Review

Jiaying Mo, Xuanqi Liu, Yutong Huang, Renke He, Yu Zhang* and Hefeng Huang*

# Developmental origins of adult diseases

https://doi.org/10.1515/mr-2022-0027
Received August 29, 2022; accepted October 11, 2022;
published online November 11, 2022

**Abstract:** The occurrence and mechanisms of developmental adult diseases have gradually attracted attention in recent years. Exposure of gametes and embryos to adverse environments, especially during plastic development, can alter the expression of certain tissue-specific genes, leading to increased susceptibility to certain diseases in adulthood, such as diabetes, cardiovascular disease, neuropsychiatric, and reproductive system diseases, etc. The occurrence of chronic disease in adulthood is partly due to genetic factors, and the remaining risk is partly due to environmental-dependent epigenetic information alteration, including DNA methylation, histone modifications, and noncoding RNAs. Changes in this epigenetic information potentially damage our health, which has also been supported by numerous epidemiological and animal studies in recent years. Environmental factors functionally affect embryo development through epimutation, transmitting diseases to offspring and even later generations. This review mainly elaborated on the concept of developmental origins of adult diseases, and revealed the epigenetic mechanisms underlying these events, discussed the theoretical basis for the prevention and treatment of related diseases.

**Keywords:** embryos development; epigenetic; gametes; non-communicable diseases.

## Introduction

Do the origins of adult disease lie in early life events? How is individual susceptibility to adult disease programmed by gametes and embryonic developmental environmental conditions? Answers to these questions are at the center of the emerging field, the "developmental origins of health and disease (DOHaD)" hypothesis. This hypothesis is initially proposed by Barker 50 years ago, linking the state of health in adult life with the environmental conditions of early life, based on his observation on epidemiology [1, 2] Suboptimal perinatal environment influences susceptibility to non-communicable diseases (NCDs) in adulthood, as demonstrated by numerous epidemiological and genome-wide studies [3]. Previous studies mostly focused on the metabolic and cardiovascular system related diseases [4]. However, the scope of the developmental origin of adult diseases has now been expanded, and the types of diseases have gradually expanded from metabolic and cardiovascular diseases to mental and reproductive-related diseases [5, 6]. Here, we will fill in the gaps in terms of disease diversity.

NCDs, mainly cardiovascular diseases, cancers, diabetes, and chronic respiratory diseases, are responsible for 71% of global deaths [7]. The rising incidence of these diseases, which cannot be explained by genes alone, indicates that epigenetic but not genetic inheritance may play an important role in disease development [8]. Environment-induced epigenetic information perturbations, including DNA methylation, histone modifications, and noncoding RNA, are observed in various adult diseases

Jiaying Mo and Xuanqi Liu These authors equally contributed to this work.

***Corresponding authors: Yu Zhang**, Obstetrics and Gynecology Hospital, Institute of Reproduction and Development, Fudan University, No. 131 Dong'an Road, Xuhui District, Shanghai 200032, China, E-mail: yuzhang0327@126.com; and **Hefeng Huang**, Department of Obstetrics and Gynecology, The Fourth Affiliated Hospital, International Institutes of Medicine, Zhejiang University School of Medicine, Yiwu 322000, Zhejiang Province, China; The Key Laboratory of Reproductive Genetics (Zhejiang University), Ministry of Education, Zhejiang University School of Medicine, No.866 Yuhangtang Road, Xihu District, Hangzhou 310058, Zhejiang Province, China; Obstetrics and Gynecology Hospital, Institute of Reproduction and Development, Fudan University, Shanghai 200032, China; and Research Units of Embryo Original Diseases, Chinese Academy of Medical Sciences (No. 2019RU056), Shanghai 200032, China, E-mail: hhf57@zju.edu.cn. https://orcid.org/0000-0003-4344-8019
**Jiaying Mo and Renke He,** Department of Obstetrics and Gynecology, The Fourth Affiliated Hospital, International Institutes of Medicine, Zhejiang University School of Medicine, Yiwu, Zhejiang Province, China; and The Key Laboratory of Reproductive Genetics (Zhejiang University), Ministry of Education, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China
**Xuanqi Liu and Yutong Huang,** The Key Laboratory of Reproductive Genetics (Zhejiang University), Ministry of Education, Zhejiang University School of Medicine, Hangzhou, Zhejiang Province, China

and proved to be important in the etiology [8–11]. Moreover, parental lifestyles, including diet, environmental factors and lifestyle stress, and even infectious and inflammatory events during pregnancy, can negatively impact the health of the offspring through modified epigenetic features in gametes and embryos [12–15]. Multiple epidemiological and experimental animal studies revealed how epigenetic information affects fetal development intergenerationally or even across generations [14, 16, 17]. Among them, the importance of germline-mediated intergenerational inheritance has not been fully recognized in the field of developmental diseases, which is also a research hotspot in recent years [12–14, 18]. For example, our prior study elucidated that adverse maternal environment can affect offspring glucose metabolism through the impaired *Tet3*-deficient oocyte [19]. Qi Zhou and colleagues conducted a seminal study proved that a class of highly enriched small RNAs, tsRNAs, in mature spermatozoa, can act as a carrier of epigenetic information and transmit a high-fat-induced metabolic disorder phenotype from the parent to the offspring [20].

With this in mind, this review summarizes the epigenetic plasticity of various systemic diseases caused by environmental stimuli and diet, etc., and discusses how gametes and embryos act as vectors for introducing epimutations in the next generation through epigenetic mechanisms. This will help us identify critical periods for earlier prevention and more effective treatment.

## Multisystem diseases

Parental exposure to adverse environments alters various biological systems in the developing embryo, fetus, and postnatal individuals (including the metabolic system, cardiovascular system, central nervous system, reproductive system, etc.). The altered expression of certain tissue-specific genes results in widespread organ dysfunctions and susceptibility to disease in the mature offspring [10, 21] (Figure 1).

### Metabolic system

The world is now facing a global epidemic of obesity accompanied by a "double burden of malnutrition", including overweight, underweight, and micronutrient deficiency. The prevalence of metabolic diseases is increasing worldwide, and multiple researches claimed that environmental rather than genetic factors are the main drivers [22–24]. We mainly focused on how external disturbances increase the risk of chronic metabolic disease in adults (Table 1).

Growing epidemiological studies connected perinatal factors to the later risk of obesity and metabolic diseases in adults [21]. Maternal obesity is an important factor [21]. Clinical data showed that a higher pre-pregnancy body mass index (BMI, weight [kg]/height [m]$^2$) is associated

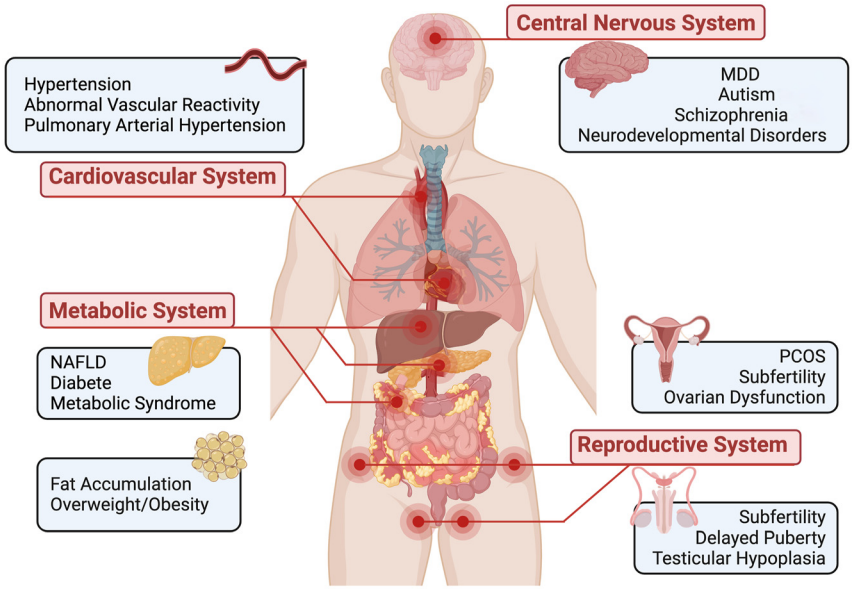


**Figure 1:** Overview of various biological system diseases caused by adverse environmental exposure of parents.Disorders of different systems are listed from left to right (indicated by the red lines): cardiovascular system (Hypertension，Abnormal vascular reactivity and Pulmonary arterial hypertension); metabolic system (Non-alcoholic fatty liver disease, Diabetes, Metabolic syndrome, Fat accumulation and Overweight/obesity); central nervous system (Major Depressive Disorder, Autism, Schizophrenia and Neurodevelopmental disorders); reproductive system (Polycystic ovary syndrome, Subfertility, Ovarian dysfunction, Delayed puberty and Testicular hypoplasia). MDD, Major Depressive Disorder; PCOS, Polycystic ovary syndrome; NAFLD, Non-alcoholic fatty liver disease.

**Table 1:** Metabolic system.

| Exposure conditions | Exposure factors | Species | Epigenetic perturbations | Offspring adverse outcomes | References |
|---|---|---|---|---|---|
| Gametogenesis | High-fat diet (HFD) | SD rats (M) | Not applicable/Hypomethylation of the Il13ra2 gene | Growth deficit in males (F1) (birth weight↓, fat pads and skeletal muscles↓), risk of potential metabolic↑, β-cell dysfunction' in female (F1) | [22, 25] |
| | Paternal obesity and F1 were fed HFD | SD rats (M) | Not applicable | Metabolic (body weight and leptin level↑) and reproductive disturbances (luteinizing hormone (LH), testosterone and LH responses to central kisspeptin-10↓) in male (F1) | [23] |
| | Maternal high BMI/ adiposity | Human | Not applicable | Overweight/obesity/circulating lipid levels↑ | [24, 26] |
| | Low-protein diet | C57/Bl6 mice (M) | Cytosine methylation patterns in sperm | Metabolic disorders (cholesterol and lipid) | [27] |
| | Hyperglycaemia | C57BL/6 n (F) | Insufficient demethylation by oocyte TET3 | Metabolic disorders (glucose intolerance) | [19] |
| | Inflammation | C57BL/6 mice (M) | Ang-mediated biogenesis of 5′-tsRNAs in sperm | Metabolic disorders (glucose intolerance and obesity) | [28] |
| | Traumatic stress | C57Bl/6J mice (M) | Small non-coding RNAs in sperm | Behavioral and metabolic disorders | [29] |
| | Low-protein diet | Rats (F) | Histone modifications at the gene enhancer region of Hnf4a | Insulin resistance (IR) and obesity | [30] |
| *In utero* | High-calorie diet (HCD) | C57BL/6J mice | Not applicable | Metabolic disorders (body weight↑, impaired glucose metabolism, insulin sensitivity↓, serum cholesterol and hepatic steatosis↑) | [31, 32] |
| | HFD | SD rats | Not applicable | IR and pancreatic beta-cell dysfunction | [33] |
| | | Japanese macaques/ C57BL/6J mice | Not applicable | Risk of nonalcoholic fatty liver disease (NAFLD) ↑ | [34–36] |
| | Nutrition deprivation | Human | Not applicable | Obesity rates↓ (last trimester of pregnancy and the first months of life) and obesity rates↑ (the first half of pregnancy)/risk of overweight, type 2 diabetes (T2DM), hyperglycemia, metabolic syndrome, and schizophrenia ↑ | [37, 38] |
| | Maternal diabetes | Human | Not applicable | Risk of diabetes and obesity↑ | [39–44] |
| | Maternal smoking | Human | Not applicable | Risk of type 1 diabetes（T1DM） | [45] |
| | Maternal obesity | Human | Not applicable | Metabolic disorders (adiposity and IR) | [46] |
| | | Human | Not applicable | Risk of being overweight↑ | [47] |
| Post-natal | Caesarean section delivery | Human | Not applicable | Risk of T1DM and obesity↑ | [48–51] |
| | Antibiotics | Human | Not applicable | Risk of being overweight↑ (normal weight mothers) and risk of overweight ↓ (overweight mothers) | [52] |
| | Low rates of fetal growth/small size at birth | Human | Not applicable | Risk of T2DM↑/high growth rates | [53] |
| | Early catch-up growth/rapid weight gain | Human | Not applicable | Risk of being overweight↑ | [54, 55] |
| | Fed with breast milk | Human | Not applicable | Risk of being overweight↓ | [56] |

with an increased risk of overweight offspring [24, 26]. Children whose mothers with a pre-pregnancy BMI ≥ 25 were 1.7 times more likely to be overweight in early childhood and twice as likely to be overweight in later childhood [24]. What's more, Catalano et al. found that obese mothers may induce fetal hyperinsulinemia accompanied with increased fetal lipogenesis [46]. Our group recently reported that maternal pre-pregnancy hyperglycemia makes offspring more susceptible to glucose intolerance through oocyte TET3 deficiency [19]. Interestingly, offspring of paternal diabetes are also at greater risk of developing diabetes [39–42, 45], which suggests that changes in sperm can also be transmitted to offspring and affect subsequent development. Carone et al. revealed that paternal exposure to a low-protein diet can affect offspring's cholesterol and lipid metabolism [27]. The female offspring, whose father has long-term exposure to a high-fat diet, are more prone to impaired glucose-insulin homeostasis [25]. Paternal inflammation [28], traumatic stress [29] can also alter the sperm epigenomic profile, leading to metabolic disturbances in offspring.

