

Annual Review of Public Health

Environmental Influences on the Epigenome: Exposure- Associated DNA Methylation in Human Populations

Elizabeth M. Martin and Rebecca C. Fry

Department of Environmental Sciences and Engineering, and Curriculum in Toxicology,
Gillings School of Global Public Health, University of North Carolina, Chapel Hill,
North Carolina 27599, USA; email: emsebas@live.unc.edu, rfry@unc.edu

**ANNUAL
REVIEWS Further**

Click here to view this article's
online features:

- Download figures as PPT slides
- Navigate linked references
- Download citations
- Explore related articles
- Search keywords

Annu. Rev. Public Health 2018. 39:309–33

First published as a Review in Advance on
January 12, 2018

The *Annual Review of Public Health* is online at
publhealth.annualreviews.org

<https://doi.org/10.1146/annurev-publhealth-040617-014629>

Copyright © 2018 Elizabeth M. Martin & Rebecca C. Fry. This work is licensed under a Creative Commons Attribution 4.0 International License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited. See credit lines of images or other third-party material in this article for license information

**Keywords**

environment, epigenetics, human studies, molecular epidemiology

Abstract

DNA methylation is the most well studied of the epigenetic regulators in relation to environmental exposures. To date, numerous studies have detailed the manner by which DNA methylation is influenced by the environment, resulting in altered global and gene-specific DNA methylation. These studies have focused on prenatal, early-life, and adult exposure scenarios. The present review summarizes currently available literature that demonstrates a relationship between DNA methylation and environmental exposures. It includes studies on aflatoxin B₁, air pollution, arsenic, bisphenol A, cadmium, chromium, lead, mercury, polycyclic aromatic hydrocarbons, persistent organic pollutants, tobacco smoke, and nutritional factors. It also addresses gaps in the literature and future directions for research. These gaps include studies of mixtures, sexual dimorphisms with respect to environmentally associated methylation changes, tissue specificity, and temporal stability of the methylation marks.

INTRODUCTION

The Epigenome: An Overview

Epigenetic machinery influences gene expression [messenger RNA (mRNA)] and subsequent protein expression levels but does not alter primary DNA sequence (83). In this way, epigenetic regulation allows for an immediate organism-level adaptation to the environment (176). Three major epigenetic regulators have been described. These include histone modifications, cytosine-phosphate-guanine (CpG) DNA methylation, and noncoding RNA expression (83). This review details studies on DNA methylation alterations in humans assessed in relation to prenatal environmental exposures, as well as studies of chronic adult exposure. We describe the state of the literature on environmental triggers for CpG methylation in human populations. We also highlight current gaps in research and future areas for study (see the sidebar titled Terms and Definitions for further explanation of terms used throughout this article).

DNA Methylation

DNA methylation is the addition of a methyl group at the fifth carbon position of the cytosine base (**Figure 1**). Typically, 5-methylcytosine (5-mC) bases are often proximal to guanine,

TERMS AND DEFINITIONS

Alu methylation: a measure of global methylation at Alu transposable elements

CpG: cytosine-phosphate-guanine

CpG methylation: addition of a methyl group to a cytosine at the 5' position

mC: a methyl (-CH₃) mark added to the 5' position of cytosine

hmC: a hydroxymethyl (-HOCH₃) mark added to the 5' position of cytosine; the first step in the active demethylation process

fmC: a formylmethyl mark added to the 5' position of cytosine; the second step of the active demethylation process

cmC: a carboxymethyl mark added to the 5' position of cytosine; the final step of the active demethylation process

CpG loci: specific locations within the genome at which methylation of cytosine is altered

DNA: deoxyribonucleic acid; the carrier of the genetic code

DNA methylation: an epigenetic mark where a methyl group is added to the 5' position of cytosine

DNMT: DNA methyltransferase; the enzyme family responsible for DNA methylation

In utero: prenatal

In vitro: experiments conducted in cell culture

In vivo: experiments conducted in live animals

LC/MS methylation: a measure of global methylation using liquid chromatography/mass spectrometry

LINE-1 methylation: a measure of global methylation utilizing methylation patterning at long interspersed nuclear elements (LINEs)

mRNA: messenger RNA, also called transcript or gene expression

RNA: ribonucleic acid; the copy of DNA that is used to create proteins

SAM: S-adenosylmethionine; the substrate needed for DNA methylation

TDG: thymine-DNA glycosylase; the primary enzyme responsible for removal of fmC and cmC

TET: ten-eleven translocation protein; the enzyme family responsible for active DNA demethylation

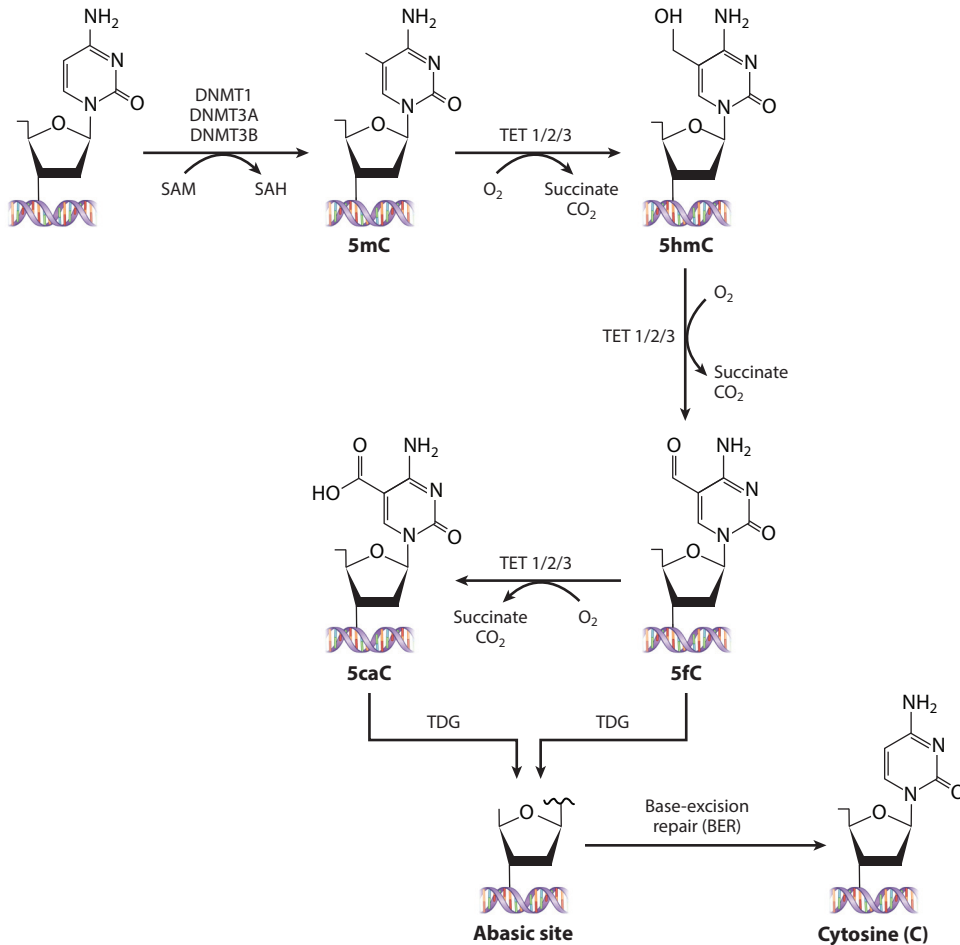


Figure 1

The diagram depicts the process of DNA methylation, namely the addition of a methyl group at the fifth carbon position of the cytosine base. The process of adding methyl groups to cytosine is carried out by the DNA methyltransferase (DNMT) enzyme family. As well as the process of the addition of methyl groups to DNA, there is also a process of active demethylation. This process is mediated by the ten eleven translocation (TET) enzyme family. Active demethylation is a multistep process whereby 5-methylcytosine is converted to 5-hydroxymethylcytosine (5-hmC), which is converted to 5-formylcytosine (5-fC) and finally 5-carboxylcytosine (5-caC). This process readies the sites for thymine-DNA glycosylase (TDG) to remove both 5-fC and 5-caC. Additional abbreviations: BER, base excision repair; OG, oxoglutarate; SAH, S-adenosyl-L-homocysteine; SAM, S-adenosyl-L-methionine.

i.e., CpG methylation, and occur within regions of the genome with a high cytosine-guanine (CG) content. These high CG content regions are often referred to as CpG islands. Sequences immediately flanking and up to two kilobases away from the islands are known as shores. The process of adding methyl groups to cytosine is carried out by the DNA methyltransferase (DNMT) enzyme family. This addition requires the cofactor S-adenosylmethionine (SAM). Within this family of enzymes, three are responsible for catalyzing the reactions of CpG methylation, namely DNMT3A, DNMT3B, and DNMT1 (92). DNMT3A and DNMT3B are responsible for de novo

methylation, e.g., methylation at sites that were not previously methylated (92). DNMT1 is primarily a maintenance methyltransferase, responsible for maintaining methyl marks during the mitotic process (92). In this way, the DNMT enzyme family adds and maintains CpG methylation across the genome.

Methyl groups can be actively removed (demethylated) from DNA, as well as added (**Figure 1**). The process of demethylation is mediated by the ten-eleven translocation (TET) enzyme family (106). Active demethylation is a multistep process characterized first by the conversion of 5-methylcytosine to 5-hydroxymethylcytosine (5-hmC) (106). Subsequently, 5-hmC is converted to 5-formylcytosine (5-fmC) and finally 5-carboxylcytosine (5-CmC) (106). This process readies the sites for thymine-DNA glycosylase (TDG) to remove both 5-fmC and 5-CmC (106). Active demethylation of the genome has been implicated as a regulatory feature that is responsible for fine-tuning CpG regulatory methylation marks.

Global DNA Methylation

Both active methylation and demethylation are responsible for creating and maintaining the CpG methylation patterns across the genome. The TET and DNMT enzymes are active during early development and also remain active throughout the life course (92, 106). Large-scale alterations of processes governing methylation, due to environmental exposure, nutritional status, or disease, are generally associated with global losses or gains of methylation particularly in early development (92). Specifically, alterations of methylation have been associated with differences in functional consequences on chromatin structure and gene expression (92). Global measures of methylation are often assessed using technologies such as LINE1, liquid chromatography–mass spectrometry (LC/MS), and Alu methylation (92). Global loss of methylation is generally associated with genomic instability and is a common phenotype of aging and cancer (56, 196). Conversely, gains in global levels of methylation, specifically in the placenta, have been associated with developmental defects, including down syndrome and gestational diabetes (91, 156). Together these show the importance of the balance of DNA methylation as it pertains to human health.

Gene-Specific Methylation

Current technologies enable the assessment of site-specific methylation, in addition to global methylation. Results of these studies have provided key insights into disease development and susceptibility because they allow for a focused study of potentially causal marks (92). For example, in the landmark Agouti mouse study that examined the effects of environmental contaminants and nutritional supplementation on methylation profiles, investigators demonstrated that methylation of the agouti coat color gene, as well as nine other CpG loci, are linked to adult health and disease susceptibility (46). Similar to global methylation, gene-specific alterations in methylation patterning have been linked to environmental exposures, especially those that occur during the prenatal period (125, 161, 189). The study by Heijmans et al. (71) was the first in a human population to show that alteration of methylation at a single gene locus resulted in changes to disease susceptibility and adult outcomes. The researchers investigated the impacts of prenatal exposure to famine during the Dutch Hunger Winter on insulin growth factor 2 (*IGF2*) methylation. This methylation was associated with lowered birth weight and a predisposition to obesity and adverse metabolic health outcomes later in life (189). These data suggest that alterations to DNA methylation that occur during the prenatal window result in later-life disease, supporting the underlying developmental origins of health and disease hypothesis (189).

