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PERSPECTIVE

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Prenatal chemical exposures and the methylome: current evidence and opportunities for environmental epigenetics

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ABSTRACT

Exposure to pollutants and chemicals during critical developmental periods in early life can impact health and disease risk across the life course. Research in environmental epigenetics has provided increasing evidence that prenatal exposures affect epigenetic markers, particularly DNA methylation. In this article, we discuss the role of DNA methylation in early life programming and review evidence linking the intrauterine environment to epigenetic modifications, with a focus on exposure to tobacco smoke, metals, and endocrine-disrupting chemicals. We also discuss challenges and novel approaches in environmental epigenetic research and explore the potential of epigenetic biomarkers in studies of pediatric populations as indicators of exposure and disease risk. Overall, we aim to highlight how advancements in environmental epigenetics may transform our understanding of early-life exposures and inform new approaches for supporting long-term health.

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Modifiable environmental exposures are significant contributors to morbidity and mortality, with nearly one-quarter of global deaths attributed to environmental factors [1]. Exposure to pollutants and toxic chemicals during critical developmental periods is of particular concern for both early-life health and later disease development [2]. Prenatal exposure to chemicals has been associated with perturbations in biological pathways involved in a broad range of adverse health outcomes, including poor birth outcomes, impaired neurodevelopment, asthma, obesity, cardiovascular disease, and cancer [2,3]. Understanding biological mechanisms, including changes in epigenetic markers, that link exposures to health is crucial for advancing public health interventions and promoting healthy environments. In this article, we discuss the role of epigenetics in early-life programming with a focus on DNA methylation (DNAm) (Figure 1). We also provide an overview of evidence regarding epigenetic signatures and biomarkers of environmental exposures and explore the potential of epigenetics in precision environmental medicine.

1. The early-life methylome

DNAm is the addition of a methyl group to C5 of cytosine forming the modified base 5-methylcytosine, primarily at cytosine-guanine (CpG) dinucleotides. DNAm is involved in regulating gene expression and cellular differentiation through tissue-specific methylation profiles. DNAm acts in concert with histone modifications and other regulatory elements to control chromatin accessibility and transcription factor binding [4]. The molecular mechanisms linking DNAm to gene expression are not fully understood and are discussed in more detail elsewhere (see [4–6]). DNAm is established and maintained by the DNA methyltransferase (DNMT) family of enzymes [7]. DNMT3A and DNMT3B are responsible for *de novo* methylation, i.e., catalyzing the addition of a methyl group to previously unmethylated cytosines. DNMT1, however, is involved in maintenance of DNAm through preferential methylation of hemimethylated cytosines. Following replication, DNMT1 adds a methyl group to the daughter DNA strand to maintain the methylation pattern of the parental strand.

Epigenetic reprogramming, which involves changes to histone modifications as well as extensive erasure and the reestablishment of the methylome, occurs during both embryogenesis and gametogenesis. Immediately after fertilization, the paternal epigenome undergoes rapid active demethylation, while the maternal genome is passively demethylated at a slower rate through DNA replication [8], processes that are crucial for cell pluripotency. Around the time of blastocyst development and implantation, the methylome is reestablished by DNMT3A and DNMT3B, corresponding with a decrease in pluripotency [9]. Imprinted genes, which are differentially expressed by parent of origin, maintain their methylation status throughout embryogenesis. Following this rapid remodeling of the methylome, DNAm of genes involved in developmental pathways is also highly dynamic throughout fetal development. Primordial germ cells differentiate early in embryogenesis and undergo nearly complete demethylation. DNAm is reestablished in a sex-specific manner: in male germ cells, *de novo*

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Article highlights

The early-life environment and epigenetic programming
- According to the Developmental Origins of Health and Disease (DOHaD) hypothesis, epigenetic responses to the intrauterine and early-life environment may increase the risk of disease later in life.
- The epigenome undergoes extensive remodeling during embryogenesis and gametogenesis, developmental windows that may be particularly sensitive to environmental insults.

Prenatal chemical exposures and epigenetic perturbations
- Prenatal chemical exposures are associated with a broad range of adverse health outcomes across the life course, including poor birth outcomes, impaired neurodevelopment, asthma, obesity, cardiovascular disease, and cancer.
- In human epidemiological studies, prenatal chemical exposures, including tobacco smoking, metals, and endocrine-disrupting chemicals, have consistently been associated with changes in DNA methylation measured at birth and in childhood.
- A limited number of epidemiological studies have evidence supporting mediation of the associations between prenatal chemical and health by DNA methylation.

