Epigenetics as a Biomarker for Early-Life Environmental Exposure

Rose Schrott[1] · Ashley Song[1] · Christine Ladd-Acosta[2]

Abstract

Purpose of Review There is interest in evaluating the developmental origins of health and disease (DOHaD) which emphasizes the role of prenatal and early-life environments on non-communicable health outcomes throughout the life course. The ability to rigorously assess and identify early-life risk factors for later health outcomes, including those with childhood onset, in large population samples is often limited due to measurement challenges such as impractical costs associated with prospective studies with a long follow-up duration, short half-lives for some environmental toxicants, and lack of biomarkers that capture inter-individual differences in biologic response to external environments.

Recent Findings Epigenomic patterns, and DNA methylation in particular, have emerged as a potential objective biomarker to address some of these study design and exposure measurement challenges. In this article, we summarize the literature to date on epigenetic changes associated with specific prenatal and early-life exposure domains as well as exposure mixtures in human observational studies and their biomarker potential. Additionally, we highlight evidence for other types of epigenetic patterns to serve as exposure biomarkers.

Summary Evidence strongly supports epigenomic biomarkers of exposure that are detectable across the lifespan and across a range of exposure domains. Current and future areas of research in this field seek to expand these lines of evidence to other environmental exposures, to determine their specificity, and to develop predictive algorithms and methylation scores that can be used to evaluate early-life risk factors for health outcomes across the life span.

Keywords Early life · Environment · Exposure · Epigenetics · Biomarker · DNA methylation

Introduction

The developmental origins of health and disease (DOHaD) hypothesis is rooted in understanding the role of the early-life environment on health outcomes across the lifespan. This hypothesis stems from evidence built over decades demonstrating that environments encountered in utero and during early life are associated with future non-communicable disease risk [1–3]. Most DOHaD studies to date have focused on growth, nutrition, stress, and other exposures that are feasible to measure using questionnaire or medical or other record-based data due to practical challenges with prospectively collecting exposure data from the prenatal and early-life windows and health outcomes in childhood, adolescence, and adulthood. Additional challenges to rigorously evaluating DOHaD include the short biologic half-life of many existing environmental toxicants (e.g., cotinine, phthalates, bisphenol A), self-report or external measures may not capture inter-individual differences in biologic response to an exposure or the "internal dose" experienced, and harmonization across studies due to different exposure measures. For these reasons, our ability to fully assess and identify prenatal and early-life risk factors associated with disease across the life course is limited. Thus, there is a need for effective molecular biomarkers that can be used to predict an individual's exposure history and are harmonizable across studies to identify early-life exposures associated with future disease risk.

Ideal biomarkers are specific, long-lasting in the body, and reflect the dose of exposure. Additionally, they must

✉ Christine Ladd-Acosta
claddac1@jh.edu

1 Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

2 Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 N. Wolfe Street, Baltimore, MD 21205, USA

be present in easily accessible biospecimens [4]. Contrary to mechanistic studies that would require examination of an affected tissue to determine the relationship between an exposure and a health outcome, assessment of an affected tissue is not required to establish an effective biomarker. However, given that many molecular modifications that are often used as biomarkers are necessarily different across tissue types, this must be accounted for and considered when establishing and implementing biomarkers, and when looking across tissue types. Additionally, many substances have short half-lives; thus, more long-lasting molecular changes that are specific to an exposure can be a more accurate representation of an individual's past exposure. Thus, the ease and accessibility of the measurement matrix is critical, and tissues such as blood, cord blood, and saliva, are often used in studies of biomarkers. These features of a biomarker are especially important when considering how the environment encountered during critical windows of development, such as early life, can influence future health and disease. Epigenetic modifications provide a possible measure of prenatal and childhood exposures that could be used to fill this purpose.

Epigenetic modifications are mitotically heritable components of cellular material that do not result in an underlying change to the DNA sequence [5]. Multiple types of epigenetic modifications exist including DNA methylation, histone modifications, non-coding RNAs, and chromatin structure. These modifications play critical roles in cellular functions and organismal development and are reversible. Studies have shown that many of these modifications differ by environmental contexts and undergo drastic changes particularly during developmental periods [5].

DNA methylation is the best-studied epigenetic modification. DNA methylation is characterized by the addition of a methyl or hydroxymethyl group at the 5' carbon position of a cytosine base when a cytosine is followed by a guanine in the nucleotide sequence [6]. We refer to this as a CpG site. Over the past decade, evidence has mounted showing DNA methylation is responsive to prenatal and early-life environments, is often specific to a particular exposure, and can persist across the life course and is detectable later in life[4], making it a useful biomarker of exposure.

Other epigenetic modifications may also have utility as biomarkers including post-translational modifications of histones (PTMs) and non-coding RNAs (ncRNAs) [7, 8]. Inside the cell, DNA is packaged into chromatin by wrapping 147 base pairs around an octamer of histone proteins [7]. Covalent modifications such as methylation, acetylation, ubiquitylation, and phosphorylation can be made to the N- or C-terminal tails of histones to regulate DNA compaction and accessibility to transcriptional machinery [7]. It is well-established that PTMs change in response to the environment [9]. Relative to DNA methylation and PTMs, ncRNAs are a more recently studied type of epigenetic modification. While ncRNAs do not encode genes, they do possess unique, and diverse functions inside of the cell, though we are learning quickly that their content can change in response to environmental cues in an exposure and temporally specific manner [8].

In this review, we will provide a summary of the current literature describing how prenatal and early-life environmental exposures, across several exposure domains, have been shown to impact epigenetic patterns, measured from birth through adulthood, in human observational studies. Our exposure domains include environmental toxicants, human behaviors, and social environments experienced during the prenatal, perinatal, and early childhood windows. We also summarize emerging evidence for epigenetic patterns to capture exposure mixtures and statistical tools to enable exposure prediction and algorithms to build methylation scores that can be utilized as an exposure dosimeter/measure of current and/or past exposure.