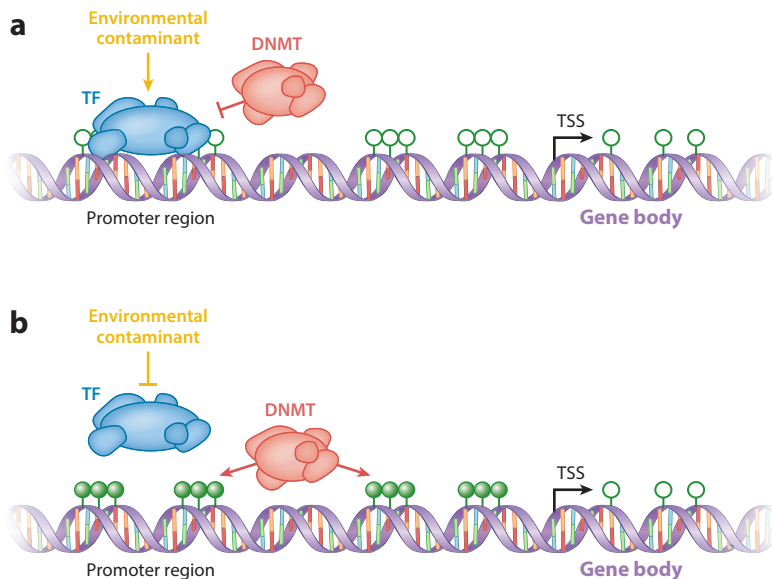


Figure 2

Diagram of the transcription factor occupancy theory. This hypothesis posits that presence or absence of transcription factors on the DNA denies or allows access to the DNA methylation machinery. In this way, transcription factors triggered by environmental exposure may influence the observed site-specific patterns of methylation. (a) Activation of transcription factors in response to an environmental contaminant as a mechanism of cellular defense/adaptation. The binding of the transcription factor may inhibit DNA methyltransferase (DNMT) from accessing the DNA for methylation of a particular gene, resulting in gene-specific hypomethylation. (b) Repression of transcription factors in response to an environmental contaminant. The lack of the transcription factor binding may allow DNMT access to particular genomic locations, resulting in gene-specific hypermethylation. Adapted from Martin & Fry 2016 (125). Additional abbreviations: TF, transcription factor; TSS, transcription start site.

Mechanisms Underlying Gene-Specific Alterations

Two often described hypotheses have been proposed to underlie environmental-induced effects on the global changes in DNA methylation. First, evidence has demonstrated the direct action of environmental chemicals on the function of DNMT and TET enzyme families. Second, evidence has also shown that chemicals may change the availability of SAM. Still, what drives gene-specific DNA methylation patterns is less clear. One hypothesis is the transcription factor occupancy theory, which proposes that presence or absence of transcription factors on the DNA denies or allows access to the DNA methylation machinery (125, 202). In this way, transcription factors triggered by environmental exposure may influence the observed site-specific patterns of methylation (Figure 2).

ENVIRONMENTAL TRIGGERS FOR DNA METHYLATION ALTERATIONS

Here, we detail numerous environmental triggers that have been associated with either global or site-specific DNA methylation alterations. Chemical exposures are the most widely studied class of environmental triggers of methylation, but nutritional status is another important factor. The studies summarized here represent currently available evidence demonstrating a relationship

between exposure to a contaminant and alteration of methylation. The studies have assessed both global and gene-specific alterations to methylation and assessed the impacts of exposure during the prenatal period and chronic exposure. In addition, many of the exposures described result in alterations of genes related to specific biological pathways of interest. They include aflatoxin B₁, air pollution, arsenic, bisphenol A, cadmium, chromium, lead, mercury, polycyclic aromatic hydrocarbons, persistent organic pollutants, tobacco smoke, nutritional factors, and nonchemical stressors (Table 1).

Table 1 Summary of exposures assessed within this review

Exposures	Global methylation	Gene-specific methylation	Exposure-associated health impact	Relevant citations
Aflatoxin B1	Hypomethylation associated with exposure	71 CpG sites associated with prenatal exposure	Hepatocellular carcinomas, reduced growth, immune deficiencies	73, 75, 185, 197
Air pollution	Hypomethylation typically associated with exposure in adults, prenatal exposure is associated with both hypo- and hypermethylation	<i>MAPK</i> pathway members, <i>ACE</i> , <i>iNOS</i> , <i>ICAM-1</i> , <i>TLR2</i> , <i>IL-6</i> , <i>TET1</i>	Accelerated lung aging, loss of lung capacity, asthma, bronchitis, emphysema, and cancer	19, 20, 28, 31, 32, 36, 39, 44, 45, 63, 69, 79, 87, 88, 98, 112, 120, 165, 168, 183
Arsenic	Hypomethylation associated with exposure with sex-specific directionality shown as well	<i>KCNQ1</i> , <i>SQSTM1</i> , sex-specific profiles	Cancer lung conditions and diabetes in adults; prenatal exposure is associated with increased incidence of infection, neurocognitive effects, and increased neonatal mortality	2, 6, 9, 13, 15, 29, 33, 34, 47, 50, 54, 65, 76, 77, 84, 97, 105, 110, 121, 136, 137, 151–153, 155, 159, 177, 184, 199
Bisphenol A	Hypomethylation associated with exposure in females, potential nonmonotonic dose responses	<i>SNORD</i> , <i>SULT2A1</i> , <i>COMT</i>	Neurocognitive effects, increased incidence of cancer, and heart conditions from prenatal exposure	52, 53, 70, 99, 133, 134
Cadmium	Hypomethylation associated with exposure	<i>DNMT1</i>	Cancer, lung, bone, and kidney disease, developmental toxicity	51, 70, 78, 103, 129, 169, 170, 187, 188
Chromium	Hypermethylation associated with exposure	Not assessed at present	Cancer	3, 192
Lead	Not assessed at present	Alterations in imprinted genes, sex-specific response	Neurotoxicity, developmental toxicity	64, 70, 114, 138, 172–174
Mercury	Not assessed at present	<i>EMID2</i> , sex-specific profiles	Neurotoxicity	14, 34, 35, 62, 70, 119
Polycyclic aromatic hydrocarbons	Hypomethylation associated with exposure	<i>HIN1</i> , <i>ESR1</i> , <i>TWIST1</i>	Cancer	48, 72, 74, 101, 112, 146, 149, 194, 195, 198

(Continued)

Table 1 (Continued)

Exposures	Global methylation	Gene-specific methylation	Exposure-associated health impact	Relevant citations
Persistent organic pollutants	Nonmonotonic association with exposure	<i>IGF2</i> , <i>TNF-α</i> , <i>NR3C1</i>	Various health effects	40, 71, 82, 100, 116, 128, 141, 162, 201
Tobacco smoke	Hypomethylation associated with exposure	<i>AHRR</i> , <i>CNTNAP2</i> , <i>MYO1G</i>	Cancer, developmental toxicity, cardiovascular disease, chronic respiratory conditions	26, 27, 37, 55, 67, 86, 89, 94, 118, 148, 157, 175, 181, 182
Nutritional factors	Hypermethylation associated with exposure	<i>IGF2</i> , <i>RXR-α</i> , <i>PLAG1</i>	Proper development	1, 17, 22, 23, 71, 93, 126, 131, 142, 154
Nonchemical stressors	Not assessed at present	<i>BDNF</i> , <i>IGF2</i>	Various health effects	7, 24, 66, 102, 117, 135, 139, 180

Abbreviations: *ACE*, angiotensin-converting enzyme; *AHRR*, aryl hydrocarbon receptor repressor; *BDNF*, brain-derived neurotrophic factor; *CNTNAP2*, contactin-associated protein-like 2; *COMT*, catechol-*O*-methyltransferase; CpG, cytosine-phosphate-guanine; *DNMT1*, DNA methyltransferase; *EMID2*, collagen type XXVI alpha 1 chain; *ESR1*, estrogen receptor 1; *HIN1*, high in normal-1; *ICAM-1*, intercellular adhesion molecule 1; *IGF2*, insulin growth factor 2; *IL-6*, interleukin 6; *iNOS*, nitric oxide synthase; *KCNQ1*, potassium voltage-gated channel subfamily Q member 1; *MAPK*, mitogen-activated protein kinase; *MYO1G*, myosin IG; *NR3C1*, nuclear receptor subfamily 3 group C member 1; *PLAG1*, PLAG1 Zinc Finger; *RXR- α* , retinoid X receptor alpha; *SNORD*, small nucleolar RNA; *SQSTM1*, sequestosome 1; *SULT2A1*, sulfotransferase family 2A member 1; *TET1*, tet methylcytosine dioxygenase; *TLR2*, toll-like receptor 2; *TNF- α* , tumor necrosis factor alpha; *Twist1*, twist family BHLH transcription factor 1.

Aflatoxin B₁

Aflatoxin B₁ (AFB₁) is a mycotoxin that can contaminate foods such as peanuts, grain, and corn (185). It is one of the most potent hepatic carcinogens and is known to induce specific DNA lesions leading to subsequent mutation and resulting in hepatocellular carcinoma (197, 200). Interestingly, hepatocellular carcinomas are known to have altered DNA methylation profiles, so investigation of AFB₁ as an epimutagen has been of interest (197, 200). To this end, studies showed that adults in two separate Taiwanese populations who were exposed to AFB₁ had lower levels of methylation in white blood cells (197, 200). These results are consistent with broader findings in cancer biology that suggest that genomic instability is a hallmark of cancer. In line with this proposition, the authors suggest that epigenetic alterations may provide an accurate way to assess cancer risk in AFB₁-exposed populations. In addition to chronic exposure and global measures, researchers have assessed gene-specific alterations in DNA methylation in response to prenatal AFB₁ exposure in Gambia. A total of 71 CpG sites related to immune response and growth factors were identified to be altered in association with AFB₁ in white blood cells (73). These data suggest that reduced growth and immune deficiencies associated with prenatal AFB₁ exposure could be mediated by methylation (185), but more research is needed to understand the impacts of AFB₁-associated methylation on a wider range of health effects.

Air Pollution

Air pollutants include a broad array of different environmental exposures, including particulate matter (PM) of various sizes and composition, ozone, nitrogen oxides, sulfur oxides, carbon monoxide, diesel exhaust fumes, and a wide variety of toxic chemicals such as benzene. In addition to these specific contaminants, broader descriptors such as urban development and traffic-related air pollution are commonly used to classify exposure in the field. These studies emphasize the effects of toxic air pollutant mixtures on the epigenome. For example, Carmona et al. (36) showed that

alterations in blood DNA methylation levels of the mitogen-activated protein kinase (MAPK) pathway are associated with exposure to generalized measures of air pollution in human populations. Furthermore, Bind et al. (19) demonstrated that exposure to air pollutants can result in functional changes to blood-based measures of protein expression and that altered DNA methylation may be indicative of susceptibility to these changes.

In addition to studies of general air pollutants, specific air pollutants have been a subject of interest. The constituents of the different types of air pollution, such as the composition of PM or ozone content, likely impact the observed relationship with gene-specific methylation patterns (31, 79). However, in adults, different constituents and pollution types are generally associated with global hypomethylation (12, 18, 44, 45, 69, 120). More recent studies have sought to differentiate the effects of hmC from mC and found that PM smaller than or equal to 10 microns in length (PM₁₀), PM smaller than or equal to 2.5 microns in diameter (PM_{2.5}), and elemental composition of PM are associated with 5hmC but not with 5mC (168). PM_{2.5} exposure is associated with decreased methylation of the angiotensin-converting enzyme (*ACE*) gene (190), the nitric oxide synthase (*iNOS*) gene (98, 166), and hypermethylation of the mitochondrial genome (32), providing a potential mechanistic link between elevated blood pressure and PM exposure. Additionally, coagulation factor II (*F2*), intercellular adhesion molecule 1 (*ICAM-1*), and toll-like receptor 2 (*TLR-2*) display hypomethylation in association with air pollution constituents, and interferon gamma (*IFN-γ*) and interleukin 6 (*IL-6*) are associated with hypermethylation (20). Of great interest is the finding that traffic-related air pollution can influence methylation at the tet methylcytosine dioxygenase 1 (*TET1*) gene, a key enzyme in DNA demethylation, resulting in changes to gene expression (178).

