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Programming by maternal obesity: a pathway to poor cardiometabolic health in the offspring

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There is an ever increasing prevalence of maternal obesity worldwide such that in many populations over half of women enter pregnancy either overweight or obese. This review aims to summarise the impact of maternal obesity on offspring cardiometabolic outcomes. Maternal obesity is associated with increased risk of adverse maternal and pregnancy outcomes. However, beyond this exposure to maternal obesity during development also increases the risk of her offspring developing long-term adverse cardiometabolic outcomes throughout their adult life. Both human studies and those in experimental animal models have shown that maternal obesity can programme increased risk of offspring developing obesity and adipose tissue dysfunction; type 2 diabetes with peripheral insulin resistance and β-cell dysfunction; CVD with impaired cardiac structure and function and hypertension via impaired vascular and kidney function. As female offspring themselves are therefore likely to enter pregnancy with poor cardiometabolic health this can lead to an inter-generational cycle perpetuating the transmission of poor cardiometabolic health across generations. Maternal exercise interventions have the potential to mitigate some of the adverse effects of maternal obesity on offspring health, although further studies into long-term outcomes and how these translate to a clinical context are still required.

Key words: Obesity: Maternal Obesity: CVD: Type 2 diabetes mellitus: Exercise therapy

Worldwide obesity has nearly tripled since 1975 with currently over 1·9 billion adults overweight or obese[1]. Obesity is a recognised global problem and was declared an epidemic by the WHO in 1997. It therefore represents a significant health and economic burden to societies, and 5 % of deaths worldwide in 2013 were attributed to obesity[2].

Both genetic and environmental factors can affect obesity risk. Overweight and obesity are known risk factors for a large range of non-communicable diseases, including cardiometabolic diseases[1], which are the leading cause of death in men and women globally[3]. Cardiometabolic diseases represent a complex cardiovascular and metabolic dysfunction phenotype characterised by insulin resistance and impaired glucose tolerance, dyslipidaemia and adiposity, hypertension and cardiovascular disease (CVD). Cardiometabolic disease is multifactorial, with diet, lifestyle, genetic and epigenetic factors influencing risk[4]. Obesity in particular is known to have a significant association with cardiometabolic disease[2].

As the prevalence of obesity increases worldwide this includes women of childbearing age. Over half of women of reproductive age in the UK are currently classed as overweight or obese[5]. Obesity during pregnancy is known to have a negative impact on maternal health, pregnancy outcome and the long-term health of

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her offspring[6,7]. This phenomenon by which exposures during early life have impacts on lifelong health is known as the developmental origins of health and disease, following studies of a UK birth cohort, where low birth weights were shown to be associated with increased risk of men developing CVD, hypertension, glucose intolerance, type 2 diabetes and other metabolic diseases in adult life[8–10]. These initial findings have since been replicated in a variety of global cohorts[11–13].

Although initial studies in the developmental origins of health and disease field focused on the detrimental impact of maternal and fetal under-nutrition, in light of the obesity epidemic recent focus has been directed towards the effects of maternal over-nutrition and obesity. Maternal obesity during pregnancy has been associated with a range of poor offspring cardiometabolic outcomes[14,15] (Fig. 1). Importantly these effects on offspring health are programmed by the maternal environment independently of the postnatal environment. Adoption studies have shown that despite different postnatal exposures than the biological parent's lifestyle, adopted offspring have a strong association for BMI with that of their biological parents. This could reflect either a genetic or programmed effect of parental obesity on offspring adiposity[16,17]. The effects of genetics *v.* programmed effects of maternal obesity can be distinguished by studies of siblings born before and after maternal bariatric surgery, thereby controlling for the genetics and lifestyle exposures of the sibling pairs. These studies showed that siblings born after maternal surgery, which resulted in significant maternal weight loss, have reduced prevalence of macrosomia at birth[18], are less obese[19], have lower fasting insulin levels[20] and improved insulin sensitivity[18,20], lower blood pressure[20] and improved cardiometabolic markers[18] in childhood, compared to their sibling born prior to maternal surgery[19]. Together this evidence suggests that exposure to maternal obesity programmes offspring health by mechanisms that are independent of and additional to genetic and postnatal environmental factors.

