REVIEW

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Developmental origins of health and disease: Impact of paternal nutrition and lifestyle

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ABSTRACT

Most epidemiological and experimental studies have focused on maternal influences on offspring's health. The impact of maternal undernutrition, overnutrition, hypoxia, and stress is linked to adverse offspring outcomes across a range of systems including cardiometabolic, respiratory, endocrine, and reproduction among others. During the past decade, it has become evident that paternal environmental factors are also linked to the development of diseases in offspring. In this article, we aim to outline the current understanding of the impact of male health and environmental exposure on offspring development, health, and disease and explore the mechanisms underlying the paternal programming of offspring health. The available evidence suggests that poor paternal pre-conceptional nutrition and lifestyle, and advanced age can increase the risk of negative outcomes in offspring, via both direct (genetic/epigenetic) and indirect (maternal uterine environment) effects. Beginning at preconception, and during utero and the early life after birth, cells acquire an epigenetic memory of the early exposure which can be influential across the entire lifespan and program a child's health. Potentially not only mothers but also fathers should be advised that maintaining a healthy diet and lifestyle is important to improve offspring health as well as the parental health status. However, the evidence is mostly based on animal studies, and well-designed human studies are urgently needed to verify findings from animal data.

KEYWORDS

Epigenetics, Mental health, Metabolic outcomes, Offspring, Paternal exposure, Telomere length

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INTRODUCTION

It is now well established that environmental stimuli in the early life stage impact offspring's health and development. Thirty years ago, Barker and colleagues first reported their findings on the association between in-utero environment and cardiovascular disease in later life.[1] Subsequently, studies from population cohorts and animal models have demonstrated that the impact of maternal undernutrition, overnutrition, hypoxia, and stress is linked to adverse offspring outcomes.[2] As a result, Barker's fetal programming hypothesis is completed with the developmental origins of the health and disease concept, which posits that not only exposures to toxins and chemicals, use of drugs, infections, and other stimulations but also imbalanced nutritional status during pregnancy and postnatal early life, increase the risk of disease and dysfunction later in life, especially cardiovascular disease and metabolic comorbidities such as obesity and type-2 diabetes (T2D).[3,4]

During the past decade, a growing body of evidence suggests that male exposure to toxins and pharmaceutical drugs, chemical weapons and ionizing radiation, under-/over-nutrition, lifestyle factors such as exercise, alcohol, and tobacco consumption, trauma and stress situations, impact fetal development and adult offspring health and disease, beyond effects on sperm quality and infertility.[4–12] The evidence supports the involvement of paternal factors in the origin of health or disease in offspring, and a new concept of paternal origins of health and diseases has emerged, stressing that the impact of paternal environmental conditions could also influence the offspring's health and development.[11] Paternal lineage is responsible for more than just its genetically encoded information. The epigenetic marks are delivered by sperm to the zygote, with evidence pointing towards the involvement of DNA methylation, histone modifications, and non-coding RNAs (ncRNAs), and further are transmissible through the germline to the next generation.[4] This review focuses on paternal diet and nutrition, lifestyle and related conditions and their potential effects on the health of future generations, and discusses the epigenetic mechanisms responsible for the transfer of information from one generation to the next.

EFFECTS OF PATERNAL DIET AND NUTRITION ON OFFSPRING

Historic studies from human cohorts and animals highlight the notion that paternal nutrition is important, with regard to health in future generations.[5–9] The Överkalix cohort study provided evidence for the transmission of effects from early nutritional exposures through the male germ line, showing that the longevity of grandchildren was determined by the grandparent's diet during pre-puberty.[5] Subsequently, the impact on grandchild cardiovascular, diabetes mellitus and all-cause mortality, and mental health is confirmed by the Överkalix cohort,[6,7] and others.[8,9] In a mouse model, a transgenerational effect on metabolic- and growth-related parameters in the offspring was shown if fathers suffered from preconceptional food deprivation.[10] Thereafter, there is strong evidence for the influence of paternal-specific nutrients on offspring's health and diseases (Table 1).

Dietary protein

The protein content of the paternal diet has been demonstrated to influence offspring in many aspects mostly by animal studies. Paternal low protein diet (LPD) increases female-to-male ratio and fetal weight, with reduced placental weight and junctional zone area, and perturbed fetal skeletal development whereas dietary methyl-donor supplementation alters placental morphology and gene expression differentially to that observed with the LPD alone.[13–15] Also, paternal LPD impairs adult offspring's cardiovascular function with relative hypotension and elevated heart rate, by modifying renin-angiotensin system activity and calcium signaling.[13,16] Studies on offspring metabolism indicate that pups derived from fathers with the LPD are more prone to increased adiposity and body weight, impaired glucose tolerance, perturbed hepatic gene expression, symptomatic of nonalcoholic fatty liver disease, altered lipid metabolism and gut bacterial profiles.[17–19] Furthermore, daughters of LPD fathers have higher rates of mammary cancer, with the AMP-activated protein kinase pathway suppressed and consequent mammalian target of rapamycin signaling activated.[20] Conversely, in animal models, consumption of the high protein diet (HPD) by fathers improves body composition, insulin sensitivity, β cell mass and plasticity, circulating satiety hormones, and cecal short-chain fatty acids with altered gut microbial composition in the offspring.[21,22] Although few studies have been reported on the association of paternal HPD with offspring health in general populations, subjects with an HPD resulted in higher branched-chain amino acid concentration may activate the mammalian target of rapamycin (mTOR) complex 1 and reduce insulin-stimulated glucose uptake, and thus leading to an increased risk for T2D, nonalcoholic fatty liver disease, and possibly cardiovascular diseases.[23–25] Further studies demonstrate that a higher intake of animal protein instead of plant protein is associated with insulin resistance and risk of prediabetes and T2D,[25] and that compared to a conventional diabetes diet, an isocaloric carbohydrate-reduced high-protein diet reduces HbA1c and hepatic fat content in individuals with T2D.[26] A hypercaloric (50% higher) high protein/high sucrose and low-fat diet increases ectopic fat accumulation in the liver and muscle, and reduces energy expenditure, although its effect is smaller compared to an isocaloric low protein/ high sucrose and high-fat diet.[27]

TABLE 1 Effects of paternal nutrition and lifestyle on offspring health.