Challenges and future direction in environmental epigenetics
- Novel technology and statistical methods have advanced the study of environmental exposure and epigenome-wide DNA methylation data, but not without unique obstacles.
- Environmental epigenetic studies must consider sex-specific effects, the relationship between DNA methylation and cellular heterogeneity, selection of appropriate tissues, and gene-epigene interactions, among other challenges.
- Longitudinal birth cohorts and consortia studies have provided opportunities to study DNA methylation changes over time with increased power and generalizability.
- Future research should focus on linking environment-associated epigenetic changes to downstream health outcomes and may leverage novel DNA methylation-based biomarkers as surrogate measures integrating multiple biological pathways.

methylation of prospermatogonia occurs before birth with additional epigenetic remodeling during spermatogenesis [10], whereas in female germ cells, DNAm is established after birth during meiotic arrest [11].

DNAm is essential to the transition from pluripotent embryonic stem cells to differentiated progenitor and mature cells. Cell types have unique methylation signatures, which are highly conserved between individuals [12]. Cell-type specific unmethylated regions correspond to open chromatin in regions involved in gene regulation. DNAm is also strongly dependent on biological sex. X-inactivation in XX female cells to suppress gene expression as a dosage compensation mechanism is accompanied by increased DNAm [13]. It is also well-established that autosomal DNAm differs between male and female individuals with tissue-specific patterns. Sex differences have primarily been studied in adult blood [14–18], with an overall trend toward greater methylation levels in female compared to male samples. In cord blood, similar patterns have been observed with greater methylation among samples from female newborns [19–21]. In placental samples, however, differentially DNAm is largely greater in male compared to female samples [20,22,23]. Interindividual variation in DNAm signatures is also attributed to genetic variation [24]. DNAm quantitative trait loci (meQTLs), or methylation loci with levels associated with genetic variants, have been identified at as many as 45% of CpG sites [25]. meQTLs may also be sex-specific, with significant interaction between sex and genetic variants on methylation heritability [26]. In summary, the human methylome is a highly complex set of epigenetic markers representing interactions between tissue type, biological sex, and genetic variations, factors which must all be considered in the relationship between the environment, DNAm, and downstream health.

2. Epigenetic programming and the environment

The epigenome is particularly susceptible to the effects of environmental exposures during developmental periods. Beyond predictable transitions in methylation levels, changes in DNAm reflect developmental plasticity – adjustments to gene expression that optimize an organism's (or human's) ability to survive and thrive in a given environment [27]. Alterations to DNAm in response to the intrauterine environment may be mitotically maintained, affecting gene regulation and biological pathways after birth and into adulthood. As outlined in the Developmental Origins of Health and Disease (DOHaD) hypothesis [28], plasticity of the epigenome decreases with age, and if phenotypic changes are mismatched with future environmental conditions, disease risk may increase. Additionally, environmental exposures may alter programming of germ cells during fetal development. Consequently, exposure during gestation can simultaneously affect disease risk across three generations (mother, daughter, and grandchildren).

The relationship between maternal diet and offspring health in adulthood is a frequently cited example of the life-course implications of prenatal epigenetic reprogramming and non-genetic inter- and transgenerational transmission of environment-related health risks. Maternal malnutrition during gestation, as observed during the 1944–1945 Dutch Famine, has been associated with increased rates of obesity in both male [29] and female [30] adult offspring, as well as changes in DNAm [31]. In particular, DNAm of the insulin-like growth factor II (*IGF2*) gene, a maternally imprinted gene involved in growth and development, was found to be hypomethylated among individuals exposed to the famine during periconception compared to their unexposed same-sex sibling [32]. The results were time-dependent, with a significant association observed for periconceptional exposure, but not for exposure later in gestation. This example helps illustrate the potential effects of chemical exposures during development. For instance, prenatal exposure to exogenous endocrine-disrupting chemicals has been shown to have obesogenic effects in children [33], potentially mediated in part by epigenetic reprogramming in response to changes in maternal metabolism or direct exposure through the placenta.