This review will summarise the evidence from epidemiological studies and animal models for a programmed phenotype (Fig. 1), explore the underlying mechanisms that mediate the programming of adverse offspring cardiometabolic outcomes by maternal obesity, and therefore the opportunities for maternal interventions to prevent transmission of poor cardiometabolic health from mother to child.

Programming of offspring obesity by maternal obesity

Evidence from human studies

Fetal macrosomia is regarded as one of the greatest immediate risks of obese pregnancies, and obese pregnancies have been shown to be associated with a 2–3-fold increase in prevalence of fetal macrosomia at term[21]. This is associated with increased absolute fetal size and infant fat mass[22,23]. This change in body composition of the offspring continues throughout childhood, adolescence and adulthood, with various studies showing that maternal obesity leads to increased incident of offspring obesity[24–30], including alterations in offspring body composition with higher childhood fat mass[26–29,31]. Some studies have also suggested that the programming of offspring obesity by maternal obesity may be, in part, sex specific, with male offspring having increased susceptibility to increased adiposity compared to female offspring of obese mothers[26].

Evidence of offspring adiposity from animal models

Animal models are useful tools to help define the mechanisms underlying the programming of increased offspring adiposity by maternal obesity. A variety of model species, including rodents[32–40], sheep[39,41,42] and non-human primates[43], have all recapitulated the observations made in human cohorts that offspring of obese mothers have increased risk of developing obesity compared to offspring of control mothers, with increased offspring body weight and fat mass observed[44].

Sheep models have shown that fetuses of obese ewes have increased fat depots at both mid- and late-gestation compared to fetuses of lean mothers[41,42]. This may be in part driven by adipocyte hypertrophy as increased adipocyte cell size has been observed in late-gestation sheep[42] fetuses of obese mothers compared to lean controls, with similar findings reported in the mouse[45]. Adult offspring of obese rodent dams show a similar phenotype, with increased fat mass driven by a combination of adipocyte hypertrophy and hyperplasia. Rat models have shown male offspring of obese dams have adipocyte hypertrophy compared to controls[32–35]. However reports of adipocyte hyperplasia are more conflicted with some showing evidence of increased adipocyte hyperplasia[34], while others have shown it to be impaired[32]. Furthermore, while increased white adipose tissue mass has been seen in offspring of both sexes, the mechanisms for this expansion may be sexually dimorphic. Rat models of maternal obesity showing increased adipocyte cell size in males, did not see a similar increase in female offspring adipocytes[34,35]. However, conversely, in a baboon model of pre-weaning over-nutrition, offspring adipocyte hypertrophy was seen in only female offspring at 5 years of age[43].

There is also evidence of altered adipocyte metabolism and increased fatty acid accumulation in fetuses of obese pregnancies, with increased expression of fatty acid and glucose transporters and of fatty acid biosynthesis enzymes in fetal sheep adipose tissue in response to maternal obesity[42]. This is accompanied by altered expression of genes which regulate adipogenesis, lipogenesis and the synthesis of adipokines[46], leading to increased lamb fat mass observed in early postnatal life[46]. Increased fetal insulin concentration and the development of fetal insulin resistance may also contribute to increased fetal fat accretion, with fetuses of mice fed with a high-fat diet before and throughout pregnancy showing evidence of adipose tissue insulin resistance[45]. Furthermore, increased inflammation of the subcutaneous adipose tissue has been reported in fetal mice of high-fat diet-fed dams[45]. Similarly postnatally, a rat model of