Paternal exposure	Subjects	Offspring outcomes	Potential mechanisms	References
Food supply				
	Human	Survival shortening in male offspring with a surfeit of food for the paternal grandfather during the slow growth period (SGP).		5
		Mortality risk ratio of grandsons and granddaughters linked to food access for paternal grandfather and grandmother respectively, with exposure during SGP.		6, 8
		Low cardiovascular disease mortality with paternal and paternal grandmother famine, high diabetes mortality with a surfeit of food for paternal grandfather during SGP.		7
		Higher mental health scores for the third generation, if their paternal grandfather (maternal grandmother) was exposed to famine during SGP.	Evolutionary correction and possible epigenetic modifications of the gametes.	9
	Mouse	Decrease in serum glucose with paternal food deprivation.		10
Protein intake				
Low	Mouse	Impaired cardiovascular and metabolic function.	Modified DNA methylation, histone modifications, and RNA methylation in F1 testes; elevated TNF-α, and reduced calcium signaling and metabolism in male offspring.	13, 16
		Perturbed placental development, fetal growth, and skeletal development.	Altered expression of Dnmt3b, Dnmt1, and Dnmt3L, and imprinted genes.	14, 15
		Altered lipid metabolism in adipocytes.	Altered genes are involved in lipogenesis and oxidation.	17
		Altered cholesterol and lipid metabolism reprogramming of metabolic gene expression.	Altered genes associated with lipid and cholesterol biosynthesis, DNA methylation, histone H3K9me2.	18, 175
		Increased adiposity, glucose intolerance, nonalcoholic fatty liver disease, and altered gut bacterial profiles.	Paternal sperm global hypomethylation is associated with reduced testicular expression of DNA methylation and folate-cycle regulators.	19
		Increased risk of breast cancer and tumors.	Alterations in noncoding RNAs in mammary glands and tumors.	20
High	Mouse	Beneficial for body composition, insulin sensitivity, and gut microbiota; prevention of obesity and diabetes.	β cell plasticity; altered expression of Dnmt1 and Dnmt3b intergenerationally.	21, 22
High	Human and general population	Increased risk for T2D, nonalcoholic fatty liver disease, and cardiovascular diseases.	mTOR activation and reduced insulin sensitivity.	23, 24

(Continues)

TABLE 1 (Continued)

Paternal exposure	Subjects	Offspring outcomes	Potential mechanisms	References
High-fat intake and/or obesity				
	Mouse	Delayed development, reduced placental size and litter size, and disturbed embryo growth and development.	Increase in spermatogonia and S-phase population, decrease in Dnmt transcript and global DNA methylation levels, and histone H3K9me2 in germline	28, 29, 33, 34
		Increased body weight; metabolic dysregulation; repaired insulin sensitivity and adverse effects on β-cell development and function.	Changes in adipokine promoter epigenetics in the offspring for multiple generations; sperm miRNA 193b, 204 and H3K9me2, altered Nr1h3 DNA methylation at paternal germ cells; altered Igf2/H19 DNA methylation paternal sperm and offspring liver; altered DNA methylation signature and expression of sncRNA, including miRNA and piRNA in paternal spermatozoa and offspring; enrichment in H3K4me1, H3K4me3, and H3K9/K27me3 in genes implicated in offspring metabolic, inflammatory and developmental processes.	32, 35, 38–41, 173, 174, 180, 181
		Increased risk of chronic kidney disease.	Decreased lncRNA XR-146683.1 expression and increased Cd300lf promoter methylation	45, 46
	Human	High birth weight, and childhood BMI z score; increased risk of LGA, or SGA, and macrosomia	Altered DNA methylation in cord blood.	30, 31
High sugar intake				
	Mouse, Drosophila	Disturbed liver metabolism and function; alterations of gut microbiota.	Increased NFκB, SOCS3, JNK, TNF-α, IL1-β, and IL6 levels with upregulated expression of Srebp-1c and Fas.	47, 48, 52
		Obesity and abnormal energy metabolism.	Altered sperm-borne mRNAs; H3K9/K27me3-dependent reprogramming of metabolic genes in germline and zygotic windows.	53–55
		Abnormal adipokines, BP, and uric acid concentrations indicate elevated cardiovascular risk.		49
		Decrease in reward-seeking; anxiety-like behavior; high body weight.		50–52
Methyl donor intake				
Low folate intake	Mouse	Reduced pregnancy rate, post-implantation loss, and increased birth defects.	Altered imprinted gene methylation in paternal sperm and offspring; sperm histone H3 methylation or DNA methylation.	59, 60
Low intake of folate, methionine, and choline	Rat, Mouse	Increased risks of development and chronic diseases, depression-like behavior, anxiety-like behavior, and fear memory.	Differential expression of memory-related genes (Camk2α and PP1) and promoter methylation of the PP1 gene.	61, 62

(Continues)

TABLE 1 (Continued)