A strong relationship between female dietary intake and physical activity during pregnancy and offspring metabolism is supported by epidemiological and animal studies [21]. Numerous animal studies have demonstrated that a high-fat diet or dietary restrictions during pregnancy can lead to impaired glucose homeostasis [31, 33] and lipid homeostasis [32] in offspring adulthood, leading to increased morbidity of obesity [31], non-alcoholic fatty liver disease (NAFLD) [34–36], diabetes, metabolic syndrome and so forth. Other studies revealed that excess weight gain during pregnancy increases the risk of childhood being overweight, independent of pre-pregnancy BMI [57]. In addition, a classic early cohort study found starvation during pregnancy is also associated with obesity in adulthood [37, 38]. Sandovici et al. showed that maternal low-protein diets in rats result in low expression of the islet *Hnf4a* gene in offspring. At the molecular level, this low expression is partly attributable to histone modification changes in the enhancer region of *Hnf4a* [30]. Last but not the least, Gestational Diabetes Mellitus (GDM), one of the most common pregnancy disorders, may increase long-term metabolic risks in offspring, such as diabetes [43, 44] and obesity [47].

Interestingly, the mode of delivery also affects the risk of chronic metabolic disease in offspring. There is evidence suggesting that offspring born by cesarean section have a significantly higher risk of diabetes, although the overall risk is small [48]. More epidemiological investigations have shown that cesarean delivery is also associated with early offspring overweight [49, 50]. Furthermore, childhood overweight in offspring caused by different delivery methods may be related to differences in the microbial flora colonizing the mother's vagina and the infant's gastrointestinal tract [51, 52]. Nutritional status in early life can also affect long-term metabolism in offspring. One example is that growing too fast in early life may lead to a higher risk of developing type 2 diabetes in adulthood [53]. Other similar cases declared that excessive weight gain in infancy is positively associated with obesity in childhood [54, 55] and adolescence [56].

In conclusion, there are now substantial evidence showing that exposure to different environments, including gametes, embryos, fetuses, and neonates, is associated with the risk of developing chronic metabolic diseases in offspring adulthood. With the advent of metabolomics and early imaging of the placenta and fetus, the understanding and prediction of metabolic diseases in adults will be further developed.

## Cardiovascular system

The most influential early epidemiology of DOHaD theory focus on this system [2] (Table 2). Adverse intrauterine environments, usually derived from pregnancy complications, are closely related to abnormal cardiovascular development in offspring. Epidemiologic studies showed that offspring born to mothers with preeclampsia have higher childhood blood pressures and body mass index which increase the risk of cardiovascular disease (CVD) later in life [58]. Intrauterine growth restriction (IUGR), accompanied by preeclampsia, can lead to a higher risk of developing CVD in later life. Shah et al. performed sham or myocardial infarction (MI) surgery in adult rat offspring exposed to prenatal hypoxia (11% $O_2$) or normoxia (21% $O_2$) *in utero*. It turns out that male offspring exposed to prenatal hypoxia have increased cardiac superoxide levels and tend to have an ischemic myocardial injury [59]. These studies indicated that early prevention aiming at pregnancy complications is of great importance for the cardiovascular development of offspring.

The maternal nutrition state during pregnancy is also significant for the cardiovascular development of offspring. A number of animal studies have demonstrated that a high-fat diet during pregnancy affects the aorta and vascular development in adult offspring [67, 76–79]. Mdaki et al. reported that maternal high-fat diet, additively with diabetes, can cause diastolic/systolic cardiac dysfunction in offspring. It attributes to a high-fat diet-induced metabolic stress and mitochondrial dysfunction [80]. High fructose

**Table 2:** Cardiovascular system.

| Exposure conditions | Exposure factors | Species | Epigenetic perturbations | Offspring adverse outcomes | References |
|---|---|---|---|---|---|
| Gametogenesis | Low-protein diet | C57BL/6 mice (M) | DNA methylation, histone modifications and RNA methylation in testes | Adverse effect on vascular function and RAS pathway function | [60] |
| | | MF-1mice (F) | Not applicable | Impaired vasodilation, elevated serum and pulmonary ACE activity, and significantly attenuated mesenteric arterial response to the β-adrenoceptor agonist isoproterenol in male offspring | [61] |
| | High-fructose diet | C57 BL/6 | Not applicable | Increase the cardiovascular risk in later life | [62] |
| | PM2.5 | Rat (M) | Increased expressions of AT1R and GRK4 in the kidney of their offspring | Hypertension in male offspring | [63] |
| | Smoking | Human (M) | Not applicable | Increased risk of adult-onset hypertension and congenital heart defects (CHDs) in offspring | [64] |
| | Reproductive technologies | C57BL/6J | Not applicable | Elevated systoloc blood pressure | [65, 66] |
| *In utero* | Preeclampsia; prenatal hypoxia | Human | Not applicable | Increased risk of cardiovascular disease in the offspring | [58, 59] |
| | High-fat diet | Rabbits | Leptin receptor↑ and BDNF expression↑ | Hypertension | [67] |
| | High-fructose diet | C57BL/6J | Not applicable | Hypertension, insulin resistance, and obesity | [68] |
| | | Rats | Not applicable | Exacerbates post-weaning high-fat diet-induced programmed hypertension in male offspring | [69] |
| | Minocycline, cyclosporine, gentamicin, tenofovir, glucocorticoids | C57BL/6 mice; rat | Not applicable | High blood pressure, hypertension | [70–74] |
| | Tobacco exposure | Human | Increased CYP1A1 expression through DNA methylation | Fetal growth restriction | [75] |

intake during pregnancy can lead to cardiometabolic disturbances in offspring, which is a major risk factor for cardiovascular disease [68, 69]. Malnutrition during pregnancy can also be harmful. Maternal low-protein diets in the pre-pregnancy period affect gamete development, and result in abnormal cardiovascular development in offspring [61, 81–83].

The effect of medication intake during pregnancy on offspring has been a wide concern, and its effect on long-term cardiovascular development in offspring is one of the most important topics [84]. Though antibiotics are effective and potentially life-saving for pregnant women with infections, their side effects are not yet known. The usage of minocycline, a tetracycline, during pregnancy causes the elevation of BP in adult male offspring by shaping the offspring's gut microbiome [70]. Apart from these, a series of animal studies have demonstrated that drug intake during pregnancy can also affect cardiovascular development, including cyclosporine [71], gentamicin [72], tenofovir [73], and glucocorticoids [74].

There are also plenty of evidences showing that the cardiovascular outcomes of offspring in later life may be closely related to paternal exposure, such as unhealthy diet [60, 85], smoking, and environmental pollutants [86]. A paternal low-protein diet can alter the angiotensin-converting enzyme (ACE) activities of offspring, which makes the offspring's blood vessels respond abnormally to vascular inhibitors and dilators. The above phenomenon passes on to F2 offspring by modified testicular expression of central epigenetic regulators in F1 male offspring, including DNA methylation, histone modifications and RNA methylation [60]. Another animal study found male

**Table 3:** Central nervous system.

| Exposure conditions | Exposure factors | Species | Epigenetic perturbations | Offspring adverse outcomes | References |
|---|---|---|---|---|---|
| Gametogenesis | Paternal age | Mice (M) | Sperm small RNAs (sRNAs) have been identified as vector | Anxiety levels↑ and social communication defects | [92] |
| | Depression-like model | C57BL/6J mice (M) | Sperm microRNAs | Depression-like symptoms (F1) | [93] |
| *In utero* | HFD | C57Bl/6J mice (F) | Not applicable | Structural and neurobehavioral deficits in males; behavioral abnormalities and neuro-developmental disorders | [94, 95] |
| | HFD/Fructose | Mice(M) | Methylation of the *Bdnf* gene promoter↑ | Cognitive impairments | [96] |
| | | SD rats | DNA methylation | Cognitive performance and hippocampal neurogenesis↓ | [97] |
| | High-fiber diet | Mice | Microbiota-metabolites-brain axis | Cognitive impairments and social dysfunction↑ | [98] |
| | Hyperglycemia | ICR mice | Methylated modification of F1 sperm | Memory impairment; neurological disorders (F1 and F2) | [99] |
| | Cadmium | CD-1 mice | Placenta-fetal-brain axis | Cognitive impairments in male | [100] |
| | Manganese (Mn) | SD rats | Not applicable | Memory and learning impairment | [101] |
| | Lead (Pb)/Pb and stress | SD rats/Human | Not applicable | Learning and memory deficits; impaired infant neuro-development | [102, 103] |
| | Bisphenol a (BPA) | CD-1 mice | Not applicable | Cognitive and neuro-developmental impairments in male (F1) | [104] |
| Post-natal | Preterm birth | Human | Placental DNA methylation | Neurodevelopmental impairment | [105] |

offspring born to a paternal high-fructose diet have higher BP and uric acid, which may increase the cardiovascular risk in later life [62]. These results indicate that a paternal unhealthy diet has profound consequences for offspring.

Environment toxicants exposure such as smoking and PM2.5 can increase the level of reactive oxygen species (ROS) in sperm and negatively impact the cardiovascular outcomes of offspring. In rat, researchers revealed that paternal chronic exposure to PM2.5 impairs urine output and sodium excretion and lead to hypertension in the male offspring. An antioxidant used in combination with PM2.5 in paternal rats can reverse the hypertension phenotype of offspring [63]. Human epidemiology indicates paternal smoking may be associated with the increased risk of adult-onset hypertension and congenital heart defects (CHDs) in offspring [64, 87]. Similarly, smoking is a risk factor for exposure during pregnancy, which can lead to dysregulation of placental gene expression, which further affects fetal growth by altering DNA methylation [75].

Except for maternal and paternal exposure, assisted reproductive technologies, such as embryo culture, can also lead to elevated systolic blood pressure in offspring [65, 66, 88]. In sum, we should pay close attention to the exposures which may increase the incidence of cardiovascular disease in early life.

## Central nervous system

Substantial evidence from human epidemiologic and animal studies revealed that the challenges in early life, including the pre-, peri-and early postnatal periods, may have profound effects on offspring neurodevelopment [89] (Table 3). The intrauterine period, in particular, is the most discussed period when maternal exposure can disrupt fetal neural development and lay a potential risk for neuropsychiatric disorders [90]. According to human epidemiological studies, maternal Immune Activation (MIA) resulting from bacterial or viral infection during pregnancy is a risk factor for two neurodevelopmental disorders, autism (ASD) and schizophrenia (SZ) [5]. Many MIA animal models have shown that the production of cytokines by maternal immune cells rather than the infection itself is responsible for neuronal dysregulation in offspring. For example, Choi et al. [91] constructed an MIA model by intraperitoneal injection of synthetic double-stranded RNA (dsRNA) (poly [I: C]) rodents at E12.5, and found the cortical defects and associated ASD behaviors in offspring resulted from the increased maternal IL-17a, suggesting that TH17 cells in susceptible pregnant mothers may be a therapeutic target to prevent bearing children with inflammation-induced ASD-like phenotypes. In addition, the covid-19 virus is

also a hot spot in today's society, but the relevant epidemiological and animal model studies about the effects of pregnancy infection on the nervous system of offspring have not yet been reported, which is also a direction worthy of our attention in the future.

In recent years, the worldwide obesity epidemic has increased the prevalence of pregnancy-associated obesity [106]. Maternal obesity can cause adverse outcomes on the long-term health of offspring, including not only metabolic syndrome and cardiovascular defects, but also neurodevelopmental disorders [107]. Some clinical studies have shown that high maternal body mass index is correlated with lower offspring cognitive function and social behavior problems [108, 109]. Mouse fed with a high-fat diet during gestation and lactation can increase offspring's DNA methylation at the *Bdnf* promoter and drive the release of inflammatory factors in the brain, which may explain cognitive deficit in offspring [94, 97]. On the other hand, some researches support that maternal microbial ecology is the mediator between maternal obesity and the cognition of offspring [95, 98]. Maternal obesity can disrupt the synaptic structure and microglia maturation, and cause social and cognitive impairments in offspring. These negative effects can be reserved by a high fiber maternal diet, which reshapes the gut microbiome in both mother and offspring mice [98].

In addition to maternal obesity, paternal obesity also plays an important role in offspring neurodevelopment [90]. A prospective cohort study has shown that paternal obesity increases the risk of offspring failing in personal-social tasks [17]. In a mouse model, diet-induced paternal obesity can also elevate CpG methylation in the *Bdnf* promoter region in HFD-fed F0 spermatozoa and this epigenetic change may be transmitted to F1 and cause cognitive impairment [96]. Hyperglycemia, which is usually accompanied by overnutrition, can cause serious consequences as well [110]. Fetus exposed to intrauterine hyperglycemia suffers memory impairment and this phenotype can pass on to F2 through the abnormally methylated F1 sperm [99]. All indications support that the parental metabolic state is crucial for the neurodevelopment of offspring.