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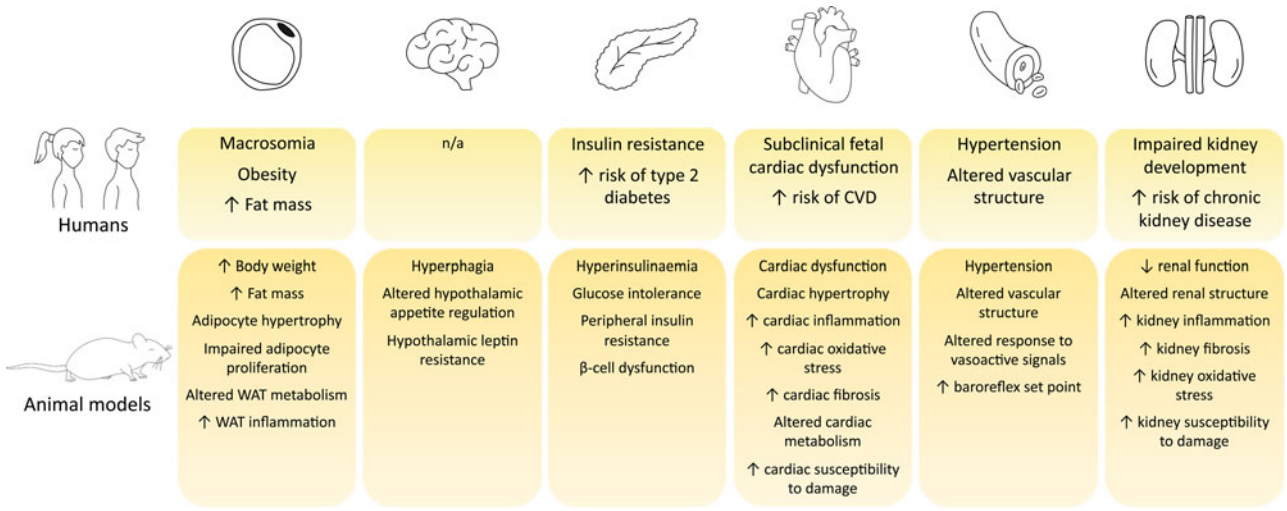

Fig. 1. Summary of the programmed effects of maternal obesity on offspring cardiometabolic health in human subjects and animal models. WAT, white adipose tissue.

maternal diet-induced obesity showed dysregulated expression of adipogenic and lipogenic genes at both 2 weeks and 2 months of age in offspring of obese dams compared to controls[47]. Adult mouse offspring also show evidence of increased adipose tissue inflammation[40,48]. This may be sex specific as mouse offspring of obese dams, when themselves are exposed to a high-fat diet challenge in adulthood, showed increased visceral adipose tissue inflammation in male, but not female, offspring[40]. Altered miRNA expression is one potential mechanism for programming of adipose tissue inflammation, with one mouse model of maternal diet-induced obesity showing reduced expression of miR-706 (known to regulate inflammatory protein expression) in adipose tissue from male offspring[49].

Evidence of offspring hyperphagia from animal models

Maternal obesity has also been shown to programme offspring obesity via offspring hyperphagia and thus increased energy intake. Offspring hyperphagia has been observed in several different rodent models of maternal obesity, in both male and female offspring[50–53]. It is thought that this hyperphagic phenotype may be driven by altered development and function of the hypothalamic circuits which regulate appetite and energy expenditure. Both leptin and insulin, which are altered in the maternal circulation during obesity, are known to affect neural development and have therefore both been implicated as factors mediating the programming effects of hypothalamic development.