Prenatal exposure to air pollution appears to differentially affect methylation patterns depending on the developmental window of exposure. Specifically, exposure during the first trimester is associated with decreased LINE-1 methylation, whereas exposure later in pregnancy is associated with increased LINE-1 methylation (28, 88). In addition to these global measures, researchers have investigated the relationship between pollutants and gene-specific methylation. For example, prenatal exposure to airborne vanadium has been linked to alteration of DNA methylation in genes interleukin 4 (*IL-4*) and *INF-γ* (95). Prenatal exposure to PM_{2.5} has been associated with hypomethylation of the leptin gene (165), sites around poly(ADP-ribose) polymerase 1 (*PARP1*) promoter (4), and the mitochondrial genome (87). In addition to these findings, untargeted analyses of the genome have revealed associations between prenatal air exposure and CpG methylation related to xenobiotic metabolism and oxygen and gas transport (63). In utero exposure to diesel exhaust and allergens has been linked to alterations in CpG methylation related to cell adhesion, protein metabolism, and vascular development (39). DNA methylation alterations accumulated later in life that are associated with air pollution found in peripheral blood do not appear to be stable, as compared with those accumulated during the prenatal period and during childhood, which do appear to be stable (183). Taken together, these data suggest the potential for developmental reprogramming of the epigenome with respect to in utero air pollution.

Arsenic

Arsenic exposure is currently impacting the lives of hundreds of millions around the globe (38). Arsenic has been associated with altered methylation patterns in both chronically exposed adults and prenatally exposed infants. Global measures of methylation in blood samples from adults, children, and infants exposed in utero have been negatively associated with increased arsenic exposure. These data support the role of arsenic in global hypomethylation (15, 76, 84, 97, 110). In contrast with these studies, some have demonstrated that arsenic exposure is associated with

global hypermethylation (121, 136, 153), including one study conducted in children (2), and another focused on CD-4-positive T cell profiling (50). More recent studies have demonstrated that arsenic is associated with global methylation changes in a sex-dependent manner. Two studies of cord blood from prenatally exposed infants in Bangladesh found a positive association between methylation and arsenic exposure in male infants and a negative relationship between methylation and arsenic exposure in female infants (137, 152). Furthermore, studies in adults have shown that female adults display an inverse relationship between exposure and LINE-1 methylation, but males display a nonsignificant relationship (76). In addition to sex dependence, emerging research is focusing on differentiating the effects of arsenic on hmC and mC. At present, a single study from a US-based cohort found that both blood profiles of hmC and mC displayed negative correlations in association with arsenic (184).

In addition to studies of global methylation, numerous studies have been conducted on gene-specific DNA methylation alterations in adults chronically exposed to arsenic (9, 13, 155, 177, 199), as well as infants exposed to arsenic in utero (29, 33, 34, 65, 105, 159). The majority of these studies have assessed methylation patterns in blood; however, two studies have assessed the relationship between exposure and methylation in potential target tissues: placenta (33, 65) and exfoliated urothelial cells (155). In addition, one study has examined the relationship between methylation and gene expression, suggesting that not all methylation marks have functional consequences (159). Additionally, there is no overlap among the genes that have been identified as targets of arsenic exposure in utero (8, 125) and those identified in adults (8). The majority of these studies have found that most of the loci are hypermethylated in association with arsenic (6). These studies have implicated genes that influence arsenic-associated birth and health outcomes. As a specific example, methylation of potassium voltage-gated channel subfamily Q member 1 (*KCNQ1*) has been associated with lower birth weight (159). Methylation of *p16* and *p53* has been associated with various cancers (77, 84), and altered sequestosome 1 (*SQSTM1*) methylation has been associated with diabetes (9). As detailed in this section, the current body of epigenetic literature focused on arsenic exposure includes assessment of the impacts of sex, functional consequence, and tissue specificity on DNA methylation response. Taken together these studies suggest that arsenic-associated methylation may result in genomic instability and may play a role in arsenic-associated disease development in the context of both prenatal and chronic exposure.

Bisphenol-A

Bisphenol A (BPA) is an endocrine-disrupting chemical of public health concern because of its ubiquitous exposure and accumulation in the environment (42). Given the unclear nature of the health effects and dose-response relationship, BPA has been an area of active investigation. In studies of blood-based methylation alterations, it appears that BPA induces hypomethylation in women (70) and in young girls (99); however, its effects in males are unclear. Further complicating the study of DNA methylation and BPA exposure, fetal liver methylation alterations associated with prenatal exposure to BPA display a nonmonotonic association with BPA level (53). In gene-specific analyses of CpG methylation as it relates to prenatal BPA exposure, altered methylation patterns were observed in diverse tissues, including placenta, fetal liver and fetal kidney. Among the differentially methylated loci associated with BPA were the small nucleolar RNA (*SNORD*) complex of genes (53), sulfotransferase family 2A member 1 (*SULT2A1*), and catechol-*O*-methyltransferase (*COMT*) (133). Methylation patterning associated with BPA may be specific to different tissue types (134). Generally, BPA has also been shown to induce hypomethylation of CpG targets on the X chromosome (99) and alter methylation associated with immune function, transport activity, and metabolism (52, 53, 99, 133, 134). Taken together, the present evidence supports sexual

dimorphism and a nonmonotonic dose response of DNA methylation associated with BPA, resulting in a need for more research to understand the complicated functional consequences of BPA-associated DNA methylation alterations.

Cadmium

Cadmium exposure is of concern because it has a long half-life, ranging up to three decades, and is associated with numerous health effects, including kidney dysfunction, pregnancy and reproductive disorders, developmental toxicity, and cancer (170). Additionally, exposure is of concern because it accumulates in the bones over an individual's life course and is released during pregnancy. This phenomenon magnifies prenatal exposure to cadmium and increases risk for cadmium-associated pregnancy disorders (170). In general, cadmium has been inversely associated with blood-based measures of LINE-1 methylation in women from the Argentinean Andes (78) and in prenatally exposed infants from the United States (22). More specifically, cadmium has been linked to blood-based methylation alterations in key genes related to DNA methylation machinery, including *DNMT1*, observed in adult cohorts in Thailand and Argentina (78, 188). Prenatal cadmium exposure in a US-based cohort has been associated with alterations in placental methylation that could drive observed differences in fetal growth (51). Exposure to cadmium has also been associated with sex-specific differences in methylation alterations, and a subset of the marks are associated with alterations in birth size (103, 129, 187). In addition to focusing on either maternal or fetal outcomes, one US-based study looked at cadmium-associated DNA methylation patterns in both infants and their mothers. The study found that cadmium-associated methylation profiles in the infants differed from those in the mother (169). Taken together, specific gene targets of epigenetic dysregulation by cadmium could provide a basis for understanding cadmium-associated reproductive effects.

Chromium

Chromium, specifically hexavalent chromium, is a known carcinogen (30). Unlike most toxic metals, it is known to form mutagenic lesions (30). In addition, in contrast with most metals whereby the carcinogenic effects are derived primarily from exposure through ingestion, chromium is primarily an inhaled carcinogen; limited evidence suggests carcinogenicity through ingestion routes (30). A study of workers occupationally exposed to chromate showed increased accumulation in peripheral red blood cells (192). Chromate was also associated with DNA hypomethylation, a hallmark of cancer (192). The authors suggest that this association may be due to an interplay between chromate and folate, a donor to the SAM pool (192). The study suggests that chromate may also be able to induce folate deficiency in conjunction with its action as a direct mutagen, increasing its carcinogenic properties. In a separate cohort, lung cells from chromate-exposed workers who developed lung cancer were associated with aberrant methylation patterns that differed from methylation profiles of lung cancers from individuals who were not exposed to chromate (3). Chromium-associated methylation remains an understudied area, and further research is needed to investigate these relationships.

Lead

Lead is a known neurotoxicant, impacting the growth and development of children (138). Both 5-mC and 5-hmC are altered in response to prenatal lead exposure. There is a clear sex-specific response, where a unique set of loci are differentially methylated in males and females in response

to lead (64, 172, 173). Studies have also found that a core set of loci is changed in both males and females who were exposed to lead in utero (64, 172, 173). In addition, children who were prenatally exposed to lead in US-based cohorts display variable methylation patterns in imprinted genes, suggesting an increased risk of childhood obesity and cardiometabolic disease in adulthood (64, 138). A recent US-based study that utilized dried blood spots suggested that a grandmother's exposure to lead could leave imprints on her grandchild's methylome, suggesting a role for transgenerational inheritance of human epigenetic marks (174). Among adults, a general loss of methylation in blood has been correlated with increased blood lead levels (114). Among women undergoing in vitro fertilization, hypomethylation of collagen type I alpha 2 chain (*COL1A2*) has been observed (70). In general, lead has been associated with an altered methylation pattern that has the potential to explain lead-associated health effects, particularly in the context of prenatal and early-life exposures.

Mercury

As with lead, mercury exposure is of concern because it is a known neurotoxicant (35, 119). Prenatal exposure to mercury can modulate methylation patterns in both infants (14, 34) and the placenta (119). The alterations observed in blood are indicative of shifts in immune cell proportions (14, 34), emphasizing the importance of controlling blood-based methylation for white blood cell populations. In contrast, placental DNA methylation alterations associated with mercury have been associated with adverse neurological outcomes, a relationship that is potentially mediated through collagen type XXVI alpha 1 chain (*EMID2*). A recent study has similarly found that mercury-associated alterations in methylation that persisted throughout childhood were also related to cognitive performance during childhood (35). This study identified sex-specific differences in altered methylation profiles as well as methylation changes that persisted into early childhood (35). The sex specificity of methylation alterations associated with mercury has also been identified in adults (62). The studies of mercury-associated alterations of CpG methylation are among the first studies to assess the stability of epigenetic marks longitudinally, and they have also assessed sex specificity. The present findings suggest a need for further investigation because a potential role for methylation as a mediator of mercury-associated neurotoxicity has been identified.

Polycyclic Aromatic Hydrocarbons

Polycyclic aromatic hydrocarbons (PAHs) are persistent organic pollutants (POPs) and known genotoxicants that have been associated with numerous adverse health outcomes. Prenatal exposures to PAHs have been associated with decreased global methylation in China and the United States (72, 112), as have adult exposures in China, Poland, and the United States (48, 140, 146, 147). In addition, methylation of key genes related to breast cancer, including retinoic acid receptor beta (*RARβ*) and adenomatous polyposis coli tumor suppressor (*APC*), has been associated with the presence of PAH adducts in breast and breast tumor tissue as well as with various sources of PAH exposure (194, 195). Specifically, synthetic log use has been associated with secretoglobin family 3A member 1 (*HINI*), environmental tobacco smoke was associated with estrogen receptor 1 (*ESR1*), and current smoking status was associated with twist family BHLH transcription factor 1 (*TWIST1*) (195). PAHs from tobacco smoke were also shown to alter methylation patterns of genes associated with cardiovascular disease and cancer in a Chinese population (203). Additional genes that display altered methylation in association with more general measures of PAH exposures are associated with insulin resistance (101), childhood asthma status (74, 149), and cancer (198). All the genes described above display hypermethylation in relationship with PAHs,

suggesting a potential role for PAHs as an environmental factor that can silence gene expression through epigenetic regulation at site-specific loci. The studies of PAH-associated modifications of DNA methylation highlight the impact of hydrocarbon mixtures and suggest a role for the epigenome in PAH-associated carcinogenicity.