Methods

The two main databases queried for this literature review were PubMed and Google Scholar. We restricted most of our search to the last 5 years (2017–2022, inclusive). For each search, we used combinations of keywords, examples of which are provided below. For exposures, we used keywords that referred to the broad class of exposure (e.g., "Pesticide," "Metal," "Phthalates," "Smoking," "Socioeconomic Position") as well as individual toxicants or factors (e.g., "Lead," "Folic Acid," "BPA," "Stress," "Tobacco"). We used these terms in combination with the exposure window (e.g., "Maternal," "in utero," "childhood"), and the measurement window (e.g., "birth," "childhood," "adolescence," "adulthood"). We also used terms specific to the tissue type (e.g., "cord blood," "placenta," "saliva," "blood," "buccal cell") that the epigenetic measurement was performed in. Terms specific to the type of epigenetic modification included "methylation," "chromatin," "histone," "microRNA," and "ncRNA," and "mixtures" was included when identifying studies of mixtures. An example of a complete search is as follows: "'prenatal' 'maternal smoking' 'DNA Methylation' 'cord blood'." For a comprehensive list of search terms used, please see Supplementary File 1.

Results

We queried the literature to identify reports of DNA methylation changes, present in any biospecimen type at birth, infancy (< 1 year of age), childhood, adolescence, or in adulthood, associated with prenatal and/or early-life

exposure to environmental factors with a focus on studies from 2017 to 2022. We did not assess inter- or transgenerational inheritance, nor did we summarize studies in animal or in vitro models because we focus on relevance to human studies seeking to utilize epigenetic biomarkers in epidemiology framework. We report these findings in Table 1, organized by the following exposure domains: (1) toxicant environmental exposures which included metals, endocrine disrupting compounds (EDCs), air pollutants, persistent organic pollutants (POPs), and pesticides; (2) behavioral including smoking (tobacco and nicotine), alcohol, illicit substance use, and diet and nutrition; and (3) social environmental factors including stress, socioeconomic position, and adverse childhood experiences (ACEs). Tables 2 and 3 report studies of early-life exposure across the same domains that identify methylation changes resulting from exposure to

environmental mixtures, or that report changes in epigenetic material other than DNA methylation, respectively.

DNA Methylation Changes Associated with Specific Environmental Factors

Most studies across all environmental exposures are focused on the effects of prenatal exposure on methylation changes in tissues collected at birth (Table 1). More than 20 studies assessed the impact of maternal metal exposure on DNA methylation changes at birth, though just two studies examined the impact of childhood metal exposure on the methylome [95, 96], identifying a gap in research that should be addressed. One study specifically assessed the persistent effects of prenatal mercury exposure on DNA methylation across the life course through repeated biospecimen

Table 1 Summary of studies between 2017 and 2022 of early-life exposures and DNA methylation changes across the life course

Exposure timing and type		Methylation Data Measurement Life Stage			
		Birth and Infancy < 1	**Childhood**	**Adolescence**	**Adulthood**
Environmental toxicant exposures					
Pre- and perinatal	Metals	Cord blood (*n* = 16 studies)[10●●, 11–25] Bloodspots (*n* = 1 study)[26] placenta (*n* = 2 studies) [27, 28]	Blood (*n* = 5 studies) [10●●, 11, 14, 17, 29] saliva (*n* = 1 study)[30]	Blood (*n* = 1 study) [31]	Buccal cells (*n* = 1 study)[32]
	EDCs (phthalates, bisphenols, flame retardants)	Cord blood (*n* = 12 studies)[33–44] placenta (*n* = 4 studies) [45–48]	Buccal cells (*n* = 1 study)[49] blood (*n* = 1 study)[50]	*none*	*none*
	Air Pollution	Cord blood (*n* = 12 studies)[51●, 52–62] placenta (*n* = 11 studies)[58, 61, 63–71]	Blood (*n* = 2 studies) [57, 72]	Blood (*n* = 1 study) [72] Saliva (*n* = 1 study) [73]	*none*
	POPs (Dioxins, PCBs, PAHs, PFAS)	Cord blood (*n* = 11 studies)[74–84] placenta (*n* = 3 studies) [85–87]	*none*	*none*	Blood (*n* = 1 study)[88●]
	Pesticides	Cord blood (*n* = 4 studies)[89–92]	Blood (*n* = 1 study) [93]	*none*	Blood (*n* = 1 study)[94●]
Childhood	Metals		Blood (*n* = 2 studies) [95, 96]	*none*	*none*
	EDCs (phthalates, bisphenols, flame retardants)		Blood (*n* = 3 studies) [97–99]	Blood (*n* = 1 study)[100●]	*none*
	Air pollution		Buccal cells (*n* = 1 study)[101] blood (*n* = 3 studies) [102–104] nasal epithelium (*n* = 2 studies)[105, 106]	*none*	*none*
	POPs (dioxins, PCBs, PAHs, PFAS)		Blood (*n* = 1 study) [107]	*none*	*none*
	Pesticides		*none*	*none*	*none*

Table 1 (continued)