The timing of the rodent neonatal leptin surge is a critical window for hypothalamic neuronal circuitry development and maturation. Neonatal rats born from obese mothers have an enhanced and prolonged postnatal leptin surge[52]. In contrast in lambs, maternal obesity has been shown to result in a reduced neonatal leptin surge[54]. However, despite the reduced neonatal leptin surge in lambs exposed to maternal obesity *in utero*, postnatally they have increased subcutaneous adipose tissue fat mass and adipose tissue leptin gene expression compared to offspring of controls[55]. As the hypothalamus requires the correct levels and timings of exposure in order to correctly develop, any perturbations leading to either under- or over-exposure to leptin during these critical developmental windows can have negative impacts. Furthermore, rat fetuses of high-fat diet-fed dams have hypothalamic leptin resistance, with reduced expression of downstream leptin signalling components despite elevated plasma leptin levels compared to fetuses from healthy pregnancies, which is accompanied by increased mRNA expression of the orexigenic neuropeptides neuropeptide Y and agouti-related protein[56]. This leptin resistance persists postnatally in adult rodent offspring exposed to either gestational or lactational overnutrition[52,53], and leptin infusion into these offspring fails to reduced food intake in offspring of both sexes[52].

In addition to leptin, neonatal insulin signalling also plays an important role in regulation of hypothalamic development. Maternal obesity in mice has been shown to result in impaired offspring proopiomelanocortin neurone projection development, which was corrected by inhibition of insulin signalling in proopiomelanocortin neurones[57]. The fetal hypothalamus also develops insulin resistance in a maternal obesogenic environment, and both mid- and late-gestation rodent fetuses of obese dams have reduced downstream insulin signalling despite increased serum insulin levels[56,58]. The inability of these offspring to appropriately respond to satiety signals may therefore contribute to the programming of offspring hyperphagia, and thus the risk of developing increased adiposity and obesity.

Overall, maternal obesity can lead to increased offspring adiposity accompanied by altered adipose tissue metabolism, inflammation and insulin resistance, as well as dysregulation of appetite regulation in the hypothalamus, thus predisposing them to obesity in later life (Fig. 1).

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Programming of offspring type 2 diabetes by maternal obesity

Evidence from human studies

Maternal obesity is known to result in increased risk of offspring developing type 2 diabetes, characterised by insulin resistance and β-cell dysfunction[59]. Studies in human subjects have shown that maternal obesity leads to increased fetal insulin resistance compared to lean controls[60]. This insulin resistance persists into childhood, where maternal obesity is associated with increased risk of insulin resistance[29,61], developing type 2 diabetes[62] and the metabolic syndrome[63]. This association continues in adulthood, with maternal obesity increasing the risk of insulin resistance[64] and type 2 diabetes[14,65,66].

Evidence of offspring insulin resistance from animal models

Consistent with human studies, animal models have also shown that maternal obesity results in the development of altered offspring insulin sensitivity. Although the exact offspring phenotype varies depending on the species and model of maternal over-nutrition/obesity, the programming of offspring metabolic dysfunction is consistently observed. Indeed, several rodent models have shown that maternal over-nutrition results in offspring hyperinsulinaemia[67–73], glucose intolerance[38,67,74] and insulin resistance[38,67–69,75–77]. Studies in Agouti yellow mice, a model of normoglycemic obesity, have highlighted that maternal obesity alone, in the absence of maternal hyperinsulinaemia, is sufficient to impair offspring insulin signalling and glucose tolerance[78,79]. While many early studies focused mainly on the phenotype of male offspring[67,70,73,75], studies investigating both offspring sexes have revealed some sex-specific differences in the programming of offspring metabolic dysfunction by maternal obesity. However, whether males[40,79,80] or females[78,81,82] are more susceptible to the programming of insulin resistance and glucose intolerance by maternal obesity varies between studies.

Skeletal muscle is a key insulin responsive tissue, with insulin promoting glucose uptake into muscle cells. Thus, impairment of the skeletal muscle response to insulin can contribute to the pathogenesis of type 2 diabetes. In an ovine model of diet-induced obesity, late-gestation fetuses were shown to have impaired skeletal muscle insulin action with decreased Akt phosphorylation despite higher circulating levels of insulin compared to fetuses of control ewes[83]. However, conversely, in mice, high-fat diet feeding prior to conception resulted in increased fetal and neonatal activation of insulin signalling in skeletal muscle, compared to offspring of lean control mothers[84]. However, in adult offspring, maternal obesity has been shown consistently to cause skeletal muscle insulin resistance[85], with disrupted expression of key downstream insulin signalling molecules seen in both sheep[86] and rodent[87,88] models of maternal obesity. Similarly, rat offspring of cafeteria diet-fed dams had altered skeletal muscle metabolism at weaning indicative of insulin resistance[89].

