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REVIEW

Early life programming and the risk of non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is associated with obesity, insulin resistance, type 2 diabetes and cardiovascular disease and can be considered the hepatic manifestation of the metabolic syndrome. NAFLD represents a spectrum of disease, from the relatively benign simple steatosis to the more serious non-alcoholic steatohepatitis, which can progress to liver cirrhosis, hepatocellular carcinoma and end-stage liver failure, necessitating liver transplantation. Although the increasing prevalence of NAFLD in developed countries has substantial implications for public health, many of the precise mechanisms accounting for the development and progression of NAFLD are unclear. The environment in early life is an important determinant of cardiovascular disease risk in later life and studies suggest this also extends to NAFLD. Here we review data from animal models and human studies which suggest that fetal and early life exposure to maternal under- and overnutrition, excess glucocorticoids and environmental pollutants may confer an increased susceptibility to NAFLD development and progression in offspring and that such effects may be sex-specific. We also consider studies aimed at identifying potential dietary and pharmacological interventions aimed at reducing this risk. We suggest that further human epidemiological studies are needed to ensure that data from animal models are relevant to human health.

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Background

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver disease ranging from simple steatosis (NAFLD) to non-alcoholic steatohepatitis (NASH) and cirrhosis, occurring in the absence of excessive alcohol intake.[1] NAFLD is considered to be the hepatic manifestation of the metabolic syndrome and as such its worldwide prevalence is increasing alongside the increasing prevalence of obesity. The National Health and Nutrition Examination Survey found the prevalence of simple steatosis in the U.S. adult population to be around 20–30%, rising to ~69% in obese subjects or those with type 2 diabetes.[2] Despite previously being considered almost entirely a disease of adults, NAFLD now has an estimated 9.6% incidence in children.[3,4] Whilst the majority of patients with NAFLD have simple steatosis, around 10–30% of cases progress to NASH, which is characterized by inflammation and hepatocellular injury[5] and confers an increased risk of hepatocellular carcinoma and cirrhosis, potentially resulting in end-stage liver failure necessitating liver transplantation.[6] Indeed, NASH is currently the third most common indication for liver transplantation in the United States, and could soon become the most common.[7] NAFLD also confers increased cardiometabolic risk, so that cardiovascular disease is a major cause of mortality in affected individuals.[8]

Although the pathophysiology of NAFLD is not completely understood,[9] insulin resistance (IR), which is strongly associated with obesity, is thought to be of particular importance.[10] The hepatic accumulation of triglycerides results from an imbalance in lipid uptake, metabolism and release by the liver. In the context of obesity and IR, peripheral lipolysis and *de novo* lipogenesis is increased, resulting in additional free fatty acid (FFA) influx to the liver.[10,11] After reaching the liver, lipids undergo either β-oxidation in mitochondria or esterification with glycerol to form triglycerides. The increase in FFAs can overwhelm the β-oxidation process resulting in mitochondrial dysfunction, oxidative stress and overproduction of reactive oxygen species.[10] These factors, together with decreased hepatic very low-density lipoprotein secretion contribute to the hepatic accumulation of triglycerides in the context of obesity and overnutrition. The risk factors determining the risk of progression to NASH are also unclear.[1] The 'multiple parallel hits' model proposes that multiple insults drive the progression of NAFLD to NASH;[3,12] steatosis is often regarded as the first 'hit', inducing increased susceptibility to injury from further insults such as mitochondrial dysfunction, oxidative stress and IR.[12] These additional 'hits' result in apoptosis, inflammation and fibrosis and progression to NASH.[3] In addition, ethnic differences in susceptibility to NAFLD suggest genetic predisposition may be important[13,14] and single nucleotide polymorphisms have been identified in association with increased NAFLD risk.[15]

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It is now recognized that the environment experienced in early life can have a profound influence on health. Many studies have now shown that exposure to adverse conditions during periods of developmental plasticity in early life alters tissue development, organogenesis and metabolism; resulting in the 'programming' of an increased risk of cardiovascular disease, obesity and the metabolic syndrome.[16–18] Given the association of NAFLD with obesity and the metabolic syndrome, it is not surprising that a number of reports in both humans and in animal models suggest that adverse early life conditions can also lead to an increased risk of NAFLD. Here we review the evidence demonstrating a link between early life factors and the risk of NAFLD.