Paternal exposure	Subjects	Offspring outcomes	Potential mechanisms	References
Low intake of methionine, folate, betaine, choline	Human	Longer gestation and altered birth weight.	Paternal global DNA hydroxymethylation; offspring global and IGF2 DNA methylation.	56, 57
High intake of methionine, betaine, choline, and vitamin B	Mouse	Deficits in learning and memory; increase in tumor volume and hepatic lipids.	Altered spermatozoal miRNAs and lncRNAs, and offspring Kcnmb2 promoter methylation.	64–66
High vitamin B12 intake	Human	Associated with a higher risk of childhood brain tumors.		58
Physical activity				
Exercise	Mouse	Decreased risk for obesity with higher glucose tolerance and insulin sensitivity; lower inflammation and oxidation; improved metabolic profile in the liver.	Normalized abundance of X-linked sperm microRNAs; induced expression of pancreatic microRNAs (let7d-5p, 194-5p); altered expression of metabolic genes in the testes and epididymis of the sires.	71, 72, 74, 182
Long-term exercise	Mouse	Increased risk for obesity with glucose intolerance, and insulin insensitivity.	Altered methylation patterns and micro-RNA content in the sperm of fathers.	73
Climbing resistance exercise	Mouse	Muscle homeostasis maintenance; modulation on calcaneal tendon proteome and left ventricle proteome.	Altered expression of genes relevant for key skeletal muscle remodeling pathways and inflammatory profiles; positive regulation of protein metabolism.	75–77
Treadmill exercise	Mouse	Improved spatial learning and memory capability.	Increased expression of Bdnf.	78
Wheel running exercise or cage activity	Mouse	Modulation on placental weight, inflammation and nutrient transporter, and fetal weights.	Decreased miRNA 193b expression and increased miRNA 204 in paternal sperm, with decreased expression of H3K9me2.	31
Active smoking				
	Human or mouse	Increased body fat and weight, with a transgenerational effect across four generations.	Altered paternal spermatozoal miRNAs.	6, 79–81, 90
	Human	High risk for childhood asthma; lower lung function.	Altered lung and gonad DNA methylation and histone 3 and 4 acetylations, and PPARγ expression.	86, 88, 89
		Poorer mental health (particularly hyperactivity/ADHD).		82
		An increase in SGA, birth defects such as congenital heart defects, orofacial clefts, cancers, brain tumors, and acute lymphoblastic leukemia.		83
		Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with tobacco smoking and conduct disorder symptoms in offspring.		91, 92

(Continues)

TABLE 1 (Continued)

Paternal exposure	Subjects	Offspring outcomes	Potential mechanisms	References
Alcohol consumption				
	Mouse	A prolonged period of fetal gestation and an increased incidence of intrauterine growth restriction; have deleterious effects on embryonic development.	Altered expression of genes within the pro-fibrotic TGF-β signaling pathway and the LiverX/RetinoidX/FarnesoidX receptor pathways; alterations in DNA methylation, ncRNAs (tsRNA, piwiRNA), as well as damage in DNA integrity in the testicular germline and sperm.	93–95
		Increase in activity and sensorimotor integration deficits, decreased balance, coordination, and short-term motor learning; altered behavioral responses and responses to repetitive mild traumatic brain injury.	Altered sensitivity to the GABAergic drug midazolam; modified expression of many genes and telomere length.	96–98
	Human	Higher risk of substance-related disorders; increased risks of anxiety/depression and sleep problems in girls at age 4, and somatic complaints and rule-breaking behaviors in boys at age 6; increased fetal birth defect risk; increased risk of total congenital heart diseases; shorter anogenital distance especially in boys.		100–104
Drug exposure				
	Human and mouse	Negative impacts on future generations, ranging from behavioral to molecular and physiological changes.	Regulation on the hypothalamic-pituitary-adrenal axis with increased corticosterone levels, as well as changes in dopaminergic signaling; changes in imprinted genes and microRNAs and genes related to glutamatergic and neurotrophic factor signaling.	12, 105, 106
Age				
Increasing paternal age	Human and mouse	Birth defects include musculoskeletal anomalies; psychiatric disorders like autism, schizophrenia and bipolar disorders, and childhood cancer.	Epigenetic changes, DNA mutations along with chromosomal aneuploidies in sperm and testes; longer telomere length.	83, 112–115, 118–120
Increasing paternal age	Human	Risk factors for early-onset type 1 diabetes and obesity.		110, 111

Therefore, the relationship between protein intake and health is complex and influenced by overall diet composition, total energy intake, and even body weight. The habitual high-protein intake with no reductions in carbohydrate and energy intake may contribute to the increased disease risk in themselves,[23] and offspring when it occurs in paternal preconception.

High-fat intake

Besides the effects on subfertility in subsequent generations,[28] paternal obesity induced by a high-fat diet (HFD) has significant negative effects on blastocyst attachment, growth, and implantation due to increased spermatogonia and S-phase population, and

DNA hypomethylation, resulting in delayed development, reduced placental size and litter size, and disturbed embryo growth and development.[29–33] Both in human and animal models, paternal HFD may impact offspring's postnatal obesity and metabolic outcomes, but the results are inconsistent.[34–37] The whole-body and skeletal muscle insulin sensitivity in offspring early life is enhanced by paternal HFD feeding,[34] but metabolic syndrome-like phenomena are induced, including weight and fat gain, glucose intolerance, hypertriglyceridemia, abnormal adipocytokine levels, and hypertension in adulthood of offspring, via endoplasmic reticulum stress and elevated expression of phosphoenolpyruvate carboxykinase.[35,38,39] Furthermore, programming by paternal HFD has demonstrated adverse effects on β-cell development and function, and numerous adipose metabolic pathways in offspring,[40,41] and an additive effect on offspring for two generations.[35] However, in a rat study with parental HFD food intake at mating/conception, maternal but not paternal HFD predisposes for offspring metabolic health (obesity, hyperleptinemia, hyperglycemia, insulin resistance) over generations. To note, this inconsistent result does not exclude the possibility that paternal HFD exposure occurs at earlier ages, that is, during critical developmental stages (gametogenesis/adolescence), for a longer time period, and/or the severity of obesity-induced.[42] Further investigation on the brain has demonstrated that male exposure to the HFD may contribute to stable behavioral variation among females in courtship, maternal care, and anxiety-like behavior,[43] as well as cognitive impairments in the offspring due to altered methylation and expression of the *BDNF* gene.[44] Moreover, paternal HFD-induced obesity is associated with renal triglyceride accumulation and histological changes in tubules, accompanied by upregulated expression of acetyl-CoA acetyltransferase 1, and epigenetic alterations of renal mRNA expression of genes (*Enpp6*, *Tmem144*, *Cd300lf*, and *Actr3b*) in offspring, implying a higher risk of chronic kidney disease.[45,46]