Exposure timing and type		Methylation Data Measurement Life Stage			
		Birth and Infancy < 1	**Childhood**	**Adolescence**	**Adulthood**
Behavioral exposures					
Pre- and perinatal	Smoking (tobacco)	Cord blood ($n=12$ studies)[108–113, 114••, 115–119] placenta ($n=5$ studies) [120–124] bloodspots ($n=1$ study)[125]	Blood ($n=9$ studies) [126–128]	Blood ($n=3$ studies) [129–131]	Blood ($n=6$ studies) [130–132, 133••, 134, 135]
	Alcohol	Cord blood ($n=1$ study)[136] buccal cells ($n=1$ study)[137] placenta ($n=3$ studies) [137–140]	Saliva ($n=1$ study) [141] blood ($n=1$ study) [141] buccal cells ($n=2$ studies)[142••, 143]	*none*	*none*
	Illicit substance use	Placenta ($n=1$ study) [144] cord blood ($n=1$ study)[145] buccal cells ($n=2$ studies)[146, 147] saliva ($n=1$ study) [148]	Blood ($n=1$ study) [149]	*none*	*none*
	Diet/nutrition (folate, B12)	Cord blood ($n=15$ studies)[150–164] placenta ($n=1$ study) [165] mesenchymal stem cells ($n=1$ study) [166] blood ($n=1$ study) [167]	Blood ($n=1$ stud) [164] saliva ($n=1$ study) [168]	*None*	Saliva ($n=1$ study) [169••]
Childhood	Smoking (tobacco)		Blood ($n=1$ study) [128]	*None*	*None*
	Alcohol		*none*	*None*	*None*
	Illicit substance use		*none*	*None*	*None*
	Diet/nutrition (folate, B12)		Saliva ($n=1$ study) [170] blood ($n=1$ study) [171]	*None*	*None*
Social environmental exposures					
Pre- and perinatal	Stress	Cord blood ($n=8$ studies)[160, 172–178] placenta ($n=4$ studies) [173, 179–181] blood ($n=1$ study) [182]	*None*	*None*	*None*
	Socio-economic position	cord blood ($n=5$ studies)[183••, 184•, 185–187] placenta ($n=1$ study) [188]	Blood ($n=2$ studies) [183••, 184•]	Blood ($n=2$ studies) [183••, 184•]	*None*
	Adverse childhood experiences (ACEs)				

Table 1 (continued)

Exposure timing and type		Methylation Data Measurement Life Stage			
		Birth and Infancy < 1	**Childhood**	**Adolescence**	**Adulthood**
Childhood	Stress		*None*	*None*	*None*
	Socio-economic position		Buccal cells (*n* = 1 study)[189]	*none*	Blood (*n* = 2 studies) [190, 191]
	Adverse childhood experiences (ACEs)		Saliva (*n* = 3 studies) [192–194] blood (*n* = 2 studies) [193, 195] buccal cells (*n* = 1 study)[196] postmortem brain tissues (*n* = 1 study) [197]	Saliva (*n* = 1 study) [194] blood (*n* = 1 study) [198]	Blood (*n* = 10 studies) [190, 193, 199, 200••, 201–206] saliva (n = 5 studies) [193, 207–210] buccal cells (n = 2 studies)[200••, 211] bloodspots (n = 1 study) [212]

Table 2 Summary of studies of early-life exposure to mixtures and DNA methylation changes across the life course

Exposure timing and type		Methylation data measurement life stage		
		Birth and infancy < 1	**Childhood**	**Adulthood**
Environmental toxicant exposures				
Pre- and perinatal	Metals	Cord blood (*n* = 2)[213••, 214]	*None*	*None*
	EDCs (phthalates, bisphenols, flame retardants)	Placenta (*n* = 3)[215–217]	*None*	*None*
	POPs (dioxins, PCBs, PAHs, PFAS)	Cord blood (*n* = 1)[79] Placenta (*n* = 2)[85, 86]	*None*	*None*
	Air pollution	*None*	*None*	*None*
	Pesticides	*None*	*None*	*None*
Childhood	Metals, EDCs, POPs, Air pollution, Pesticides		*none*	*none*
Behavioral exposures				
Pre- and perinatal	Smoking, alcohol, illicit substance use, diet/nutrition	*None*	*None*	*None*
childhood	Smoking, alcohol, illicit substance use, diet/nutrition		*None*	*None*
Social environmental exposures				
Pre- and perinatal	Composite socioeconomic position (education, income, neighborhood, etc.)	Cord blood (*n* = 4)[183••, 186, 187, 218]	Blood (*n* = 1)[183••]	*None*
	ACEs, Stress	*None*	*None*	*None*
Childhood	Composite socioeconomic position (education, income, neighborhood, etc.)		Blood (*n* = 1)[189]	Blood (*n* = 4) [190, 191, 219, 220] adipose tissue (*n* = 1)[220]
	ACEs, Stress		*None*	*None*

measures and demonstrated that blood methylation changes associated with prenatal mercury exposure persisted into early and mid-childhood [10••].

As shown in Table 1, more than 15 human observational studies conducted in the last 5 years have documented DNA methylation changes in tissues collected

Table 3 Summary of epidemiology studies of early-life exposures and non-methylation based epigenetic changes across the life course

Exposure timing and type		Epigenetic material measurement time period		
		Birth and infancy < 1	Childhood	Adulthood
Environmental toxicant exposures				
Pre- and perinatal	Metals	ncRNA (*n* = 1 study)[221●]	*None*	*None*
	EDCs (phthalates, bisphenols, flame retardants)	ncRNA (*n* = 4 studies)[222–225]	*None*	*None*
	Air pollution	ncRNA (*n* = 1 study)[226] PTM (*n* = 1 study)[227]	*None*	*None*
	Pesticides	PTM (*n* = 1 study)[92]	*None*	*None*
	POPs	*None*	*None*	*None*
Childhood	Air pollution		ncRNA (*n* = 2 studies)[228●, 229]	*None*
	Metals, EDCs, pesticides, POPs		*None*	*None*
Behavioral exposures				
Pre- and perinatal	Smoking	ncRNA (*n* = 2 studies)[230, 231]	PTM (n = 1 study)[232●●]	*None*
	Alcohol	ncRNA (*n* = 2 studies)[233, 234]	*None*	*None*
	Illicit Substance Use, Diet/Nutrition	*none*	*None*	*None*
Childhood	Smoking, alcohol, illicit substance use, diet/nutrition	*None*	*None*	*None*
Social environmental exposures				
Pre- and perinatal	Stress, SEP, ACEs	*None*	*None*	*None*
Childhood	ACEs		PTM (*n* = 1 study)[235]	miRNA (*n* = 2 studies)[236, 237] PTM (*n* = 1 study)[238]
	Stress, SEP		*none*	*none*

**PTM* posttranslational modification of histones, *ncRNA* noncoding RNAs including lncRNAs and miRNAs

from birth, childhood, or adolescence related to prenatal exposure to EDCs including phthalates [33–38, 45, 46], bisphenols [33, 39–43, 47, 49, 50, 239, 240], and flame retardants [48]. Though most of the literature is focused on prenatal exposure to these chemicals (Table 1), work from the Spanish INMA-Granada birth cohort identified peripheral blood DNA methylation changes at the brain-derived neurotrophic factor (*BDNF*) locus in adolescents with childhood bisphenol A (BPA) exposure [100●].