Environmental toxicants such as Cd, bisphenol-A, Pb, and manganese are public health concerns. Early life exposure to these environmental pollutants is associated with cognitive deficits and behavioral abnormalities in later life [111, 112]. Gestational Cd exposure inhibits placental estrogen synthesis via activating GCN2 signaling, thus downregulating the expression of synapse-associated proteins in the fetus's brain and causing cognitive dysfunction [100]. Lead (Pb) and manganese (Mn) are common neurotoxins, they can cause neurodevelopmental disorders independently [101–103]. Recent research proved that the effect of co-exposure to Mn and Pb is greater than single metal exposure in early life [113]. Researchers established a rat model exposed to Mn or Pb or both from weaning to postnatal day. It turns out that co-exposure to Pb and Mn causes microglial and astrocytic activation, and this activation likely leads to more pronounced inhibitory effects on the hippocampal long-term potentiation [113]. Apart from metal toxicants, endocrine-disrupting chemicals (EDCs) such as bisphenol-A also impacts the behaviors of offspring [114]. The expression of hippocampal PSD-95 and Synapsin-1 are significantly downregulated after exposure to BPA perinatally, but only in male offspring [104]. This sex-specific manner may be associated with differential methylation pattern in ERα promoters of different sexes. Based on these scientific results, measures should be taken to avoid early life exposure to environmental pollutants.

Last but not the least, parental stress can store a great amount of environmental information ("epigenetic memory") in their germ cells and pass it on to the next generation. The stress-induced paternal differential DNA Methylation Regions (DMRs) can partially survive offspring embryonic reprogramming, which is attributed to enriched sncRNAs (Small non-coding RNAs) in sperm [92, 115]. Using a chronic mild stress-induced F0 males of depression-like model, researchers found that F1 offspring are susceptible to depression-like symptoms [93]. Sperm small RNAs, particularly microRNAs, reshape the early embryonic transcriptional profiles and explain depressive-like phenotypes in F1 offspring [93]. A longitudinal observational cohort study showed that prenatal maternal anxiety or depression can impair fetal brain metabolism and hippocampal growth, and decrease infant social-emotional scores in 18 months old mice [116]. The mechanism underlying this phenomenon is complicated. Serotonin (5-hydroxytryptamine [5-HT]) is considered as an important mediator in regulating fetal brain development [117]. The synthetic pathway of 5-HT in the placenta can be disturbed by a change of maternal tryptophan precursor and thus affect fetal affect neurogenesis [118]. Besides, excessive secretion of maternal glucocorticoid can influence offspring behavior in epigenetic ways [105, 119]. All these studies remind us to pay close attention to the intergeneration inheritance of mental illness.

## Reproductive system

Parental environmental factors and lifestyles, including a wide range of endocrine-disrupting chemicals, nutrition and lifestyle stressors, influence the reproductive system of the next generation through the epigenetic remodeling in gametes and embryos (Table 4). Chronic parental arsenic,

**Table 4:** Reproductive system.

| Exposure conditions | Exposure factors | Species | Epigenetic perturbations | Offspring adverse outcomes | References |
|---|---|---|---|---|---|
| Gametogenesis | Chronic arsenic exposure | Rats (F/M) | Ggenotoxic damage (DNA strand breaks) ↑; global DNA methylation in gonadal tissue ↓ | Alterations in physical and reproductive parameters; aberrant morphology in the ovaries (F0 and F1) and testicles (F1–F3); quality of sperm (F0–F3, except F2) ↓ | [120] |
| | Chronic low dose uranium exposure | SD rats (F/M) | Global DNA methylation in testes tissue↑, but in ovaries↓ | Not applicable | [6] |
| | Methoxychlor | SD rats (F) | Epimutation in DNA methylated regions | Incidence of kidney disease, ovary disease, and obesity↑ (F1 and F3), multiple diseases in F3↑ | [121] |
| | Permethrin and DEET | SD rats (F) | Epimutation in DNA methylated regions | Incidence of total diseases↑ (F1 and F3), especially pubertal abnormalities, testis disease, and ovarian disease in F3 | [122] |
| | NH4Cl and/or Na2S | Mice (M) | ERα-related DNA methylation and histone methylation pathways | Transgenerational disruption in spermatogenesis | [128] |
| *9 In utero* | Hypercaloric diet | Wistar rats | Not applicable | Early peripubertal development (F1 and F2); reproductive parameters were affected (F0–F2) | [126] |
| | Streptozotocin- and high-fat and high-sugar-induced | Wistar rats | Not applicable | Maternal effect: Spermatid number↓, daily sperm production↓, caput/corpus sperm number↓, TNF-α↓ and CAT↑ in epididymis; paternal effect: Absolute testis weight↑, serum testosterone↓, GST↓ and CP↓ in epididymis; interaction effect: Spermatid number↓, daily sperm production↓, CP↓ in epididymis | [127] |
| | | C57BL/6J mice | Histone methylation and acetylation | Fertility problems (negatively affect folliculogenesis) | [129] |
| | Low protein maternal diet | Rats | Not applicable | Testis weight, epididymal sperm count, number of sertoli cells, testosterone (T) concentration and luteinizing hormone (LH) concentration↓ | [130] |
| | Bisphenol A/E/S (BPA/E/S) | CD-1 mice | Disruption of DNA methylations and histone marks in the neonatal and/or adult testis | Sperm counts and/or motility↓ and disrupted the progression of germ cell development; dysregulated serum estradiol-17β and testosterone; DNA methylation modified (F3) | [131] |
| | | Rare minnow *Gobiocypris rarus* | DNA methylation and histone trimethylation | Inhibited ovary development (the number of mature oocytes↓, the steroidogenic genes (cyp11a1, cyp17a1, cyp19a1a and star) were significantly affected). [a]The negative effects were reversible. | [132] |
| | Stress | Human | Not applicable | Total sperm count, number of progressive motile sperm and morning serum testosterone concentration↓ | [133] |

**Table 4:** (continued)

| Exposure conditions | Exposure factors | | Species | Epigenetic perturbations | Offspring adverse outcomes | References |
|---|---|---|---|---|---|---|
| | | | Wistar rats | Not applicable | Neurotransmitter levels and sexual behavior testosterone levels↓, delayed latency to the first mount and first intromission, number of ejaculations↓ | [134] |
| | | | Mice | Not applicable | Sexual behavior and fertility↓, latencies to mount and to achieve intromission and ejaculation ↑ | [135] |
| | Environment toxicant exposure | Nicotine and ethanol | Mice | DNA methylation have changed | Testicular and sperm parameters (seminiferous tubules, sperm number, motility, viability↓, DNA fragmentation↑) | [136] |
| | | PM2.5 | C57BL/6 mice | Inhibin B hypermethylation and activate the p21/Cleaved Caspase-3 pathway | Sperm motility, the number of offspring ↓; vacuolization in the sertoli cells ↑; inhibin and testosterone ↓, LH and FSH ↑ | [137] |
| | | DEHP | C57BL/6J mice | Sperm transcriptome and methylome have changed | Symptoms similar to the human testicular dysgenesis syndrome | [138] |
| | | CYP | Rats | Sperm global hypermethylation and H19 DMR hypomethylation | Effects on gonadal steroidogenesis, gametogenesis and sperm epigenome | [139] |
| | | ATZ | CD1 mice | Not applicable | Affected meiosis, spermiogenesis and reduces the spermatozoa number (F3) | [140] |
| | | Diuron | Medaka (*Oryzias melastigma*) | DNA methylation | Hatching of F1 ↓; ovarian development was retarded (F1) | [141] |
| | | Benzo (a) pyrene | Zebrafish | DNA methylation | Spawned egg number, fertilization rate and hatching success ↓ | [142] |

uranium, and methoxychlor exposure cause changes in global DNA methylation with negative transgenerational effects on the adult-onset reproductive phenotypes in female and male rats [6, 120, 121]. Permethrin and DEET exposure also increase abnormal puberty, testicular disease, and ovarian disease (primordial follicle loss and polycystic ovary disease) in F3 generation animals [122]. The paternal or maternal intake of high-fat diets has been shown to affect not only the metabolism [123–125] but also the reproductive health of both male and female offspring. The maternal effect seems to be more pronounced than the paternal effect [126, 127].

The causes of male subfertility are wide-ranging in the majority of cases, in addition to genetic and direct spermatogenesis impairment, there is increasing evidence showing that male reproductive function may be regulated by early life environment [143, 144]. Several early prenatal exposures, primarily endocrine disrupting chemicals (EDCs) such as pesticides, chemicals, plasticizers, phthalates, etc., are proved to have direct and transgenerational effects on male reproductive development [145]. Bisphenol A (BPA) is a well-known reproductive toxicant that can affect male and female fertility and have transgenerational effects on reproductive function [131, 132, 146, 147]. This transgenerational inheritance may also be explained by the gamete transmission of dysregulated epigenetic marks, such as markedly reduced overall DNA methylation in the testis and ovary in zebrafish [148], the levels of histone acetylation in the reproductive system of male rats [149], and the altered mRNA levels of DNA methyltransferases, histone methyltransferases, and their associated factors in rare minnow germ cells [150]. Although human health is impaired by environmental exposure at any time, the potential effects of exposures during pregnancy are magnified during the most critical developmental period for male fetal development [151]. Maternal exposures to low dietary protein, high milk, alcohol, and nicotine [136] may adversely affect male fertility through epigenetic mechanisms [151]. Epidemiological and experimental studies have shown that exposure to a maternal low dietary protein during pregnancy reduces male

fertility in adult male rats [130]. Exposure to stressful life events in early pregnancy is also associated with reduced reproductive function in adult males in a prospective longitudinal cohort [133]. Extensive animal experimental studies have shown that male offspring exposed to maternal stress prenatally have decreased fertility, decreased sexual activity, and delayed puberty compared to controls [134, 135]. In addition, exposure to environmental toxicants during pregnancy is noxious for offspring reproductive health. Environmental factors such as PM2.5 [137], NH4Cl and/or Na2S [128], and even the endocrine disruptors bis(2-ethylhexyl) phthalate (DEHP) [138], cypermethrin [139] and atrazine [140] can alter epigenetic marks in the germline, resulting in testicular hypoplasia in offspring.

The ovary plays an important role in the female reproductive system, which is affected by various factors. Epidemiological studies of maternal effects on offspring fertility are rare, but the possible correlation between maternal environment and female offspring reproductive function has been explored through animal models [151]. Some environmental pollutants mentioned above have a significant impact on the reproductive health of offspring. Prenatal exposure to some toxic substances, especially a class of endocrine disruptors, such as phthalates [152], metoclopramide [121], etc., may directly target the ovary and affect follicular development, alter the epigenetic information in oocytes, and lay out epigenetic effects across generations [153]. Long-term exposure to environmental diuron in F0 marine medaka inhibits F1 ovary development [141]. DNA methyltransferases are significantly upregulated in adult ovaries, suggesting a possible mechanism related to the altered expression of epigenetic modifiers [141]. Exposure of embryos to BaP resulted in markedly elevated DNA methylation of the gonadotropin-releasing hormone (GnRH) gene *gnrh3* in the adult zebrafish brain, resulting in abnormal female reproduction through physiological changes in the brain-pituitary-gonadal axis [142]. In addition, female offspring from gestational diabetes dams are prone to fertility problems later in life [129]. The underlying mechanism of this fertility issue may be correlated with impaired fetal epigenome reprogramming, which manifests in ovarian dysfunction and subfertility in adulthood [129]. Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders in women and a leading cause of female infertility [154]. PCOS has a strong genetic component [155]. Daughters born to mothers with PCOS have a 60%–70% chance of developing this disease [156, 157]. Due to the complexity of the disease, the specific mechanisms have not yet been elucidated, and the epigenetic changes associated with PCOS have not been interpreted. In 2008, an accepted explanation for the etiology of PCOS claimed that intrauterine androgen overexposure may interfere with epigenetic reprogramming of fetal germ cells, leading to susceptibility to PCOS in offspring [158]. Recently, Mimouni et al. proved that PCOS neuroendocrine reproductive and metabolic dysfunction is transmitted in PAMH (prenatal AMH exposed) mice through altered DNA methylation and gene expression for at least three generations [159].

Adult lifestyle and environmental conditions are important factors affecting male and female fertility, and also the reproductive health of their offspring. We need early prevention and intervention for these factors. Thus, a healthy and nutritious diet and regular exercise is very important for reproductive health.

## Epigenetic regulation in developmental diseases

Recently studies have slowly identified the mechanisms linking the environment to parental and offspring health. One connection between environmental exposure and disease is epigenetic regulation-Environments trigger epigenetic changes, while the altered epigenetic modification generates the unique birth phenotype [8, 9, 160]. Epigenetic modifications, including DNA methylation, histone modifications, RNA methylation, genomic imprinting, noncoding RNA, etc., refer to stable heritable changes in biological phenotype or gene expression without changes in nucleotide sequence [161]. It plays an important role in normal development. Disordered epigenetic information can disrupt gene expression and lead to the occurrence of various diseases, such as tumors, senile diseases, and developmental diseases [162]. A large number of studies have found that epigenetic dysregulation may play an essential role in the occurrence of developmental diseases [10, 163–165] (Figure 2).