High sugar intake

The consumption of a high-sugar diet (HSD) or high-sugar/fat diet by fathers is associated with adverse effects on liver metabolism and function, and alterations of gut microbiota in adult male offspring.[47,48] Consumption of a fructose-rich diet by the father, the mother, or both negatively affects blood pressure, adipokines, and uric acid concentrations of mature offspring, which correspond to markers of elevated cardiovascular risk in progeny.[49] Le et al. found that paternal sucrose self-administration experience results in a decrease in reward-seeking and induces anxiety-like behavior in the offspring of rats.[50] Also, paternal HFD and HSD cause significant phenotypic changes in the offspring, including higher body weight, hypothalamic inflammation, altered energy homeostasis, gut microbiota, stress reactivity, and social behavior.[51–53] In a Drosophila model, paternal sugar-induced intergenerational metabolic reprogramming (lipid metabolism, immune response, obesity, etc.) is attributable to modification of sperm and offspring chromatin state, and histone methylation associated gene transcription, and this similar pathway may be involved in obesity susceptibility and phenotype variation in mice and humans.[54,55]

Vitamin or methyl donor in diet

There are emerging shreds of evidence that paternal vitamin or methyl donor (methionine, folate, betaine, choline) intake impacts the offspring's health and disease onset. Human studies demonstrate that an increase in paternal folate intake is associated with longer gestation,[56] and that methionine/betaine intake is negative, but choline intake is positively associated with birth weight.[57] In a case-control study, paternal preconception high intake of folate, B_6 or B_{12} is associated with an increased risk of childhood brain tumors.[58] In rodent models, paternal folate deficiency or low intake decreases sperm counts[59] and alters the sperm and placenta epigenome and genes' expression implicated in the development of chronic diseases such as cancer, diabetes, autism, and schizophrenia, thus linking to adverse pregnancy outcomes, such as a reduced pregnancy rate, post-implantation loss, increased birth defects, increased postnatal-preweaning mortality and risks of developmental and chronic diseases.[59,60] Offspring of paternal methyl donor (folate) deficient diet shows greater depression-like behavior, anxiety-like behavior, and fear memory, accompanied by differences in the expression of memory-related genes and gene promoter methylation in the hippocampus.[61,62] Paternal over intake of folic acid and methionine also results in deficits in hippocampus-dependent learning and memory, impaired hippocampal synaptic plasticity and theta oscillations, and impaired metabolic functions in the offspring.[63–65] Meanwhile, a stepwise increase in tumor volume and hepatic triglycerides and cholesterol in female offspring has been found with increasing paternal B vitamin intake prior to mating.[66] Studies on other vitamins display that paternal consumption of vitamin E can improve offspring's negative parameters resulting from feeding fathers with trans-fatty acids.[67]

To summarize, the above-mentioned imbalanced nutrient intake, encompassing high-fat/sugar intake, lower intake of fiber, vitamins, minerals, and so forth in populations including preconception fathers, which are resulted from refined grains, processed and red meat, desserts, and drinks in the

prevailing western dietary pattern, may exert a negative impact on offspring health outcomes.

EFFECTS OF PATERNAL LIFESTYLE ON OFFSPRING

A growing body of literature has provided strong evidence for a clustered and co-occurring unhealthy pattern such as smoking, alcohol, physical inactivity, and poor diet in adult populations, particularly males and those with greater social disadvantage.[68] Beyond its contribution to the development of chronic diseases such as cardiovascular diseases and cancer in adults themselves, this clustered behavioral pattern may adversely affect sperm, which modulates both the genotype and phenotype of progeny in intergenerational or transgenerational inheritance.

Physical activity

Paternal exercise training, mostly in animal models, has been shown to impact various physiological systems, benefit cognitive development, and combat the development of metabolic dysfunction in offspring.[69,70] Increases in risk of T2D and metabolic impairments in offspring when the father consumes an HFD, can be normalized when the father also exercises during preconception. This protection may occur by increasing insulin signaling potential within offspring skeletal muscle, normalizing adiposity, attenuating fibrosis, inflammatory profile, and redox status, and restoring pancreatic islet cell morphology and ncRNA expression in sperm.[70–72] However, Murashov et al. reported that offspring from fathers subjected to long-term exercise are more susceptible to low energy expenditure and increased risk for obesity in mice, potentially via microRNA (miRNA)-induced modification of sperm.[73] Effects on other systems demonstrate that paternal exercise training can improve the metabolic profile in the liver of the progeny, thereby ameliorating the negative effects of obesity.[74] Meanwhile, key skeletal muscle remodeling pathways and inflammatory profiles are altered in offspring from exercised fathers, with positive regulation of proteins essential for the homeostasis maintenance of tendon integrity.[75,76] Moreover, paternal regular training demonstrates to be an important intervention capable of inducing beneficial effects on the left ventricle proteome and associated homeostasis maintenance in offspring.[77] As well, paternal treadmill exercise improves the spatial learning and memory capability of male pups, which is accompanied by increased expression of BDNF and Reelin.[78] In addition, in a mouse model of paternal HFD, the reduction in placental and fetal tissue weights, up-regulation in nutrient transporter gene expression, and inflammatory gene expression, are reversed by paternal exercise in a sex-specific manner, which may reduce offspring T2D risk.[31]

