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Crosstalk between Maternal Life and Fetal Epigenome; A Review Article

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ABSTRACT

Background: It is important to say that maternal lifestyle during gestation could affect embryonic development and health consequences. **Objectives**: Many endogenous and exogenous factors affect the epigenetics of the germ cells during their division and subsequently affect the embryogenesis. **Methods**: This systematic review outline various studies that link the different environmental factors and modification in the fetal epigenome. **Conclusion**: Aberrant fetal epigenome modification subsequently affects the healthy embryonic growth and their contribution to the phenotypic changes and chronic disease development later in life.

Keywords: *Epigenetic modifications; Covid; Histone remodeling; Prenatal health; Radiation.*

INTRODUCTION

Epigenetics refer to the heritable change in the level of genes expression without affecting the DNA sequence of the genes[1]. Enzymatic removal or transfer of chemical agent to DNA and/or Histon could change genes expression. Methylation of DNA CpG islands together with hypoacetylated and hypermethylated histones mainly induce gene silencing. This effect refers to long-range epigenetic silencing (LRES) usually caused by DNA methyl transferase (DNMT) family[2]. In addition, ten-eleven translocation (TET) protein family methyl cytosine dioxygenases considered the major family for DNA demethylation regulation via the removal of a methyl group from 5-mC[3]. In addition, histones post translation modification induced by histone acetyltransferases (HATs), histone deacetylase (HDACs) histone methyltransferases (HMTs) and histone demethylases (HDMs) induce chromatin remodeling and subsequently affecting genes expression[4,5]. Epigenetic related noncoding RNAs (ncRNAs) including microRNAs (miRNAs), small interfering RNA (siRNAs), Piwi-interacting RNA (piRNAs) and long noncoding RNAs (lncRNA) could also induce genes silencing[6,7]. Different epigenetic mechanisms involved in genes regulations are summarized in **Figure1**.

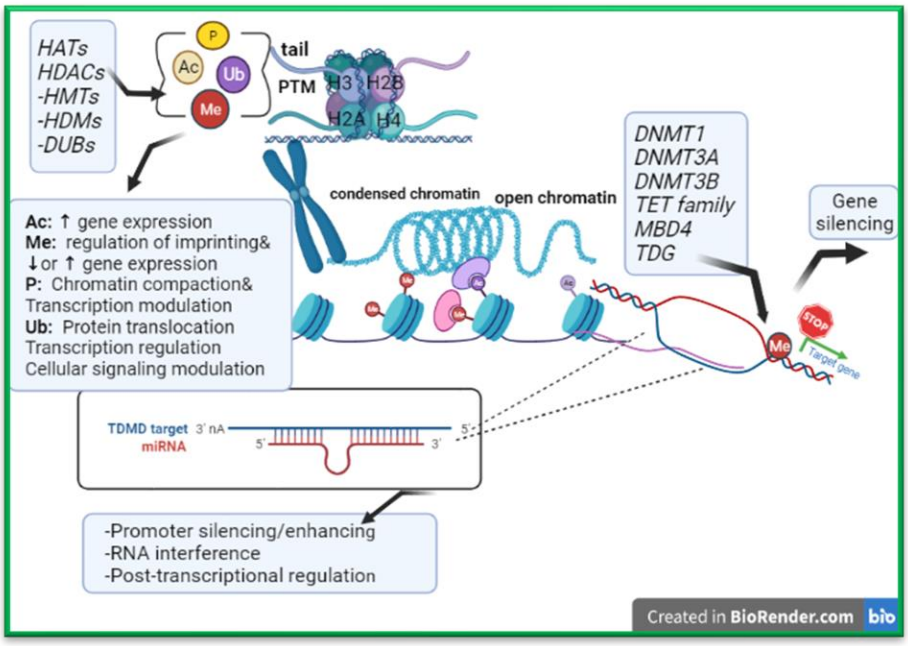

Figure 1. Different epigenetic mechanisms involved in genes regulation.