### DNA methylation

DNA methylation is vital epigenetic information that can be altered across the life course and transited to the next generation. It is characterized by the addition of a methyl group at the carbon-5 position of the cytosine base (5-methylcytosine [5mC]), which usually occurs in the CpG dinucleotide context. The DNMT methyltransferase family contains a conserved set of DNA-modifying enzymes,

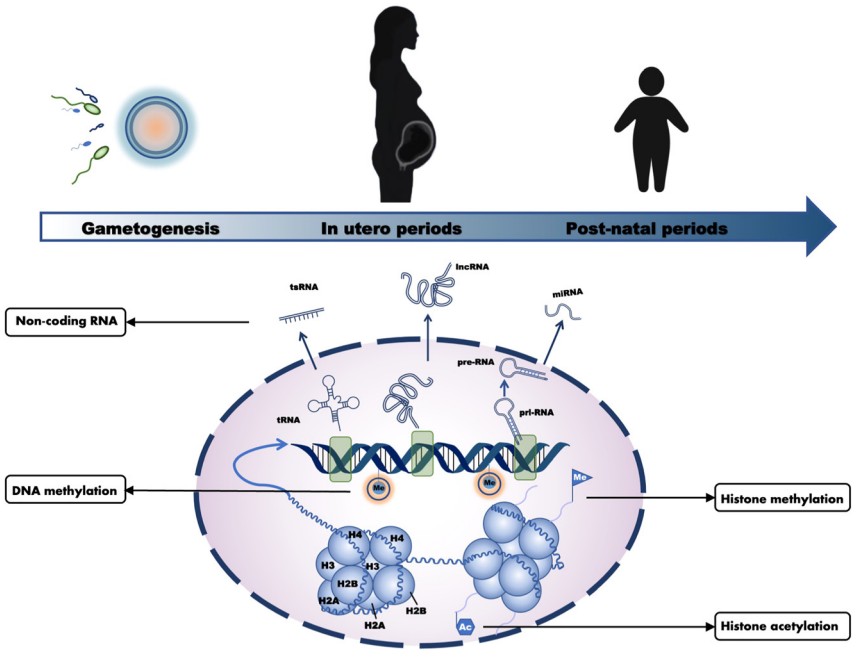


**Figure 2:** Links of epigenetic modifications to developmental diseases. The timeline represents three distinct time periods of disease exposure: gametogenesis, *in utero* periods, and post-natal periods; The black arrows represent the mechanisms of four different epigenetic modifications during disease development, which play different roles at the DNA (DNA methylation), histone (acetylation and methylation), and RNA (non-coding RNAs) levels, respectively.

including DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L [166]. The establishment of *de novo* DNA methylation needs DNMT3A, DNMT3B, and DNMT3L, while the maintenance of DNA methylation pattern requires DNMT1. Ten-eleven translocation (TET) family of enzymes can actively reverse DNA methylation by oxidizing 5-methylcytosine (m5C) to produce 5-hydroxymethylcy tosine (hm5C), 5-formylcytosine (f5C) and 5-carboxy lcytosine (ca5C) [167]. Global DNA demethylation happens after fertilization to erase the gametic epigenome. Early adverse exposure in life can change DNA methylation in germ cells or embryos by regulating the activity of corresponding enzymes [19, 168, 169]. Abnormalities in demethylation may affect the healthy development of offspring [170]. Our recent study revealed that pregestational hyperglycemia can reduce the expression of TET3 in oocytes, result in hypermethylation of the *Gck* gene at the paternal alleles and lead to glucose intolerance in offspring [19]. This is vital evidence showing that gamete cell is sensitive to environmental factors and influence the epigenetic landscape of offspring. The intrauterine environment can also alter parental DNA methylation and have long-term effects on the health of offspring [171, 172]. For example, maternal exercise can activate the AMPK-IDH-αKG-TET signaling pathway in the fetal liver, which controls DNA demethylation at the promoters of glucose metabolic genes and improve offspring health [173].

Genomic imprinting is a critical epigenetic feature that is regulated by differential DNA methylation inherited from the parental germline [174]. Imprinted gene typically contains an ICR (imprinting control region) which harbors parental-allele-specific methylation and controls the allelic expression of genes [175]. Subtle changes in ICRs in the germline can influence the long-term health of offspring. Our previous research reported that intrauterine hyperglycemia can cause abnormal methylation of ICR and downregulate the expression of imprinted genes *Igf2* and *H19*. This altered genomic imprinting pattern retains in F1 sperm and thus contributes to transgenerational transmission [176]. Similarly, exposure to a high-fat diet during pregnancy can cause the loss of Dlk1 imprinting, a paternally expressed imprinted gene, in offspring, Dysregulation of *Dlk1* can pass on to F2 generation [14]. This evidence indicated that imprinted gene plays an important role in transgenerational inheritance.

## Histone modifications

The nucleosome is the basic structural unit of chromosomes, consisting of a histone octamer (one H2A–H2B tetramer and two H3–H4 dimers) and 146–147 bp of DNA wrapped around the outside [177]. The amino acids in the free N-and C-terminal tails of histones that make up the core region of the nucleosome can undergo different modifications under the action of related enzymes. These modifications regulate chromatin state and transcriptional activity by altering the electronic charge and structure of

these histones [177, 178]. The main types of histone modifications are acetylation, methylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation. Interestingly, Zhang and colleagues [179] described a newly discovered histone modification, lactation, derived from the cellular metabolite lactate, which directly stimulated gene transcription in chromatin. Compared with other types of protein modifications, lactation modification research is still in its infancy, but considering the existence of aerobic glycolysis during the growth of many cells in the living body [180]. Therefore, lactation modification is closely related to a variety of physiological and pathological processes, and also provides new ideas for disease research [180]. For example, lipopolysaccharide regulates histone lactate modification through Toll-like receptor/BCAP signaling, which ultimately affects the process of macrophage polarization [181]. The most common modification forms are histone methylation and acetylation [182, 183]. Histone acetylation is a post-translational modification that mostly occurs at specific lysine residues in the N-terminal basic amino acid concentration region of core histones, and is very important for the regulation of chromatin structure, transcription, and DNA repair. Two competing enzyme families, histone lysine acetyltransferases (HATs) and histone deacetylases (HDACs) regulate histone acetylation [183, 184]. HATs catalyze the transfer of acetyl groups from acetyl-CoA to the amino groups of histone lysine residues. Acetylation of histone tails can neutralize positively charged lysine, which is thought to disrupt the interaction between the tails and negatively charged nucleosomal DNA, thereby promoting the opening of chromatin for positive transcription [184]. There are lots of lysine residues in histones that can be acetylated, including H3K4, H3K9, H3K27, H3K36, H3K79, H4K5, H4K12, H4K20, etc. Among them, H3K27ac is the most well-studied one.

To date, histone modifications in adult-onset diseases following IUGR, including type 2 diabetes and hypertension, have been extensively investigated [185, 186] For example, studies revealed that the acetylation of H3/H4 at the proximal promoter of *Pdx1* in IUGR fetal pancreatic islets is significantly reduced, and the downregulation of *Pdx1* gene expression alters β-cell function, ultimately leads to insulin resistance and susceptibility to type 2 diabetes [187, 188]. Other study also reported that the histone acetylation level in the promoter of endothelin 1 (*ET-1*) gene in pulmonary vascular endothelial cells of IUGR rats was increased. This change may cause varying degrees of Pulmonary Arterial Hypertension (PAH) or pulmonary vascular remodeling in later life [189].

Histone methylation typically occurs at arginine (Arg or R) and lysine (Lys or K) residues of H3 and H4. These arginine and lysine can be mono- or dimethylated, and lysine can be trimethylated. This methylation is regulated by histone methyltransferases (HMTs) and histone demethylases (HDMs) [177]. Unlike acetylation modification, methylated histone lysine residues can either activate or repress gene transcription, depending on the specific situation (such as methylation site, state, etc.). Histone methylation is involved in developmental gene expression from the onset of pre-fertilization to the late postnatal period, so methylation defects caused by environmental factors affect early embryogenesis and have profound effects on organ development [183, 190, 191]. A recent study reported that the ectopic increase of H3K4me3 in *In Vitro* Fertilization (IVF) extraembryonic ectoderm tissues resulted in the ectopic expression of the epiblast gene in IVF extraembryonic tissues, which is also an important cause of abnormal development of IVF extraembryonic tissues [192]. Parental nematodes can transmit obesity signals to offspring, and histone H3K4me3 modification was identified as a contributing factor to the transgenerational epigenetic inheritance (TEI) of obesity effect [193]; Additionally, another study also reported that H3K9me2 was involved in heat shock-induced TEI [194]. A father's health and lifestyle can also impact his children's health, but the role of sperm chromatin in the non-genetic inheritance of metabolic disorders remains unknown. To study the epigenetic role of histone retention in sperm on embryonic development and intergenerational epigenetics, Siklenka targets the methylation of H3K4, an epigenetic mark associated with developmental genes in sperm [170]. Overexpression of the histone demethylase KDM1A during mouse spermatogenesis shows a decrease in H3K4me2 at the transcription start site (TSS) of more than 2000 genes in sperm. Loss of H3K4me2 enrichment in sperm is associated with abnormal gene expression in embryos, and severe birth defects in offspring [170]. Recent studies have demonstrated that these epigenomic changes at the chromatin level can be transmitted through sperm, thereby altering embryonic gene expression, development, and offspring health [170, 195]. Sperm H3K4me3 can be altered by folate deficiency and influences embryonic development and gene expression [195]. In addition, sperm H3K4me3 acts as a metabolic sensor and is associated with the paternal transmission of obesity-related diseases in offspring [196]. Identification of epigenetic mechanisms that are transmitted from sperm to affect offspring health, especially in the context of toxicant screening, could help to better assess paternal effect models and improve paternal preconception advice.

### Non-coding RNAs, ncRNAs

It is now generally accepted that genetic information in the germline can be encoded at the transcriptional and/or post-transcriptional level, not just DNA sequences [197]. Non-coding RNAs (ncRNAs) refer to RNAs that do not encode proteins, including short-chain microRNAs (miRNAs) and long-chain lncRNAs, which have the properties of regulating gene expression and protein function [177]. More and more studies have shown that ncRNAs are involved in a variety of complex biological processes and may be key regulators in the occurrence and development of diseases [198–200]. miRNAs can bind to target mRNAs in a complementary manner at the post-transcriptional level, leading to their translational repression or degradation [184, 201, 202]. Compared with miRNAs, lncRNAs also act in a variety of human diseases [203–205], but their regulatory mechanisms are more complex, involving chromosomal imprinting, epigenetic regulation, and transcriptional processes. A recent review by Arzua et al. [206] described an association between dysregulation of ncRNA biogenesis and abnormal brain development related to environmental factors (alcohol, narcotics, nicotine, and viral infections). miRNAs and lincRNAs are dysregulated in various animal and human models following early alcohol exposure. Inhibition of miR-9 in zebrafish and mouse resulted in a highly similar phenotype to patients with Fetal Alcohol Syndrome (FAS) [207]. Recently, lncRNA Lrap knockout was shown to have increased alcohol consumption and preference in early rats [208].

The discovery of RNA (mRNA and noncoding RNA) in sperm unlocked its role in providing paternal genetic information [18]. There is growing evidence supporting that microRNAs (miRNAs), transfer RNA (tRNA)-derived small RNAs (tsRNAs), and long RNAs (lRNAs) (mRNAs and long noncoding RNAs) play essential roles in epigenetic transmission [29, 209]. They can mediate the intergenerational transmission of paternal phenotypes, including psychiatric problems [29, 210] and metabolic abnormalities [20, 211]. For example, a high-fat diet (HFD) [219] and inflammation (LPS) [28] induce changes in sperm tsRNA and lead to metabolic-related phenotypes in their offspring. Traumatic stress [29] and stress [210] alter miRNA expression in mice, resulting in behavioral and metabolic abnormalities in offspring. Depressed mouse sperm miRNAs can also mediate intergenerational inheritance and play a key role in the process of passing phenotypes from parent to offspring [93]. Genetic information carriers based on non-DNA sequences all have the potential to encode and store information and may be passed on to offspring in a coordinated manner. Recently, it has been reported that a paternal low-protein diet affects the binding activity of the transcription factor ATF7, alters the histone modification levels of its target genes and the generation of non-coding small RNAs (sncRNAs), ultimately leading to changes in the expression profiles of offspring liver genes [212]. A high-fat diet during pregnancy induces irreversible changes in microRNA expression in developing oocytes that are associated with Dlk1 dysregulation in subsequent F2 generations [14].