A recent epigenome-wide meta-analysis was among the first to identify several differentially methylated CpG sites in newborns that are significantly associated with prenatal particulate air pollution exposure [51●]. These CpG sites were annotated to genes previously implicated in lung-related health outcomes [51●]. Exposure to air pollution during childhood is associated with methylation changes in children themselves (Table 1), but we were unable to identify studies that examined whether DNA methylation patterns associated with prenatal or childhood exposure to air pollution could be detected in adolescent or adult biospecimens.

Similar to the other classes of environmental toxicants, most of the persistent organic pollutant (POP) literature focused on prenatal exposure and methylation patterns at birth [74–87] (Table 1). In these studies, maternal urine or serum was assayed for detection of PFAS [75, 76, 81–83, 87], PAHs [77, 78, 80], and PCBs [74, 79, 84, 85] to determine exposure levels during this critical window. One longitudinal study identified significant associations between prenatal PCB and polychlorinated dibenzofuran (PCDF) exposure levels and blood DNA methylation patterns at 20 CpG sites in early adulthood [88●]. A second recent study assessed the impact of childhood PFAS exposure on blood DNA methylation levels in school-age children; the authors identified 12 differentially methylated CpG sites and 7 differentially methylated genomic regions associated with higher levels of PFAS exposure [107].

We identified only six studies in the last 5 years that assessed the relationship between prenatal or childhood pesticide exposure and DNA methylation patterns (Table 1). Four of those studies assessed cord blood methylation [89–92] and one examined child blood methylation [93].

Recent work from the Child Health and Development Study detected DNA methylation changes at genes involved in pubertal development and breast cancer susceptibility in adulthood that were associated with prenatal DDT exposure [94•]. These results provide initial evidence to support that DNA methylation patterns, from birth through adulthood, reflect prenatal pesticide exposure and have the potential to serve as a pesticide exposure biomarker.

Across all exposure types, additional, more robust studies are needed to determine whether methylation changes resulting from a particular exposure are 1) specific to the type of chemical or toxicant; 2) persistent and thus consistently detectable across life stages; and 3) detectable across tissue types from easily accessible biological specimens. Methylation changes that meet these criteria would serve as useful biomarkers of exposure and could help inform an individual's future health and disease risk.

DNA Methylation Changes Associated with Human Behaviors

There is strong evidence to support the utility of DNA methylation as a biomarker of prenatal smoking exposure [108–113, 114••, 115–127, 129–132, 133••, 134] (Table 1). Multiple studies have identified consistent significant differential methylation in the aryl hydrocarbon receptor repressor (*AHRR*) gene [110–113, 117, 122]. Given the reproducibility of this finding, methylation changes at a specific locus within this gene are established and accepted as a biomarker of fetal exposure to tobacco smoke. Studies from the Avon Longitudinal Study of Parents and Children (ALSPAC) have identified persistent methylation changes across the life course associated with prenatal smoking exposure that are independent of postnatal and personal smoking exposures [241, 242••]. Unsurprisingly, there were no studies on the effects of childhood smoking on methylation patterns given tobacco smoking in children is rare. We did however identify one study assessing the effect of childhood secondhand smoke exposure on blood DNA methylation, though no significant associations were detected[128].

Five studies assessed the associations between prenatal exposure to alcohol and methylation patterns at birth [136–140], and just three studies examined methylation changes in children prenatally exposure to alcohol (Table 1). Candidate gene methylation studies in placenta analyzed imprinting at the *IFG2/H19* locus [139]. In children prenatally exposed to alcohol, persistent methylation changes were detected in saliva [141], blood [141], and buccal cells [142••, 143]. No longitudinal studies assessed the effects of this early-life exposure on the methylome in adolescence or adulthood. Additionally, we did not identify studies assessing the effect of childhood alcohol use on methylation across

the life course likely given the limited consumption of alcohol by children.

Few studies have assessed maternal substance use during pregnancy and DNA methylation changes. This may be due, in part, to the illicit nature of these substances leading to reporting biases by mothers, and perhaps other social confounding factors that may make it more difficult for pregnant mothers experiencing substance use issues to seek care and/or be enrolled in studies. We identified six studies that assessed the impact of exposure to opioids, cocaine, methamphetamine, and cannabis on neonatal DNA methylation patterns (Table 1). Severe maternal addiction to crack cocaine was shown to predict oxytocin receptor (*OXTR*) gene DNA methylation patterns in newborns [145], and babies born to opioid-dependent mothers sustained on methadone treatment had increased buccal cell methylation at the Opioid Receptor Mu 1 (*OPRM1*) gene [146, 148]. We identified just one epigenome-scale association study that identified DNA methylation changes in placenta that differed in opioid exposed versus unexposed infants [144]. Children with prenatal methamphetamine exposure had hypermethylated hydroxysteroid 11-beta dehydrogenase 2 (*HSD11B2)* buccal cell DNA relative to those without exposure [149].

As shown in Table 1, studies of prenatal diet and nutrition status were primarily associated with methylation changes at birth [150–164]. Dietary fat intake during pregnancy was associated with imprinted gene status in newborns [151], while folic acid supplementation for the entire duration of pregnancy was associated with methylation change at genes involved in neurodevelopment at birth [154]. A nested studying within the Aberdeen Folic Acid Supplementation Trial assessed methylation changes in adults who were prenatally exposed to two different doses of folic acid supplementation. Methylation changes at individual CpG sites, as well as across regions of the genome, were identified in buccal cells from adult offspring, demonstrating the persistence of the effects of this prenatal exposure [169••]. Further, comparing methylation changes from low and high dose-offspring identified a dose–response relationship between folic acid supplementation and the degree of methylation change, emphasizing the specificity of methylation change to the prenatal exposure [169••]. Given the widespread use of vitamins and supplements during pregnancy, studies should assess methylation changes across multiple life stages and should compare methylation changes across tissue types to establish effective biomarkers of prenatal nutrient status.