Persistent Organic Pollutants

POPs are a class of compounds that persist long after their introduction into the environment. Many of these chemicals are known to have toxic effects on wildlife and ecosystems, leading to questions about effects on human health. Examples of these compounds include dichlorodiphenyl-trichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE), as well as polybrominated diphenyl (PBDEs), polychlorinated biphenyl (PCBs), perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). Exposure to POPs impacts global measures of methylation, specifically Alu and LINE-1 elements. Prenatal, early-life, and later-life exposure to these compounds may be associated with a global hypomethylation (82, 85, 100, 162), DNA hypermethylation (40, 116, 193), and nonmonotonic associations (100, 141) in populations from the United States, Korea, Europe, and the Arctic. Specifically, PBDEs have been linked to hypomethylation of tumor necrosis factor alpha (*TNF- α*) in cord blood from a US-based cohort (43), *IGF2* in placenta from both a US-based cohort and a Chinese-based cohort (96, 201), and nuclear receptor subfamily 3 group C member 1 (*NR3C1*) in placentas from a Chinese-based cohort (201). Exposure is also associated with hypomethylation in sperm cells with exposure to POPs and PFOAs, suggesting that POPs are potential germline epimutagens and could be tied to preconception exposure (40, 113). In utero PFOA exposures also induce global hypomethylation in cord blood from a US-based population (67) as well as induce hypomethylation of *IGF2* in cord blood from a Japanese cohort (104). Researchers found associations between methylation alterations associated with POPs and neurological development in children (104). Supporting this finding, PCBs and PBDEs have been associated with hypomethylation of genes associated with autism (49, 128). Taken together, the existing literature supports the role of POPs-associated methylation as a potential mediator of POP-associated health effects in humans.

Tobacco Smoke

Tobacco smoke is an exposure of concern because it is a known carcinogen, in addition to being associated with cardiovascular disease and other chronic respiratory conditions. One of the means of carcinogenicity is genomic instability and dysregulation of the epigenome. Specifically, tobacco smoke has been associated with global hypomethylation for both in utero exposures (26, 55, 67, 89) and adult exposures (41). Of the methylation targets of tobacco smoke, aryl hydrocarbon receptor repressor (*AHRR*) has been identified as a reproducible biomarker of exposure across studies (68, 150, 157, 158, 175). The locus cg05575921 was shown to be hypomethylated across populations and altered in response to prenatal tobacco smoke exposure (16, 68, 94, 150, 157, 158, 160, 175). Additional targets include cancer, cell cycle, and metabolism-related genes (37, 59, 90, 115, 148, 167, 203). Prenatal exposure to tobacco smoke has been associated with alterations of genes related to fetal growth restriction (86, 118), development (94, 123, 171), cancer and cell growth (160), and other processes (26, 27, 181, 182, 191). Among these genes, contactin-associated protein-like 2 (*CNTNAP2*), cytochrome P450, family 1, member A1 (*CYP1A1*), and myosin IG (*MYO1G*) are common across numerous studies (125). Further support for the effect of tobacco smoke on DNA methylation comes from recent work that has demonstrated the stability of methylation patterns at a subset of the genes identified as differentially methylated in response to prenatal exposure

(27, 164). Of the assessed contaminants, the most overlap in gene-specific methylation patterns was observed for tobacco smoke (108, 125), which suggests that the observed blood modifications may be useful biomarkers in the future. Taken together, the data corroborate that tobacco smoke has a strong effect on DNA methylation that is potentially related to exposure-associated health outcomes.

Nutritional Factors

Among other environmental factors that alter CpG methylation, in addition to chemicals in the environment, nutrition should be considered. Alterations of early-life and prenatal nutritional status have been associated with developmental programming, resulting in later-life health outcomes (16, 126). In addition, given the direct relationship between one-carbon metabolism and the process of DNA methylation described earlier, it is highly likely that alterations to nutritional status could directly impact the amount and patterns of DNA methylation. Specifically, methyl donor nutrients such as methionine, folate, betaine, and choline have been implicated in alterations in methylation patterns. These nutrients are directly related to one-carbon metabolism, the process that generates SAM, the major substrate for DNA methylation.

In general, supplementation with methyl donors appears to increase global methylation levels (154), and deficiency is associated with global hypomethylation (1). Similarly, intermediates of one-carbon metabolism are also associated with decreased SAM levels (22, 58). Of these nutrients, folate is a commonly added dietary supplement because it is important for fetal development. Folate has been associated with global measures of methylation in infants (93), children (130), and adults (17, 21). Similarly, a positive relationship exists between 5-hmC and methyl donors. This effect appears to be limited to the third trimester of pregnancy (142). Meanwhile, increased paternal intake of methyl donor nutrients has been associated with increased global methylation in the cord blood of offspring (145), whereas increases in maternal methyl donors influence methylation patterns related to infant metabolism and growth (143, 144). A key mediator of this relationship may be the *H19/IGF2* locus (57, 81, 179). This same locus was shown to be altered by exposure to prenatal famine (71) and has been implicated in later-life obesity and diabetes. In addition to *H19/IGF2*, retinoid X receptor alpha (*RXR- α*) appears to be modified in association with maternal folate intake during the prenatal period (60), which is of key interest because *RXR- α* is known to play a role in later-life obesity and metabolic disorders. Among the genes altered by folate in adult pathways are those related to cancer (61, 107), inflammation (23), and fetal growth and development (5, 80). Folate intake also appears to moderate the effects of environmental contaminant exposure, including arsenic (153), chromium (192), hormonal markers (186), tobacco smoke (16) and pesticides (163).

In addition to folate donor nutrients, other micronutrients are also critical for methylation status. The vitamin B family are members of one-carbon metabolism, as well as micronutrients. Homocysteine (58), choline (22), and vitamin B12 (127) are associated with alterations in global methylation during the prenatal period. Methylation differences associated with these nutrients, when investigated on a gene-specific level, are associated with differences in alterations in imprinted genes, including PLAG1 Zinc Finger (*ZAC1/PLAG1*) (11, 80). For example, increased maternal vitamin D is associated with hypermethylation tumor suppression genes in infants (131). In addition, selenium, which has a sex-specific relationship (151), has been shown to alter methylation at genes related to Keshan disease, which arises from selenium deficiency. These results suggest that micronutrients, as well as one-carbon metabolism indicators, are important to CpG methylation alterations. Thus more consideration should be given to nutritional status during the study of perturbations of CpG methylation associated with environmental exposures.

Nonchemical Environmental Exposures

The field of epigenetics has generally focused on environmental factors such as chemical contaminants and nutrients. However, other factors related to the social environment are known to play a role in alterations related to DNA methylation. For example, numerous studies have demonstrated that socioeconomic status is related to adult (24, 109, 180) and prenatal (7, 63, 102, 109) alterations of DNA methylation. Socioeconomic status is environmental in nature because it is related to social factors that affect individuals. Some research has suggested that childhood adversity/socioeconomic status, as compared with that experienced in adulthood, is more strongly tied to adult methylation patterns and health outcomes (24, 135). Additionally, it is important to consider the mother's general health/mental state, given that the mother is the environment for the developing fetus. To this end, maternal mental health can impact methylation patterns in infants. Specifically, maternal depression during the prenatal period has been linked to altered methylation of brain-derived neurotrophic factor (*BDNF*) (25), and maternal anxiety during the prenatal period is associated with hypomethylation of the *IGF2/H19* loci (122). These changes are further related to childhood anxiety and birth weight. More broadly, prenatal and early-life social/location-based CpG alterations are related to immune function and inflammatory pathways (7, 117, 135). These findings suggest the strong need to consider social and community impacts along with more tangible measures of environmental exposure to contaminants and nutrients.

FUTURE DIRECTIONS

Environmental epigenetic studies have broadly categorized the relationship between exposure and alterations in CpG methylation for numerous contaminants, nutrients, and social factors. However, there are currently four major gaps in the scientific literature, which pertain to environmental factors and the epigenome: (a) the assessment of mixtures and contaminant/nutrient interactions, (b) sex-specific responses, (c) tissue-specific responses, and (d) stability and functional consequences of CpG methylation. One of the major limitations of the field at present is the failure to consider environmental mixtures and the interactions of numerous environmental factors. Numerous hypotheses have proposed that nutrition, exposure, and hormonal signaling can all impact methylation (111). Studies have shown that the effects of numerous contaminants are modulated by one-carbon metabolism nutrients (16, 110, 153, 163, 192). Furthermore, humans are not exposed to a single contaminant. As detailed previously, only a handful of studies have examined the relationship between multiple environmental factors and their impacts on DNA methylation. In the future, nutritional assessment in conjunction with environmental assessment as well as assessment of multiple contaminants are needed to advance the field.

In addition to multi-contaminant environmental mixtures, the sex of the exposed individual may impact the relationship between environmental factors and DNA methylation. For example, baseline differences in methylation patterns have been shown between placentas derived from male pregnancies compared with those from female pregnancies (124). Given that many of these differences pertain to metabolism and transport of environmental contaminants, these could underlie some of the observed differences in health effects between males and females (124). In support of this notion, differences in methylation patterns associated with environmental contaminants have been observed in males and females (2, 29, 82, 103, 129, 137, 172). Furthermore, sex-based differences in DNA methylation should be considered because they may influence the response to environmental exposure (152). Future studies can utilize both interaction models and stratified modeling to understand the sex-specific effects of the contaminants as well as potential disease susceptibility. Although this approach has become more standard in the study of some

contaminants, such as in studies of arsenic and cadmium (29, 82, 103, 129, 137, 152), it is still not as fully considered in others.

Tissue specificity is the third area in which improved understanding of methylation is important. Many studies have focused on blood-based methylation as biomarkers for disease; however, the meaning of these methylation marks is somewhat unclear. Although it is a readily accessible biospecimen for the study of humans, it may not reflect changes in specific tissues of interest (10, 33). In the case of some specific biomarkers, such as decreased methylation of *AHRR* in smokers, it is clear that this methylation pattern is conserved across tissue types, specifically blood and lung tissue (175). In addition, some studies have shown that imprinted gene methylation is conserved across tissue types, making these genes strong targets for study, as their methylation may represent changes across tissues (132). However, future work should examine toxicological target tissues, such as the placenta as an organ of reproductive toxicity, or use banked biopsies from target organs such as livers and kidneys.

The final gap in the literature is centered around the stability of methylation marks and their functional consequences. Only a handful of studies have assessed the stability of methylation over time (35). Although more researchers are looking to understand functional consequences by assessing gene expression, protein expression, or birth outcomes (119, 159), this is not standard practice yet. Given that methylation is a mechanism for adaptation, it would be unsurprising if methylation signatures changed over an individual's life course depending on subsequent exposure. However, given that previously described studies have shown stability of specific loci, it is possible that some of the methylation patterns observed were preprogrammed during gestation. These should be targets of further studies. To close this gap, prospective cohort studies with longitudinal measures of methylation and gene expression should be established.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

This research was supported by grants from the National Institute of Environmental Health Sciences (T32-ES007018, T32-ES007126, R01-ES0019315, P42-ES005948). We acknowledge Caroline Reed for the figure design.