The liver also plays an important role in regulation of glucose homoeostasis, with insulin signalling acting to promote hepatic storage of glucose as glycogen. Similarly to skeletal muscle, maternal obesity influences insulin signalling in the fetal liver, with dysregulated expression of miRNAs associated with insulin signalling, accompanied by increased liver lipid accumulation seen in the late-gestation primate fetal liver[90], and increased activation of fetal hepatic insulin signalling in mice[84]. A similar phenotype is also seen in the adult offspring liver in rats[70], mice[87,91] and sheep[92]. For example, maternal obesity in sheep alters the expression of key insulin signalling molecules and factors which regulate gluconeogenesis in the male and female offspring liver[92,93]. Similar to the primate fetus, this may be due to dysregulated expression of miRNAs related to insulin signalling[92]. In rodents some of these effects have been shown to be sex specific as transcriptomic analysis of livers of offspring born to obese dams has shown a male-specific dysregulation of pathways involved in insulin signalling and glycolysis/gluconeogenesis[94].

Adipose tissue is also sensitive to insulin action, where insulin promotes adipocyte glucose uptake and inhibits lipolysis. Several studies in mouse models have shown that maternal obesity impairs offspring white adipose tissue insulin signalling[72,74,87], and similar to the liver, this may be associated with altered regulatory miRNA expression in offspring adipose tissue[74].

Evidence of offspring pancreatic β-cell dysfunction from animal models

In addition to systemic insulin resistance, insufficient insulin production, processing and release from pancreatic β-cells is also characteristic of type 2 diabetes. In the initial stages of type 2 diabetes, when peripheral tissues become insulin resistant, the pancreas can attempt to compensate, increasing β-cell number, size and insulin production. However, as disease progresses β-cell exhaustion can lead to reduced function and cell death. Animal models have shown significant evidence of offspring β-cell dysfunction in response to exposure to maternal obesity.

In the fetus, maternal obesity in sheep results in increased relative pancreatic weight and β-cell number and proliferation at mid-gestation[95], but reduced pancreatic weight and β-cell numbers in late-gestation[96], with increased β-cell apoptosis and a resultant decrease in blood insulin levels and increase in glucose levels at birth[96]. Similarly, maternal obesity has been shown to significantly reduce β-cell mass in neonatal mice[97] and rats[98], resulting in neonatal hyperglycaemia[98]. However, in contrast, another model of mice fed with a high-fat diet prior to pregnancy resulted in increased fetal pancreatic β-cell mass and thus elevated fetal blood insulin levels and reduced glucose concentrations, compared to control fetuses[84]. Regardless of the exact phenotype, if these alterations to fetal pancreatic growth and function are not corrected in later life it can lead to a

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predisposition for offspring glucose intolerance and thus increased risk of developing type 2 diabetes.

In rodents, postnatal offspring of dams fed with a high-fat diet during gestation show progressive β-cell dysfunction with increased β-cell hypertrophy[77,99] and proliferation[97,99,100] seen in the young adult offspring of obese dams compared to controls, accompanied by increased β-cell insulin content[100], and enhanced glucose-stimulated insulin release[97], characteristic of the initial β-cell response to increased peripheral insulin resistance. However, as insulin resistance progresses, loss of β-cell function leads to decreased pancreatic insulin content[68,73], impaired insulin secretion from pancreatic islets[68] and offspring hypoinsulinaemia[101].