Early life growth restriction and the programming of NAFLD

Many of the early studies in the Developmental Origins of Health and Disease (DOHaD) field described the association between intrauterine growth restriction (IUGR, defined as low fetal weight for gestational age) and a higher risk of developing metabolic and cardiovascular disease.[19] Growth restriction can occur as a consequence of maternal undernutrition and/or placental dysfunction including pre-eclampsia, in which there is disruption of the normal transplacental nutrient supply and/or fetal hypoxia. In humans, being born IUGR is associated with an increased risk of abnormal liver function tests and of developing NAFLD in adulthood,[20] and this is also seen in childhood, with children born small for gestational age having an increased risk of developing NASH.[21] In addition, postnatal growth patterns may be important in determining disease risk, so that individuals showing rapid catch-up growth in the first 3 months of life have a higher risk of developing NAFLD compared with those with slower early postnatal growth.[22] The DOHaD concept also includes events occurring in infancy and childhood that also influence later disease risk and this includes the risk of NAFLD. For example, exposure to the Great Chinese Famine in early life was shown to have sex-specific association with moderate–severe NAFLD[23] and amongst individuals in the Helsinki birth cohort study, individuals who were small during early childhood and obese as adults were at the highest risk of developing NAFLD.[24]

Animal models have been developed in order to understand potential mechanisms linking IUGR with later disease risk, and these mainly involve global maternal calorie restriction or specific macronutrient restriction, usually a low-protein diet. In rodents, maternal 50% calorie restriction or protein restriction results in offspring developing microvesicular steatosis accompanied by upregulation of the master transcription factors sterol regulatory element binding protein (SREBP-1c), carbohydrate-responsive element-binding protein and peroxisome proliferator-activated receptor-γ (PPAR-γ), together with effects on downstream target genes important in lipid metabolism including fatty acid synthase (FAS), acetyl-CoA carboxylase and steroyl-CoA desaturase.[25,26] In some of these studies, hepatic steatosis and changes in hepatic gene expression occurred in the absence of obesity in the offspring, suggesting obesity-independent mechanisms.[25] Effects on SREBP-1c may be mediated through changes in nicotinamide adenine dinucleotide^{+}-dependent histone deacetylase (SIRT1) and AMP-activated protein kinase (AMPK) which are involved in the deacetylation and phosphorylation of SREBP-1c: 50% food restriction in pregnant rats resulted in increased hepatic SIRT1 activity in offspring fetal liver, but decreased hepatic SIRT1 and AMPK activity postnatally, in association with increased lipogenesis, decreased lipolysis and increased fat stores.[27] Thus, changes in hepatic gene expression in the offspring of females subjected to calorie or protein restriction predict increased lipid turnover, with an increased propensity for lipogenesis as well as lipid storage. These studies are not limited to rodents; in sheep, maternal dietary restriction promotes the accumulation of lipid in offspring liver.[28] Further, in some studies, the severity of hepatic steatosis is worsened when the offspring are also exposed to a high-fat diet.[29] Finally, although most studies have used models of maternal calorie or protein restriction, maternal vitamin D deficiency leads to increased body mass, diffuse hepatic steatosis and increased hepatic expression of FAS.[30] Details of some of the animal and human studies are summarized in Table 1.