DNA Methylation Changes Associated with Social Environmental Factors

Prenatal exposure to several different stressors has been associated with changes in DNA methylation patterns collected at birth (Table 1). Placental methylation was

measured in 92 samples from the FinnBrain Birth Cohort, whose mothers were screened for psychosocial stress and depressive symptoms during early pregnancy [179]. Maternal depressive symptoms were associated with DNA methylation at 2833 CpG sites [179]. In one study, the relationship between prenatal exposure to stress from a natural disaster and persistent methylation changes in adolescents was identified in participants from Project Ice Storm [243].

Inequities in socioeconomic position (SEP) are associated with poor health outcomes in individuals. SEP can be influenced by factors including education, occupation, income level, neighborhood, and race or ethnicity [244]. While SEP is comprised of multiple factors, several studies assessed the influence of individual SEP characteristics on DNA methylation patterns at birth [183••, 184•, 185, 188] (Table 1). An EWAS from the Extremely Low Gestational Age Newborns (ELGAN) determined that marital status, receiving supplemental nutrition assistance, education level, and health insurance status were each independently associated with placental DNA methylation at birth [188]. Higher levels of cord blood methylation at the repetitive element LINE-1 were associated with living in the most impoverished neighborhood in a Mexican–American birth cohort of 241 maternal-infant pairs [185]. Women from the Project Viva cohort who were married or cohabitating with a partner had infants with lower levels of cord blood methylation. This prospective study followed infants through early and mid-childhood and demonstrated significant associations between maternal education and global DNA methylation at both stages of life [183••]. The ALSPAC cohort performed an epigenome-scale association study of DNA methylation changes at birth, childhood, and adolescence associated with markers of SEP during pregnancy and found that maternal education was associated with cord blood methylation at birth and methylation changes in adolescence [184•].

While the relationship between adverse childhood experiences (ACEs) and childhood and adolescent methylation was assessed in seven studies, most of the literature in this domain assessed the long-lasting effect of ACEs on methylation changes in adulthood (Table 1). At both time points, altered methylation of *NR3C1* was identified as being associated with ACEs [196, 197, 199]. Genome-wide studies on the effects of ACEs on the adult methylome were performed together on blood samples from ALSPAC and buccal cells from the MRC National Survey of Health and Development (NSHD) study [200••]. Nine DMRs were significantly associated with a specific ACE measure across both NSHD and ALSPAC, including one that was associated with a cumulative measure of adversity [200••]. It is notable that these DMRs were replicated between two different cohorts and across tissue types—blood or buccal—suggesting that methylation changes resulting from childhood adversity are stable

over time, specific to the exposure, and are detectable across tissues.

DNA Methylation Patterns Associated with Exposure to Mixtures

Biomarkers that reflect exposure to mixtures can be used as a reduced complexity measure to capture the complex mixtures of chemicals that individuals are exposed to daily. This is especially important given that the mixture of chemicals that individuals regularly encounter may influence health outcomes differently as a mixture than they do as individual chemicals. Although most studies to date have focused on identifying DNA methylation patterns related to single exposures, recent statistical and exposome measurement advances have allowed researchers to begin to assess the impacts of environmental mixtures on DNA methylation patterns [245, 246]. As detailed below, mixtures studies to date have largely focused on chemical toxicant mixtures, some studies have examined multiple social exposures, and to our knowledge, no studies have examined behavioral exposure mixtures in relation to DNA methylation. Social exposure mixtures were primarily defined by composite SEP, a summative score that accounts for the individual socioenvironmental factors that comprise SEP. Future studies should continue to use newly developed statistical methods (such as Bayesian kernel machine regression) to evaluate environmental mixtures and its effect on the epigenome.

Associations between prenatal exposure to a 16-metal mixture and cord blood DNA methylation were assessed using the Bayesian kernel machine regression (BKMR) model[213••] (Table 2). A BKMR statistical model allows the joint effect of mixtures on methylation to be estimated in a way that is superior to standard regression approaches as it has features to account for the correlation structure of environmental mixtures, allowing it to overcome challenges from traditional analysis methods such as collinearity and high dimensionality [246]. No significant associations were observed between the metal mixtures and DNA methylation [213••]. Another study from the Norwegian Mother, Father, and Child Cohort assessed the effect of prenatal exposure to a mixture of 12 metals and essential elements on cord blood methylation in 631 mother–child pairs [214] (Table 2). Two-way interactions between exposures were investigated using elastic net regression, and the joint effects of the mixture on DNA methylation were assessed using quantile g-computation, a novel analysis approach that allows for an unbiased inference on the effects of mixtures [245]. Elastic net regression identified significant associations between cord blood methylation and maternal selenium, cobalt, and mercury exposure, individually [214]. However, despite the application of two novel statistical approaches to identifying

effects of exposure mixtures, no associations between prenatal metals mixtures and DNA methylation were observed.

The effect of prenatal exposure to mixtures of EDCs on DNA methylation has primarily been assessed in placenta. However, two studies took candidate gene approaches, investigating the relationship between mixtures of xenoestrogens on cord blood methylation at repetitive elements [215], as well as the effects phthalate and phenol exposures on imprinted genes in the placenta [216] (Table 2). For placenta, epigenome-scale association approaches identified methylation changes in the placenta that were associated with prenatal exposure to a mixture of xenoestrogens [217] or other POPs mixtures [79, 85, 86] (Table 2). In one study, multi-pollutant principal component analysis identified significant associations between a mixture of 57 POPs measured in maternal serum and placental DNA methylation at the insulin-line growth factor 2 (*IGF2*) imprinted locus [85]. Another multi-pollutant study used principal component analysis to evaluate the association between prenatal exposure to multiple POPs and DNA methylation in the placenta [86]. These results demonstrate that exposure to POPs mixtures is associated with DNA methylation changes, supporting the potential for DNA methylation patterns to serve as a biomarker of POPs exposure mixtures.