Ac; *acetylation,* ***Me;*** *methylation,* ***P;*** *phosphorylation,* ***Ub;*** *ubiquitination,* ***DNMT;*** *DNA methyl transferase,* ***TET****; ten-eleven translocation enzymes,* ***MBD4;*** *methyl-CpG binding protein 4,* ***TDG;*** *thymine DNA glycosylase,* ***HATs****; histone acetyltransferases,* ***HDACs****; histone deacetylase,* ***HMTs****; histone methyltransferases,* ***HDMs****; histone demethylases,* ***DUBs;*** *deubiquitinating enzymes,* ***miRNAs****; microRNAs*

Epigenetic profile of fetus performed in the early life. This profile not only affect embryo development but may also increase the susceptibility to various diseases such as diabetes, obesity, cardiovascular disease and cancer, in later life. Various researches proved that maternal lifestyle including maternal nutrition and exposure to different environmental factors as alcohol, smoking, pollution and infection modify the epigenome of fetus by different mechanisms and affect the fetus through different ways. This review will shed light on the different factors affecting the epigenomes of the fetus during the gestation period and their mechanisms in order to provide better understanding of this developmental disorder's etiology and finding the ways for preventing them.

Maternal Nutrition

Maternal nutrition during pregnancy plays crucial role in fetal health and disease framework. Balanced nutrition is the goal in this point as undernutrition and overnutrition affect fetal development negatively.

Maternal overnutrition

The availability of common methyl donors such as folate, choline, serine, and methionine from dietary sources could modulate the synthesis of the S-adenosyl-methionine (SAM) which is universal methyl donor. Increase in SAM production cause histone and DNA hypermethylation in the fetal epigenome, resulting in changes in gene expression [8].

A study conducted by Waterland et al on-mouse model showed that methyl supplementation during pregnancy induce hypermethylation at the CpG site at the agouti viable yellow (Avy) allele, resulting in transgenerational epigenetic inheritance, that induce changes in the phenotype and longevity of the offspring[9].

Although Daly et al has shown the essential role of folic acid uptake at the first four weeks of pregnancy in the growth of fetal spine and brain in addition to prevention of neural tube defects & congenital heart[10], its epigenetic role should be considered. Excessive Dietary intake of the methyl donor folic acid above the recommended dose (600 µg -1000 µg/daily) as recommended by institute of Medicine's Food and Nutrition Board (USA)) induced cytosine guanine rich region (CpG island) hypermethylation and silencing of genes involved in early growth as insulin – like growth factor 2(IGF2)[11]. Increased adiposity in children and insulin resistance is positively correlated with level of Folic acid in the maternal circulation. Yajnik et al reported that periconceptional folic acid ≥400ug/ml in

period (weeks 0-12 post conception) is associated with an increased risk of clefts lip [12].

A study conducted by Rozendaal et al in an animal model has shown that maternal high-fat diet during gestation contribute with epigenetic alterations and histone modifications of key metabolic genes that influences the risk of obesity in the offspring [13].

Maternal undernutrition

A Study performed by Strakovsky et al in an animal model showed that maternal undernutrition induced changes in the expression of genes involved in regulation of endothelial cell function in the pulmonary vasculature and promote pulmonary vascular remodeling. Mice received Caloric Restricted diet showed upregulation in endothelium fibronectin 1 (Fn1) and plasminogen activator inhibitor 1 (PAI 1) genes, while the expression of genes involved in regulation of histone acetylation was downregulated significantly [14].

It is well known that proteins are the source of amino acids like methionine, serine and glycine which act as methyl donor in methylation process of genes promotors [15]. Low protein diet during gestation induced hypomethylation in the promotor of different placental genes. Wingless-type MMTV integration site family, member 2, also known as Wnt2 (Wnt Family Member 2) is a Protein Coding gene and its promoter methylation in the placenta is essential in fetal growth and its hypomethylation induced impairment in fetus development[16].

In addition, A study performed by Reamon et al showed that prenatal low protein diet caused methylation level change in the angiotensin II receptor, type 1b (Agtr1b) gene which is associated with hypertension development in later life[17]. Moreover, maternal magnesium or calcium deficiency cause alterations of methylation in the promoter of hydroxysteroid dehydrogenase in the offspring hepatic tissues that may affect the neurobehavior and the growth of neonates [18]**. Table1** describes the epigenetic mechanisms induced by different maternal nutrition.