Maternal overnutrition and the programming of NAFLD

In humans, exposure to maternal obesity is associated with increased risk of premature mortality from cardiovascular disease[31] and maternal obesity has also been linked to increased hepatic steatosis and adiposity in offspring. Recent studies using magnetic resonance imaging in the neonatal period show a direct correlation between maternal body mass index and adipose tissue and intrahepatocellular lipid levels.[32,33]

Experimental evidence from animal models has linked exposure to maternal overnutrition during gestation and/or lactation to the development of NAFLD. Some experimental studies in animals, including rodents and non-human primates[34–37] have confirmed that the offspring of high-fat fed dams have increased body mass and adiposity. In a number of these studies, offspring exposed to maternal overnutrition have increased hepatic triglyceride accumulation and liver lipid droplets, indicative of hepatic steatosis,[35,36] although the increase in hepatic lipid levels does not always persist into adulthood.[38] However, a number of other studies have found no effects of maternal overnutrition on the offspring phenotype.[39,40]

Some of the discrepancies between studies may be explained by the different diets used in these studies which have included high-fat, high sugar, a combination of both (a 'Western-style' or 'cafeteria' diet) or supplementation with additional chocolate, sucrose and/or fructose. The offspring of dams fed on these supplemented diets display an increased percentage body fat.[41,42] The source of fat in the diet may be important to the programming of NAFLD, as demonstrated by a study in which the offspring of dams fed diets supplemented with different sources of fat had differential susceptibility to NAFLD.[43] In addition, the timing of intervention in the dams may be

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Table 1. *Overview of intrauterine growth restriction (IUGR) and undernutrition literature*

Early life insult	Species	Effect on offspring adiposity	Offspring NAFLD phenotype	References
Maternal undernutrition	Rat	Lower birthweight, reduced adipose tissue mass	Microvesicular steatosis	107
Maternal undernutrition and offspring HF diet	Sheep	No difference in fat mass to obese controls	Increased hepatic TG content, microvesicular steatosis	28
Maternal protein restriction and offspring HF diet	Rat	Female: more overweight than controls Male: similar to controls	Increased hepatic steatosis	29
Maternal low-protein and offspring HF diet	Rat	Maternal diet did not significantly influence weight gain	Increased hepatic TGs and lipid accumulation	25
Maternal hypoxia	Rat	–	Increased hepatic lipid droplets and TG	108
IUGR/SGA	Human	Obesity more common in children with NAFLD	Paediatric NAFLD	21
Accelerated infant weight gain	Human	–	Increased FLI score	22

NAFLD, non-alcoholic fatty liver disease; HF, high fat; TG, triglyceride; SGA, small for gestational age; FLI, fatty liver index.

important, with some studies starting dietary interventions pre-conception, leading to maternal obesity, whereas others commence the diets only during pregnancy. Furthermore, the maternal phenotype may be crucial; in rats, offspring exposed to maternal diabetes had vacuolar and ballooning degeneration in the liver, with a hepatitis-like phenotype.[44] Another rat model demonstrated that exposure to maternal hyperglycaemia exacerbated the effects of a postnatal high-fat diet, with offspring displaying more severe hepatic steatosis.[45]

In terms of mechanisms, altered expression of genes important in the PPAR signalling, gluconeogenesis and lipid metabolism pathways have been observed in mice born to high-fat fed dams.[41,46–48] A role for disrupted mitochondrial function in NAFLD pathogenesis has been implicated in some models,[46,49] and a number of studies have implicated increased oxidative stress, with increased markers of oxidative damage and alterations in the levels of key anti-oxidant enzymes glutathione peroxidase-1,[36,46] which can precede the development of IR.[50] Such mechanisms have also been implicated in non-human primate studies, with elevated levels of markers of oxidative stress observed in the fetal livers of Macaques born to high-fat diet fed mothers.[51] A number of studies show alterations in key mediators of inflammation in offspring of overnourished mothers, including increased circulating concentrations of the adipokine leptin, which may have a proinflammatory role in liver and play a role in the progression of fibrosis in NASH;[47,52] altered expression of toll-like receptor 4 which is important in the activation of Kuppfer cells, the resident liver macrophages;[53] and increased expression of tumour necrosis factor alpha (TNFα).[54]