## Future perspectives

This review focused on developmental diseases in multiple systems, and also discussed the associations and underlying mechanisms of parental factors in offspring adult diseases. With the continuous changes of the human living environment and pressure, these adverse environmental factors impair the development of gametes and embryos through epigenetic modifications, which further lead to a greatly increased risk of certain chronic diseases in adulthood. Epigenetic modifications may arise through our interactions with the environment. For example, obesity gained with a high-fat diet, can lead to changes in the epigenetic status of certain genes, including DNA methylation, histone modifications and small RNAs, which further bring in health potential damage [20, 79, 96]. Prof. Surani and his colleagues [213] found that the methylation process did not wipe out the entire epigenome, about 5% of the DNA appeared to resist reprogramming. These “escape” regions of the genome contain genes associated with diseases such as obesity and schizophrenia, which may play important roles in development. It provides us with a good resource for targeting potential candidate regions being passed on to the next generation, and even across generations. Several recent studies have demonstrated that these epigenomic changes at the chromatin level and small RNAs can also be transmitted through germ cells, thereby altering embryonic gene expression, development, and offspring health [28, 195, 196, 211]. For example, H3K4me3 and tsRNAs in sperm can evade epigenome reprogramming, thereby altering gene expression in offspring [20, 195]. How these altered epigenetic features escape the global reprogramming processes during PGC and early embryo development, and then pass on to offspring to cause disease still awaits further investigation, and this is a major challenge in the field. Once the epigenetic mechanisms underlying certain diseases are identified, it will be of great importance for us to develop specific drugs or manipulation to avoid this disease.

The application of epigenetic modification in clinical diagnosis and treatment is currently limited, although some clinical trials have been developed for tumor gene methylation therapy [214]. However, the diagnosis and treatment of developmental-related disorders are still in their infancy. The field is of exciting potential, including the identification of early potential biomarkers associated with the epigenetics for early prevention of disease, and the discovery of possible therapeutic targets for future translational research. Despite the positive outlook, many challenges remain. The first challenge is how to identify the epigenetic biomarkers within blood or certain tissues. It may require high-risk populations to detect changes in epigenetic modifications of targeted genes, which will facilitate the early diagnosis of diseases. For example, altered methylation status of a single CpG site in the promoter region of the RXRA nuclear receptor in umbilical cord tissue is closely associated with childhood obesity, which can be used as an early diagnostic marker [215]. Most of the current work exploring the mechanisms of developmental-related diseases utilized animal models, which may not be suitable for clinical application. The second challenge is how to develop effective interventions, such as diet or exercise interventions, which may mitigate or even prevent the development of adult disease in susceptible individuals. For example, paternal exercise before pregnancy and maternal exercise interventions during pregnancy have been shown to improve metabolic health [216]. However, to date, the intervention methods are limited. Thus, in the search for more effective therapies, we believe that further studies centered on downstream effectors such as apoptosis, mitochondrial dysfunction, and increased oxidative stress are required. Pharmacology targeting epigenetic signals may improve these components, thereby improving some of the symptoms associated with disease dysfunction.

Collectively, the booming epigenetics field helps us answer scientific questions underlying developmental diseases, opening up new and exciting research areas. It is believed that the studies of epigenetic regulation may benefit the development of early diagnosis a of developmental-related diseases, and will surely become a brand-new approach for the treatment of human diseases.

**Acknowledgments:** Figure 1 created with BioRender.com.
**Research funding:** This work is supported by the National Natural Science Foundation of China (82088102), CAMS Innovation Fund for Medical Sciences (2019-I2M-5-064), Collaborative Innovation Program of Shanghai Municipal Health Commission (2020CXJQ01), Clinical Research Plan of SHDC (SHDC2020CR1008A) and Shanghai Frontiers Science Research Base of Reproduction and Development.
**Author contributions:** Hefeng Huang and Yu Zhang conceived of the study; Jiaying Mo and Xuanqi Liu wrote the manuscript; Yutong Huang and Renke He organized figures and Tables. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.
**Competing interests:** Authors state no conflict of interest.
**Informed consent:** Informed consent was obtained from all individuals included in this study.
**Ethical approval:** The local Institutional Review Board deemed the study exempt from review.

## References

1. Barker DJ, Osmond C, Law CM. The intrauterine and early postnatal origins of cardiovascular disease and chronic bronchitis. J Epidemiol Community Health 1989;43:237–40.
2. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev 2014;94:1027–76.
3. Safi-Stibler S, Gabory A. Epigenetics and the developmental origins of health and disease: parental environment signalling to the epigenome, critical time windows and sculpting the adult phenotype. Semin Cell Dev Biol 2020;97:172–80.
4. Simeoni U, Armengaud JB, Siddeek B, Tolsa JF. Perinatal origins of adult disease. Neonatology 2018;113:393–9.
5. Tioleco N, Silberman AE, Stratigos K, Banerjee–Basu S, Spann MN, Whitaker AH, et al. Prenatal maternal infection and risk for autism in offspring: a meta–analysis. Autism Res 2021; 14:1296–316.
6. Elmhiri G, Gloaguen C, Grison S, Kereselidze D, Elie C, Tack K, et al. DNA methylation and potential multigenerational epigenetic effects linked to uranium chronic low–dose exposure in gonads of males and females rats. Toxicol Lett 2018;282: 64–70.
7. WHO. World health statistics 2020: monitoring health for the SDGs, sustainable development goals WHO: WHO; 2020. Available from: https://www.who.int/publications/i/item/9789240005105.
8. Cutfield WS, Hofman PL, Mitchell M, Morison IM. Could epigenetics play a role in the developmental origins of health and disease? Pediatr Res 2007;61:68r–75.
9. Simmons RA. Developmental origins of beta-cell failure in type 2 diabetes: the role of epigenetic mechanisms. Pediatr Res 2007; 61:64r–7.
10. Arima Y, Fukuoka H. Developmental origins of health and disease theory in cardiology. J Cardiol 2020;76:14–7.
11. Cescon M, Chianese R, Tavares RS. Environmental impact on male (in) fertility via epigenetic route. J Clin Med 2020;9: 2520.
12. Sarker G, Sun WF, Rosenkranz D, Pelczar P, Opitz L, Efthymiou V, et al. Maternal overnutrition programs hedonic and metabolic phenotypes across generations through sperm tsRNAs. Proc Natl Acad Sci USA 2019;116:10547–56.

13. Saben JL, Boudoures AL, Asghar Z, Thompson A, Drury A, Zhang W, et al. Maternal metabolic syndrome programs mitochondrial dysfunction via germline changes across three generations. Cell Rep 2016;16:1–8.
14. Van de Pette M, Galvao A, Millership SJ, To W, Dimond A, Prodani C, et al. Epigenetic changes induced by in utero dietary challenge result in phenotypic variability in successive generations of mice. Nat Commun 2022;13:2464.
15. Rando OJ, Simmons RA. I'm eating for two: parental dietary effects on offspring metabolism. Cell 2015;161:93–105.
16. Schagdarsurengin U, Western P, Steger K, Meinhardt A. Developmental origins of male subfertility: role of infection, inflammation, and environmental factors. Semin Immunopathol 2016;38:765–81.
17. Yeung EH, Sundaram R, Ghassabian A, Xie YL, Louis GB. Parental obesity and early childhood development. Pediatrics 2017;139: e20161459.
18. Chen Q, Yan W, Duan EK. Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications. Nat Rev Genet 2016;17:733–43.
19. Chen B, Du YR, Zhu H, Sun ML, Wang C, Cheng Y, et al. Maternal inheritance of glucose intolerance via oocyte TET3 insufficiency. Nature 2022;605:761–6.
20. Chen Q, Yan MH, Cao ZH, Li X, Zhang YF, Shi JC, et al. Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. Science 2016;351:397–400.
21. Hoffman DJ, Powell TL, Barrett ES, Hardy DB. Developmental origins of metabolic diseases. Physiol Rev 2021;101:739–95.
22. Lecomte V, Maloney CA, Wang KW, Morris MJ. Effects of paternal obesity on growth and adiposity of male rat offspring. Am J Physiol Endocrinol Metab 2017;312:E117–25.
23. Sanchez-Garrido MA, Ruiz-Pino F, Velasco I, Barroso A, Fernandois D, Heras V, et al. Intergenerational influence of paternal obesity on metabolic and reproductive health parameters of the offspring: male-preferential impact and involvement of kiss1–mediated pathways. Endocrinology 2018; 159:1005–18.
24. Voerman E, Santos S, Golab BP, Amiano P, Ballester F, Barros H, et al. Maternal body mass index, gestational weight gain, and the risk of overweight and obesity across childhood: an individual participant data meta-analysis. PLoS Med 2019;16: e1002744.
25. Ng SF, Lin RC, Laybutt DR, Barres R, Owens JA, Morris MJ. Chronic high-fat diet in fathers programs beta-cell dysfunction in female rat offspring. Nature 2010;467:963–6.
26. Mir SA, Chen L, Burugupalli S, Burla B, Ji S, Smith AAT, et al. Population-based plasma lipidomics reveals developmental changes in metabolism and signatures of obesity risk: a mother-offspring cohort study. BMC Med 2022;20:242.
27. Carone BR, Fauquier L, Habib N, Shea JM, Hart CE, Li R, et al. Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell 2010;143:1084–96.
28. Zhang Y, Ren L, Sun X, Zhang Z, Liu J, Xin Y, et al. Angiogenin mediates paternal inflammation-induced metabolic disorders in offspring through sperm tsRNAs. Nat Commun 2021;12:6673.
29. Gapp K, Jawaid A, Sarkies P, Bohacek J, Pelczar P, Prados J, et al. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat Neurosci 2014;17:667–9.
30. Gaillard R, Steegers EA, Tiemeier H, Hofman A, Jaddoe VW. Placental vascular dysfunction, fetal and childhood growth, and cardiovascular development: the generation R study. Circulation 2013;128:2202–10.
31. Zheng J, Zhang Q, Mul JD, Yu M, Xu J, Qi C, et al. Maternal high-calorie diet is associated with altered hepatic microRNA expression and impaired metabolic health in offspring at weaning age. Endocrine 2016;54:70–80.
32. Zheng J, Xiao X, Zhang Q, Yu M, Xu J, Wang Z. Maternal high-fat diet modulates hepatic glucose, lipid homeostasis and gene expression in the PPAR pathway in the early life of offspring. Int J Mol Sci 2014;15:14967–83.
33. Taylor PD, McConnell J, Khan IY, Holemans K, Lawrence KM, Asare-Anane H, et al. Impaired glucose homeostasis and mitochondrial abnormalities in offspring of rats fed a fat-rich diet in pregnancy. Am J Physiol Regul Integr Comp Physiol 2005; 288:R134–9.
34. Nash MJ, Dobrinskikh E, Newsom SA, Messaoudi I, Janssen RC, Aagaard KM, et al. Maternal Western diet exposure increases periportal fibrosis beginning in utero in nonhuman primate offspring. JCI Insight 2021;6:e154093.
35. McCurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE, et al. Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. J Clin Invest 2009;119: 323–35.
36. Oben JA, Mouralidarane A, Samuelsson AM, Matthews PJ, Morgan ML, McKee C, et al. Maternal obesity during pregnancy and lactation programs the development of offspring non-alcoholic fatty liver disease in mice. J Hepatol 2010;52:913–20.
37. Ravelli GP, Stein ZA, Susser MW. Obesity in young men after famine exposure in utero and early infancy. N Engl J Med 1976; 295:349–53.
38. Li C, Lumey LH. Exposure to the Chinese famine of 1959–61 in early life and long-term health conditions: a systematic review and meta-analysis. Int J Epidemiol 2017;46:1157–70.
39. Pettitt DJ, Lawrence JM, Beyer J, Hillier TA, Liese AD, Mayer-Davis B, et al. Association between maternal diabetes in utero and age at offspring's diagnosis of type 2 diabetes. Diabetes Care 2008;31:2126–30.
40. Lowe WL Jr., Lowe LP, Kuang A, Catalano PM, Nodzenski M, Talbot O, et al. Maternal glucose levels during pregnancy and childhood adiposity in the hyperglycemia and adverse pregnancy outcome follow-up study. Diabetologia 2019;62: 598–610.
41. Lawlor DA, Lichtenstein P, Langstrom N. Association of maternal diabetes mellitus in pregnancy with offspring adiposity into early adulthood: sibling study in a prospective cohort of 280, 866 men from 248, 293 families. Circulation 2011;123:258–65.
42. Lee SC, Pu YB, Chow CC, Yeung VT, Ko GT, So WY, et al. Diabetes in Hong Kong Chinese: evidence for familial clustering and parental effects. Diabetes Care 2000;23:1365–8.
43. Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 2000;49:2208–11.
44. Pettitt DJ, Baird HR, Aleck KA, Bennett PH, Knowler WC. Excessive obesity in offspring of Pima Indian women with diabetes during pregnancy. N Engl J Med 1983;308:242–5.
45. Edstorp J, Lampousi AM, Carlsson S. Parental smoking, type 1 diabetes, and islet autoantibody positivity in the offspring: a