Some studies suggest that male mouse offspring may be more vulnerable to the programming of poor β-cell development[71], function[102], survival and oxidative stress[71], with the female offspring pancreas being more protected[71]. In fact the female offspring pancreas may be primed by exposure to maternal obesity to be better able to cope with exposure to over-nutrition in postnatal life[103]. However, conflicting studies have reported a more severe phenotype in females with increased pancreatic dysfunction[78], disrupted islet metabolism[78] and significantly reduced glucose-stimulated insulin release[78] specifically in female mouse offspring of obese mothers compared to offspring of controls.

This evidence suggests that exposure to a maternal obesogenic environment has long-term effects on β-cell function and peripheral organ insulin resistance, contributing to the increased risk of offspring developing insulin resistance and type 2 diabetes (Fig. 1).

Programming of offspring cardiac dysfunction by maternal obesity

Evidence from human studies

Maternal obesity in human subjects is known to be associated with increased risk of congenital heart disease[104], however relatively little research has been carried out to study the effect of maternal obesity on other aspects of the fetal heart. At mid-gestation the effects of maternal obesity appear relatively small with evidence of reduced left and right ventricular strain suggesting impaired contractile function, but no observed effects on fetal cardiac dimensions, heart rate, blood flow velocities or standard echocardiographic parameters of systolic and diastolic function[105,106]. However, later in gestation there is persistence of reduced ventricular strain, accompanied by the development of impaired diastolic function, although no clear changes in cardiac systolic function are observed[105,107]. Additionally, there are late-gestational changes in cardiac morphology in fetuses exposed to maternal obesity with increased ventricular wall widths and reduced chamber widths[105,108]. However, there are still no observed differences in heart rate or cardiac blood flow in human fetuses of obese mothers in the third trimester, suggesting that maternal obesity does not cause overt fetal cardiac dysfunction despite the observed diastolic impairment[105,107].

In adulthood, several studies have shown a significant association between maternal BMI and increased risk of CVD in her children[14,15,109–113]. One early study in a population of 3302 Finnish men showed that a higher maternal BMI was associated with increased risk of death due to coronary heart disease in her adult offspring[109]. These results were later supported by similar results seen in a larger Scottish cohort of 37 709 men and women, where offspring of obese mothers were shown to have increased risk of hospital admissions for a cardiovascular event aged 31–64 years[15]. Data from men and women in the Helsinki Birth Cohort have also shown an association between maternal BMI and increased risk of offspring coronary heart disease and stroke[14], while offspring from the 1958 British birth cohort have shown that parental BMI is positively associated with increased CVD risk factors in offspring aged 44–45 years[111]. Furthermore, a more recent large Swedish cohort has also shown increased risk of childhood and young adult CVD with increasing maternal BMI[110]. Importantly, this association was maintained in a sibling-controlled analysis, supporting a more causal relationship between maternal BMI and offspring CVD, after controlling for shared sibling environmental and genetic factors[110].

Human studies looking more specifically at offspring cardiac structure and function in childhood have shown that high maternal BMI was associated with increased left ventricular mass and hypertrophy in 6 year old offspring[114], but not relative wall thickness[114], fractional shortening[114] or other indices of left ventricular systolic or diastolic function as assessed by echocardiography[112]. Overall, these studies suggest that, while maternal obesity does not programme overt cardiac dysfunction in early childhood, it does increase the risk of offspring developing CVD in adulthood.

Evidence of offspring cardiac dysfunction from animal models

The effects of maternal obesity on the offspring heart at the cellular and molecular levels have been investigated further using animal models. While a range of species and maternal obesity models have been used, similar cardiac phenotypes are observed across species. Despite inconsistencies in the effect of maternal obesity to increase fetal heart weights, in mid-gestation fetal sheep[115–118] and neonatal rats[119–121], although not in late-gestation sheep[115,116] or baboons[122], there is consistent evidence that maternal obesity leads to offspring cardiomyocyte hypertrophy. Indeed, increased cell size and expression of hypertrophy markers have been consistently reported in the hearts of fetal sheep[115,123] and neonatal minipigs[124] and rodents[119–121]. In adulthood, mouse offspring of obese mothers have also been shown to exhibit increased left ventricular mass and area[125–127], with increased cardiomyocyte cell size in 3-[127] and 8-[125–128]week-old male offspring, although this was a transient phenotype which was lost by 12 weeks of age[127]. This increased cardiomyocyte cell size was accompanied by re-expression of fetal genes and miRNAs associated with pathological hypertrophy in young adult