Alterations in DNA methylation and histone modifications have also been proposed to be important in the programming of NAFLD. In Macaques, Aagaard-Tillery *et al.*[55] reported decreased expression of the histone deacetylase HDAC1 in offspring exposed to maternal high-fat diet and histone hyperacetylation at H3K14 in association with increased expression of retinal dehydrogenase 12 (*Rdh12*), a gene essential to the circadian rhythm controlled feeding pattern in hepatic tissue[55] which could lead to abnormal feeding behaviour.[56] Changes in DNA methylation patterns were also identified, with altered hepatic expression of the DNA methyltransferase Dnmt1,[55] suggesting that exposure to gestational insults may cause alterations in the DNA methylation machinery in offspring. However, whether these changes are causative or simply a consequence of the induced disease state remains to be determined.

Finally, as with models of maternal undernutrition, exposure to a high-fat diet postnatally can exacerbate the effects of exposure to maternal overnutrition. Mice born to females maintained on a high-fat diet during gestation, which were then exposed to a high-fat diet after weaning developed more severe hepatic steatosis and characteristics of NASH, including fibrosis.[49,57] Other studies have demonstrated comparable findings, with the offspring of high-fat fed dams showing microvesicular steatosis, progressing to macrovesicular steatosis if animals were also fed a high-fat diet postnatally.[58,59] Studies showing an association of maternal undernutrition with offspring NAFLD are summarized in Table 2.

Glucocorticoids and the programming of NAFLD

Prenatal glucocorticoid overexposure has also been implicated in the programming of cardiometabolic disease. In humans, such exposure may occur as a consequence of maternal stress, resulting in increased fetal exposure to maternal glucocorticoids, or exposure to exogenous glucocorticoids. Maternal stress during pregnancy, for example as a consequence of bereavement, has been associated with an increased risk of offspring metabolic dysfunction including overweight.[60–62] Synthetic glucocorticoids are administered to women with threatened preterm labour, and while this undoubtedly accelerates fetal lung development and increases survival, excess synthetic glucocorticoid exposure can reduce birthweight and increase the risk of later IR.[63,64] Although glucocorticoid overexposure therefore appears to increase the risk

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Table 2. *Overview of maternal obesity and high-fat (HF) diet literature*

Early life insult	Species	Effect on offspring adiposity	Offspring NAFLD phenotype	References
High maternal BMI	Human	Increased adipose tissue in neonates	Increased intrahepatic lipid levels in neonates	32
High maternal BMI and GDM	Human	Increased birthweight	Increased intrahepatic fat	33
Maternal HF diet	Mouse	Increased body mass	Increased hepatic TG and hepatic steatosis	36
Maternal HF diet	Mouse	Males: increased body weight Females: decreased fat mass	Males: hepatic steatosis	109
Maternal HF diet	Mice	Larger epididymal fat pad	Lipid vacuoles, increased hepatic TGs	110
Maternal HF diet	Rat (male)	No effect on weight gain	Hepatic steatosis at weaning	38
Maternal obesity	Mouse	Increased food consumption and body weight	Biochemical and histological evidence of hepatic steatosis	35
Maternal HF diet	Non-human primates	Increased % body fat	Increased hepatic TGs and inflammation	51
Maternal HF diet and HF post weaning diet	Mouse	Greater total fat mass	NASH	49
Maternal HF diet and offspring HF diet	Mouse	Increased adiposity	Macrovesicular steatosis and inflammation	59
Maternal HF diet and offspring HF diet	Mouse	Increased body mass	Macrovesicular steatosis and activated stellate cells	58
Maternal HF diet and HF post weaning diet	Mouse (female)	Increased body weight and adiposity	Non-alcoholic steatohepatitis and hepatic fibrosis	57
Maternal diabetes	Rat	Increased birthweight	Fatty change, ballooning degeneration hepatitis-like phenotype	44
Maternal hyperglycaemia	Rat	Reduced birthweight and growth inhibition	Exacerbated the effects of HF diet: more profound hepatic steatosis	45
Maternal fat supplementation	Rat	Greater WAT mass	Histological signs of NAFLD	43
Maternal chocolate + fructose	Rat (male)	Increased % body fat	NAFLD	42
Maternal chocolate + sucrose	Rat	Increased body fat mass	Increased hepatic TGs	41

NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; GDM, gestational diabetes mellitus; TG, triglyceride; NASH, non-alcoholic steatohepatitis; WAT, white adipose tissue.

of cardiometabolic disease, there are no studies reporting any effects on the risk of NAFLD in the offspring.

In animal models, prenatal glucocorticoid overexposure as a consequence of maternal stress or synthetic glucocorticoid exposure reduces birthweight and has been linked to the programming of cardiovascular disease, hypertension, glucose intolerance and the disruption of the hypothalamic–pituitary–adrenal axis.[64] In rats, administration of the synthetic glucocorticoid dexamethasone to pregnant females reduces birthweight and leads to IR in adipose and hepatic tissue.[65] In rats, maternal dexamethasone exposure in late gestation increased liver triglycerides in their male offspring, particularly when offspring were maintained on a high-fat diet,[66] and induced hepatocellular apoptosis,[67] a feature linked with the progression and initiation of NAFLD.[68] In contrast, another study in Sprague Dawley rats found that prenatal exposure to high dose dexamethasone had no significant effect on triglyceride accumulation in male offspring, however there were differences in females, with increased numbers of steatotic cells.[69] Perhaps surprisingly, the prenatal glucocorticoid exposure-induced increase in hepatic steatosis was not paralleled by an increase in obesity, despite the offspring having low birthweight.[66,69]

The mechanisms involved in the programming of NAFLD in glucocorticoid programming may differ from those observed as a consequence of maternal overnutrition. Prenatal exposure to dexamethasone resulted in decreased hepatic PPAR-γ and AMPK2 mRNA expression, in contrast to the upregulation observed in offspring exposed to maternal high-fat diets.[66] There were depot-specific alterations in gene expression in adipose tissue, with upregulation of SREBP-1c in subcutaneous but not omental fat in dexamethasone-exposed animals.[66] Rats born to dams exposed to restraint stress had higher liver lipid levels compared with controls, with increased expression of hepatic 11-beta hydroxysteroid dehydrogenase type 1 (11β-HSD1), which reactivates inactive glucocorticoids, increasing local tissue glucocorticoid concentrations,[70] predicted to increase local IR. Thus, prenatal overexposure to glucocorticoids has programming effects on lipid metabolism, inducing an increased susceptibility to hepatic steatosis. However, the differences between studies, notably in differential effects on males and females which may stem from the use of different animal strains and differences in experimental protocols merit further investigation.

Environmental pollutants and the programming of NAFLD

Bisphenol A

There is much interest in the potential role of environmental pollutants in programming adverse effects on metabolism in offspring. Bisphenol A (BPA) is a chemical widely used in the

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production of plastics and epoxy resins and exposure is widespread in humans, with detectable levels in the urine of ~95% of a sample population.[71] Evidence from animal studies suggests that gestational exposure to BPA can program an increased risk of developing the metabolic syndrome.[72–74] Dietary BPA exposure during gestation and lactation results in adverse effects in the offspring including increases in body weight, hepatic triglycerides, microvesicular steatosis, altered expression of triglyceride synthesis and β-oxidation-related genes and a liver histology resembling mild NAFLD.[75,76] Again, postnatal exposure to a high-fat diet exacerbates the effects of prenatal BPA exposure, with increases in the concentrations of the liver enzymes aspartate aminotransferase, alanine aminotransferase and alkaline phosphate (ALP), suggestive of liver injury, and liver histology showing diffuse lipid droplets, balloon degeneration and signs of inflammation.[74] However, the applicability of this study to human populations is unclear, as the 100 μg/kg/day dose used is far higher than the estimated human typical daily exposure (0.5–4.8 μg/kg/day).