systematic review and meta-analysis. Diabet Med 2022;39: e14830.
46. Catalano PM, Presley L, Minium J, Hauguel-de Mouzon S. Fetuses of obese mothers develop insulin resistance in utero. Diabetes Care 2009;32:1076–80.
47. Gomes D, von Kries R, Delius M, Mansmann U, Nast M, Stubert M, et al. Late-pregnancy dysglycemia in obese pregnancies after negative testing for gestational diabetes and risk of future childhood overweight: an interim analysis from a longitudinal mother-child cohort study. PLoS Med 2018;15: e1002681.
48. Cardwell CR, Stene LC, Joner G, Cinek O, Svensson J, Goldacre MJ, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. Diabetologia 2008;51: 726–35.
49. Kuhle S, Tong OS, Woolcott CG. Association between caesarean section and childhood obesity: a systematic review and meta-analysis. Obes Rev 2015;16:295–303.
50. Yuan C, Gaskins AJ, Blaine AI, Zhang C, Gillman MW, Missmer SA, et al. Association between cesarean birth and risk of obesity in offspring in childhood, adolescence, and early adulthood. JAMA Pediatr 2016;170:e162385.
51. Mueller NT, Mao G, Bennet WL, Hourigan SK, Dominguez–Bello MG, Appel LJ, et al. Does vaginal delivery mitigate or strengthen the intergenerational association of overweight and obesity? Findings from the boston birth cohort. Int J Obes 2017; 41:497–501.
52. Ajslev TA, Andersen CS, Gamborg M, Sorensen TI, Jess T. Childhood overweight after establishment of the gut microbiota: the role of delivery mode, pre-pregnancy weight and early administration of antibiotics. Int J Obes 2011;35:522–9.
53. Forsen T, Eriksson J, Tuomilehto J, Reunanen A, Osmond C, Barker D. The fetal and childhood growth of persons who develop type 2 diabetes. Ann Intern Med 2000;133:176–82.
54. Ong KK, Ahmed ML, Emmett PM, Preece MA, Dunger DB. Association between postnatal catch-up growth and obesity in childhood: prospective cohort study. BMJ 2000;320:967–71.
55. Stettler N, Zemel BS, Kumanyika S, Stallings VA. Infant weight gain and childhood overweight status in a multicenter, cohort study. Pediatrics 2002;109:194–9.
56. Gillman MW, Rifas-Shiman SL, Camargo CA Jr., Berkey CS, Frazier AL, Rockett HR, et al. Risk of overweight among adolescents who were breastfed as infants. JAMA 2001;285: 2461–7.
57. Badon SE, Quesenberry CP, Xu F, Avalos LA, Hedderson MM. Gestational weight gain, birthweight and early-childhood obesity: between- and within-family comparisons. Int J Epidemiol 2020;49:1682–90.
58. Dyess NF, Kinsella JP. Cardiovascular implications for offspring born to mothers with preeclampsia. J Pediatr 2021; 228:11–2.
59. Shah A, Matsumura N, Quon A, Morton JS, Dyck JRB, Davidge ST. Cardiovascular susceptibility to in vivo ischemic myocardial injury in male and female rat offspring exposed to prenatal hypoxia. Clin Sci 2017;131:2303–17.
60. Morgan HL, Paganopoulou P, Akhtar S, Urquhart N, Philomin R, Dickinson Y, et al. Paternal diet impairs F1 and F2 offspring vascular function through sperm and seminal plasma specific mechanisms in mice. J Physiol 2020;598:699–715.
61. Watkins AJ, Lucas ES, Torrens C, Cleal JK, Green L, Osmond C, et al. Maternal low-protein diet during mouse pre-implantation development induces vascular dysfunction and altered renin-angiotensin-system homeostasis in the offspring. Br J Nutr 2010;103:1762–70.
62. Ornellas F, Carapeto PV, Aguila MB, Mandarim-de-Lacerda CA. Sex-linked changes and high cardiovascular risk markers in the mature progeny of father, mother, or both father and mother consuming a high-fructose diet. Nutrition 2020;71:110612.
63. Hu C, Tao Y, Deng Y, Cai Q, Ren H, Yu C, et al. Paternal long-term PM2.5 exposure causes hypertension via increased renal AT1R expression and function in male offspring. Clin Sci 2021;135: 2575–88.
64. de Jonge LL, Harris HR, Rich-Edwards JW, Willett WC, Forman MR, Jaddoe VW, et al. Parental smoking in pregnancy and the risks of adult-onset hypertension. Hypertension 2013;61:494–500.
65. Watkins AJ, Platt D, Papenbrock T, Wilkins A, Eckert JJ, Kwong WY, et al. Mouse embryo culture induces changes in postnatal phenotype including raised systolic blood pressure. Proc Natl Acad Sci U S A 2007;104:5449–54.
66. Aljahdali A, Airina R, Velazquez MA, Sheth B, Wallen K, Osmond C, et al. The duration of embryo culture after mouse IVF differentially affects cardiovascular and metabolic health in male offspring. Hum Reprod 2020;35:2497–514.
67. Lim K, Burke SL, Marques FZ, Jackson KL, Gueguen C, Sata Y, et al. Leptin and melanocortin signaling mediates hypertension in offspring from female rabbits fed a high-fat diet during gestation and lactation. Front Physiol 2021;12:693157.
68. Saad AF, Dickerson J, Kechichian TB, Yin H, Gamble P, Salazar A, et al. High-fructose diet in pregnancy leads to fetal programming of hypertension, insulin resistance, and obesity in adult offspring. Am J Obstet Gynecol 2016;215:378.e1–6.
69. Tain YL, Lee WC, Wu KLH, Leu S, Chan JYH. Maternal high fructose intake increases the vulnerability to post-weaning high-fat diet-induced programmed hypertension in male offspring. Nutrients 2018;10:56.
70. Hsu CN, Chan JYH, Wu KLH, Yu HR, Lee WC, Hou CY, et al. Altered gut microbiota and its metabolites in hypertension of developmental origins: exploring differences between fructose and antibiotics exposure. Int J Mol Sci 2021;22:2674.
71. Slabiak-Blaz N, Adamczak M, Gut N, Grajoszek A, Nyengaard JR, Ritz E, et al. Administration of cyclosporine a in pregnant rats-the effect on blood pressure and on the glomerular number in their offspring. Kidney Blood Press Res 2015;40:413–23.
72. Chahoud I, Stahlmann R, Merker HJ, Neubert D. Hypertension and nephrotoxic lesions in rats 1 year after prenatal exposure to gentamicin. Arch Toxicol 1988;62:274–84.
73. Gois PH, Canale D, Luchi WM, Volpini RA, Veras MM, Nde SC, et al. Tenofovir during pregnancy in rats: a novel pathway for programmed hypertension in the offspring. J Antimicrob Chemother 2015;70:1094–105.
74. Tain YL, Sheen JM, Chen CC, Yu HR, Tiao MM, Kuo HC, et al. Maternal citrulline supplementation prevents prenatal dexamethasone–induced programmed hypertension. Free Radic Res 2014;48:580–6.
75. Suter M, Abramovici A, Showalter L, Hu M, Shope CD, Varner M, et al. Utero tobacco exposure epigenetically modifies placental CYP1A1 expression. Metabolism 2010;59:1481–90.
76. Slater-Jefferies JL, Hoile SP, Lillycrop KA, Townsend PA, Hanson MA, Burdge GC. Effect of sex and dietary fat intake on

the fatty acid composition of phospholipids and triacylglycerol in rat heart. Prostaglandins Leukot Essent Fatty Acids 2010;83: 219–23.
77. Khan I, Dekou V, Hanson M, Poston L, Taylor P. Predictive adaptive responses to maternal high-fat diet prevent endothelial dysfunction but not hypertension in adult rat offspring. Circulation 2004;110:1097–102.
78. Menting MD, Mintjens S, van de Beek C, Frick CJ, Ozanne SE, Limpens J, et al. Maternal obesity in pregnancy impacts offspring cardiometabolic health: systematic review and meta-analysis of animal studies. Obes Rev 2019;20:675–85.
79. Suter M, Bocock P, Showalter L, Hu M, Shope C, McKnight R, et al. Epigenomics: maternal high-fat diet exposure in utero disrupts peripheral circadian gene expression in nonhuman primates. Faseb J 2011;25:714–26.
80. Mdaki KS, Larsen TD, Wachal AL, Schimelpfenig MD, Weaver LJ, Dooyema SD, et al. Maternal high-fat diet impairs cardiac function in offspring of diabetic pregnancy through metabolic stress and mitochondrial dysfunction. Am J Physiol Heart Circ Physiol 2016;310:H681–92.
81. Watkins AJ, Lucas ES, Wilkins A, Cagampang FR, Fleming TP. Maternal periconceptional and gestational low protein diet affects mouse offspring growth, cardiovascular and adipose phenotype at 1 year of age. PLoS One 2011;6:e28745.
82. Watkins AJ, Wilkins A, Cunningham C, Perry VH, Seet MJ, Osmond C, et al. Low protein diet fed exclusively during mouse oocyte maturation leads to behavioural and cardiovascular abnormalities in offspring. J Physiol 2008;586:2231–44.
83. Goyal R, Van-Wickle J, Goyal D, Longo LD. Antenatal maternal low protein diet: ACE-2 in the mouse lung and sexually dimorphic programming of hypertension. BMC Physiol 2015;15:2.
84. Jose PA, Raj D. Gut microbiota in hypertension. Curr Opin Nephrol Hypertens 2015;24:403–9.
85. Watkins AJ, Sinclair KD. Paternal low protein diet affects adult offspring cardiovascular and metabolic function in mice. Am J Physiol Heart Circ Physiol 2014;306:H1444–52.
86. Eberle C, Kirchner MF, Herden R, Stichling S. Paternal metabolic and cardiovascular programming of their offspring: a systematic scoping review. PLoS One 2020;15:e0244826.
87. Cresci M, Foffa I, Ait-Ali L, Pulignani S, Gianicolo EA, Botto N, et al. Maternal and paternal environmental risk factors, metabolizing GSTM1 and GSTT1 polymorphisms, and congenital heart disease. Am J Cardiol 2011;108:1625–31.
88. Velazquez MA, Sheth B, Smith SJ, Eckert JJ, Osmond C, Fleming TP. Insulin and branched-chain amino acid depletion during mouse preimplantation embryo culture programmes body weight gain and raised blood pressure during early postnatal life. Biochim Biophys Acta, Mol Basis Dis 2018;1864: 590–600.
89. Chan JC, Nugent BM, Bale TL. Parental advisory: maternal and paternal stress can impact offspring neurodevelopment. Biol Psychiatr 2018;83:886–94.
90. Bodden C, Hannan AJ, Reichelt AC. Of 'junk food' and 'brain food': how parental diet influences offspring neurobiology and behaviour. Trends Endocrinol Metab 2021;32:566–78.
91. Choi GB, Yim YS, Wong H, Kim S, Kim H, Kim SV, et al. The maternal interleukin-17a pathway in mice promotes autism-like phenotypes in offspring. Science 2016;351:933–9.
92. Liang GL, Zhu XJ, Zhang ZX, Chen L, Feng HJ, Zhan SB, et al. microRNAs in aged sperm confer psychiatric symptoms to offspring through causing the dysfunction of estradiol signaling in early embryos. Cell Discov 2022;8:63.
93. Wang YB, Chen ZP, Hu HH, Lei JQ, Zhou Z, Yao B, et al. Sperm microRNAs confer depression susceptibility to offspring. Sci Adv 2021;7:eabd7605.
94. Graf AE, Lallier SW, Waidyaratne G, Thompson MD, Tipple TE, Hester ME, et al. Maternal high fat diet exposure is associated with increased hepcidin levels, decreased myelination, and neurobehavioral changes in male offspring. Brain Behav Immun 2016;58:369–78.
95. Buffington SA, Di Prisco GV, Auchtung TA, Ajami NJ, Petrosino JF, Costa-Mattioli M. Microbial reconstitution reverses maternal diet-induced social and synaptic deficits in offspring. Cell 2016; 165:1762–75.
96. Zhou Y, Zhu H, Wu HY, Jin LY, Chen B, Pang HY, et al. Diet-induced paternal obesity impairs cognitive function in offspring by mediating epigenetic modifications in spermatozoa. Obesity 2018;26:1749–57.
97. Yamazaki M, Yamada H, Munetsuna E, Ishikawa H, Mizuno G, Mukuda T, et al. Excess maternal fructose consumption impairs hippocampal function in offspring via epigenetic modification of BDNF promoter. Faseb J 2018;32:2549–62.
98. Liu XN, Li X, Xia B, Jin X, Zou QH, Zeng ZH, et al. High-fiber diet mitigates maternal obesity-induced cognitive and social dysfunction in the offspring via gut-brain axis. Cell Metabol 2021;33:923–38.e6.
99. Zou KX, Ren J, Luo SS, Zhang JY, Zhou CL, Tan CX, et al. Intrauterine hyperglycemia impairs memory across two generations. Transl Psychiatry 2021;11:434.
100. Liu WB, Zhu HL, Xiong YW, Lv J, Huang YC, Wang H. Environmental cadmium exposure during gestation impairs fetal brain and cognitive function of adult offspring via reducing placenta-derived E2 level. Chemosphere 2022;307:135668.
101. Amos-Kroohs RM, Davenport LL, Atanasova N, Abdulla ZI, Skelton MR, Vorhees CV, et al. Developmental manganese neurotoxicity in rats: cognitive deficits in allocentric and egocentric learning and memory. Neurotoxicol Teratol 2017;59:16–26.
102. Gu X, Bi N, Wang T, Huang C, Wang R, Xu Y, et al. Probiotic Lactobacillus rhamnosus GR-1 supplementation attenuates Pb-induced learning and memory deficits by reshaping the gut microbiota. Front Nutr 2022;9:934118.
103. Guo XR, Jiang SW, Xu J, Tian Y, Ouyang FX, Yu XD, et al. Effects of single and combined exposure to lead and stress during pregnancy on offspring neurodevelopment. Dev Cognit Neurosci 2022;56:101124.
104. Zhang C, Wu XC, Li S, Dou LJ, Zhou L, Wang FH, et al. Perinatal low-dose bisphenol AF exposure impairs synaptic plasticity and cognitive function of adult offspring in a sex-dependent manner. Sci Total Environ 2021;788:147918.
105. van Dokkum NH, Bachini S, Verkaik–Schakel RN, Baptist DH, Salavati S, Kraft KE, et al. Differential placental DNA methylation of NR3C1 in extremely preterm infants with poorer neurological functioning. Front Pediatr 2022;10:876803.
106. Johnson JL, Farr SL, Dietz PM, Sharma AJ, Barfield WD, Robbins CL. Trends in gestational weight gain: the pregnancy risk assessment monitoring system, 2000–2009. Am J Obstet Gynecol 2015;212:806.e1–8.
107. Godfrey KM, Reynolds RM, Prescott SL, Nyirenda M, Jaddoe VW, Eriksson JG, et al. Influence of maternal obesity on the long-term health of offspring. Lancet Diabetes Endocrinol 2017;5:53–64.