Smoking

The Avon Longitudinal Study of Parents and Children cohort study first reported an association between prepubertal (<11 years) start of father's smoking and raised body mass index in adolescence in their sons,[79,6] with a transgenerational effect across four generations.[80] In the Respiratory Health in Northern Europe, Spain, and Australia study, fathers' smoking onset before conception of the offspring (onset ≥15 years) is associated with higher body mass index in the offspring's adulthood.[81] Systematic reviews and meta-analyses demonstrate that paternal smoking during pregnancy is related to greater odds of attention deficit hyperactivity disorder,[82] an increase in small for gestational age, birth defects such as congenital heart defects and orofacial clefts, cancers, brain tumors, and acute lymphoblastic leukemia in offspring.[83] Recently, to rule out maternal passive smoke, several studies have indicated that just preconception paternal smoking can affect offspring's health and development. For example, it has been reported that only preconception smoking exposure or both pre- and post-conception exposure is significantly associated with offspring overweight/obesity in boys.[84] Preconception paternal smoking may be associated with congenital heart diseases, limb abnormalities, and neural tube defects in the offspring, and infants whose fathers stopped or decreased smoking during pregnancy are at lower risk of these defects.[85] A hospital-based birth retrospective observational birth cohort study showed that either only paternal smoking or only maternal smoking increases the risk of childhood asthma, and paternal cessation of smoking during pregnancy reduces the risk of asthma regardless of maternal smoking.[86] Another study reported that the risk of childhood asthma is highest if the father starts smoking before age 15 years, even if he stopped more than 5 years before conception.[87] Additionally, not only fathers' smoking in prepuberty but also paternal grandmothers' smoking in pregnancy may cause lower lung function in three generations.[88] Mechanistic studies have shown that paternal smoking exposure regulates gonad DNA methylation and histone 3 and 4 acetylations, or spermatozoa miRNAs, which may become permanently programmed and transferred through the germline to subsequent generations, thus enhancing the risks of respiratory- and metabolic-related diseases in offspring.[89,90] These data suggest that, unlike other factors, use of alcohol and caffeine or physical activity, which impact offspring outcomes via direct germline transmission, paternal smoking may affect intrauterine development by both direct pathways (germline transmission) with preconception smoking and indirect pathways (altering maternal environment and physiology) with post-conception smoking and resulted in maternal passive smoke. However, an Australian birth cohort study has found insufficient evidence for an association between

paternal smoking during pregnancy and the risk of tobacco smoking and conduct disorder symptoms in offspring.[91] As well, a meta-analysis reveals that offspring exposed to maternal but not paternal prenatal tobacco smoking are at an increased risk of tobacco smoking/dependence.[92] These data suggest that paternal smoking affects offspring outcomes in a disease-specific manner. Therefore, further differentiations between the impact on offspring outcomes of paternal smoke exposure in the preconception stage, and during and after pregnancy, remain to be a challenge.

Alcohol exposure

Paternal alcohol exposure (PAE) is found to cause histological and epigenetic changes, as well as damage in DNA integrity in the testicular germline and sperm, which give rise to deleterious effects on embryonic development and to testicular and spermatic changes in the offspring.[93–95] Besides, PAE can induce several developmental aberrations and alters learning and locomotor activity, affective behavior, and sensitivity to the rewarding properties of alcohol in offspring.[12] Notably, the PAE effects are in a sex-specific manner with a negative impact on offspring neocortical development, causing deficits in activity and sensorimotor integration deficits and decreased balance, coordination, and short-term motor learning postnatally.[96] Female and male offspring display unique responses to repetitive mild traumatic brain injury and paternal experiences (exercise, caffeine, and alcohol), showing male instead of female offspring are affected by paternal alcohol treatment.[98] Also, reduced sensitivity to stress-induced hyperthermia is induced by PAE, selectively in male offspring.[97] Additionally, PAE negatively affects fetal growth in the male offspring to a greater extent than the females, and the growing deficits in males may persist into adult life with insulin hypersensitivity, increased markers of hepatic fibrosis, and alterations in immune signaling.[93] By contrast, the male offspring of alcohol-exposed sires are found resistant to HFD-induced obesity and improved glucose homeostasis via programmed increases in hepatic LXRα expression.[99] In humans, preconceptional paternal alcohol consumption increases offspring risks of substance-related disorders, anxiety/depression, sleep problems, somatic complaints and rule-breaking behaviors, fetal birth defects including total congenital heart diseases, and shorter anogenital distance.[100–104]

Drug exposure

An extensive body of literature firmly establishes that preconception exposure to drugs of abuse has impacts on future generations, ranging from behavioral to molecular and physiological changes.[12,105,106] Human literature suggests that paternal exposure to the drug (alcohol, cocaine, opioids, cannabinoids, and nicotine) has inconsistent or even contradictory results on vulnerability to drug abuse in offspring, but a few similarities do arise.[105] Preconception exposure, particularly in the case of ethanol, cocaine, and opiates, decreases addiction to that particular drug in the offspring, but offspring of morphine-exposed dams showed a higher propensity to take cocaine. Another area that revealed consistencies across studies involves hypothalamic-pituitary-adrenal axis regulation with increased corticosterone levels, as well as changes in dopaminergic signaling and reward circuitry in the brain.[106] Moreover, drug-sired offspring show epigenetic-mediated changes in imprinted genes and miRNAs and genes related to glutamatergic and neurotrophic factor signaling, which, in some instances, occur simultaneously in sire sperm and the brains of offspring, resulting in developmental and physiological abnormalities, deficits in cognitive and emotional domains and addiction-like behaviors.[12]

PATERNAL AGE

Since the correlation between increasing paternal age and genetic defects and disorders was first suggested in the late 1800s by Weinburg and strengthened in 1955 by Penrose, many other genetic disorders with single DNA errors have been considered to be associated with increasing paternal age, such as achondroplasia and osteogenesis imperfecta, as well as neurofibromatosis and Marfan syndrome.[107,108] Thereafter, a series of studies demonstrate an association of advanced paternal age (>50 years) at conception with infertility and adverse outcomes, which is less pronounced as compared to the effect of advanced maternal age showing increased risks of prolonged time to pregnancy, infertility, spontaneous abortions, and trisomy (>35 years), and risks of preterm births and stillbirths (>40 years).[109] More recently, an association with the risk of more common disorders, diabetes mellitus,[110] obesity,[111] birth defects including musculoskeletal anomalies, psychiatric disorders like autism, schizophrenia and bipolar disorders, and childhood cancer in offspring is increasing with advanced paternal age, particularly when they are 50 years or older.[83,112–117] In a large cohort study in Swedish, with every 10-year increase in paternal age at the time of conception, the risk of an offspring having schizophrenia increased by 1.47 times, while offspring with younger fathers (<21 years) were also at a higher risk of schizophrenia and attention-problems compared to the fathers aged 21–24 years at the time of conception.[118,119] Thus, paternal age shows an inverted U-shape relation with neurodevelopment and psychiatric disorders, with the offspring of younger and older fathers at a disadvantage.[115,118,119] By contrast, Frans et al. found that an old grandmother's age increased the risk of schizophrenia in a grandchild but not the grandfather's age.[120] In addition, several large studies have evaluated the risk of