Gestational *Diabetes Mellitus* (GDM)

Gestational diabetes mellitus (GDM) is a pregnancy complication first detected in the second or third trimester in women that did not show evident glucose intolerance or diabetes before gestation. It increases the susceptibility to developing chronic diseases for both the mother and the baby later in life. Under GDM conditions, the intrauterine environment becomes hyperglycemic, while also showing high concentrations of fatty acids and proinflammatory cytokines, producing morphological, structural, and molecular modifications in the placenta, affecting its function; these alterations may predispose the baby to disease in adult life[33]. Molecular alterations include epigenetic mechanisms such as DNA and RNA methylation, chromatin remodeling, histone modifications, and expression of noncoding RNAs (ncRNAs). Gestational Diabetes mellitus & obesity can induce potential alterations in the methylation pattern of several genes, including those involved in the metabolic pathway in placenta and cord blood[34]. Obesogenic diets have decreased DNA methylation in the zinc finger protein 423(Zfp423) promoter, a crucial transcriptional component. Zfp423 dysregulation elevate adipogenic tissue differentiation during fetal development and cause adiposity [35]. Studies also showed that maternal obesity and high fat diet increase the level of hepatic triglyceride (TG) in neonates due to upregulation of Stearoyl-CoA desaturase-1(SCD1) gene that involved in TG accumulation. This lead to transgenerational nonalcoholic fatty liver (NAFLD) disease development[36,37].

Maternal stress

Different reports showed that Maternal depression, has been linked to fourfold increase in the risk of the depression development in the child [38,39]. Stress induced plasticity in the developing brain that resulting in a serious impact on the behavioral and cognitive–emotional systems[40]. Prenatal exposure to maternal depression can induce epigenetic alterations in newborns, resulted in gain in methylation level in the fetal glucocorticoid receptor gene Nuclear Receptor Subfamily 3 Group C Member 1(NR3C1) promoter region in cord blood. This modification lead to impairment in the glucocorticoid response [41].

Tobacco smoking

Maternal smoking is one of the major medical concerns as it is associated with development of preterm birth baby, child behavioral problems and intrauterine growth restrictions [42,43]. Previous study proved that maternal cigarette smoking is contributed with increased risk for spontaneous abortion[44].

Smoking during gestation also has been found to induce pathologic changes to the placenta, including aberrant patterns of DNA methylation and reduced mature neural content, effects that are likely predisposed by nicotine[45]. Smoking cause in utero hypomethylation of cytochrome P450 family 1 subfamily A member 1(CYP1A1) gene promotor. CYP1A1gene considered the major metabolic enzyme that catalyze the conversion of polycyclic aromatic hydrocarbons into harmful hydrophilic DNA adducts. This yield subsequently adverse outcome in the development of offspring [46].

Several reports showed a correlation between maternal smoking and later development of attention deficit hyperactivity disorder (ADHD)and psychiatric disorder [47-50].

Table 1. Epigenetic Mechanisms induced by different maternal nutrition

Nutrition	Epigenetic mechanisms	References
Overfeeding (High calorie diet)	Deacetylation and methylation in the multiple genes as adiponectin, and leptin.	19
High fat	Histone acetylation of H3K9, H3K18 and H3K14 Histone acetylation of fetal surtuin 1. Hypermethylation in GHSR	20
Methyl donors	Methylation of the runt-related transcription factor 3 (Runx3), Histone modification Sirt1 and pmrt1 expression Hypomethylation of PGC-1α Hypomethylation of Ptpn22 and PPAR-α	21 22
Folate and Multivitamins	Hypomethylation of IGF2 2R and GTL2-2	23
DHA	LINE1 hypermethylation and increase INFγ/IL13 methylation ratio	24
Choline	Hypermethylation of CRH, NR3C1 in placenta; hypomethylation of CRH, NR3C1 in cord blood leukocyte; increase H3K9me2	25
Folate	Hypomethylation of LINE1 Hypermethylation of IGF2 DMR Hypomethylation of PEG3 and LINE1; and Hypermethylation of IGF2	26 27
Free fatty acid	Hypermethylation in PGC-1α	28
Green tea polyphenols (EGCG)	DNMT, HAT, HDAC inhibition Decreased MeCP2 MiRNAs modulation	29
Vitamin B12	Decrease methylation levels of (IGFBP-3) gene.	30
Undernutrition (Low calorie diet)	Histone (H3, H4) acetylation of CEBPB, PEPCK	31
Low Protein	Hypermethylation of Wnt promoter DNA methylation Agtr1b promoter Decrease DNMT1 expression. Interaction between Hnf4a enhancer and p2 promoter Hypermethylation of IGF2 and H19 ICR Hypermethylation of X-receptor promoter	16 32