108. Coo H, Fabrigar L, Davies G, Fitzpatrick R, Flavin M. Are observed associations between a high maternal prepregnancy body mass index and offspring IQ likely to be causal? J Epidemiol Community Health 2019;73:920–8.
109. Girchenko P, Lahti-Pulkkinen M, Lahti J, Pesonen AK, Hamalainen E, Villa PM, et al. Neonatal regulatory behavior problems are predicted by maternal early pregnancy overweight and obesity: findings from the prospective PREDO Study. Pediatr Res 2018;84:875–81.
110. Bianco ME, Josefson JL. Hyperglycemia during pregnancy and long-term offspring outcomes. Curr Diabetes Rep 2019;19:143.
111. Braun K, Champagne FA. Paternal influences on offspring development: behavioural and epigenetic pathways. J Neuroendocrinol 2014;26:697–706.
112. Kundakovic M, Champagne FA. Epigenetic perspective on the developmental effects of bisphenol A. Brain Behav Immun 2011; 25:1084–93.
113. Guan RL, Wang T, Dong XR, Du KJ, Li J, Zhao F, et al. Effects of co-exposure to lead and manganese on learning and memory deficits. J Environ Sci 2022;121:65–76.
114. Lopez-Rodriguez D, Aylwin CF, Delli V, Sevrin E, Campanile M, Martin M, et al. Multi- and transgenerational outcomes of an exposure to a mixture of endocrine-disrupting chemicals (EDCs) on puberty and maternal behavior in the female rat. Environ Health Perspect 2021;129:87003.
115. Zheng XG, Li ZH, Wang GS, Wang HS, Zhou YC, Zhao XZ, et al. Sperm epigenetic alterations contribute to inter-and transgenerational effects of paternal exposure to long-term psychological stress via evading offspring embryonic reprogramming. Cell Discov 2021;7:101.
116. Wu Y, Espinosa KM, Barnett SD, Kapse A, Quistorff JL, Lopez C, et al. Association of elevated maternal psychological distress, altered fetal brain, and offspring cognitive and social–emotional outcomes at 18 months. JAMA Netw Open 2022;5:e229244.
117. Cote F, Fligny C, Bayard E, Launay JM, Gershon MD, Mallett J, et al. Maternal serotonin is crucial for murine embryonic development. Proc Natl Acad Sci USA 2007;104:329–34.
118. Bonnin A, Goeden N, Chen K, Wilson M, King J, Shih JC, et al. A transient placental source of serotonin for the fetal forebrain. Nature 2011;472:347–50.
119. Appleton AA, Lester BM, Armstrong DA, Lesseur C, Marsit CJ. Examining the joint contribution of placental NR3C1 and HSD11B2 methylation for infant neurobehavior. Psychoneuroendocrinology 2015;52:32–42.
120. Nava-Rivera LE, Betancourt-Martinez ND, Lozoya-Martinez R, Carranza-Rosales P, Guzman-Delgado NE, Carranza-Torres IE, et al. Transgenerational effects in DNA methylation, genotoxicity and reproductive phenotype by chronic arsenic exposure. Sci Rep 2021;11:8276.
121. Manikkam M, Haque MM, Guerrero-Bosagna C, Nilsson EE, Skinner MK. Pesticide methoxychlor promotes the epigenetic transgenerational inheritance of adult-onset disease through the female germline. PLoS One 2014;9:e102091.
122. Manikkam M, Tracey R, Guerrero-Bosagna C, Skinner MK. Pesticide and insect repellent mixture (permethrin and DEET) induces epigenetic transgenerational inheritance of disease and sperm epimutations. Reprod Toxicol 2012;34:708–19.
123. Jazwiec PA, Sloboda DM. Nutritional adversity, sex and reproduction: 30 years of DOHaD and what have we learned? J Endocrinol 2019;242:T51–68.
124. Fleming TP, Watkins AJ, Velazquez MA, Mathers JC, Prentice AM, Stephenson J, et al. Origins of lifetime health around the time of conception: causes and consequences. Lancet 2018;391: 1842–52.
125. Gu L, Liu HL, Gu X, Boots C, Moley KH, Wang Q. Metabolic control of oocyte development: linking maternal nutrition and reproductive outcomes. Cell Mol Life Sci 2015;72:251–71.
126. Oshio LT, Andreazzi AE, Lopes JF, de Sa JP, Bolotari M, Costa VMG, et al. A paternal hypercaloric diet affects the metabolism and fertility of F1 and F2 Wistar rat generations. J Dev Orig Hlth Dis 2020;11:653–63.
127. Sertorio MN, Cesar H, de Souza EA, Mennitti LV, Santamarina AB, Mesquita LMD, et al. Parental high-fat high-sugar diet intake programming inflammatory and oxidative parameters of reproductive health in male offspring. Front Cell Dev Biol 2022;10:867127.
128. Han X, Zhang PF, Shen W, Zhao Y, Zhang HF. Estrogen receptor-related DNA and histone methylation may be involved in the transgenerational disruption in spermatogenesis by selective toxic chemicals. Front Pharmacol 2019;10:1012.
129. Sinha N, Biswas A, Nave O, Seger C, Sen A. Gestational diabetes epigenetically reprograms the cart promoter in fetal ovary, causing subfertility in adult life. Endocrinology 2019;160: 1684–700.
130. Ajuogu PK, Al-Aqbi MAK, Hart RA, McFarlane JR, Smart NA. A low protein maternal diet during gestation has negative effects on male fertility markers in rats – a Systematic Review and Meta-analysis. J Anim Physiol Anim Nutr 2021;105:157–66.
131. Shi M, Whorton AE, Sekulovski N, MacLean JA, Hayashi K. Prenatal exposure to bisphenol A, E, and S induces transgenerational effects on male reproductive functions in mice. Toxicol Sci 2019;172:303–15.
132. Zhu L, Liu Y, Xue X, Yuan C, Wang Z. BPA's transgenerational disturbance to transcription of ovarian steroidogenic genes in rare minnow gobiocypris rarus via DNA and histone methylation. Sci Total Environ 2021;762:143055.
133. Brauner EV, Hansen AM, Doherty DA, Dickinson JE, Handelsman DJ, Hickey M, et al. The association between in-utero exposure to stressful life events during pregnancy and male reproductive function in a cohort of 20-year-old offspring: the Raine Study. Hum Reprod 2019;34:1345–55.
134. Gerardin DCC, Pereira OCM, Kempinas WG, Florio JC, Moreira EG, Bernardi MM. Sexual behavior, neuroendocrine, and neurochemical aspects in male rats exposed prenatally to stress. Physiol Behav 2005;84:97–104.
135. Crump CJ, Chevins PFD. Prenatal stress reduces fertility of male offspring in mice, without affecting their adult testosterone levels. Horm Behav 1989;23:333–43.
136. Pabarja A, Hakemi SG, Musanejad E, Ezzatabadipour M, Nematollahi-Mahani SN, Afgar A, et al. Genetic and epigenetic modifications of F1 offspring's sperm cells following in utero and lactational combined exposure to nicotine and ethanol. Sci Rep 2021;11:12311.
137. Liu JH, Huang J, Gao LQ, Sang YJ, Li XY, Zhou GQ, et al. Maternal exposure to PM2.5 disrupting offspring spermatogenesis through induced sertoli cells apoptosis via inhibin B hypermethylation in mice. Ecotoxicol Environ Saf 2022;241: 113760.
138. Stenz L, Escoffier J, Rahban R, Nef S, Paoloni-Giacobino A. Testicular dysgenesis syndrome and long-lasting epigenetic