leukemia and cancers in the offspring of fathers with advanced age, indicating an increased risk of acute lymphoblastic leukemia [116,117] but no protective effect on the risk of acute myeloid leukemia,[117,121] and decreased risk of cancers of the female genitalia as well as cancers of the respiratory and intrathoracic organs in offspring.[112,113] Although the current data implies that aging impairs sperm quality, which can affect fertility status and offspring outcomes, the results are conflicting. Given that most aged fathers are partnered with aged mothers, the complications of confounding factors, and the lack of systemic definitions and study design has contributed to the difficulty in interpreting data. Also, there is no clear definition of advanced paternal age in the current literature.[114] A survey on assistant reproduction technology (ART) in European countries indicates that the legal maximum age for sperm donation ranges from 35 years old in Hungary, Kazakhstan, Russia, and Slovakia to 55 years old in Slovenia, and that male maximum age for ART access is legally set in Portugal (60 years) and is recommended in Finland (60 years) and Sweden (56 years).[122] Therefore, advanced paternal age should be evaluated while accounting for normal or abnormal semen parameters, the age of the female partner, and the mode of conception.

MECHANISMS

The environment influences the health and well-being of progeny by working through the germline to introduce spontaneous genetic mutations as well as a variety of epigenetic changes. In evolutionary terms, these changes create the phenotypic diversity that fuels the fires of natural selection. However, such variation may also generate a plethora of pathological disease states ranging from dominant genetic disorders to an increased risk of developing diseases or metabolic disorders in the next generation(s).[123,124] Unique maternal factors include altered structure/function of reproductive organs, alterations in the vaginal or gut microbiome, mitochondrial DNA (mtDNA) inheritance, placental function, or epigenetic phenotypes in female germ cells. By contrast, unique paternally mediated effects on offspring implicate indirect effects on the fetal component of the placenta, telomere length (TL), sperm epigenetic, or seminal fluid protein mechanisms.[125,126] Herein, we focus on genetic/epigenetic information and/or shorter TL that are associated with the transgenerational nature of phenotypic changes observed in offspring.[123]

Telomere length

Mammalian telomeres are composed of non-coding DNA repeats that form nucleoprotein complexes and are located at the extremities of chromosomes. They preserve genomic integrity by protecting chromosome ends from degradation as well as preventing end-to-end fusions.[127] TL inherited by the father, is heterogeneous within cells presenting a Gaussian distribution and undergoes progressive age-dependent shortening in somatic cells while elongating in the male germline.[128,129] Several large cohort studies confirm that a strong positive association exists between paternal age at birth and participant leukocyte TL, with a weak inverse or no association with maternal age,[129–131] and that a 1-year increase in father's age corresponds to a 0.26% increase in offspring TL at age 53.[132] A cross-sectional study recruited subjects from 30 to 80 years of age shows that an increase of 17–22 bp is seen in children's TL per year of increasing paternal age.[130,133] Moreover, the association of paternal age at birth with longer TL in offspring is cumulative across multiple generations.[134,135]

The possible mechanisms underlying the effect of paternal age at conception on offspring TL, include sperm telomere extension due to telomerase activity, and age-dependent changes in the spermatogonia stem cell population, representing an intergenerational adaptation with increased maintenance effort to lower extrinsic mortality and delay reproduction.[136,137] While TL dynamics in the growing fetus/newborn are influenced by polymorphisms in the maternal mtDNA in the end, the paternal age at conception effect on the offspring TL may largely (and ironically) reflect variation in the mitochondrial genome that is derived from the offspring's paternal grandmother.[128] In addition, telomere biology varies considerably across species[138,139] and the effect of paternal age at conception on TL appears to vary considerably as well.[136,140] Thus, even strong experimental evidence of the biological mechanisms accounting for the paternal age at conception effect in one species should not be extrapolated uncritically to other species.[135]

The length of telomeres becomes shortened after each chromosomal replication event[127] and occurs concurrently with aging in most proliferating tissues.[141] It has been found that short TL are implicated in instigating cell senescence, as well as genetic and epigenetic instability that increase the risk of cancer,[142] and further are transmitted to future generations through their gametes.[143] Numerous studies have shown that telomere shortening is associated with aging and aging-related diseases, including AD, atherosclerosis, and chronic obstructive pulmonary disease.[144] Reduced TL in early childhood is independently associated with arterial wall thickness in later childhood, indicating a marker of vascular disease risk.[145] Despite consistency across studies on the association between paternal age and offspring TL, it is needed to further assess the impact of this association on offspring health and aging outcomes.

Epigenetics

Although DNA damage or mutations are often suggested as the biological background for father-child effects

from various environmental exposures, it is confirmed that the offspring's epigenetic profile and health status are influenced by paternal pre-conceptional insults, such as exposures to endocrine disruptors or toxins, ionizing radiation,[146] and nutritional status.[18,147–149] Ng et al. first reported that the female offspring mice from fathers with an HFD has an early onset of impaired insulin secretion and glucose tolerance, with altered expression of several associated genes and DNA hypomethylation.[147] Meanwhile, Carone et al. found that male mice consuming an LPD from weaning until sexual maturity produce offspring with increased methylation at the key lipid transcription factor PPARα in the liver.[18] Offspring of pre-diabetic fathers exhibit impaired glucose tolerance and insulin insensitivity, altered expression of genes involved in glucose metabolism, and differential DNA methylation patterns in the pancreatic islets.[150] Subsequently, in humans, the Newborn Epigenetics Study shows significant differences in DNA methylation at differentially methylated regions (DMRs) of several imprinted genes (IGF2, H19) if the father is obese.[148,149] DNA methylation marks are known to establish during gametogenesis, and deregulation of methylation at DMRs is related to chronic diseases or metabolic disorders in the offspring.[151,152] Since then, an increasing number of studies demonstrate that the information transferred from sire to progeny may occur through epigenetic marks in sperm, encompassing alterations in DNA methylation, histone modification, and/or small ncRNAs (Table 1).[123]