3. The growing field of pediatric environmental epigenetics

Over the past decade, the study of environmental epigenetics has emerged as a promising tool for understanding disease etiology, predicting disease risk, and estimating exposures. As regulators of gene expression changes, epigenetic markers can provide insights into the pathways involved in the development of environment-related diseases. DNAm may also be a uniquely valuable signature of chemical exposures and future disease risk. Because DNAm is both responsive to

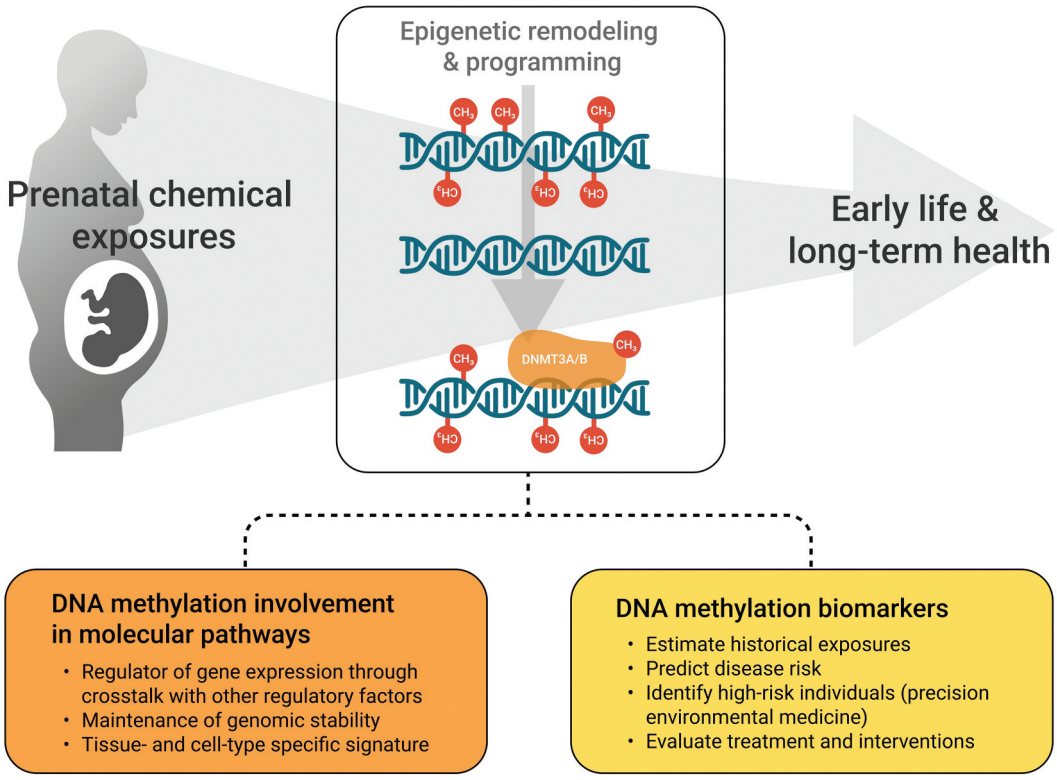

Figure 1. Overview of article focus. Epigenetic remodeling and programming in early life may be involved in linking prenatal chemical exposures to health. DNA methylation signatures may help identify pathways involved in disease etiology and may be leveraged as non-causal biomarkers of environmental exposures and disease risk.

environmental insults and mitotically stable, it can offer a record of cumulative or historical exposures. Specific DNAm patterns have also been linked to disease development, particularly in conditions with common environmental risk factors.

DNAm and other epigenetic markers are now commonly investigated in longitudinal birth and child cohort studies, providing increasing evidence of their role in linking the intrauterine environment to health. DNAm can be measured in noninvasive and accessible samples (e.g., cord blood, placenta, peripheral blood, or saliva) using whole-genome sequencing and array-based platforms. Illumina Infinium BeadChips have emerged as a popular technology due to their high-throughput design, relatively low cost, and single-nucleotide resolution, which now covers > 900,000 cytosine-guanine (CpG) dinucleotides. Similar to genome-wide association studies, epigenome-wide association studies (EWAS) use methylation levels at individual CpG sites to identify methylation signals related to exposures and phenotypes. Building on early approaches to integrate environmental epidemiology and epigenetics, research consortia have been developed to aggregate or meta-analyze data from thousands of samples and diverse populations, enhancing the power and generalizability of findings. The Pregnancy And Childhood Epigenetics (PACE) consortium, established over 10 years ago, integrates data from over 30 pregnancy and pediatric cohort and case-control studies in the United States, Europe, and Australia [34]. More recently, the Environmental Influences on Child Health Outcomes (ECHO) Program, comprised of over 40 observational cohorts in the United States, has created a harmonized dataset and portal for investigators to analyze prenatal exposures, DNAm, and health outcomes [35].