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male mouse offspring of obese mothers[125–128]. One potential mechanism for the programming of this pathological remodelling is hyperinsulinaemia-induced overactivation of cardiac insulin signalling. Consistent with this hypothesis, in a mouse model of maternal diet-induced obesity, although insulin receptor levels were reduced in the hearts of offspring of obese dams, the downstream signalling components were upregulated[126].

Changes in fetal cardiomyocyte growth have been reported to be accompanied by changes in cardiomyocyte structure with irregular orientation of myofibrils in mid- and late-gestational fetal sheep[115,116,123] and rats[120,121] exposed to maternal obesity, in parallel with altered expression of contractile proteins which could affect cardiac ionotropic function[115,116,123]. Indeed, cardiomyocytes isolated from fetuses of obese ewes showed impaired contractility and calcium handling[123]. Furthermore, hearts isolated from late-gestational fetal sheep showed impaired cardiac function as they were unable to maintain increased contractile performance when subjected to a higher workload, although baseline cardiac function was unaffected by maternal obesity[105,107,129]. Similarly, neonatal rats[120] and pigs[124] when exposed to maternal obesity and diabetes *in utero* showed cardiac systolic and diastolic *in vivo* dysfunction.

Impaired cardiac contractility programmed by maternal obesity persists into adulthood, with a mouse model of diet-induced obesity showing impaired *in vivo* systolic and diastolic function, as assessed by echocardiography in male offspring of obese dams compared to controls at 8 weeks of age[125,128], and in *ex vivo* Langendorff preparations at 12 weeks of age[127]. Furthermore, administration of parasympathetic and sympathetic agents to these heart preparations showed a blunted response to parasympathetic stimulation, but enhanced contractile response to sympathetic stimulation, indicative of sympathetic dominance, a marker of heart failure, in the hearts of offspring of obese dams[127].

Further changes in the fetal heart in response to maternal obesity include increased lipid droplet accumulation in fetal sheep[115] and neonatal rat[120], and increased fibrosis in fetal sheep and neonatal mouse[119] which may increase cardiac stiffness, potentially leading to impaired cardiac function[116,122,130]. Increased cardiac fibrosis was also seen in 8-week-old mouse offspring of obese dams, when challenged with a high-fat diet in postnatal life[125].

There is also increased cardiac inflammation seen in the hearts of fetal sheep exposed to maternal obesity[115], as well as attenuated sensitivity to insulin[129], and reduced expression of the cardioprotective AMP-activated protein kinase signalling pathway, which may be involved in metabolic regulation and substrate metabolism[129]. Altered energy metabolism was also seen in the hearts of neonatal pigs and fetal mice born to high-fat diet-fed mothers suggestive of changes in cardiomyocyte energy metabolism shifting from glycolytic towards oxidative cardiac metabolism[124,131].

Maternal obesity in rodents has been shown to result in impaired offspring mitochondrial structure and function in both early and adult life[120,121,132,133], which may lead to impaired mitochondrial function, cellular metabolism and increased reactive oxygen species production. Indeed, neonatal rat cardiomyocytes of obese dams had lower basal oxygen consumption[120], and increased cardiac oxidative stress[119,120,134] and reactive oxygen species production[119]. Increased oxidative stress and reactive oxygen species production in the heart has also been seen in adult male offspring of obese mouse dams[126], although this result has not been recapitulated in every study[125].