DNA methylation

DNA methylation, a process by which a methyl group is added to a cytosine residue at cytosine-guanine dinucleotides as well as other dinucleotide pairings,[153] is an important regulator of gene expression globally involved in gene regulation, and more specifically, in transposon silencing, genomic imprinting, maintenance of genome integrity or X chromosome inactivation.[154,155] During mammalian life, DNA methylation is a dynamic modification that is erased and reset during two major genome-wide epigenetic reprogramming events. One takes place in primordial germ cells (PGCs) during gametogenesis with genome-wide DNA demethylation, removal and resetting of parental imprints, histone modifications, and inactive-X-chromosome reactivation. The other one occurs in the preimplantation embryo when cells experience DNA demethylation, the removal, and resetting of parental imprints, and histone modifications.[154–156] Epidemiological studies and various animal models demonstrate that DNA methylation in sperm and offspring exhibits alterations when the father is exposed to environmental stress, such as diet,[156] mental stress,[157,158] and metabolic disorders.[159]

Gene imprinting, a form of DNA methylation, plays an important role in modulating fetal-placental growth and resource acquisition, postnatal growth and energy homeostasis, and transgenerational inheritance.[160,162] Imprinted genes together with transposable elements and some regions of the male pronuclei may escape the demethylation process during gametogenesis and preimplantation and pass through to descendants.[163,164] Many studies show that methylation alterations in DMRs of imprinted genes are found in exposed sires' sperm and their offspring.[165–167] Abnormalities in imprinting genes caused by epigenetic aberrations, mutations, and deletions can result in loss of imprinting and imprinting disorders, such as complex syndromes of neurodevelopmental disabilities, cognitive problems, and metabolic diseases.[168]

Histone modification

The role of histones in conveying epigenetic information in mature spermatozoa was doubted because a few studies have focused on these epigenetic marks. It is clear that most histone proteins are replaced by protamine during late spermatogenesis, facilitating a highly condensed state of the chromosomes, repressing transcriptional activity, and preventing DNA damage.[169] However, 2% and 5%–10% of the mouse and human histones persist in the sperm nucleus and remain unchanged, respectively.[170–172] The modifications present on these histone proteins in sperm provide one mechanism for epigenetic transmission, that relates to the selective establishment of specific DNA methylation patterns of developmental genes, including imprinted genes, miRNAs, and homeobox genes.[172] For example, paternal HFD or HSD induces H3K4me1 enrichment at transcription regulatory genes, and H3K4me3, H3K9/K27me3 in genes implicated in metabolic, inflammatory, and developmental processes in the offspring, which are associated with metabolic dysfunction and corresponded to genes enriched in embryos.[55,173,174] The LPD-induced and ATF7-dependent histone H3K9me2 in testicular germ cells play an important role in paternal diet-induced metabolic reprogramming in offspring.[175]

Noncoding RNA

It is known that regulatory ncRNAs are involved in transcriptional, posttranscriptional, and translational regulation for gene expression by interacting with histone modifications and the DNA methylation status of genes.[176,177] Two large subsets of ncRNAs are long ncRNAs and short ncRNAs (sncRNAs) like miRNAs, short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs).[178] Recently, sncRNAs in sperm have seemed crucial to the transmission of paternal epigenetic information to offspring.[179] The alteration in the abundance of specific ncRNAs in sperm, induced by paternal environmental

exposure including HFD and drugs, impacts the development of the embryo following fertilization and ultimately, behavioral and metabolic outcomes in the offspring.[106,179–182] When dysregulated ncRNAs in the sperm of male animals with metabolic diseases are injected into fertilized embryos sired by healthy parents, the offspring display behavioral and physiological changes comparable to those offspring born from sires with metabolic diseases.[183,184] In another study, paternal exposure to the stress hormone corticosterone altered miRNA-98, miRNA-144, and miRNA-190b, which may interact with *IGF2* and *BDNF* in the sires' sperm, resulting in anxiety behavior increased in the offspring.[185] However, more studies should focus on the origin of RNA alteration, the target of RNA regulation, and their roles in preventing offspring diseases.[179]

Effects from both sperm and seminal plasma

Besides the effects of sperm, maternal health, and post-fertilization development during early pregnancy may be influenced by the seminal plasma, which contains bioactive signaling factors that encourage uterine remodeling by inducing a maternal immune response, including the clearance of excess sperm and microorganisms from the vagina and cervix, endometrial cytokine production, immune cell infiltration and activation in the reproductive tract.[186] Being different from sperm-mediated embryo programming, the seminal plasma impacts offspring growth and metabolic and vascular health via the uterine environment. Several human and animal studies have observed that repeated exposure to a partner's seminal plasma leads to better fertilization, lower prevalence of preeclampsia and inflammation in gestation, and altered expression of genes involved in the cell cycle and growth, indicating that an increased duration of exposure to partner's semen may be beneficial for a woman's gestational wellbeing.[187–193] In contrast, less time exposure to a partner's semen or changing partner places a woman at an increased risk of developing preeclampsia.[194,195] Mice without seminal fluid have reduced fertility, impaired glucose tolerance, and exhibited obesity, placental hypertrophy, and hypertension in male offspring.[196]

The novel data from animal studies reveal the impact of sub-optimal paternal nutrition on offspring well-being, programming offspring health through both sperm and seminal plasma-specific mechanisms over successive generations.[197] In a mouse model, besides sperm contribution, seminal plasma-specific pathways are also indicated to mediate the effects of paternal preconception LPD on offspring health programming, including growth, adiposity, glucose metabolism, liver metabolic function, and gut microbiota.[19] Likewise, either LPD sperm or seminal fluid at conception impairs adult offspring's vascular function in response to both vasoconstrictors and dilators with modified expression profiles of epigenetic regulators in adult F1 male testes.[23] Other components of semen, including exosomes and its containing sncRNAs, may be important for sperm maturation and associated with metabolic diseases in their offspring.[184,198]