LITERATURE CITED

1. Agodi A, Barchitta M, Quattrocchi A, Maugeri A, Canto C, et al. 2015. Low fruit consumption and folate deficiency are associated with LINE-1 hypomethylation in women of a cancer-free population. *Genes Nutr.* 10:30
2. Alegría-Torres JA, Carrizales-Yáñez L, Díaz-Barriga F, Rosso-Camacho F, Motta V, et al. 2016. DNA methylation changes in Mexican children exposed to arsenic from two historic mining areas in San Luis Potosí. *Environ. Mol. Mutagen.* 57:717–23
3. Ali AH, Kondo K, Namura T, Senba Y, Takizawa H, et al. 2011. Aberrant DNA methylation of some tumor suppressor genes in lung cancers from workers with chromate exposure. *Mol. Carcinog.* 50:89–99
4. Alvarado-Cruz I, Sánchez-Guerra M, Hernández-Cadena L, De Vizcaya-Ruiz A, Mugica V, et al. 2017. Increased methylation of repetitive elements and DNA repair genes is associated with higher DNA oxidation in children in an urbanized, industrial environment. *Mutat. Res.* 813:27–36

5. Amarasekera M, Martino D, Ashley S, Harb H, Kesper D, et al. 2014. Genome-wide DNA methylation profiling identifies a folate-sensitive region of differential methylation upstream of ZFP57-imprinting regulator in humans. *FASEB J.* 28:4068–76
6. Ameer SS, Engström K, Hossain MB, Concha G, Vahter M, Broberg K. 2017. Arsenic exposure from drinking water is associated with decreased gene expression and increased DNA methylation in peripheral blood. *Toxicol. Appl. Pharmacol.* 321:57–66
7. Appleton AA, Armstrong DA, Lesueur C, Lee J, Padbury JF, et al. 2013. Patterning in placental 11-B hydroxysteroid dehydrogenase methylation according to prenatal socioeconomic adversity. *PLOS ONE* 8:e74691
8. Argos M. 2015. Arsenic exposure and epigenetic alterations: recent findings based on the Illumina 450K DNA methylation array. *Curr. Environ. Health Rep.* 2:137–44
9. Argos M, Chen L, Jasmine F, Tong L, Pierce BL, et al. 2015. Gene-specific differential DNA methylation and chronic arsenic exposure in an epigenome-wide association study of adults in Bangladesh. *Environ. Health Perspect.* 123:64–71
10. Armstrong DA, Lesueur C, Conratt E, Lester BM, Marsit CJ. 2014. Global and gene-specific DNA methylation across multiple tissues in early infancy: implications for children's health research. *FASEB J.* 28:2088–97
11. Azzi S, Sas TC, Koudou Y, Le Bouc Y, Souberbielle J-C, et al. 2014. Degree of methylation of ZAC1 (PLAGL1) is associated with prenatal and post-natal growth in healthy infants of the EDEN mother child cohort. *Epigenetics* 9:338–45
12. Baccarelli A, Wright RO, Bollati V, Tarantini L, Litonjua AA, et al. 2009. Rapid DNA methylation changes after exposure to traffic particles. *Am. J. Respir. Crit. Care Med.* 179:572–78
13. Bailey KA, Wu MC, Ward WO, Smeester L, Rager JE, et al. 2013. Arsenic and the epigenome: interindividual differences in arsenic metabolism related to distinct patterns of DNA methylation. *J. Biochem. Mol. Toxicol.* 27:106–15
14. Bakulski KM, Lee H, Feinberg JI, Wells EM, Brown S, et al. 2015. Prenatal mercury concentration is associated with changes in DNA methylation at TCEANC2 in newborns. *Int. J. Epidemiol.* 44:1249–62
15. Bandyopadhyay AK, Paul S, Adak S, Giri AK. 2016. Reduced LINE-1 methylation is associated with arsenic-induced genotoxic stress in children. *Biometals* 29:731–41
16. Beach SRH, Lei MK, Ong ML, Brody GH, Dogan MV, Philibert RA. 2017. MTHFR methylation moderates the impact of smoking on DNA methylation at AHRH for African American young adults. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* 174:608–18
17. Bednarska-Makaruk M, Graban A, Sobczyńska-Malefora A, Harrington DJ, Mitchell M, et al. 2016. Homocysteine metabolism and the associations of global DNA methylation with selected gene polymorphisms and nutritional factors in patients with dementia. *Exp. Gerontol.* 81:83–91
18. Bellavia A, Urch B, Speck M, Brook RD, Scott JA, et al. 2013. DNA hypomethylation, ambient particulate matter, and increased blood pressure: findings from controlled human exposure experiments. *J. Am. Heart Assoc.* 2:e000212
19. Bind MA, Baccarelli A, Zanobetti A, Tarantini L, Suh H, et al. 2012. Air pollution and markers of coagulation, inflammation, and endothelial function: associations and epigenome-environment interactions in an elderly cohort. *Epidemiology* 23:332–40
20. Bind MA, Lepeule J, Zanobetti A, Gasparrini A, Baccarelli A, et al. 2014. Air pollution and gene-specific methylation in the Normative Aging Study: association, effect modification, and mediation analysis. *Epigenetics* 9:448–58
21. Binder AM, Michels KB. 2013. The causal effect of red blood cell folate on genome-wide methylation in cord blood: a Mendelian randomization approach. *BMC Bioinform.* 14:353
22. Boeke CE, Baccarelli A, Kleinman KP, Burriss HH, Litonjua AA, et al. 2012. Gestational intake of methyl donors and global LINE-1 DNA methylation in maternal and cord blood: prospective results from a folate-replete population. *Epigenetics* 7:253–60
23. Bollati V, Favero C, Albetti B, Tarantini L, Moroni A, et al. 2014. Nutrients intake is associated with DNA methylation of candidate inflammatory genes in a population of obese subjects. *Nutrients* 6:4625–39
24. Borghol N, Suderman M, McArdle W, Racine A, Hallett M, et al. 2012. Associations with early-life socio-economic position in adult DNA methylation. *Int. J. Epidemiol.* 41:62–74

25. Braithwaite EC, Kundakovic M, Ramchandani PG, Murphy SE, Champagne FA. 2015. Maternal prenatal depressive symptoms predict infant NR3C1 1F and BDNF IV DNA methylation. *Epigenetics* 10:408–17
26. Breton CV, Byun HM, Wenten M, Pan F, Yang A, Gilliland FD. 2009. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. *Am. J. Respir. Crit. Care Med.* 180:462–67
27. Breton CV, Siegmund KD, Joubert BR, Wang X, Qui W, et al. 2014. Prenatal tobacco smoke exposure is associated with childhood DNA CpG methylation. *PLOS ONE* 9:e99716
28. Breton CV, Yao J, Millstein J, Gao L, Siegmund KD, et al. 2016. Prenatal air pollution exposures, DNA methyl transferase genotypes, and associations with newborn LINE1 and Alu methylation and childhood blood pressure and carotid intima-media thickness in the Children's Health Study. *Environ. Health Perspect.* 124:1905–12
29. Broberg K, Ahmed S, Engström K, Hossain MB, Jurkovic Mlakar S, et al. 2014. Arsenic exposure in early pregnancy alters genome-wide DNA methylation in cord blood, particularly in boys. *J. Dev. Origins Health Dis.* 5:288–98
30. Brocato J, Costa M. 2013. Basic mechanics of DNA methylation and the unique landscape of the DNA methylome in metal-induced carcinogenesis. *Crit. Rev. Toxicol.* 43:493–514
31. Byun HM, Motta V, Panni T, Bertazzi PA, Apostoli P, et al. 2013. Evolutionary age of repetitive element subfamilies and sensitivity of DNA methylation to airborne pollutants. *Part. Fibre Toxicol.* 10:28
32. Byun HM, Panni T, Motta V, Hou L, Nordio F, et al. 2013. Effects of airborne pollutants on mitochondrial DNA methylation. *Part. Fibre Toxicol.* 10:18
33. Cardenas A, Houseman EA, Baccarelli AA, Quamruzzaman Q, Rahman M, et al. 2015. In utero arsenic exposure and epigenome-wide associations in placenta, umbilical artery, and human umbilical vein endothelial cells. *Epigenetics* 10:1054–63
34. Cardenas A, Koestler DC, Houseman EA, Jackson BP, Kile ML, et al. 2015. Differential DNA methylation in umbilical cord blood of infants exposed to mercury and arsenic in utero. *Epigenetics* 10:508–15
35. Cardenas A, Rifas-Shiman SL, Agha G, Hivert M-F, Litonjua AA, et al. 2017. Persistent DNA methylation changes associated with prenatal mercury exposure and cognitive performance during childhood. *Sci. Rep.* 7:2888
36. Carmona JJ, Sofer T, Hutchinson J, Cantone L, Coull B, et al. 2014. Short-term airborne particulate matter exposure alters the epigenetic landscape of human genes associated with the mitogen-activated protein kinase network: a cross-sectional study. *Environ. Health* 13:94
37. Cheng L, Liu J, Li B, Liu S, Li X, Tu H. 2016. Cigarette smoke-induced hypermethylation of the *GCLC* gene is associated with COPD. *Chest* 149:474–82
38. Chung J-Y, Yu S-D, Hong Y-S. 2014. Environmental source of arsenic exposure. *J. Prev. Med. Public Health* 47:253–57
39. Clifford RL, Jones MJ, MacIsaac JL, McEwen LM, Goodman SJ, et al. 2017. Inhalation of diesel exhaust and allergen alters human bronchial epithelium DNA methylation. *J. Allergy Clin. Immunol.* 139:112–21
40. Consales C, Toft G, Leter G, Bonde JP, Uccelli R, et al. 2016. Exposure to persistent organic pollutants and sperm DNA methylation changes in Arctic and European populations. *Environ. Mol. Mutagen.* 57:200–9
41. Conway K, Edmiston SN, Parrish E, Bryant C, Tse CK, et al. 2017. Breast tumor DNA methylation patterns associated with smoking in the Carolina Breast Cancer Study. *Breast Cancer Res. Treat.* 163:349–61
42. Corrales J, Kristofco LA, Steele WB, Yates BS, Breed CS, et al. 2015. Global assessment of bisphenol A in the environment: review and analysis of its occurrence and bioaccumulation. *Dose-Response* 13:1559325815598308
43. Dao T, Hong X, Wang X, Tang WY. 2015. Aberrant 5'-CpG methylation of cord blood TNF α associated with maternal exposure to polybrominated diphenyl ethers. *PLOS ONE* 10:e0138815
44. De Prins S, Koppen G, Jacobs G, Dons E, Van de Mieroop E, et al. 2013. Influence of ambient air pollution on global DNA methylation in healthy adults: a seasonal follow-up. *Environ. Int.* 59:418–24
45. Ding R, Jin Y, Liu X, Ye H, Zhu Z, et al. 2017. Dose- and time- effect responses of DNA methylation and histone H3K9 acetylation changes induced by traffic-related air pollution. *Sci. Rep.* 7:43737
46. Dolinoy DC. 2008. The agouti mouse model: an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome. *Nutr. Rev.* 66(Suppl. 1):S7–11