Mitochondrial dysfunction and increased oxidative stress have again been implicated as important drivers of NAFLD development in these models. Prenatal BPA exposure leads to an early decrease in hepatocyte mitochondrial respiratory complex activity, increased production of reactive oxygen species and reduced mitochondrial ATP production indicative of impaired hepatic mitochondrial function and increased oxidative stress.[75] A decrease in the expression of the key β-oxidation enzyme carnitine palmitoyltransferase (Cpt1a) following prenatal BPA exposure supports the argument that dysfunctional β-oxidation is a 'hit' involved in NAFLD pathogenesis.[76] Prenatal BPA exposure coupled with a high-fat diet postnatally predisposes offspring to increased oxidative stress, with decreased levels of antioxidants and an increased level of the lipid peroxidation product malondialdehyde, a biomarker of oxidative stress.[74]

Overall, the evidence suggests that in rodent models, prenatal BPA exposure combined with postnatal obesity results in an increases predisposition to hepatic steatosis, with mitochondrial dysfunction and oxidative stress acting as a 'hit', leading to a more severe NAFLD phenotype. However, there are issues with the extrapolation of these animal studies to humans due to differences in BPA metabolism. Rats have an increased ability to glucuronidate BPA, meaning humans may be exposed to a higher oestrogenic burden at the same dose.[77] Studies in non-human primates and longitudinal epidemiological studies linking BPA detection in the mothers' urine with offspring's future health may prove useful. The recent lowering of the tolerable daily intake (TDI) to 4 μg/kg/day from 50 μg/kg/day means that some studies have used inappropriately high doses and future studies should use lower doses to better reflect both the TDI and estimated daily intake in order to be relevant to human populations.

Phthalates

Phthalates are ubiquitous environmental pollutants used as plasticizers in a range of consumer products with widespread human exposure demonstrated by studies showing that metabolites were detectable in urine in over 75% of a U.S. study population.[78] Phthalates are thought to impede the function of nuclear receptors involved in lipid and glycogen metabolism, such as PPARs.[79] Studies showing reduced liver ALP levels suggestive of hepatocellular membrane damage and increased hepatic acid phosphatase levels indicative of liver injury in the offspring of male and female Wistar rats exposed to polychlorinated biphenyl (PCB, a xenoestrogen) and diethylphthalate (DEP) suggest these chemicals may have a synergistic interactive toxic effect.[80] Histologically, livers from offspring exposed to DEP showed mild vacuolation, with pups exposed to both PCB and DEP having more severe vacuolation and hepatic steatosis. Again, studies have used doses that may be much higher than those to which humans are exposed. Prenatal di-(2-ehtylhexyl)phthalate exposure at a dose of 100 mg/kg (a much higher dose than the estimated median human daily exposure of 1.32 μg/kg/day[81]) resulted in reduced glycogen storage and hepatic steatosis at weaning, which seemed to improve with age.[82] Thus, although there is some evidence to suggest that prenatal phthalate exposure could affect hepatic development and metabolism, there is limited literature to support the persistence of these effects into adulthood and further studies using phthalates at doses relevant to human exposure are needed.