4. Evidence of DNA methylation signatures of prenatal exposures and disease risk

As interest in developmental programming and environmental epigenetics grows, there is increasing evidence linking a broad range of prenatal exposures to changes in DNAm. Although a comprehensive review of epigenetic studies on prenatal chemical exposures is beyond the scope of this article, we offer a brief overview of epigenome-wide human epidemiological research on smoking, metals, and endocrine-disrupting chemicals – exposures that pose substantial health risks to pediatric populations – to highlight unique aspects of studying early-life exposures.

Maternal smoking during pregnancy increases the risk of a broad range of adverse birth and child health outcomes, including preterm birth, low birth weight, impaired neurodevelopment, obesity, asthma, and decreased lung function [36]. Tobacco smoke is one of the most extensively studied exposures in environmental epigenetics, with consistent smoking-associated changes in DNAm identified across various tissues and exposure levels [37]. Differential methylation of the *AHRR* gene is among the most persistent and reproducible signals of current and former smoking, and smoking-associated changes in *AHRR* expression have been observed in transcription-wide association studies [38]. The PACE consortium has conducted

meta-analyses examining the association between maternal smoking during pregnancy and DNAm in newborn cord blood ($N = 6,685$) [39] and placenta samples ($N = 1,700$) [40]. These analyses identified common differentially methylated CpGs, including loci within *AHRR*, and tissue-specific signals. Differentially methylated CpGs were also identified in a subset of older children, suggesting persistence of effects and consistent with other studies of adolescents and adults prenatally exposed to smoking. In another European-based meta-analysis of adolescents and adults, exposure to prenatal smoking was associated with differential methylation consistent with the PACE study of cord blood [41]. DNAm has also been studied as a mediator between prenatal tobacco smoke exposure and adverse health of offspring. In a study of $N = 78$ children aged 7–12 years, lower methylation of *AHRR* significantly mediated the association between maternal smoking during pregnancy and higher liver fat content, triglycerides, and alanine aminotransferase levels and lower HDL cholesterol in children [42]. In another study of $N = 954$ mother-infant dyads, DNAm of *AHRR*, *GFI1*, and *CYP1A1* explained 68% of the association between maternal smoking and decreased birth weight [43]. Mendelian analysis using GWAS summary data has also provided evidence of a causal link of smoking-associated CpGs with inflammatory bowel disease and schizophrenia [41].

There is increasing evidence linking prenatal exposure to metals with changes in DNAm. As previously reviewed [44], recent studies have focused on non-essential toxic metals such as lead, arsenic, and mercury. Multiple studies have identified epigenome-wide significant associations between metal exposures, commonly measured in maternal biospecimens during pregnancy, and DNAm in cord blood or placenta. Despite this evidence, reproducible epigenetic signatures of prenatal metal exposures are still lacking. For example, prenatal lead exposure has been associated with DNAm at birth in several small studies: in a US-based cohort ($N = 96$), blood lead levels measured in neonatal blood spots was significantly associated with DNAm at 33 CpGs [45]; in a Mexico-based birth cohort ($N = 89$), first and second trimester maternal blood and bone lead was associated with DNAm at 3, 2, and 2 CpGs, respectively [46]; and in a Korea-based cohort ($N = 364$), maternal blood lead in pregnancy was associated with DNAm of 18 CpGs among male newborns [47]. Conversely, in a Mexico-based cohort ($N = 420$), prenatal lead exposure (measured in maternal blood and bone and cord blood) was not associated with cord blood DNAm [48]. Prenatal arsenic exposure, even at low levels of exposure, has been consistently associated with differential DNAm at birth [49–56]. However, the extent of the epigenetic signal has varied greatly across studies (e.g., ranging from 1 CpG in cord blood associated with maternal drinking water arsenic ($N = 45$) [49] to almost 5,000 CpGs in cord blood associated with maternal urinary arsenic ($N = 38$) [54]), and few differentially methylated positions have been found to be in common across studies. This may be due in part to small sample sizes, variability in exposure levels, and unmeasured confounding factors. Additionally, the epigenetic effects of prenatal metal exposures may vary by tissue [49], newborn sex [47,55,57], and timing of exposure during pregnancy [46,47,56]. Mediation of the association between prenatal toxic metals and health by DNAm has been investigated in a limited number of studies. Two studies of prenatal arsenic in Bangladesh, which used an epigenome-wide approach to first identify candidate CpGs associated with exposure, found evidence that DNAm is a mediator between arsenic and gestation age ($N = 569$) [58] and insulin-like growth factor-binding protein 3 (IGFBP3) concentrations in children ($N = 551$) [50].