47. Drobná Z, Martin E, Kim KS, Smeester L, Bommarito P, et al. 2016. Analysis of maternal polymorphisms in arsenic (+3 oxidation state)-methyltransferase AS3MT and fetal sex in relation to arsenic metabolism and infant birth outcomes: implications for risk analysis. *Reprod. Toxicol.* 61:28–38
48. Duan H, He Z, Ma J, Zhang B, Sheng Z, et al. 2013. Global and MGMT promoter hypomethylation independently associated with genomic instability of lymphocytes in subjects exposed to high-dose polycyclic aromatic hydrocarbon. *Arch. Toxicol.* 87:2013–22
49. Dunaway KW, Islam MS, Coulson RL, Lopez SJ, Vogel Ciernia A, et al. 2016. Cumulative impact of polychlorinated biphenyl and large chromosomal duplications on DNA methylation, chromatin, and expression of autism candidate genes. *Cell Rep.* 17:3035–48
50. Engström K, Wojdacz TK, Marabita F, Ewels P, Käller M, et al. 2017. Transcriptomics and methylomics of CD4-positive T cells in arsenic-exposed women. *Arch. Toxicol.* 91:2067–78
51. Everson TM, Armstrong DA, Jackson BP, Green BB, Karagas MR, Marsit CJ. 2016. Maternal cadmium, placental *PCDHAC1*, and fetal development. *Reprod. Toxicol.* 65:263–71
52. Faulk C, Kim JH, Anderson OS, Nahar MS, Jones TR, et al. 2016. Detection of differential DNA methylation in repetitive DNA of mice and humans perinatally exposed to bisphenol A. *Epigenetics* 11:489–500
53. Faulk C, Kim JH, Jones TR, McEachin RC, Nahar MS, et al. 2015. Bisphenol A-associated alterations in genome-wide DNA methylation and gene expression patterns reveal sequence-dependent and non-monotonic effects in human fetal liver. *Environ. Epigenet.* 1:dvv006
54. Ferrario D, Gribaldo L, Hartung T. 2016. Arsenic exposure and immunotoxicity: a review including the possible influence of age and sex. *Curr. Environ. Health Rep.* 3:1–12
55. Flom JD, Ferris JS, Liao Y, Tehranifar P, Richards CB, et al. 2011. Prenatal smoke exposure and genomic DNA methylation in a multiethnic birth cohort. *Cancer Epidemiol. Biomark. Prev.* 20:2518–23
56. Fraga MF, Esteller M. 2007. Epigenetics and aging: the targets and the marks. *Trends Genet.* 23:413–18
57. Fryer AA, Emes RD, Ismail KM, Haworth KE, Mein C, et al. 2011. Quantitative, high-resolution epigenetic profiling of CpG loci identifies associations with cord blood plasma homocysteine and birth weight in humans. *Epigenetics* 6:86–94
58. Fryer AA, Nafee TM, Ismail KM, Carroll WD, Emes RD, Farrell WE. 2009. LINE-1 DNA methylation is inversely correlated with cord plasma homocysteine in man: a preliminary study. *Epigenetics* 4:394–98
59. Gilliland FD, Harms HJ, Crowell RE, Li Y-F, Willink R, Belinsky SA. 2002. Glutathione S-transferase P1 and NADPH quinone oxidoreductase polymorphisms are associated with aberrant promoter methylation of P16^{INK4a} and O⁶-methylguanine-DNA methyltransferase in sputum. *Cancer Res.* 62:2248–52
60. Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, et al. 2011. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. *Diabetes* 60:1528–34
61. Gonseth S, Roy R, Houseman EA, de Smith AJ, Zhou M, et al. 2015. Periconceptional folate consumption is associated with neonatal DNA methylation modifications in neural crest regulatory and cancer development genes. *Epigenetics* 10:1166–76
62. Goodrich JM, Basu N, Franzblau A, Dolinoy DC. 2013. Mercury biomarkers and DNA methylation among Michigan dental professionals. *Environ. Mol. Mutagen.* 54:195–203
63. Goodrich JM, Reddy P, Naidoo RN, Asharam K, Batterman S, Dolinoy DC. 2016. Prenatal exposures and DNA methylation in newborns: a pilot study in Durban, South Africa. *Environ. Sci. Process. Impacts* 18:908–17
64. Goodrich JM, Sánchez BN, Dolinoy DC, Zhang Z, Hernandez-Ávila M, et al. 2015. Quality control and statistical modeling for environmental epigenetics: a study on in utero lead exposure and DNA methylation at birth. *Epigenetics* 10:19–30
65. Green BB, Karagas MR, Punshon T, Jackson BP, Robbins DJ, et al. 2016. Epigenome-wide assessment of DNA methylation in the placenta and arsenic exposure in the New Hampshire Birth Cohort Study (USA). *Environ. Health Perspect.* 124:1253–60
66. Gudsnuk K, Champagne FA. 2012. Epigenetic influence of stress and the social environment. *ILAR J.* 53:279–88
67. Guerrero-Preston R, Goldman LR, Brebi-Mieville P, Ili-Gangas C, Lebron C, et al. 2010. Global DNA hypomethylation is associated with in utero exposure to cotinine and perfluorinated alkyl compounds. *Epigenetics* 5:539–46

68. Gunter TD, Philibert RA. 2015. Smoking, methylation at AHRR, and recidivism risk in a community correction sample of individuals at high risk for recidivism. *Behav. Sci. Law* 33:691–700
69. Guo L, Byun H-M, Zhong J, Motta V, Barupal J, et al. 2014. Effects of short-term exposure to inhalable particulate matter on DNA methylation of tandem repeats. *Environ. Mol. Mutagen.* 55:322–35
70. Hanna CW, Bloom MS, Robinson WP, Kim D, Parsons PJ, et al. 2012. DNA methylation changes in whole blood is associated with exposure to the environmental contaminants, mercury, lead, cadmium and bisphenol A, in women undergoing ovarian stimulation for IVF. *Hum. Reprod.* 27:1401–10
71. Heijmans BT, Tobi EW, Stein AD, Putter H, Blauw GJ, et al. 2008. Persistent epigenetic differences associated with prenatal exposure to famine in humans. *PNAS* 105:17046–49
72. Herbstman JB, Tang D, Zhu D, Qu L, Sjodin A, et al. 2012. Prenatal exposure to polycyclic aromatic hydrocarbons, benzo[α]pyrene-DNA adducts, and genomic DNA methylation in cord blood. *Environ. Health Perspect.* 120:733–38
73. Hernandez-Vargas H, Castelino J, Silver MJ, Dominguez-Salas P, Cros MP, et al. 2015. Exposure to aflatoxin B1 in utero is associated with DNA methylation in white blood cells of infants in The Gambia. *Int. J. Epidemiol.* 44:1238–48
74. Hew KM, Walker AI, Kohli A, Garcia M, Syed A, et al. 2015. Childhood exposure to ambient polycyclic aromatic hydrocarbons is linked to epigenetic modifications and impaired systemic immunity in T cells. *Clin. Exp. Allergy* 45:238–48
75. Ho SM, Johnson A, Tarapore P, Janakiram V, Zhang X, Leung YK. 2012. Environmental epigenetics and its implication on disease risk and health outcomes. *ILAR J.* 53:289–305
76. Hossain K, Suzuki T, Hasibuzzaman MM, Islam MS, Rahman A, et al. 2017. Chronic exposure to arsenic, LINE-1 hypomethylation, and blood pressure: a cross-sectional study in Bangladesh. *Environ. Health* 16:20
77. Hossain MB, Vahter M, Concha G, Broberg K. 2012. Environmental arsenic exposure and DNA methylation of the tumor suppressor gene *p16* and the DNA repair gene *MLH1*: effect of arsenic metabolism and genotype. *Metallomics* 4:1167–75
78. Hossain MB, Vahter M, Concha G, Broberg K. 2012. Low-level environmental cadmium exposure is associated with DNA hypomethylation in Argentinean women. *Environ. Health Perspect.* 120:879–84
79. Hou L, Zhang X, Zheng Y, Wang S, Dou C, et al. 2014. Altered methylation in tandem repeat element and elemental component levels in inhalable air particles. *Environ. Mol. Mutagen.* 55:256–65
80. Hoyo C, Daltveit AK, Iversen E, Benjamin-Neelon SE, Fuemmeler B, et al. 2014. Erythrocyte folate concentrations, CpG methylation at genomically imprinted domains, and birth weight in a multiethnic newborn cohort. *Epigenetics* 9:1120–30
81. Hoyo C, Murtha AP, Schildkraut JM, Jirtle RL, Demark-Wahnefried W, et al. 2011. Methylation variation at *IGF2* differentially methylated regions and maternal folic acid use before and during pregnancy. *Epigenetics* 6:928–36
82. Huen K, Yousefi P, Bradman A, Yan L, Harley KG, et al. 2014. Effects of age, sex, and persistent organic pollutants on DNA methylation in children. *Environ. Mol. Mutagen.* 55:209–22
83. Inbar-Feigenberg M, Choufani S, Butcher DT, Roifman M, Weksberg R. 2013. Basic concepts of epigenetics. *Fertil. Steril.* 99:607–15
84. Intarasunanont P, Navasumrit P, Waraprasit S, Chaisatra K, Suk WA, et al. 2012. Effects of arsenic exposure on DNA methylation in cord blood samples from newborn babies and in a human lymphoblast cell line. *Environ. Health* 11:31
85. Itoh H, Iwasaki M, Kasuga Y, Yokoyama S, Onuma H, et al. 2014. Association between serum organochlorines and global methylation level of leukocyte DNA among Japanese women: a cross-sectional study. *Sci. Total Environ.* 490:603–9
86. Ivorra C, Fraga MF, Bayón GF, Fernández AF, Garcia-Vicent C, et al. 2015. DNA methylation patterns in newborns exposed to tobacco in utero. *J. Transl. Med.* 13:25
87. Janssen BG, Byun HM, Gyselaers W, Lefebvre W, Baccarelli AA, Nawrot TS. 2015. Placental mitochondrial methylation and exposure to airborne particulate matter in the early life environment: An ENVIRONAGE birth cohort study. *Epigenetics* 10:536–44
88. Janssen BG, Godderis L, Pieters N, Poels K, Kiciński M, et al. 2013. Placental DNA hypomethylation in association with particulate air pollution in early life. *Part Fibre Toxicol.* 10:22

89. Janssen BG, Gyselaers W, Byun H-M, Roels HA, Cuypers A, et al. 2017. Placental mitochondrial DNA and *CYP1A1* gene methylation as molecular signatures for tobacco smoke exposure in pregnant women and the relevance for birth weight. *J. Transl. Med.* 15:5
90. Jimenez-Garza O, Baccarelli AA, Byun HM, Marquez-Gamino S, Barron-Vivanco BS, Albores A. 2015. CYP2E1 epigenetic regulation in chronic, low-level toluene exposure: relationship with oxidative stress and smoking habit. *Toxicol. Appl. Pharmacol.* 286:207–15
91. Jin S, Lee YK, Lim YC, Zheng Z, Lin XM, et al. 2013. Global DNA hypermethylation in down syndrome placenta. *PLOS Genet.* 9:e1003515
92. Jones PA. 2012. Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat. Rev. Genet.* 13:484–92
93. Joubert BR, den Dekker HT, Felix JF, Bohlin J, Ligthart S, et al. 2016. Maternal plasma folate impacts differential DNA methylation in an epigenome-wide meta-analysis of newborns. *Nat. Commun.* 7:10577
94. Joubert BR, Håberg SE, Nilsen RM, Wang X, Vollset SE, et al. 2012. 450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. *Environ. Health Perspect.* 120:1425–31
95. Jung KH, Torrone D, Lovinsky-Desir S, Perzanowski M, Bautista J, et al. 2017. Short-term exposure to PM_{2.5} and vanadium and changes in asthma gene DNA methylation and lung function decrements among urban children. *Respir. Res.* 18:63
96. Kappil MA, Li Q, Li A, Dassanayake PS, Xia Y, et al. 2016. *In utero* exposures to environmental organic pollutants disrupt epigenetic marks linked to fetoplacental development. *Environ. Epigenet.* 2:dvv013
97. Kile ML, Baccarelli A, Hoffman E, Tarantini L, Quamruzzaman Q, et al. 2012. Prenatal arsenic exposure and DNA methylation in maternal and umbilical cord blood leukocytes. *Environ. Health Perspect.* 120:1061–66
98. Kile ML, Fang S, Baccarelli AA, Tarantini L, Cavallari J, Christiani DC. 2013. A panel study of occupational exposure to fine particulate matter and changes in DNA methylation over a single workday and years worked in boilermaker welders. *Environ. Health* 12:47
99. Kim JH, Rozek LS, Soliman AS, Sartor MA, Hablas A, et al. 2013. Bisphenol A-associated epigenomic changes in prepubescent girls: a cross-sectional study in Gharbiah, Egypt. *Environ. Health* 12:33
100. Kim K-Y, Kim D-S, Lee S-K, Lee I-K, Kang J-H, et al. 2010. Association of low-dose exposure to persistent organic pollutants with global DNA hypomethylation in healthy Koreans. *Environ. Health Perspect.* 118:370–74
101. Kim YH, Lee YS, Lee DH, Kim DS. 2016. Polycyclic aromatic hydrocarbons are associated with insulin receptor substrate 2 methylation in adipose tissues of Korean women. *Environ. Res.* 150:47–51
102. King K, Murphy S, Hoyo C. 2015. Epigenetic regulation of newborns' imprinted genes related to gestational growth: patterning by parental race/ethnicity and maternal socioeconomic status. *J. Epidemiol. Community Health* 69:639–47
103. Kippler M, Engström K, Mlakar SJ, Bottai M, Ahmed S, et al. 2013. Sex-specific effects of early life cadmium exposure on DNA methylation and implications for birth weight. *Epigenetics* 8:494–503
104. Kobayashi S, Azumi K, Goudarzi H, Araki A, Miyashita C, et al. 2017. Effects of prenatal perfluoroalkyl acid exposure on cord blood *IGF2/H19* methylation and ponderal index: the Hokkaido Study. *J. Expo. Sci. Environ. Epidemiol.* 27:251–59
105. Koestler DC, Avissar-Whiting M, Houseman EA, Karagas MR, Marsit CJ. 2013. Differential DNA methylation in umbilical cord blood of infants exposed to low levels of arsenic in utero. *Environ. Health Perspect.* 121:971–77
106. Kohli RM, Zhang Y. 2013. TET enzymes, TDG and the dynamics of DNA demethylation. *Nature* 502:472–79
107. Kok DE, Dhonukshe-Rutten RA, Lute C, Heil SG, Uitterlinden AG, et al. 2015. The effects of long-term daily folic acid and vitamin B12 supplementation on genome-wide DNA methylation in elderly subjects. *Clin. Epigenetics* 7:121
108. Ladd-Acosta C, Shu C, Lee BK, Gidaya N, Singer A, et al. 2016. Presence of an epigenetic signature of prenatal cigarette smoke exposure in childhood. *Environ. Res.* 144:139–48
109. Lam LL, Emberly E, Fraser HB, Neumann SM, Chen E, et al. 2012. Factors underlying variable DNA methylation in a human community cohort. *PNAS* 109(Suppl. 2):17253–60