Maternal smoking and alcohol intake and the programming of NAFLD

Smoking during pregnancy has long been known to have a deleterious effect on offspring development, particularly lung function.[83] Human epidemiological studies suggest that maternal tobacco use during pregnancy increases a child's risk of obesity.[84] Maternal smoking during pregnancy has been associated with increased circulating triglycerides and lower high-density lipoprotein cholesterol in females[85] and the adult offspring of mothers that smoked during pregnancy had higher body mass index and circulating triglycerides when compared with non-smokers.[86]

Benzo[a]pyrene (BaP) is a carcinogenic polycyclic aromatic hydrocarbon to which humans are typically exposed through tobacco, in addition to air pollution and grilled foods.[87] In the model organism *Xenopus tropicalis*, BaP exposure disrupted hepatic cholesterol and lipid metabolism.[88] In female mice, *in utero* exposure to BaP led to increased visceral adipose depot, increased body weight and increased hepatic lipid content.[87] Histologically, these mice displayed features of NAFLD, such as mild inflammatory infiltrates and steatosis despite being fed a low-fat diet. This hepatic steatosis was accompanied by an increased in expression of PPAR-γ and UCP2.

Despite previously being believed to cause less harm, there is growing evidence that gestational exposure to nicotine, the major psychoactive chemical in tobacco, may also have harmful effects.[89] Exposure to nicotine during gestation has been shown to affect the metabolic processes of multiple generations in rats, with the second (F2) generation offspring of rats exposed

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to nicotine *in utero* displaying increased IR compared with controls.[90] In a study by Ma *et al.*, male and female offspring of female rats treated with daily nicotine injections pre-conceptually and through to weaning, had increased levels of hepatic triglycerides at postnatal day 180 with males also having increased circulating triglycerides. This was associated with an increase in hepatic expression of FAS and its regulator LXRα, suggestive of increased *de novo* triglyceride synthesis,[91] an established mechanism in NAFLD pathogenesis.

Moderate to heavy ethanol consumption during pregnancy can have teratogenic effects in humans, with severity varying from a slight reduction in cognitive abilities and low birthweight to fetal alcohol syndrome, characterized by facial abnormalities, pre/postnatal growth retardation and neurocognitive deficits.[92] In rats, prenatal ethanol exposure (PEE) increases the risk of developing the metabolic syndrome in association with hypothalamic–pituitary–adrenal axis-associated neuroendocrine programming.[93] Offspring had increased IR, hyperglycaemia and total cholesterol, with lipid accumulation present in the liver. PEE induces increased susceptibility to high-fat diet-induced NAFLD with macrovesicular steatosis and increased insulin like growth factor 1 (IGF-1), glucose and triglyceride levels in female Wistar rats.[94] Proposed mechanisms for this include the dysregulation of hepatic glucose and lipid metabolism and the influence of changing glucocorticoid concentrations, in response to ethanol-induced IUGR, on IGF-1 concentrations during catch-up growth.

Potential interventions

Interventions for chronic diseases such as NAFLD are generally initiated in later life when response to treatments may be suboptimal. The fetal and early life period is a time of developmental plasticity, when small changes can have a large impact on future disease risk, highlighting this period as a critical window for interventions.[95] In the case of maternal high-fat diet induced NAFLD, dietary interventions and nutrient supplements in mothers and offspring have had varying levels of success in reducing the risk of NAFLD development. For example, in non-human primates chronically fed a high-fat diet, switching the mothers onto a low-fat diet during pregnancy helped to partially normalize their offspring's hepatic triglyceride levels, reducing but not eliminating the offspring's risk.[51] However, achieving compliance with long-term lifestyle modifications such as improving diet has proved difficult in human studies, meaning dietary supplementation may prove to be easier to implement.

In rats, taurine (an amino sulphonic acid) supplementation has been shown to alleviate high-fat diet induced liver lipid accumulation[96] and supplementation during pregnancy was demonstrated to ameliorate maternal hepatic steatosis and IR.[97] However, there was increased neonatal mortality in this study, and previous work by the same group demonstrated that maternal taurine supplementation in addition to a high-fat diet aggravated hepatic steatosis in some offspring.[98] Fish oil contains anti-inflammatory n-3 polyunsaturated fatty acids (PUFAs) and supplementation helps prevent hepatic steatosis in obese animal models.[99] Fish oil administration after weaning reversed some of the adverse programming caused by a maternal low-protein diet, reducing serum triglyceride levels, hepatic SREBP-1C expression and hepatic steatosis in offspring.[100] These beneficial effects seem to occur through suppression of hepatic lipogenesis and upregulation of β-oxidation. Omega-9 supplementation also has a protective effect against the developmental programming of NAFLD, with the offspring of high-fat dams which were fed an omega-9 supplemented diet after weaning having reduced serum and hepatic triglycerides and reduced steatosis compared with controls.[101]