Fewer studies have investigated associations between prenatal exposure to essential trace metals and offspring DNAm. Although essential metals are necessary for healthy fetal development due to their roles as cofactors and allosteric components for enzymes, high levels of essential metals can be detrimental to health [59,60]. Copper concentrations measured in placenta ($N = 447$) [61] and maternal red blood cells during pregnancy ($N = 361$) [55] have been associated with differentially methylated regions in placenta and cord blood samples, respectively, although associations with individual CpGs did not reach epigenome-wide significance. Additional essential metals, including magnesium, manganese, selenium, and zinc, were studied in a US-based cohort with metal concentrations measured in maternal red blood cells and DNAm measured in cord blood ($N = 361$) and mid-childhood blood ($N = 333$) [55]. Manganese concentrations were associated with differentially methylated CpGs among infants overall and stratified by sex, most of which were nominally significant in childhood; all metals were associated with at least one differentially methylated region. Although these studies offer insights to the link between prenatal essential metal exposures and early-life epigenetic regulation, they are limited by the range of exposure levels and investigation of linear, rather than non-linear, effects.

Endocrine-disrupting chemicals, such as bisphenol A (BPA), are major concerns for early-life health due to their ubiquity of exposure and ability to cross the placenta and the blood-brain barrier. Prenatal and early-life exposure to these chemicals increases the risk of adverse birth, adiposity, and metabolic outcomes, with sex-specific effects [62,63]. In a mother-child cohort study conducted in Germany ($N = 101$), maternal urinary BPA concentrations in pregnancy were associated with DNAm at two CpG sites in cord blood [64]. Mediation analysis found that the association between BPA and children's BMI *z*-score at one year was mediated by DNAm of *MEST*, an imprinted gene associated with obesity. DNAm of another imprinted gene, *IGF2*, involved in growth and development, was also found to be associated with BPA measured in maternal urine samples during pregnancy ($N = 59$) [65]. In a Japan-based cohort ($N = 277$), BPA concentrations have also been linked to sex-specific changes in DNAm in cord blood [66]. Similar sex-specific effects were observed for associations of maternal urinary BPA during pregnancy with cord blood DNAm of target genes measured by pyrosequencing, in particular *IGF2* [67]. Results from studies of BPA highlight the importance of sex-specific effects and DNAm of imprinted genes involved in maintaining parent-of-origin expression. The downstream effects of changes to DNAm may be particularly susceptible to environmental insults during development due to the functionally haploid nature of imprinted genes.

5. Challenges and opportunities

Environmental epigenetics is a relatively nascent but growing field. As knowledge and interest in environmental epigenetics increases, so do challenges and opportunities for investigators, with unique considerations when studying prenatal and early-life exposures. Below and in Table 1, we address challenges in the field and strategies for overcoming them. We also discuss how advancements in the study of epigenetics and DNAm-based biomarkers create new research prospects.

Rapid advancements in laboratory and computational tools have provided both challenges and opportunities for researchers. The HumanMethylation27K BeadChip, introduced in 2008, was quickly adopted as a robust platform for measuring DNAm in human epidemiological studies. New BeadChip designs have since increased reliability, coverage of the epigenome (i.e., >900,000 CpG sites on the Illumina Infinium MethylationEPIC v2.0), and suitability for population health studies. However, this progress has also posed challenges such as increased computational demands and harmonization of BeadChip types in longitudinal and consortia studies. Likewise, multiple data processing pipelines and statistical approaches, developed to address technical artifacts specific to the methylation BeadChips and to allow for analysis of high dimensional and spatially correlated DNAm data [68], have created obstacles for replication and evaluation of results across studies.