In addition to environmental mixtures, studies have focused on the effect of composite early-life SEP—a way to assess the cumulative impact of the factors that contribute to socioeconomic status and adversity—on DNA methylation across the life course [186, 187] (Table 2). Work from the NEST cohort demonstrated that hypermethylation of the *DLK1/MEG3* imprinting locus in cord blood samples was associated with lower composite SEP, where SEP was assessed as a principal components factor of six individual SEP measures [218]. In addition to work from Project Viva looking at how individual SEP factors associated with global DNA methylation, this study also detected locus specific methylation changes at birth and in childhood that were associated with prenatal composite SEP. Low prenatal SEP was associated with DNA methylation of the gene Leucine Rich Repeat Neuronal *4* (*LRRN4)* at birth, and those methylation changes persisted into early childhood [183••]. Studies of the association between childhood composite SEP and DNA methylation identified methylation changes in children themselves [189], as well as persistent changes to the methylome in blood [190, 191] and adipose tissues (Table 2). A study from the Cebu Longitudinal Health and Nutrition Survey—a pregnancy cohort of women from the Philippines—identified epigenome-wide leukocyte methylation changes in adults that were associated with their composite SEP in childhood [191].

In sum, there is evidence showing DNA methylation changes are associated with exposure to EDC and POPs mixtures, as well as composite SEP. As next steps, it will be important to determine whether these changes are persistent over time and may have utility in helping us understand how these mixtures may contribute to adverse health outcomes, especially in the context of how they may compare to the effects of individual chemical toxicants on health outcomes. Future research is also needed to determine the specificity of these DNA methylation changes and to investigate other types of exposure mixtures, including across other exposure domains and windows of exposure.

Posttranslational Histone Modification and Noncoding RNA Changes Associated with Environmental Exposures

To date, studies investigating DNA methylation changes associated with prenatal and early-life exposures have largely focused on DNA methylation. This is mainly due to the ease and stability of collecting this measure in epidemiology samples, commercially available cost-effective measurement methods, and because we understand it best at a biologic level. However, other types of epigenetic material, such as posttranslational modifications of histones (PTMs), and noncoding RNAs (ncRNAs), have also been shown to differ by environmental context and play important roles in development and health. As our understanding of how these molecular modifications change in response to the environment expands, we highlight a largely unmet opportunity to consider whether non-methylation-based epigenetic changes may have utility as an exposure biomarker in human epidemiologic studies. Below, and in Table 3, we summarize the evidence to date showing prenatal and early-life exposure associations with PTMs and ncRNAs.

We found limited evidence of any studies investigating the association between prenatal metal exposure and PTMs at any developmental period. We identified one study that examined the relationship between prenatal cadmium exposure and long noncoding RNA (lncRNA) expression in placenta[221•] (Table 3). There was a significant relationship between prenatal cadmium concentrations and expression of four lncRNAs in placenta [221•]. Bioinformatic analysis demonstrated that *MIR22HG*, the lncRNA whose placental expression was most significantly associated with prenatal cadmium exposure, was associated with gene modules involved in organ development and cellular respiration.

Prenatal exposure to phthalates and phenols has been associated with placental ncRNA expression [222–225] (Table 3). A study that co-enrolled women from the Harvard Epigenetic Birth Cohort and the Predictors of Preeclampsia Study assessed the relationship between exposure to multiple EDCs and placental micro RNA (miRNA)expression [225]. Maternal urine was collected to measure phthalate and phenol metabolites, and targeted expression of 29 miRNAs was measured via real-time quantitative reverse

transcription polymerase chain reaction [225]. Of the 29 miRNAs assessed, three had significant associations with urinary phthalate or phenol metabolite levels [225]. Other studies identified associations between prenatal phthalate exposure and placental lncRNA expression [222, 223]. Additional comprehensive studies are needed to establish ncRNA biomarkers of early-life EDC exposure across multiple tissue types and life stages. Future work should also assess the impact of EDC exposure on PTMs.

Prenatal gas and particulate air pollution exposure was associated with altered expression of a cluster of miRNAs in cord blood [226], while studies of childhood air pollution exposure detected changes in miRNA expression in serum [228•] and saliva [229] (Table 3). We found just one study that identified PTM changes in cord blood that were associated with prenatal exposure to ambient air pollution [227] (Table 3). This recent work assessed histone H3 methylation in cord blood from 609 mother-newborn pairs and found significant changes associated with $PM_{2.5}$ and black carbon exposure during pregnancy [227].

As with the DNA methylation data available for early-life exposure to pesticides, epidemiologic studies on the effects of pesticide exposure on PTMs or ncRNAs were limited, and population-based studies of the epigenetic consequences of exposure to a pesticide mixture were sparse. We identified one recent study that examined the relationship between in utero exposure to chlordecone and its impact on PTMs in cord blood [92] (Table 3). A prospective study in the French West Indies collected cord blood samples at birth for PTM analyses, and maternal plasma was assayed for chlordecone concentration. Quantitative immunofluorescence analysis of PTMs in the nuclei of cord blood cells and found significant decreases in H3K4me3 and H3K9me3 levels in cord blood from chlordecone exposed individuals relative to the unexposed controls [92]. This work combined their epidemiologic work with in vitro approaches to experimentally validate their findings and assess the relationship between histone occupancies and changes in gene expression [92].