Drug treatments targeting the PPAR transcription factors have been explored. Bezafibrate is a pan-PPAR activator that is used clinically to improve glycaemic control in diabetic patients.[102] In mice exposed to an obesogenic maternal diet, bezafibrate treatment resulted in lowered hepatic triglycerides, an increased PPAR-α/SREBP-1c ratio and reduced hepatic steatosis compared with non-treated mice.[103] The proposed mechanism behind this is the reduction of the proinflammatory adipokine profile in WAT and increased β-oxidation in response to the upregulation of PPAR-α. Therefore, pharmaceutical interventions targeting the PPAR transcription factors may prove useful in reversing developmental programming of increased NAFLD risk.

Finally, breastfeeding may also be protective against the developmental programming of NAFLD in humans. Breastfeeding may reduce a child's risk of becoming overweight[104] and may help prevent NAFLD progression; a study of 191 children demonstrated that breastfeeding was protective against NASH and liver fibrosis, with a longer duration of breastfeeding conferring an increased benefit.[105] Potential mechanisms include the effect of long chain-PUFAs present in breast milk that can affect gene expression of enzymes (e.g. FAS), leading to the inhibition of hepatic glycolysis and *de novo* lipogenesis.[106]

Conclusions

There is compelling evidence from epidemiological clinical studies and experimental research to suggest that an adverse fetal and early life environment can programme increased susceptibly to NAFLD development and progression. Some of the factors which may increase the risk of NALFD are summarized in Fig. 1. Evidence from human and animal studies demonstrate that maternal over- and undernutrition during pregnancy confers increased susceptibly to NAFLD development, as well as exacerbating the effects of a postnatal obesogenic diet and increasing the offspring's risk of a more severe phenotype such as NASH. In animal models, gestational overexposure to glucocorticoids leads to an increased risk of NAFLD in offspring without an associated increased susceptibly to obesity. Finally, experimental evidence from animal models suggests that environmental pollutants have developmental toxicity, however, the use of inappropriate treatment doses make it difficult to assess whether they have a large impact at typical human exposure concentrations. Finally, studies suggest that interventions

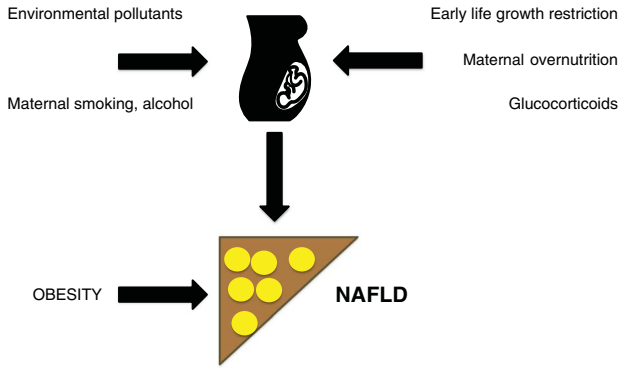

Fig. 1. The environment in early life influences the risk of non-alcoholic fatty liver disease (NAFLD). Environmental factors which may mediate this include early growth restriction, maternal nutrition, glucocorticoid exposure, environmental pollutants and maternal smoking and/or alcohol use. The effect of early life exposure to an adverse environment may be amplified by the development of obesity.

in early life can at least partially reverse the adverse developmental programming leading to NAFLD development and progression. However, further controlled clinical trials in humans are necessary to establish treatment doses and the safety profiles of these interventions before they can be implemented.

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Conflicts of Interest

None.

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