Table (1): *(**Agtr1b**) angiotensin II receptor, type 1b , (**CEBPB**),CCAAT Enhancer Binding Protein Beta, (**CRH**)Corticotropin-releasing hormone receptor 1, , (**DNMT**) DNA methyl transferase, growth hormone secretagogue receptor (**GHSR**), gene trap locus 2 (**GTL2-2**), Histone H3 Lys9 (**H3K9**), Histone deacetylase (HDAC), Histone acyetyl transferase(**HAT**), (**Hnf4a**) hepatocyte nuclear factor 4 alpha, Interferon gamma (**IFN-γ**) , **IGF2R** insulin like growth factor 2 receptor,), Interleukin 13 (**IL-13**), Insulin Like Growth Factor Binding Protein 3) (**IGFBP-3**) , (**LINE1**) Type Transposase Domain Containing 1), Methyl-CpG binding protein 2 (**MeCP2**), Nuclear Receptor Subfamily 3 Group C Member 1(**NR3C1**), **PMRT1**, a Plasmodium specific parasite plasma membrane transporter, Protein tyrosine phosphatase non-receptor type 22 (**Ptpn22**), Peroxisome proliferator-activated receptor-gamma coactivator (**PGC**)-1alpha, Peroxisome proliferator-activated receptor alpha (**PPARα**), Phosphoenolpyruvate carboxykinase (**PEPCK**), **PEG3** (Paternally Expressed 3), (**Runx3**) runt-related transcription factor 3, , serine proteinase inhibitor (**surtuin 1**).*

Higher degree of DNA methylation in exon 6 of the brain-derived neurotrophic factor (BDNF) observed in infant exposed to in utero maternal tobacco smoking. BDNF plays an important role in brain development, such modification may modulate the overall neurodevelopmental outcomes, including depression [51]. Moreover, study conducted by *Patil et al* demonstrate that prenatal maternal smoking modulates the DNA methylation of IL13 gene that induce asthma related lung function in offspring[45].

Alcohol consumption

Studies demonstrated that gestational alcohol exposure can induce long-lasting changes to the fetal epigenome. Fetal alcohol spectrum disorder (FASD), the term that is used to describe alcohol-related neonatal abnormalities, include growth retardation and central nervous system (CNS) deficiencies[52,53]. Chronic alcohol consumption during the pregnancy associated with increase the activity of DNMT, resulting in reduced the expression of methyl-CpG binding protein 2 (MeCP2).

Methyl-CpG binding protein 2 is important for the function of several types of cells including the neurons so its reduced expression resulting in neurodevelopmental deficit. Study conducted by liu et al in-mouse embryos has shown that alcohol exposure altered DNA methylation, and expression of several genes, including those involved in cell cycle, growth, apoptosis which can modulate early fetal development [54].

Study conducted by Halder et al reported an alteration in the gene expression involved in brain development. Nuclear factor one alpha (Nf1a) gene and N-methyl-d-aspartate (Nmda) receptor family were down-regulated in brain hippocampus. These TF regulate the expression of different genes involved in control gliogenesis, cell proliferation and neuronal cells survival[53].

Pollution

Environmental exposures, such as bushfire smoke, during pregnancy have the potential effect on the pregnant woman and their offspring with elevated levels of PM2.5 (fine particulate matter <2.5 µm in size) [55]. Exposed pregnant women to air pollutant have been associated with epigenetic alteration which lead to poor perinatal outcomes, such as preterm birth, and the development of asthma [56].

Being born early or small constitutes a risk for the child's future health, such as an rise the risk of cardiovascular, respiratory and metabolic diseases later in life [57]. In mothers, adverse relation were also detected between wildfire smoke exposure and gestational diabetes and pregnancy induced hypertension [58].

According to studies, maternal exposure to PM2.5, PM10, NO2, SO2, and O3 was linked to a higher risk of birth abnormalities[59]. According to Feng et al., the hypermethylation level of the G protein-coupled receptor 61(GPR61) gene is evident in both mothers and neonates, confirming the effect of air pollution exposure on pregnant women and their unborn children due to alteration in DNA methylation [60]. Some studies investigate the relationship between air pollution from traffic and the risk of developing autism spectrum condition. Rats' offspring have been found to have epigenetic changes in the proteins methyl CpG binding protein 2 (MeCP2), SH3 and multiple ankyrin repeat domains 3 (Shank3), tri-methylatable lysine 4 on histone H3 (H3K4me3), and tri-methylatable lysine 27 on histone H3 protein (H3K27me3). [61].

Radiation

The smartphone is the most advanced technological device in the mobile phone market today, comprising the features of both computers and mobile phones in one small device [62]. Many people today rely on their smartphones to carry out their daily tasks and for a variety of purposes, including education, communication, and shopping. However, researchers have reported that technological devices emit harmful, non-ionizing, electromagnetic field (EMF) radiation at a high-frequency level (100 kHz–300 GHz) [63].