While studies on the impact of smoking on the methylome are extensive, there is a dearth of epidemiologic literature on the effects of prenatal smoking on PTMs or ncRNAs. Work from the LINA mother–child cohort assessed the role of maternal smoking on chromatin architecture and PTMs in children around four years of age [232••] (Table 3). Chromatin immunoprecipitation sequencing (ChIP-Seq) was performed in blood for six mother–child pairs (three who smoked, three who did not). Two activating and two repressive histone modifications were assessed, and the authors identified a shift from a repressive to an activate chromatin state in cord blood from children prenatally exposed to maternal smoking relative to controls [232••]. Though their sample size was small, this represents one of the few studies that has looked at the effect of prenatal smoking on

PTMs, and their findings suggest that additional work is warranted. One study of miRNAs assessed expression of two microRNAs in 441 cord blood samples from a prospective mother–child study of prenatal tobacco smoke exposure [230] (Table 3). They found altered miR-223 expression in cord blood following prenatal tobacco smoke exposure, that was further associated with low numbers of regulatory T cells at birth, and increased allergy risk in childhood [230]. A second study of maternal cigarette smoking assessed the expression of four miRNAs in 25 placentas samples [231] (Table 3). Despite a smaller sample size, authors found that expression of three of the four miRNAs—miR-16, miR-21, and mi-146a—was downregulated in placentas from smoke-exposed individuals compared to controls [231].

Two studies identified associations between prenatal alcohol exposure and microRNA content at birth [233, 234] (Table 3). Plasma extracellular circulating miRNAs were isolated from infants from the Cape Town cohort of mothers and infants [234]. Alcohol-consuming mothers drank on average 1–2 days/week during pregnancy. Offspring miRNA expression was altered in plasma from 2-week-old and 6.5-month-old infants. Confirmatory factor analysis identified three-factor models that explained the variance in expression of miRNAs associated with prenatal alcohol expression at both time points[234].

Micro-RNAs (miRNAs) and histone modification changes related to childhood trauma have been detected in adults, and thus may serve as a useful biomarker [247] (Table 3). Peripheral blood measures of miR-15a showed elevated levels of expression in adults with childhood trauma compared to age and gender matched individuals with no history of early-life trauma or stress [236] (Table 3). More recently, downregulation of miRNA 125b-1-3p was observed in blood from adults that experienced childhood trauma compared to those who did not [237] (Table 3). Related work on the epigenetic eraser, histone-deacetylase 1 (*HDAC1*) demonstrated elevated levels of *HDAC1* expression in patients with schizophrenia who experienced early-life stress compared to patients who did not [238]. Finally, analysis of six PTMs in the amygdala of postmortem brain samples showed changes in the histone landscape in individuals who experienced severe childhood trauma compared to controls [235] (Table 3).

Development of Epigenetic Prediction Tools

In line with demonstrating the utility of DNA methylation as an exposure biomarker, studies have built epigenetic prediction tools that use DNA methylation measures to estimate an individual's current and previous exposures. These tools are extremely powerful because they provide an opportunity to accurately determine whether an individual incurred an exposure, or to what extent they were exposed to a chemical

or stressor, when that data is otherwise unattainable. Additionally, aggregate methylation score tools can have several advantages over traditional exposure ascertainment measures because (1) they include a collection of methylation loci to represent a particular exposure or multiple exposures which can provide greater statistical efficiency over individual CpGs, and (2) they may capture inter-individual biologic responses to similar measures of external exposures, i.e., serve as an "exposure dosimeter" [248, 249].

There are two main approaches to working with methylation-based predictive tools. The first is based on the development and implementation of a methylation score. Here, CpG sites that were previously determined to be significantly associated with an environmental exposure are used to build a single numeric score that is a weighted sum of the selected CpG methylation levels, often using methylation data from an epigenome-scale analysis. This score is then used in linear regression models to determine an association with an exposure of interest [248, 249]. A study from the Norwegian Mother and Child Cohort Study (MoBa) developed and tested a numeric DNA methylation score using 28 CpG sites associated with sustained smoke exposure. [114••]. When applied to a test dataset of cord blood samples, their numeric methylation score was able to predict prenatal smoke exposure with a greater than 90% specificity [114••]. A methylation score of prenatal smoke exposure that persisted into adulthood was developed from the ALSPAC cohort. DNA methylation changes at 568 CpG sites that were previously demonstrated to be associated with prenatal smoke exposure in cord blood were used to create a DNA methylation score to successfully predict whether adults sustained prenatal smoke exposure in utero (AUC 0.69) [133••]. A second score from the same study was derived from 19 CpG sites from children's peripheral blood that were associated with prenatal smoke exposure. This score was even more successful at predicting prenatal smoke exposure in adult blood samples (AUC 0.72), despite being derived from childhood biospecimens rather than newborn tissues [133••].

In addition to score-based prediction tools that can be used as biomarkers of exposure, machine learning approaches can be used to detect patterns in methylation data in an unsupervised manner that can ultimately be used to predict an individual's exposure status [248, 249]. Work from the Study to Explore Early Development (SEED) was among the first to use predictive tools to determine whether DNA methylation changes at 26 CpG sites associated with prenatal smoke exposure in cord blood could similarly predict prenatal smoke exposure in childhood [250••]. Using a support vector machine classifier, with tenfold cross validation, prenatal smoke exposure was predicted in children with a greater than 86% accuracy when it was compared to maternal reports of smoking during pregnancy [250••]. Machine learning techniques have also been used to predict

fetal alcohol exposure in children and adolescents. DNA methylation changes at 648 CpG sites initially identified in buccal cells from children and adolescents with fetal alcohol spectrum disorder (FASD) were used in a gradient boosting machine learning model to generate an algorithm capable of predicting FASD status in an independent set of individuals [142••]. When tested on buccal cell samples from children and adolescents, the algorithm was able to predict dichotomous FASD status with a specificity of 75% [142••].

Discussion

There are potential advantages to using epigenetic biomarkers instead of traditional external exposure measures. First, epigenetic changes can reflect an internal dosimeter or represent the biologic response to exposure which could explain inter-individual variation. Second, epigenetic changes that are specific to an exposure can address exposure misclassification such as incorrect self-report or other reporting errors or biases. Third, epigenetic analyses of environmental mixtures can overcome statistical concerns and difficulties modeling multi-exposures.