WINDOWS OF SUSCEPTIBILITY FOR PATERNAL INFLUENCE

Epigenetic programs are particularly dynamic in germ cells undergoing erasure, re-establishment, and maintenance of patterns, and these events, potentially susceptible to prenatal and/or postnatal exposures, may have amplified long-lasting effects.[199] Based on epigenetic alterations during the development of the paternal germ line, zygote, and embryo, four windows of susceptibility are defined during the father's lifespan where environmental effects can impact the epigenetic profile of his gametes, as follows: (i) during migration of PGCs to the genital ridge in early embryos, when genome-wide epigenetic reprogramming by demethylation or methylation remaining occurs; (ii) before puberty, from PGC (or gonocytes) to spermatogonia, during which methylation profiles are largely established; (iii) during each reproductive cycle, from spermatogonium to spermatocyte and finally the spermatozoon, when DNA methylation is also fully established; (iv) in the zygote, when the acquired methylation marks need to withstand post-zygotic epigenetic reprogramming at specific regions (e.g. imprinted genes), and the modifications present on histone proteins in sperm may relate to the selective establishment of specific DNA methylation patterns.[146] Disappointedly, current studies on the effects of internal and external factors are not enough to differentiate which stage of sperm development is influenced both in animals and humans, and this needs to be strengthened in the future.[4,11,146] Nonetheless, these data indicate that, from a father's perspective, pre-puberty/puberty, adulthood, and the zygote phase are all valuable windows to start potential nutritional interventions and avoidance of environmental insult to maximize sperm epigenetic integrity and promote adequate fetal growth and development, thus preventing chronic diseases in adulthood.

CONCLUSION

In summary, based mostly on animal studies, paternal risk factors such as obesity, high-fat, high-sugar, or low-protein diet, undernutrition, diabetes mellitus, hyperglycemia, advanced age, smoking as well as drug exposure may affect offspring health leading to adverse outcomes. These paternal factors regulate offspring development via both direct (genetic/epigenetic) and indirect (maternal uterine environment) effects. The mechanisms responsible for this inter-and trans-generational inheritance are beginning

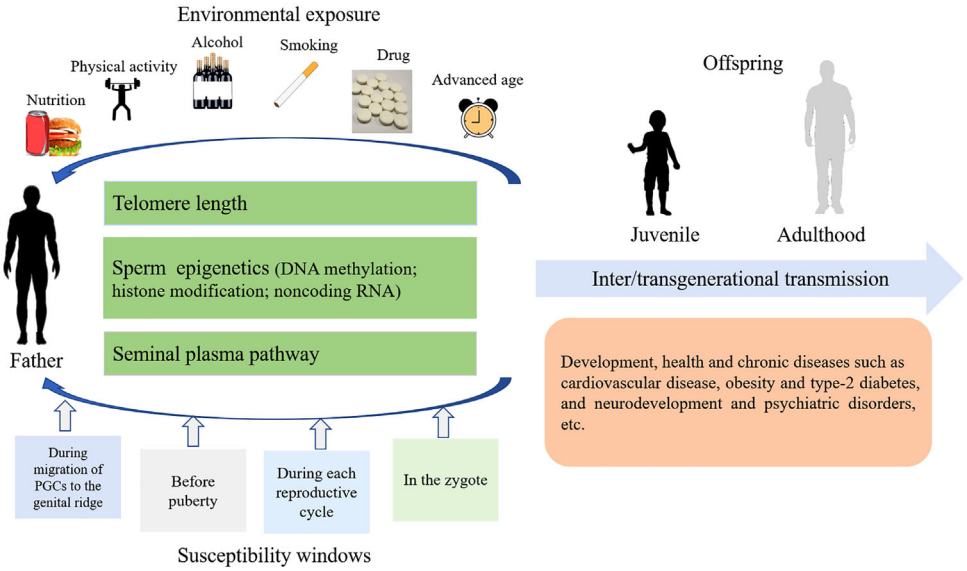

FIGURE 1 Effects of paternal environmental factors on offspring health. Paternal exposure to environmental factors including unhealthy diets, malnutrition, lifestyle, such as smoking as well as drug exposure, and advanced age, may affect offspring health, development, and chronic diseases. These unique paternally mediated effects on offspring implicate indirect effects on the fetal component of the placenta, telomere length, sperm epigenetic, or seminal fluid protein mechanisms. The epigenetic marks are delivered by sperm to the zygote, with evidence pointing towards the involvement of DNA methylation, histone modifications, and non-coding RNAs, and further are transmissible through the germline to the next generation. Four windows of susceptibility during the father's lifetime where environmental effects can impact the epigenetic profile of his gametes are as follows: during migration of primordial germ cells (PGCs) to the genital ridge; before puberty; during each reproductive cycle and zygote formation. Appropriate care during the closed circle of life including pre-puberty/puberty, adulthood, and the zygote phase, specialized in medical, behavioral, and social health interventions is very important to reduce the risk of negative environmental exposures, and consequently to improve offspring health as well as the parental health status.

to be better understood, with evidence pointing towards the involvement of DNA methylation, histone modifications, and above all, ncRNAs. All these events can interfere with each other and are transmissible through the germline to the next generation without the intervention of genetic mechanisms. In addition, the seminal plasma, a complex fluid that interacts with the sperm and the female reproductive tract, can impact maternal gestational health, post-fertilization, and postnatal development. Appropriate care during the closed circle of life including pre-puberty/puberty, adulthood, and the zygote phase, specialized in medical, behavioral, and social health interventions, is very important to reduce the risk of negative environmental exposures, and consequently to improve offspring health as well as the parental health status (Figure 1). Owing to those findings from animal studies that cannot be directly related to human populations, where exposures, outcomes, physiology, and social contexts are very different, caution should be taken in extrapolating findings from animal models to humans. Nonetheless, preventive and educational approaches should include both mothers and fathers (to be), to reduce adverse health outcomes in their offspring caused by modifiable diet and lifestyle, and environmental risk factors. To attain this, well-crafted human study designs are urgently needed and indispensable to verify findings from animal data.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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