Several studies have investigated the biological interaction between the human body and exposure to this radiation. The evidence indicates that the absorption of EMF radiation by the human body is linked with detrimental health impacts, including respiratory problems [64],(muscle pains, headaches [65], and male infertility problems [66]. According to [67], it is reported that the EMF radiation of mobile phones that is absorbed by pregnant women can cause changes in the fetal temperature.

Many reviewed studies supported the presence of risks on pregnancy, birth, and infant outcomes among pregnant mothers exposed to EMF radiation. For example, Karuserci et al showed that pregnant women who were exposed to EMF radiated from TVs were more likely to give birth to infants with small head circumference [68], Meanwhile, Lu et al showed that pregnant women who use their mobile phones excessively tend to give birth to infants with small chest circumference, as compared to women who use their mobile phones moderately[69].

One cross-sectional study found that using mobile phones during pregnancy increased the chances of giving birth to children with speech problems [70]. However, there is a lack of evidence related to the association between EMF radiation exposure and epigenetic changes in pregnant women. The reviewed studies provide evidence for the urgent need for more research which assesses the impacts of EMF radiation exposure on epigenetic changes in pregnancy, birth, and infant outcomes.

COVID-19 infection

The COVID-19 pandemic represents a collective trauma that may have enduring stress effects during sensitive periods, such as pregnancy[71,72]. Maternal stress during pregnancy may be specifically linked with alterations of the temperamental profile of the infant [73-75]. A previous study showed that Prenatal stress may result in epigenetic signatures of stress-related genes (e.g., the serotonin transporter gene, *SLC6A4*) that may in turn influence infants' behavioral development [76].

In 2021, Provenzi *et al* launched a longitudinal cohort study to assess the behavioral and epigenetic vestiges of COVID-19-related prenatal stress exposure in mothers and infants. COVID-19-related prenatal stress was retrospectively assessed at birth. *SLC6A4* methylation was assessed in thirteen CpG sites in mothers and infants' buccal cells. Infants' temperament was assessed at 3-month-age. Greater COVID-19-related prenatal stress was significantly associated with higher infants' *SLC6A4* methylation in seven CpG sites [77].

Another study examined the potential link between maternal infection & altered DNA Methylation (DNAm)where there was consequent alterations occurring in the DNAm of specific genes involved in the regulation of stress and cognitive development of the fetus [78]. A DNAm analysis on the heart and kidney of murine models with SARS-CoV-2 infection identified more than 200 differentially methylated regions (DMRs)

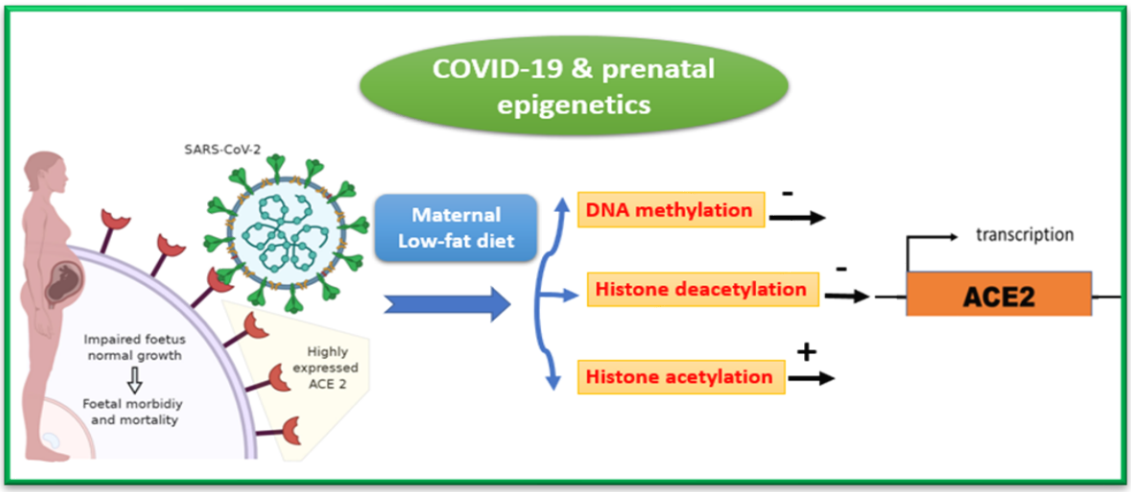

Figure 2. Effect of epigenetic modulation of maternal nutrition for tissue specific expression of ACE2 gene in COVVID-19 infection[88].

in the genome of both organs, one tenth of which were associated with two particular genes with prenatal implications.