Epigenetic biomarkers need to be assessed in easily accessible tissues [4]. At birth, this typically includes cord blood and placenta tissues. We saw that the majority of studies presented in this review were from cord blood samples collected at birth, from which epigenetic measures were generated. Later in life, saliva and saliva-derived buccal cells, and whole blood, represent two tissue types that can be easily sampled across different stages of life to measure epigenetic biomarkers of exposure. This is consistent with the tissues that were commonly sampled in childhood, adolescence, and adulthood in the studies that we reviewed here. The work summarized in this review provided excellent examples of the utility of epigenetic biomarkers of early-life exposure that are detectable across tissue types and life stages, that are specific to the exposure of interest, and that are predictive of disease outcomes. This emphasizes the effectiveness of epigenetic exposure biomarkers and motivates future research to continue to use exposure biomarkers to identify potential interventions that could mitigate disease risk.

Literature on epigenetic biomarkers of early-life exposure is overwhelmingly focused on DNA methylation. This was true across all exposure domains, exposure timepoints, and measurement timepoints included in this review. However, there were a limited number of observational studies that followed participants from birth through adolescence or adulthood, with repeated sampling of biospecimens to measure methylation changes over time. One question that remains is whether persistent methylation changes associated with prenatal exposures were similarly identifiable following childhood exposures. The data presented here is somewhat

inconclusive. For example, childhood metal exposure was associated with methylation changes at novel loci that had not previously been identified following prenatal exposures [95, 96]. Conversely, prenatal and childhood exposures to stress were associated with DNA methylation changes at the *NR3C1* locus [243, 251–255], demonstrating that methylation changes here seemed to be more specific to the type of exposure rather than the developmental window that the exposure occurred. Similarly, childhood exposure to BPA was associated with *BDNF* methylation [100•], and work in animal models found that gestational BPA exposure in mice was associated with persistent DNA methylation changes in offspring of *Bdnf*, and that boys with high levels of BPA exposure in utero had aberrant *BDNF* methylation in cord blood [100•, 256]. Contrary to the metals studies, this suggests that perhaps for BPA exposure, the epigenetic effects are specific to the chemical exposure and not necessarily the timing of the exposure. Finally, childhood air pollution was associated with differential methylation of nitric oxide synthase genes, a finding that was similarly detectable in adults with exposure to air pollution [257, 258]. To establish effective biomarkers, rigorous investigations are needed to identify whether methylation patterns associated with environmental influences are more specific to a class of chemicals or a developmental window of exposure.

While the importance of DNA methylation studies in advancing the field of epigenetics cannot be overstated, we were surprised to see the shortage of studies that assessed how early-life exposures during the in utero and childhood time periods were associated with non-methylation epigenetic changes, particularly histone PTMs and ncRNAs. In these instances, work in animal models far surpasses epidemiologic studies [247, 259, 260]. However, those studies provide a strong scientific rationale for investigating the effects of exposure on epigenetic patterns in population-based work. The studies we did find highlight associations between PTMs [7, 89, 92, 227, 235] and ncRNAs [221•, 223, 226, 229, 230, 237] and exposures. Thus, future studies should focus on development and implementation of non-methylation-based biomarkers of early-life exposure.

Recent advances in the development and implementation of epigenetic prediction tools have demonstrated the ability for composite DNA methylation changes to reconstruct an individual's exposure history when that data is otherwise unavailable. Once developed and tested for accuracy and reliability, these predictive tools can be applied to observational studies to characterize an individual's exposure history, and to better understand their potential future disease risk. Multiple studies have demonstrated the utility of these numeric methylation scores and machine learning predictive algorithms at predicting prenatal exposures across the life course, and across tissue types [114••, 133••, 142••, 250••]. However, additional methylation tools are needed to

comprehensively predict early-life exposures across the three domains covered in this review. Further, these tools should be used to advance the development of biomarkers of the exposome to better understand an individual's comprehensive exposure history and future disease risk.

There are unique advantages and disadvantages to the methylation score and machine learning approaches to predictive modeling of biomarker development. For example, one disadvantage to using DNA methylation scores is that the algorithm requires a mean methylation value for the "exposed" and "unexposed" groups. Thus, it cannot be used to predict exposure status when that data is otherwise unavailable. One could use the mean values that the score was initially developed with in the test dataset, but the inter-experiment conditions, such as the presence of batch effects and other laboratory variables, could greatly impede the accuracy of this approach. However, an advantage to using methylation scores is that they can reflect an internal dosimeter of an individual's exposure when quantifying an exposure in a biospecimen might not be feasible. Given that methylation scores are weighted, a higher score, for example, might be reflective of a higher level of exposure to a certain toxicant earlier in life. Machine learning approaches do not have this same capability. The output from these predictive algorithms is typically dichotomous, i.e., "yes" or "no," for a particular exposure or outcome of interest, so no individual metrics about the magnitude of an exposure would be ascertained in that case. However, machine learning is advantageous given that once the algorithm is trained, no exposure history data is needed to predict the binary outcome of whether an individual is or is not exposed. Investigators need to carefully consider the data they have available, and the scientific question that they are trying to address, when choosing an approach to developing biomarkers through predictive modeling.

Conclusions

In summary, the evidence provided in this review strongly supports epigenomic biomarkers of exposure are detectable across the lifespan across a range of exposure domains. Of note, we did not address the transgenerational effects of early-life exposure on the epigenome, or how inheritance of an aberrant epigenetic profile might be associated with disease risk in subsequent generations. Studies have begun to develop biomarkers for intergenerational and transgenerational exposures, and future work should be supported in this area. We have identified promising new directions that would address current gaps in research. These include the ability to capture an epigenetic biomarker of the exposome through mixtures analysis, the derivation and implementation of non-methylation biomarkers of exposure, and

the development and use of epigenetic prediction tools. Together, these research avenues will help advance our understanding of how exposures early in life shape health and disease across a generation.

Declarations

Conflict of Interest Dr. Ladd-Acosta reports receiving consulting fees from the University of Iowa for providing expertise on autism spectrum disorder epigenetics outside of this work. Drs. Schrott and Song declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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