTLs. However, our overall conclusions are in line with these reviews.

Of the three exposures (body size, nutrition and SEP) examined in this review, the majority of papers investigated body size in early life particularly birth weight. Birth weight can be considered as a proxy for the in utero environment, which may subsume maternal diet and parental SEP. This time in the life course marks a period of rapid development during which epigenetic processes, including DNAm are becoming established [10]. Therefore, it is no surprise that this sensitive time period has been the subject of the majority of epigenetic studies to date. However, the results from these studies have been inconsistent and the direction of the association, particularly in cross-sectional studies, remains unclear. One of the interesting findings from the Dutch Hunger Famine study is that nutritional insults in early gestation are more sensitive to lasting changes in DNAm compared with later gestation. Using birth weight as a proxy for the entire gestational period may mask these time-specific effects. There are fewer studies on the impact of post-natal body size, nutrition and SEP. There is some weak and inconsistent evidence to support the impact of body composition, childhood body size, breastfeeding, intake and biomarkers of nutrition related methyl-donors in early life as well as SEP on DNAm that can last into later life. There is also evidence from intervention studies suggesting folic acid and fish oil supplementation during pregnancy or early life results in changes in DNAm [124–126], which were outside the scope of our review.

The inability to come to a conclusive interpretation based on studies in this systematic review is due to extensive heterogeneity in the study designs, statistical analyses and small sample sizes. This is no surprise given that the field of epigenetics in relation to life course epidemiology is in its infancy. Since DNAm can be influenced by stochastic, genetic and environmental exposures, effect sizes, even if they represent causal effects, are likely to be small and therefore difficult to find in small studies [11]. The sources of heterogeneity common to other systematic reviews of observational studies are a concern here. For example, there is inconsistency in how exposures were recorded or measured between the studies which may have introduced heterogeneity. Similarly, not all studies adjusted for the same confounding factors, nor are we clear about what those confounders should be. Of particular concern is the oversight of some relevant studies to control for maternal smoking which is to date the strongest known environmental exposure to impact DNA methylation [127], and cellular heterogeneity [128]. Another source of heterogeneity is the method through which studies account (or do not account) for multiple testing with some studies using a Bonferroni correction and others using false discovery rate. It has been argued that using a Bonferroni correction in epigenome wide association studies may be too conservative due to potential patterns of co-methylation [129]. However, the potential for false positives makes for cautious interpretation of any positive findings in studies which don’t account appropriately for multiple testing. In addition, reproducibility of these findings will be an important goal for future research [128]. One of the unique characteristics of studying DNAm compared to genetics is that DNAm is tissue-specific [128]. The majority of studies included in this review have examined blood due to the ease of accessibility. It may be the case that the impact of e.g. nutrition in early life on DNAm may be more evident in adipose or other target tissues compared with blood.

A major limitation of all the studies is that knowledge of the epigenome, and DNAm, is still limited [128]. Most of the studies included in this review have focused on candidate genes, similar to how early genetic studies were carried out. A variety of assays were used to measure DNAm, which have been discussed in previous papers [129, 130]. As technology has advanced, the study of genome-wide methylation has increased. However, even the relatively advanced methods such as Illumina 450k (or the new 850k) covers an estimated <2% of the epigenome.
This implies that sites of interest may be missed. These technological issues have been discussed extensively by Mill and Heijmans [128].

In addition to these statistical and technological issues, interpreting the functional consequences of some of the identified DNAm sites remains relatively unexplored, as is the potential impact of these DNAm changes on phenotypic health outcomes. A recent paper from the Dutch Hunger Famine study providing evidence that DNAm may mediate the link between adversity in early life and health outcomes in adulthood is one of the first to support this hypothesis [131].

In light of findings from this review and suggestions from previous commentaries [128, 132, 133], we propose the following recommendations for future studies: 1) use of longitudinal studies to assess the impact of early life environmental exposures on the dynamics of the epigenome through the life course 2) full consideration of statistical issues, such as adjustment for confounding, ensuring sufficient power, control for multiple testing, and reproducibility 3) control for cell heterogeneity and examine associations across different tissue types 4) assess the functional consequence of identified epigenetic marks through second-generation EWAS as part of an integrated functional genomics strategy 5) examine if DNAm mediates the relationship between early life exposures and health outcomes in later life and use of novel methods to assess causality e.g. Mendelian Randomisation.

Overall, evidence for the impact of body size, nutrition and/or SEP in early life on concurrent or subsequent DNAm is inconclusive. However, findings to date are supportive of the continued investigation using well designed studies which capitalise on emerging technologies to test these hypotheses. Whether these early life-mediated DNAm profiles translate into health outcomes in later life is something that should be incorporated into future studies.

Supporting information

S1 Table. Search terms.

S2 Table. PRISMA 2009 checklist.

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