110. Lambrou A, Baccarelli A, Wright RO, Weisskopf M, Bollati V, et al. 2012. Arsenic exposure and DNA methylation among elderly men. *Epidemiology* 23:668–76
111. Lee DH, Jacobs DR Jr., Porta M. 2009. Hypothesis: a unifying mechanism for nutrition and chemicals as lifelong modulators of DNA hypomethylation. *Environ. Health Perspect.* 117:1799–802
112. Lee J, Kalia V, Perera F, Herbstman J, Li T, et al. 2017. Prenatal airborne polycyclic aromatic hydrocarbon exposure, LINE1 methylation and child development in a Chinese cohort. *Environ. Int.* 99:315–20
113. Leter G, Consoles C, Eleuteri P, Uccelli R, Specht IO, et al. 2014. Exposure to perfluoroalkyl substances and sperm DNA global methylation in Arctic and European populations. *Environ. Mol. Mutagen.* 55:591–600
114. Li C, Yang X, Xu M, Zhang J, Sun N. 2013. Epigenetic marker (LINE-1 promoter) methylation level was associated with occupational lead exposure. *Clin. Toxicol.* 51:225–29
115. Li W, Deng J, Wang SS, Ma L, Pei J, et al. 2014. Association of methylation of the RAR- β gene with cigarette smoking in non-small cell lung cancer with Southern-Central Chinese population. *Asian Pac. J. Cancer Prevent.* 15:10937–41
116. Lind L, Penell J, Luttrupp K, Nordfors L, Syvänen AC, et al. 2013. Global DNA hypermethylation is associated with high serum levels of persistent organic pollutants in an elderly population. *Environ. Int.* 59:456–61
117. Loucks EB, Huang YT, Agha G, Chu S, Eaton CB, et al. 2016. Epigenetic mediators between childhood socioeconomic disadvantage and mid-life body mass index: the New England Family Study. *Psychosom. Med.* 78:1053–65
118. Maccani JZ, Koestler DC, Houseman EA, Marsit CJ, Kelsey KT. 2013. Placental DNA methylation alterations associated with maternal tobacco smoking at the *RUNX3* gene are also associated with gestational age. *Epigenomics* 5:619–30
119. Maccani JZ, Koestler DC, Lester B, Houseman EA, Armstrong DA, et al. 2015. Placental DNA methylation related to both infant toenail mercury and adverse neurobehavioral outcomes. *Environ. Health Perspect.* 123:723–29
120. Madrigano J, Baccarelli A, Mittleman MA, Wright RO, Sparrow D, et al. 2011. Prolonged exposure to particulate pollution, genes associated with glutathione pathways, and DNA methylation in a cohort of older men. *Environ. Health Perspect.* 119:977–82
121. Majumdar S, Chanda S, Ganguli B, Mazumder DN, Lahiri S, Dasgupta UB. 2010. Arsenic exposure induces genomic hypermethylation. *Environ. Toxicol.* 25:315–18
122. Mansell T, Novakovic B, Meyer B, Rzehak P, Vuillermin P, et al. 2016. The effects of maternal anxiety during pregnancy on *IGF2/H19* methylation in cord blood. *Transl. Psychiatry* 6:e765
123. Markunas CA, Xu Z, Harlid S, Wade PA, Lie RT, et al. 2014. Identification of DNA methylation changes in newborns related to maternal smoking during pregnancy. *Environ. Health Perspect.* 122:1147–53
124. Martin E, Smeester L, Bommarito PA, Grace MR, Boggess K, et al. 2017. Sexual epigenetic dimorphism in the human placenta: implications for susceptibility during the prenatal period. *Epigenomics* 9:267–78
125. Martin EM, Fry RC. 2016. A cross-study analysis of prenatal exposures to environmental contaminants and the epigenome: support for stress-responsive transcription factor occupancy as a mediator of gene-specific CpG methylation patterning. *Environ. Epigenet.* 2:dvv011
126. Mathers JC. 2007. Early nutrition: impact on epigenetics. *Forum Nutr.* 60:42–48
127. McKay JA, Groom A, Potter C, Coneyworth LJ, Ford D, et al. 2012. Genetic and non-genetic influences during pregnancy on infant global and site specific DNA methylation: role for folate gene variants and vitamin B₁₂. *PLOS ONE* 7:e33290
128. Mitchell MM, Woods R, Chi LH, Schmidt RJ, Pessah IN, et al. 2012. Levels of select PCB and PBDE congeners in human postmortem brain reveal possible environmental involvement in 15q11-q13 duplication autism spectrum disorder. *Environ. Mol. Mutagen.* 53:589–98
129. Mohanty AF, Farin FM, Bammler TK, MacDonald JW, Afsharinejad Z, et al. 2015. Infant sex-specific placental cadmium and DNA methylation associations. *Environ. Res.* 138:74–81
130. Montrose L, Ward TJ, Semmens EO, Cho YH, Brown B, Noonan CW. 2017. Dietary intake is associated with respiratory health outcomes and DNA methylation in children with asthma. *Allergy Asthma Clin. Immunol.* 13:12

131. Mozhui K, Smith AK, Tylavsky FA. 2015. Ancestry dependent DNA methylation and influence of maternal nutrition. *PLOS ONE* 10:e0118466
132. Murphy SK, Huang Z, Hoyo C. 2012. Differentially methylated regions of imprinted genes in prenatal, perinatal and postnatal human tissues. *PLOS ONE* 7:e40924
133. Nahar MS, Kim JH, Sartor MA, Dolinoy DC. 2014. Bisphenol A-associated alterations in the expression and epigenetic regulation of genes encoding xenobiotic metabolizing enzymes in human fetal liver. *Environ. Mol. Mutagen.* 55:184–95
134. Nahar MS, Liao C, Kannan K, Harris C, Dolinoy DC. 2015. In utero bisphenol A concentration, metabolism, and global DNA methylation across matched placenta, kidney, and liver in the human fetus. *Chemosphere* 124:54–60
135. Needham BL, Smith JA, Zhao W, Wang X, Mukherjee B, et al. 2015. Life course socioeconomic status and DNA methylation in genes related to stress reactivity and inflammation: the multi-ethnic study of atherosclerosis. *Epigenetics* 10:958–69
136. Niedzwiecki MM, Hall MN, Liu X, Oka J, Harper KN, et al. 2013. A dose-response study of arsenic exposure and global methylation of peripheral blood mononuclear cell DNA in Bangladeshi adults. *Environ. Health Perspect.* 121:1306–12
137. Niedzwiecki MM, Liu X, Hall MN, Thomas T, Slavkovich V, et al. 2015. Sex-specific associations of arsenic exposure with global DNA methylation and hydroxymethylation in leukocytes: results from two studies in Bangladesh. *Cancer Epidemiol. Biomark. Prev.* 24:1748–57
138. Nye MD, King KE, Darrah TH, Maguire R, Jima DD, et al. 2016. Maternal blood lead concentrations, DNA methylation of *MEG3* DMR regulating the *DLK1/MEG3* imprinted domain and early growth in a multiethnic cohort. *Environ. Epigenet.* 2:dvv009
139. Olden K, Lin YS, Gruber D, Sonawane B. 2014. Epigenome: biosensor of cumulative exposure to chemical and nonchemical stressors related to environmental justice. *Am. J. Public Health* 104:1816–21
140. Ouyang B, Baxter CS, Lam H-M, Yeramane S, Levin L, et al. 2012. Hypomethylation of *dual specificity phosphatase 22* promoter correlates with duration of service in firefighters and is inducible by low-dose benzo[a]pyrene. *J. Occup. Environ. Med.* 54:774–80
141. Park SY, Kim K-S, Lee Y-M, Kim M-J, Jacobs DR Jr., et al. 2015. Persistent organic pollutants and promoter hypermethylation of the *O⁶-methylguanine-DNA methyltransferase* gene. *Biomarkers* 20:136–42
142. Pauwels S, Duca RC, Devlieger R, Freson K, Straetmans D, et al. 2016. Maternal methyl-group donor intake and global DNA (hydroxy)methylation before and during pregnancy. *Nutrients* 8:474
143. Pauwels S, Ghosh M, Duca RC, Bekaert B, Freson K, et al. 2017. Dietary and supplemental maternal methyl-group donor intake and cord blood DNA methylation. *Epigenetics* 12:1–10
144. Pauwels S, Ghosh M, Duca RC, Bekaert B, Freson K, et al. 2017. Maternal intake of methyl-group donors affects DNA methylation of metabolic genes in infants. *Clin. Epigenet.* 9:16
145. Pauwels S, Truijen I, Ghosh M, Duca RC, Langie SAS, et al. 2017. The effect of paternal methyl-group donor intake on offspring DNA methylation and birth weight. *J. Dev. Origins Health Dis.* 8:311–21
146. Pavanello S, Bollati V, Pesatori AC, Kapka L, Bolognesi C, et al. 2009. Global and gene-specific promoter methylation changes are related to anti-B[a]PDE-DNA adduct levels and influence micronuclei levels in polycyclic aromatic hydrocarbon-exposed individuals. *Int. J. Cancer* 125:1692–97
147. Pavanello S, Pesatori AC, Dioni L, Hoxha M, Bollati V, et al. 2010. Shorter telomere length in peripheral blood lymphocytes of workers exposed to polycyclic aromatic hydrocarbons. *Carcinogenesis* 31:216–21
148. Peluso ME, Munnia A, Bollati V, Srivatanakul P, Jedpiyawongse A, et al. 2014. Aberrant methylation of hypermethylated-in-cancer-1 and exocyclic DNA adducts in tobacco smokers. *Toxicol. Sci.* 137:47–54
149. Perera F, Tang W-Y, Herbstman J, Tang D, Levin L, et al. 2009. Relation of DNA methylation of 5'-CpG island of *ACSL3* to transplacental exposure to airborne polycyclic aromatic hydrocarbons and childhood asthma. *PLOS ONE* 4:e4488
150. Philibert RA, Beach SR, Brody GH. 2012. Demethylation of the aryl hydrocarbon receptor repressor as a biomarker for nascent smokers. *Epigenetics* 7:1331–38
151. Pilsner JR, Hall MN, Liu X, Ahsan H, Ilievski V, et al. 2011. Associations of plasma selenium with arsenic and genomic methylation of leukocyte DNA in Bangladesh. *Environ. Health Perspect.* 119:113–18
152. Pilsner JR, Hall MN, Liu X, Ilievski V, Slavkovich V, et al. 2012. Influence of prenatal arsenic exposure and newborn sex on global methylation of cord blood DNA. *PLOS ONE* 7:e37147