The two genes, PEG10 and ECE1, were demonstrated to be neighbored by multiple DMRs. Located on chromosome 7, PEG10 is a paternally expressed imprinted gene, containing several DMRs within its first exon. The presence of these DMRs may render PEG10 subject to epigenetic modifications in the form of unspecified altered DNAm following SARS-CoV-2 infection, in the murine models of COVID-19.

The clinical prominence of this finding is in that the loss of function of PEG10 can lead to early embryonic death [79]. A proteolytic enzyme encoded by ECE1 on the first chromosome, endothelin converting enzyme 1 regulates the processing of potent vasoconstrictors, including endothelin 1–3. Unfunctional copies of ECE1 are correlated with cardiac defects and autonomic dysfunctions in neonates.

Several DMRs were also identified, by the same analysis, upstream to the transcription start site of ECE1, whose hypermethylation were associated with downregulation of ECE1 [79]. This might potentially explain the hypotensive state observed frequently in patients with critical COVID-19, necessitating administration of vasopressors [80], however, such speculations need to be confirmed by prospective studies.

There is accumulating evidence suggesting that ACE2, the host cell receptor for the spike (S) protein of the SARS-CoV-2, mediates viral entry and infection, is under epigenetic control[81]. Here, many studies suggested a nutritional strategy for down-regulating ACE2 expression in tissues of offspring through the phenomenon of maternal epigenomic reprogramming mediated by maternal diet[82,83].

Their analysis of the proposed mechanism for "early life programming" via nutritional modulation of histone acetylation and DNA methylation goes beyond the physiological consequence of boosting the innate cellular resistance to a viral transmission[84]. During the pandemic, where there was still no specific antiviral drug or a widely disseminated vaccine for COVID-19, SO they hypothesize that an epigenomic nutrition approach may be a practical approach to help mitigate viral transmission offspring.

Since it has been found that ACE2 is highly expressed in the maternal-fetal interface cells [85], it is speculated that there is atheoretical basis to consider a low-fat diet as a practical intervention for pregnant mothers by induction of histone deacetylation at the promoters of ACE[86]. There was much evidence that a low-fat diet, which is composed mainly of a plant-based diet, can lead to epigenetically mediated down-regulation of ACE2. perinatal nutritional interventions may offer a critical window of opportunity for infants to acquire not just COVID-19 resistance, but also empower mothers to activate epigenetic priming mechanisms to extend the biological effects over multiple generations[87] (**Figure 2**).

CONCLUSION

Reports confirm that there is a cross talk between maternal lifestyle and fetal epigenetic modification. Thus, strategies for preventing this aberrant modification in fetal epigenome by regular maternal exercise, healthy balanced nutrition and avoiding the devasting environmental factors considered

an urgent issue. In addition to the discussed environmental factors that affect fetal epigenome described in this review, we should take into consideration daily exposure to radiation from different sources as microwaves, mobiles and consequently the study of their possible effects on fetal epigenome and subsequently fetal health will be a challenge.

Abbreviations

LRES; long-range epigenetic silencing, **DNMT**; DNA methyl transferase, **TET**; ten-eleven translocation enzymes, **HATs**; histone acetyltransferases, **HDACs**; histone deacetylase, **HMTs**; histone methyltransferases, **HDMs**, histone demethylases; **ncRNAs**; noncoding RNAs, **miRNAs**; microRNAs, **siRNA**; small interfering RNA, **piRNAs**; Piwi-interacting RNA, **lncRNA**; long noncoding RNAs, **SAM**; S-adenosyl-methionine, **Fn1**; Fibronectin 1, **Sperine 1**; plasminogen activator inhibitor1, **Agtr1b**; Angiotensin receptor type1b, **TF**; Transcription factor, **NAFLD**; Nonalcoholic fatty liver disease, **SCD1**; Stearoyl-CoA desaturase-1, **GDM** ;Gestational Diabetes mellitus**, ADHD**; attention deficit hyperactivity disorder, **BDNF**; brain-derived neurotrophic factor, **FASD**; Fetal alcohol spectrum disorder, **CNS**; central nervous system, **MeCP2**; methyl-CpG binding protein 2, **Nf1a**; Nuclear factor one alpha, **Nmda**; N-methyl-d-aspartate, **EMF**; electromagnetic field, **CVS,** Cardiovascular disease.

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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