Research in recent years has also advanced our understanding of biological mechanisms and pathways in the context of environmental epigenetics. Differential methylation is now recognized as reflecting complex biological processes beyond observed changes in DNAm levels. DNAm signatures are specific to cell types, and consequently, variation in methylation may indicate shifts in cell type composition. Multiple cell-type deconvolution methods are now available to control for confounding by cell type, including reference-based and reference-free algorithms [69]. While adjusting for estimated cellular heterogeneity is now common practice in EWAS, investigators should still approach interpretation of environment-related DNAm signals with caution: even after accounting for major cell types, differences in the proportions of cell subtypes can influence observed associations with environmental exposures [70]. Although cell type heterogeneity is commonly viewed as a source of unwanted variation, DNAm-based surrogates of cell types can also be studied as outcomes of interest. The novel field of immunomethylomics aims to leverage estimates of cell subtypes to understand exposure- or disease-related shifts in immune profiles of peripheral blood.

Similarly, DNAm signatures of exposure are unique to the tissue studied. Epidemiological studies commonly rely on non-invasive biospecimens, which may not be the target tissue of interest. However, leveraging studies across tissue types (e.g., cord blood, placenta) and including information from existing resources comparing cross-tissue concordance (e.g., the Blood-Brain Epigenetic Concordance application [71]) can strengthen evidence of environment-related epigenetic variations. For studies of prenatal exposures, although target tissues are not readily available in human studies, placental samples may offer unique insights to developmental pathways relevant to long-term health. The placenta functions as the maternal-fetal interface, responsible for transferring nutrients and acting as a barrier between the developing fetus and extrauterine environment. Alterations in placenta function and structure increase risk of adverse birth and child health outcomes [72], and changes in placental DNA have been associated with maternal health before and during pregnancy, birth outcomes, and multiple prenatal chemical and non-chemical exposures [73]. However, studies of the placental epigenome must also take into consideration its unique methylation profile, including lower levels of global methylation and greater number of partially methylated regions, and high degree of plasticity, which may not reflect methylation changes in fetal tissues.

DNAm is impacted by genetic variation. Functional genetic variants can create (or remove) transcription factor binding sites, thereby influencing local DNAm levels [74]. In turn, CpG sites related to genetic variation (i.e., meQTLs) are associated with chromatin accessibility and other epigenetic markers [75]. To limit spurious associations due to genetic variants, CpG sites with known nearby SNPs are commonly dropped from

Table 1. Overview of common challenges in environmental epigenetic studies.

Challenge	Considerations & strategies to overcome challenge
Cell-type heterogeneity	• When available, use reference-based methods to estimate cell type composition of samples, including reference sets developed for cord blood or placenta. • Use reference-free deconvolution methods for tissue types without reference information.
Analysis of surrogate tissue	• Determination of target and surrogate tissues must consider both exposure response the phenotypic relevance. • Analyze multiple surrogate tissues to identify tissue-independent signals. • Interpret results in the context of physiological function of the tissue studied. • Use existing resources comparing cross-tissue concordance to infer similarity with target tissue.
Genetic influence on DNA methylation	• Remove CpG located at or near known SNPs before analysis. • Control for genetic principal components or DNA methylation-based surrogates.
Linking DNA methylation changes to health	• Leverage data from longitudinal studies to investigate the sequelae of early -life exposures, DNA methylation changes, and health. • Combine multiple omics layers, including transcriptomics, proteomics, and metabolomics, to understand downstream effects.
Reproducibility of findings	• All data processing and quality-control steps should be well-documented and use validated methods. • Use data from an external study to validate findings. • Leverage existing consortia of early -life epigenetic studies to increase power and generalizability.

downstream analyses. Potential SNP-associated CpGs can in specific populations also be identified computationally [76]. Like genetic association studies, population stratification is adjusted for using genetic ancestry principal components, if available, or surrogates for ancestry inferred from DNAm data [77,78]. Unique study designs (e.g., twin or paired-sibling studies [32]) may also limit the influence of genetic variants. Beyond removing the effects of genetic variants from analyses of epigenetic data, directly studying meQTLs and other gene-epigene interactions is important for understanding how multiple omics affect environment-associated disease risk.