153. Pilsner JR, Liu X, Ahsan H, Ilievski V, Slavkovich V, et al. 2007. Genomic methylation of peripheral blood leukocyte DNA: influences of arsenic and folate in Bangladeshi adults. *Am. J. Clin. Nutr.* 86:1179–86
154. Pusceddu I, Herrmann M, Kirsch SH, Werner C, Hubner U, et al. 2016. Prospective study of telomere length and LINE-1 methylation in peripheral blood cells: the role of B vitamins supplementation. *Eur. J. Nutr.* 55:1863–73
155. Rager JE, Tilley SK, Tulenko SE, Smeester L, Ray PD, et al. 2015. Identification of novel gene targets and putative regulators of arsenic-associated DNA methylation in human urothelial cells and bladder cancer. *Chem. Res. Toxicol.* 28:1144–55
156. Reichetzeder C, Dwi Putra SE, Pfab T, Slowinski T, Neuber C, et al. 2016. Increased global placental DNA methylation levels are associated with gestational diabetes. *Clin. Epigenet.* 8:82
157. Reynolds LM, Magid HS, Chi GC, Lohman K, Barr RG, et al. 2017. Secondhand tobacco smoke exposure associations with DNA methylation of the aryl hydrocarbon receptor repressor. *Nicotine Tob. Res.* 19:442–51
158. Reynolds LM, Wan M, Ding J, Taylor JR, Lohman K, et al. 2015. DNA methylation of the aryl hydrocarbon receptor repressor associations with cigarette smoking and subclinical atherosclerosis. *Circ. Cardiovasc. Genet.* 8:707–16
159. Rojas D, Rager JE, Smeester L, Bailey KA, Drobná Z, et al. 2015. Prenatal arsenic exposure and the epigenome: identifying sites of 5-methylcytosine alterations that predict functional changes in gene expression in newborn cord blood and subsequent birth outcomes. *Toxicol. Sci.* 143:97–106
160. Rotroff DM, Joubert BR, Marvel SW, Håberg SE, Wu MC, et al. 2016. Maternal smoking impacts key biological pathways in newborns through epigenetic modification in utero. *BMC Genom.* 17:976
161. Ruiz-Hernandez A, Kuo CC, Rentero-Garrido P, Tang WY, Redon J, et al. 2015. Environmental chemicals and DNA methylation in adults: a systematic review of the epidemiologic evidence. *Clin. Epigenet.* 7:55
162. Rusiecki JA, Baccarelli A, Bollati V, Tarantini L, Moore LE, Bonfeld-Jorgensen EC. 2008. Global DNA hypomethylation is associated with high serum-persistent organic pollutants in Greenlandic Inuit. *Environ. Health Perspect.* 116:1547–52
163. Rusiecki JA, Beane Freeman LE, Bonner MR, Alexander M, Chen L, et al. 2017. High pesticide exposure events and DNA methylation among pesticide applicators in the agricultural health study. *Environ. Mol. Mutagen.* 58:19–29
164. Rzehak P, Saffery R, Reischl E, Covic M, Wahl S, et al. 2016. Maternal smoking during pregnancy and DNA-methylation in children at age 5.5 years: epigenome-wide-analysis in the European Childhood Obesity Project (CHOP)-study. *PLOS ONE* 11:e0155554
165. Saenen ND, Vrijens K, Janssen BG, Roels HA, Neven KY, et al. 2017. Lower placental leptin promoter methylation in association with fine particulate matter air pollution during pregnancy and placental nitrosative stress at birth in the ENVIRONAGE cohort. *Environ. Health Perspect.* 125:262–68
166. Salam MT, Byun HM, Lurmann F, Breton CV, Wang X, et al. 2012. Genetic and epigenetic variations in inducible nitric oxide synthase promoter, particulate pollution, and exhaled nitric oxide levels in children. *J. Allergy Clin. Immunol.* 129:232–39.e1–7
167. Sanchez-Cespedes M, Decker PA, Doffek KM, Esteller M, Westra WH, et al. 2001. Increased loss of chromosome 9p21 but not p16 inactivation in primary non-small cell lung cancer from smokers. *Cancer Res.* 61:2092–96
168. Sanchez-Guerra M, Zheng Y, Osorio-Yanez C, Zhong J, Chervona Y, et al. 2015. Effects of particulate matter exposure on blood 5-hydroxymethylation: results from the Beijing truck driver air pollution study. *Epigenetics* 10:633–42
169. Sanders AP, Smeester L, Rojas D, DeBusscher T, Wu MC, et al. 2014. Cadmium exposure and the epigenome: exposure-associated patterns of DNA methylation in leukocytes from mother-baby pairs. *Epigenetics* 9:212–21
170. Schoeters G, Den Hond E, Zuurbier M, Naginiene R, van den Hazel P, et al. 2006. Cadmium and children: exposure and health effects. *Acta Paediatr. Suppl.* 95:50–54
171. Schwender K, Holtkötter H, Johann KS, Glaub A, Schürenkamp M, et al. 2016. Sudden infant death syndrome: exposure to cigarette smoke leads to hypomethylation upstream of the growth factor independent 1 (GFI1) gene promoter. *Forensic Sci. Med. Patbol.* 12:399–406

172. Sen A, Cingolani P, Senut MC, Land S, Mercado-Garcia A, et al. 2015. Lead exposure induces changes in 5-hydroxymethylcytosine clusters in CpG islands in human embryonic stem cells and umbilical cord blood. *Epigenetics* 10:607–21
173. Sen A, Heredia N, Senut MC, Hess M, Land S, et al. 2015. Early life lead exposure causes gender-specific changes in the DNA methylation profile of DNA extracted from dried blood spots. *Epigenomics* 7:379–93
174. Sen A, Heredia N, Senut MC, Land S, Hollocher K, et al. 2015. Multigenerational epigenetic inheritance in humans: DNA methylation changes associated with maternal exposure to lead can be transmitted to the grandchildren. *Sci. Rep.* 5:14466
175. Shenker NS, Ueland PM, Polidoro S, van Veldhoven K, Ricceri F, et al. 2013. DNA methylation as a long-term biomarker of exposure to tobacco smoke. *Epidemiology* 24:712–16
176. Skinner MK. 2015. Environmental epigenetics and a unified theory of the molecular aspects of evolution: a neo-Lamarckian concept that facilitates neo-Darwinian evolution. *Genome Biol. Evol.* 7:1296–302
177. Smeester L, Rager JE, Bailey KA, Guan X, Smith N, et al. 2011. Epigenetic changes in individuals with arsenicosis. *Chem. Res. Toxicol.* 24:165–67
178. Sominen HK, Zhang X, Biagini Myers JM, Kovacic MB, Ulm A, et al. 2016. Ten-eleven translocation 1 (TET1) methylation is associated with childhood asthma and traffic-related air pollution. *J. Allergy Clin. Immunol.* 137:797–805.e5
179. Steegers-Theunissen RP, Obermann-Borst SA, Kremer D, Lindemans J, Siebel C, et al. 2009. Periconceptional maternal folic acid use of 400 microg per day is related to increased methylation of the *IGF2* gene in the very young child. *PLOS ONE* 4:e7845
180. Subramanyam MA, Diez-Roux AV, Pilsner JR, Villamor E, Donohue KM, et al. 2013. Social factors and leukocyte DNA methylation of repetitive sequences: the multi-ethnic study of atherosclerosis. *PLOS ONE* 8:e54018
181. Suter M, Abramovici A, Showalter L, Hu M, Shope CD, et al. 2010. In utero tobacco exposure epigenetically modifies placental CYP1A1 expression. *Metabolism* 59:1481–90
182. Suter M, Ma J, Harris A, Patterson L, Brown KA, et al. 2011. Maternal tobacco use modestly alters correlated epigenome-wide placental DNA methylation and gene expression. *Epigenetics* 6:1284–94
183. Tao MH, Zhou J, Rialdi AP, Martinez R, Dabek J, et al. 2014. Indoor air pollution from solid fuels and peripheral blood DNA methylation: findings from a population study in Warsaw, Poland. *Environ. Res.* 134:325–30
184. Tellez-Plaza M, Tang WY, Shang Y, Umans JG, Francesconi KA, et al. 2014. Association of global DNA methylation and global DNA hydroxymethylation with metals and other exposures in human blood DNA samples. *Environ. Health Perspect.* 122:946–54
185. Turner PC, Collinson AC, Cheung YB, Gong Y, Hall AJ, et al. 2007. Aflatoxin exposure in utero causes growth faltering in Gambian infants. *Int. J. Epidemiol.* 36:1119–25
186. Ulrich CM, Toriola AT, Koepf LM, Sandifer T, Poole EM, et al. 2012. Metabolic, hormonal and immunological associations with global DNA methylation among postmenopausal women. *Epigenetics* 7:1020–28
187. Vidal AC, Semenova V, Darrah T, Vengosh A, Huang Z, et al. 2015. Maternal cadmium, iron and zinc levels, DNA methylation and birth weight. *BMC Pharmacol. Toxicol.* 16:20
188. Virani S, Rentschler KM, Nishijo M, Ruangyuttikarn W, Swaddiwudhipong W, et al. 2016. DNA methylation is differentially associated with environmental cadmium exposure based on sex and smoking status. *Chemosphere* 145:284–90
189. Wadhwa PD, Buss C, Entringer S, Swanson JM. 2009. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. *Semin. Reprod. Med.* 27:358–68
190. Wang C, Chen R, Cai J, Shi J, Yang C, et al. 2016. Personal exposure to fine particulate matter and blood pressure: a role of angiotensin converting enzyme and its DNA methylation. *Environ. Int.* 94:661–66
191. Wang IJ, Chen SL, Lu TP, Chuang EY, Chen PC. 2013. Prenatal smoke exposure, DNA methylation, and childhood atopic dermatitis. *Clin. Exp. Allergy* 43:535–43
192. Wang TC, Song YS, Wang H, Zhang J, Yu SF, et al. 2012. Oxidative DNA damage and global DNA hypomethylation are related to folate deficiency in chromate manufacturing workers. *J. Hazard. Mater.* 213–214:440–46

193. Watkins DJ, Wellenius GA, Butler RA, Bartell SM, Fletcher T, Kelsey KT. 2014. Associations between serum perfluoroalkyl acids and LINE-1 DNA methylation. *Environ. Int.* 63:71–76
194. White AJ, Chen J, McCullough LE, Xu X, Cho YH, et al. 2015. Polycyclic aromatic hydrocarbon (PAH)-DNA adducts and breast cancer: modification by gene promoter methylation in a population-based study. *Cancer Causes Control* 26:1791–802
195. White AJ, Chen J, Teitelbaum SL, McCullough LE, Xu X, et al. 2016. Sources of polycyclic aromatic hydrocarbons are associated with gene-specific promoter methylation in women with breast cancer. *Environ. Res.* 145:93–100
196. Wilson AS, Power BE, Molloy PL. 2007. DNA hypomethylation and human diseases. *Biochim. Biophys. Acta* 1775:138–62
197. Wu HC, Wang Q, Yang HI, Tsai WY, Chen CJ, Santella RM. 2013. Global DNA methylation in a population with aflatoxin B1 exposure. *Epigenetics* 8:962–69
198. Yang P, Ma J, Zhang B, Duan H, He Z, et al. 2012. CpG site-specific hypermethylation of p16INK4 α in peripheral blood lymphocytes of PAH-exposed workers. *Cancer Epidemiol. Biomark. Prev.* 21:182–90
199. Yang TY, Hsu LI, Chiu AW, Pu YS, Wang SH, et al. 2014. Comparison of genome-wide DNA methylation in urothelial carcinomas of patients with and without arsenic exposure. *Environ. Res.* 128:57–63
200. Zhang Y-J, Wu H-C, Yazici H, Yu M-W, Lee P-H, Santella RM. 2012. Global hypomethylation in hepatocellular carcinoma and its relationship to aflatoxin B₁ exposure. *World J. Hepatol.* 4:169–75
201. Zhao Y, Liu P, Wang J, Xiao X, Meng X, Zhang Y. 2016. Umbilical cord blood PBDEs concentrations are associated with placental DNA methylation. *Environ. Int.* 97:1–6
202. Zhu H, Wang G, Qian J. 2016. Transcription factors as readers and effectors of DNA methylation. *Nat. Rev. Genet.* 17:551–65
203. Zhu X, Li J, Deng S, Yu K, Liu X, et al. 2016. Genome-wide analysis of DNA methylation and cigarette smoking in a Chinese population. *Environ. Health Perspect.* 124:966–73