silencing of mouse sperm genes involved in the reproductive system after prenatal exposure to DEHP. PLoS One 2017;12: e0170441.
139. Irani D, Borle S, Balasinor N, Singh D. Maternal cypermethrin exposure during perinatal period dysregulates gonadal steroidogenesis, gametogenesis and sperm epigenome in F1 rat offspring. Reprod Toxicol 2022;111:106–19.
140. Hao CX, Gely-Pernot A, Kervarrec C, Boudjema M, Becker E, Khil P, et al. Exposure to the widely used herbicide atrazine results in deregulation of global tissue-specific RNA transcription in the third generation and is associated with a global decrease of histone trimethylation in mice. Nucleic Acids Res 2016;44:9784–802.
141. Bao Y, Zhou Y, Tang R, Yao Y, Zuo Z, Yang C. Parental diuron exposure causes lower hatchability and abnormal ovarian development in offspring of medaka (oryzias melastigma). Aquat Toxicol 2022;244:106106.
142. Gao D, Lin J, Ou K, Chen Y, Li H, Dai Q, et al. Embryonic exposure to benzo (a) pyrene inhibits reproductive capability in adult female zebrafish and correlation with DNA methylation. Environ Pollut 2018;240:403–11.
143. Skakkebaek NE, Rajpert-De Meyts E, Louis GMB, Toppari J, Andersson AM, Eisenberg ML, et al. Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. Physiol Rev 2016;96:55–97.
144. Punab M, Poolamets O, Paju P, Vihljajev V, Pomm K, Ladva R, et al. Causes of male infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. Hum Reprod 2017;32:18–31.
145. Juul A, Almstrup K, Andersson AM, Jensen TK, Jorgensen N, Main KM, et al. Possible fetal determinants of male infertility (vol 10, pg 553, 2014). Nat Rev Endocrinol 2014;10:553–62.
146. Chianese R, Troisi J, Richards S, Scafuro M, Fasano S, Guida M, et al. Bisphenol A in reproduction: epigenetic effects. Curr Med Chem 2018;25:748–70.
147. Trapphoff T, Heiligentag M, Hajj NE, Haaf T, Eichenlaub-Ritter U. Chronic exposure to a low concentration of bisphenol A during follicle culture affects the epigenetic status of germinal vesicles and metaphase II oocytes. Fertil Steril 2013; 100:1758–67.e1.
148. Liu Y, Zhang Y, Tao S, Guan Y, Zhang T, Wang Z. Global DNA methylation in gonads of adult zebrafish Danio rerio under bisphenol A exposure. Ecotoxicol Environ Saf 2016;130:124–32.
149. Chen Z, Zuo X, He D, Ding S, Xu F, Yang H, et al. Long–term exposure to a 'safe' dose of bisphenol A reduced protein acetylation in adult rat testes. Sci Rep 2017;7:40337.
150. Zhu L, Yuan C, Wang M, Liu Y, Wang Z, Seif MM. Bisphenol A-associated alterations in DNA and histone methylation affects semen quality in rare minnow Gobiocypris rarus. Aquat Toxicol 2020;226:105580.
151. Dupont C, Cordier AG, Junien C, Mandon-Pepin B, Levy R, Chavatte-Palmer P. Maternal environment and the reproductive function of the offspring. Theriogenology 2012;78:1405–14.
152. Jiang HH, Du YY, Li YF. Ovarian toxicity and epigenetic mechanisms of phthalates and their metabolites. Curr Med Sci 2021;41:236–49.
153. Zama AM, Uzumcu M. Epigenetic effects of endocrine–disrupting chemicals on female reproduction: an ovarian perspective. Front Neuroendocrinol 2010;31:420–39.
154. Dumesic DA, Oberfield SE, Stener-Victorin E, Marshall JC, Laven JS, Legro RS. Scientific statement on the diagnostic criteria, epidemiology, pathophysiology, and molecular genetics of polycystic ovary syndrome. Endocr Rev 2015;36: 487–525.
155. Gorsic LK, Dapas M, Legro RS, Hayes MG, Urbanek M. Functional genetic variation in the anti-mullerian hormone pathway in women with polycystic ovary syndrome. J Clin Endocrinol Metab 2019;104:2855–74.
156. Crisosto N, Ladron de Guevara A, Echiburu B, Maliqueo M, Cavada G, Codner E, et al. Higher luteinizing hormone levels associated with antimullerian hormone in postmenarchal daughters of women with polycystic ovary syndrome. Fertil Steril 2019;111:381–8.
157. Risal S, Pei Y, Lu H, Manti M, Fornes R, Pui HP, et al. Prenatal androgen exposure and transgenerational susceptibility to polycystic ovary syndrome. Nat Med 2019;25:1894–904.
158. Li Z, Huang H. Epigenetic abnormality: a possible mechanism underlying the fetal origin of polycystic ovary syndrome. Med Hypotheses 2008;70:638–42.
159. Mimouni NE, Paiva I, Barbotin AL, Timzoura FE, Plassard D, Gras SL, et al. Polycystic ovary syndrome is transmitted via a transgenerational epigenetic process. Cell Metabol 2021;33: 513–30.e8.
160. Fu Q, McKnight RA, Yu X, Callaway CW, Lane RH. Growth retardation alters the epigenetic characteristics of hepatic dual specificity phosphatase 5. Faseb J 2006;20:2127–9.
161. Skvortsova K, Iovino N, Bogdanovic O. Functions and mechanisms of epigenetic inheritance in animals. Nat Rev Mol Cell Biol 2018;19:774–90.
162. Ho SM, Tang WY. Techniques used in studies of epigenome dysregulation due to aberrant DNA methylation: an emphasis on fetal-based adult diseases. Reprod Toxicol 2007;23:267–82.
163. Ganu RS, Harris RA, Collins K, Aagaard KM. Early origins of adult disease: approaches for investigating the programmable epigenome in humans, nonhuman primates, and rodents. ILAR J 2012;53:306–21.
164. Joss-Moore LA, Lane RH, Albertine KH. Epigenetic contributions to the developmental origins of adult lung disease. Biochem Cell Biol 2015;93:119–27.
165. Hsu CN, Tain YL. Developmental origins of kidney disease: why oxidative stress matters? Antioxidants 2021;10:33.
166. Lyko F. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. Nat Rev Genet 2018;19:81–92.
167. Alagia A, Gullerova M. The methylation game: epigenetic and epitranscriptomic dynamics of 5-methylcytosine. Front Cell Dev Biol 2022;10:915685.
168. Chen W, Liu NN, Shen SJ, Zhu W, Qiao J, Chang SJ, et al. Fetal growth restriction impairs hippocampal neurogenesis and cognition via Tet1 in offspring. Cell Rep 2021;37:109912.
169. Yan N, Li Y, Xing Y, Wu J, Li J, Liang Y, et al. Developmental arsenic exposure impairs cognition, directly targets DNMT3A, and reduces DNA methylation. EMBO Rep 2022;23:e54147.
170. Siklenka K, Erkek S, Godmann M, Lambrot R, McGraw S, Lafleur C, et al. Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. Science 2015;350:aab2006.
171. Fuemmeler BF, Dozmorov MG, Do EK, Zhang JJ, Grenier C, Huang Z, et al. DNA methylation in babies born to nonsmoking

mothers exposed to secondhand smoke during pregnancy: an epigenome-wide association study. Environ Health Perspect 2021;129:57010.
172. Tobi EW, Juvinao-Quintero DL, Ronkainen J, Ott R, Alfano R, Canouil M, et al. Maternal glycemic dysregulation during pregnancy and neonatal blood DNA methylation: meta-analyses of epigenome-wide association studies. Diabetes Care 2022;45: 614–23.
173. Kusuyama J, Alves-Wagner AB, Conlin RH, Makarewicz NS, Albertson BG, Prince NB, et al. Placental superoxide dismutase 3 mediates benefits of maternal exercise on offspring health. Cell Metabol 2021;33:939–56.e8.
174. Tucci V, Isles AR, Kelsey G, Ferguson-Smith AC, Imprinting GE. Genomic imprinting and physiological processes in mammals. Cell 2019;176:952–65.
175. Kelsey G, Feil R. New insights into establishment and maintenance of DNA methylation imprints in mammals. Philos Trans R Soc Lond B Biol Sci 2013;368:20110336.
176. Ding GL, Wang FF, Shu J, Tian S, Jiang Y, Zhang D, et al. Transgenerational glucose intolerance with Igf2/H19 epigenetic alterations in mouse islet induced by intrauterine hyperglycemia. Diabetes 2012;61:1133–42.
177. Jenuwein T, Allis CD. Translating the histone code. Science 2001;293:1074–80.
178. Strahl BD, Allis CD. The language of covalent histone modifications. Nature 2000;403:41–5.
179. Zhang D, Tang Z, Huang H, Zhou G, Cui C, Weng Y, et al. Metabolic regulation of gene expression by histone lactylation. Nature 2019;574:575–80.
180. Izzo LT, Wellen KE. Histone lactylation links metabolism and gene regulation. Nature 2019;574:492–3.
181. Irizarry-Caro RA, McDaniel MM, Overcast GR, Jain VG, Troutman TD, Pasare C. TLR signaling adapter BCAP regulates inflammatory to reparatory macrophage transition by promoting histone lactylation. Proc Natl Acad Sci U S A 2020;117: 30628–38.
182. Kouzarides T. Chromatin modifications and their function. Cell 2007;128:693–705.
183. Zhang Y, Sun Z, Jia J, Du T, Zhang N, Tang Y, et al. Overview of histone modification. Adv Exp Med Biol 2021;1283:1–16.
184. Bannister AJ, Kouzarides T. Regulation of chromatin by histone modifications. Cell Res 2011;21:381–95.
185. Fu Q, Yu X, Callaway CW, Lane RH, McKnight RA. Epigenetics: intrauterine growth retardation (IUGR) modifies the histone code along the rat hepatic IGF-1 gene. Faseb J 2009;23: 2438–49.
186. Xu XF, Du LZ. Epigenetics in neonatal diseases. Chin Med J 2010; 123:2948–54.
187. Pinney SE, Santos LJJ, Han Y, Stoffers DA, Simmons RA. Exendin-4 increases histone acetylase activity and reverses epigenetic modifications that silence Pdx1 in the intrauterine growth retarded rat. Diabetologia 2011;54:2606–14.
188. Park JH, Stoffers DA, Nicholls RD, Simmons RA. Development of type 2 diabetes following intrauterine growth retardation in rats is associated with progressive epigenetic silencing of Pdx1. J Clin Invest 2008;118:2316–24.
189. Xu XF, Lv Y, Gu WZ, Tang LL, Wei JK, Zhang LY, et al. Epigenetics of hypoxic pulmonary arterial hypertension following intrauterine growth retardation rat: epigenetics in PAH following IUGR. Respir Res 2013;14:20.
190. Huang JJ, Zhang HY, Wang XL, Dobbs KB, Yao J, Qin GS, et al. Impairment of preimplantation porcine embryo development by histone demethylase KDM5B knockdown through disturbance of bivalent H3K4me3-H3K27me3 modifications. Biol Reprod 2015;92:72.
191. Dahl JA, Jung I, Aanes H, Greggains GD, Manaf A, Lerdrup M, et al. Broad histone H3K4me3 domains in mouse oocytes modulate maternal-to-zygotic transition. Nature 2016;537: 548–52.
192. Bai DD, Sun J, Chen C, Jia YP, Li YH, Liu KS, et al. Aberrant H3K4me3 modification of epiblast genes of extraembryonic tissue causes placental defects and implantation failure in mouse IVF embryos. Cell Rep 2022;39:110784.
193. Wan QL, Meng X, Wang CY, Dai WY, Luo ZH, Yin ZN, et al. Histone H3K4me3 modification is a transgenerational epigenetic signal for lipid metabolism in Caenorhabditis elegans. Nat Commun 2022;13:768.
194. Das S, Min SH, Prahlad V. Gene bookmarking by the heat shock transcription factor programs the insulin-like signaling pathway. Mol Cell 2021;81:4843–60.e8.
195. Lismer A, Dumeaux V, Lafleur C, Lambrot R, Amour JB, Lorincz MC, et al. Histone H3 lysine 4 trimethylation in sperm is transmitted to the embryo and associated with diet-induced phenotypes in the offspring. Dev Cell 2021;56:671–86.e6.
196. Pepin AS, Lafleur C, Lambrot R, Dumeaux V, Kimmins S. Sperm histone H3 lysine 4 tri-methylation serves as a metabolic sensor of paternal obesity and is associated with the inheritance of metabolic dysfunction. Mol Metabol 2022;59:101463.
197. Miska EA, Ferguson-Smith AC. Transgenerational inheritance: models and mechanisms of non-DNA sequence-based inheritance. Science 2016;354:59–63.
198. Chen JF, Callis TE, Wang DZ. microRNAs and muscle disorders. J Cell Sci 2009;122:13–20.
199. Wojciechowska A, Braniewska A, Kozar-Kaminska K. MicroRNA in cardiovascular biology and disease. Adv Clin Exp Med 2017; 26:865–74.
200. Kalayinia S, Arjmand F, Maleki M, Malakootian M, Singh CP. MicroRNAs: roles in cardiovascular development and disease. Cardiovasc Pathol 2021;50:107296.
201. Bartel DP. Metazoan microRNAs. Cell 2018;173:20–51.
202. Eulalio A, Huntzinger E, Izaurralde E. Getting to the root of miRNA-Mediated gene silencing. Cell 2008;132:9–14.
203. Batista PJ, Chang HY. Long noncoding RNAs: cellular address codes in development and disease. Cell 2013;152:1298–307.
204. Fatica A, Bozzoni I. Long non-coding RNAs: new players in cell differentiation and development. Nat Rev Genet 2014;15:7–21.
205. Kung JTY, Colognori D, Lee JT. Long noncoding RNAs: past, present, and future. Genetics 2013;193:651–69.
206. Arzua T, Jiang CS, Yan YS, Bai XW. The importance of non-coding RNAs in environmental stress-related developmental brain disorders: a systematic review of evidence associated with exposure to alcohol, anesthetic drugs, nicotine, and viral infections. Neurosci Biobehav Rev 2021;128:633–47.
207. Mahnke AH, Salem NA, Tseng AM, Chung DD, Miranda RC. Nonprotein-coding RNAs in fetal alcohol spectrum disorders. Prog Mol Biol Transl Sci 2018;157:299–342.
208. Saba LM, Hoffman PL, Homanics GE, Mahaffey S, Daulatabad SV, Janga SC, et al. A long non-coding RNA (Lrap) modulates brain gene expression and levels of alcohol consumption in rats. Gene Brain Behav 2021;20:e12698.

209. Zhang YF, Shi JC, Rassoulzadegan M, Tuorto F, Chen Q. Sperm RNA code programmes the metabolic health of offspring. Nat Rev Endocrinol 2019;15:489–98.
210. Rodgers AB, Morgan CP, Leu NA, Bale TL. Transgenerational epigenetic programming via sperm microRNA recapitulates effects of paternal stress. Proc Natl Acad Sci U S A 2015;112: 13699–704.
211. Grandjean V, Fourre S, Abreu DAD, Derieppe MA, Remy JJ, Rassoulzadegan M. RNA-mediated paternal heredity of diet–induced obesity and metabolic disorders. Sci Rep 2015;5: 18193.
212. Yoshida K, Maekawa T, Ly NH, Fujita SI, Muratani M, Ando M, et al. ATF7-Dependent epigenetic changes are required for the intergenerational effect of a paternal low-protein diet. Mol Cell 2020;78:445–58.e6.
213. Tang WW, Dietmann S, Irie N, Leitch HG, Floros VI, Bradshaw CR, et al. A unique gene regulatory network resets the human germline epigenome for development. Cell 2015;161:1453–67.
214. Lam K, Pan K, Linnekamp JF, Medema JP, Kandimalla R. DNA methylation based biomarkers in colorectal cancer: a systematic review. Biochim Biophys Acta 2016;1866:106–20.
215. Godfrey KM, Sheppard A, Gluckman PD, Lillycrop KA, Burdge GC, McLean C, et al. Epigenetic gene promoter methylation at birth is associated with child's later adiposity. Diabetes 2011;60:1528–34.
216. Kusuyama J, Makarewicz NS, Albertson BG, Alves-Wagner AB, Conlin RH, Prince NB, et al. Maternal exercise-induced SOD3 reverses the deleterious effects of maternal high-fat diet on offspring metabolism through stabilization of H3K4me3 and protection against WDR82 carbonylation. Diabetes 2022;71: 1170–81.