Despite increasing evidence linking environmental exposures to DNAm, human studies of DNAm's role in molecular pathways linking the environment and health are more limited. Perspective birth cohorts have allowed for investigation of DNAm as mediator between prenatal exposures and child health (e.g., [42,50]). However, it is important not to conflate statistical mediation and a causal mechanistic link [79]. DNAm may also be a molecular mediator in the sense that it reflects and reinforces transcriptional changes; however, changes in methylation themselves may not directly cause alterations in gene expression. Establishing a causal association is beyond the reach of most observational epigenetic studies, but combining evidence from multiple omics layers, including transcriptomics, proteomics, and metabolomics, will help elucidate biological pathways affected by epigenetic changes. Furthermore, designing studies to establish temporality and limit bias and confounding and replicating findings in other systems including animal models will help to advance understanding of the mechanistic role of DNAm.

While studies of epigenetic markers can offer insights into the biological mechanisms linking exposures to health, there is growing interest in DNAm as a *non-causal* biomarker of exposures and disease risk, independent of a direct mechanistic role. Epigenetic clocks are a prominent example of such biomarkers. These clocks, or DNAm-based algorithms designed to estimate chronological age and aging-related phenotypes, are strong predictors of morbidity and mortality in adults and have been linked to growth and developmental stages in children and adolescents. By integrating multiple biological pathways, epigenetic clocks may also capture functional changes related to environmental exposures. Indeed, epigenetic aging has been associated with chemical exposures [80], including those occurring prenatally [81]. Although epigenetic clocks have primarily been developed for adult populations, an increasing number of clocks are trained specifically for pediatric populations [82] and tailored for use with tissue types readily available in birth and early-life epidemiological studies (e.g., cord blood [83,84], placenta [85], pediatric buccal epithelial cells [86], and pediatric peripheral blood [87]). Clocks trained on samples collected across the life course have also been shown to be correlated with gestational age and chronological age in pediatric samples [88,89]. However, the relationship between epigenetic aging and health may differ between adults and newborns or children. For example, epigenetic age acceleration is associated with mortality and chronic diseases in adults but may be indicative of greater developmental maturity at birth. Therefore, the development of epigenetic clocks for pediatric populations, including training on multiple tissue types and composite measures of development, is important for advancing the use of these biomarkers in early-life environmental epigenetic studies.

EWAS seldom integrate transcriptomics or further downstream omics layers (e.g., proteomics, metabolomics), making it difficult to understand effects of changes in DNAm. DNAm-based surrogates may be used to estimate disease-relevant physiological changes. For example, epigenetic scores have been demonstrated to be highly predictive biomarkers of plasma protein levels [90]. Epigenetic biomarkers may also be developed to assess chronic and historical environmental exposures. For instance, DNAm-based risk scores have been shown to be good classifiers of prenatal smoking exposure in adult blood samples [91]. Similarly, a DNAm-based surrogate of lead exposure has been developed [92] and has been associated with cardiovascular disease risk in an independent cohort [93]. Advancing novel epigenetic biomarkers holds promise for new approaches in precision environmental health. Measurement of DNAm in a single sample could provide information on past exposure to multiple environmental toxicants as well as future disease risk, enabling timely interventions to minimize long-term disease risk. Epigenetic biomarkers may be particularly valuable for capturing early-life exposures that are challenging to quantify but have long-lasting effects on health.

6. Future perspective

The intrauterine environment may shape long-term health through epigenetic perturbations. In this article, we provided an overview of research linking chemical exposures during embryogenesis and fetal development, a time of epigenetic remodeling, with DNAm changes. While strong evidence indicates that prenatal exposures impact DNAm – evident from studies on smoking, toxic metals, and endocrine-disrupting chemicals – the lack of replication of epigenome-wide signals and evidence of mechanistic involvement and downstream health effects, including changes in gene expression, remains a limitation. Utilizing longitudinal data and efforts by multi-cohort consortia, including PACE and ECHO, may help to overcome some challenges in identifying reproducible methylation signals and associated health outcomes. Additionally, novel computational methods could facilitate the development of epigenetic biomarkers for early-life exposures, changes in the proteome or metabolome, and disease risk, which may help to identify high-risk individuals and evaluate the efficacy of treatments and interventions. As recent advancements highlight, rapidly evolving approaches in environmental epigenetics have the potential to transform our understanding of early-life health risks and enhance long-term wellbeing.

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Author contributions

Anne K Bozack: conceptualization, writing – original draft, writing – review & editing; Leonardo Trasande: conceptualization, writing – review & editing. All authors reviewed and approved the final version of the manuscript and agreed on the journal for publication.

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