Importantly, many of these differences in cardiac structure and function have been observed in the absence of a difference in body weight between the offspring of obese and lean dams, and thus show that in rodents maternal obesity is able to programme cardiac function independent of offspring obesity[126,127]. Potential mechanisms for the programming of altered cardiac function include epigenetic alterations. Rat offspring exposed to maternal high-fat diet have differential histone modifications linked to altered regulation of genes involved in metabolic stress and cardiac dysfunction[135], and altered histone marks and DNA methylation resulting in the de-repression of pro-fibrotic and pro-hypertrophic genes[136]. Furthermore, dysregulation of miRNA expression may also play a role, and analysis of miRNA expression in the hearts of fetal baboons found altered expression of miRNAs associated with adult CVD, cardiac hypertrophy, enhanced fibrosis, growth, proliferation and cellular development[122].

Exposure to maternal obesity also increases susceptibility of the offspring heart to damage from subsequent challenges. This includes a more severe cardiac phenotype when offspring of obese mothers are exposed to high-fat diet feeding in adult life with enhanced cardiac contractile dysfunction, cardiac hypertrophy, fibrosis, lipid accumulation, inflammation, reactive oxygen species accumulation, mitochondrial dysfunction and apoptosis seen in both rodent and sheep models[137,138]. Another postnatal stress via transverse aortic constriction in rats also resulted in exacerbated cardiac dysfunction if offspring were exposed to a maternal high fructose diet[139]. Programming by maternal obesity also increases susceptibility to ischaemia-reperfusion injury in offspring of obese dams in both rats and mice[140,141]. While some phenotypes appear shared by both male and female offspring[119,133], there is inconsistent evidence in both rat and mouse models that some programming of cardiac dysfunction by maternal obesity shows sexual dimorphism, with male-specific cardiac hypertrophy[140] and susceptibility to ischaemia-reperfusion injury[140,141] in offspring of obese dams, but female-specific impairment of systolic and diastolic function in offspring of obese mice[133].

Together this shows that maternal obesity effects offspring cardiac development and function, thus predisposing offspring to increased risk of developing CVD (Fig. 1).

Programming of offspring hypertension by maternal obesity

Evidence of offspring hypertension from human studies

Blood pressure is primarily influenced by a combination of cardiac output and systemic vascular resistance.

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Cardiac output in turn is affected by blood volume, cardiac contractility, heart rate and afterload, while systemic vascular resistance can be affected by increased vasoconstriction and arterial stiffness. Cardiac function (discussed earlier), kidney function, vascular responsiveness to vasoactive signals and vascular compliance therefore all play a role in the regulation of blood pressure.

A variety of global cohorts have shown an association between maternal obesity during pregnancy and increased risk of hypertension with raised blood pressure in her children at various ages from early childhood to adulthood[28,64,142–148]. Some studies and meta-analyses have reported that observations of increased childhood blood pressure are independent of childhood BMI[28,142,149]. However, another systematic review has suggested hypertension may be at least partially programmed secondary to the programming of increased adiposity in offspring of obese mothers[150]. Controlling for childhood BMI was also shown to significantly decrease the association between maternal pre-pregnancy BMI and offspring hypertension in childhood[28,143] and adulthood[111,151], although a significant effect of maternal obesity did remain, indicating both direct and indirect programming mechanisms may be involved. One potential mechanism by which maternal obesity programmes increased offspring hypertension is by alterations in vascular function. This is supported by observations that maternal obesity is associated with increased carotid intima-media thickness[152], and increased retinal vessel tortuosity[142], a non-invasive assessment of alterations in the microcirculation, in her children.

Evidence of offspring hypertension from animal models

Animal models of maternal obesity have shown similar phenotypes to those seen in clinical studies. In particular, many different rodent models have shown an increased risk of hypertension in adult offspring of obese mothers compared to lean controls[38,73,125,153–157]. In a rat model of maternal diet-induced obesity, offspring hypertension was observed in juvenile offspring, prior to the development of offspring adiposity, providing evidence for the direct programming of offspring hypertension by maternal obesity, independent of offspring obesity[156]. Furthermore, mouse models have shown the effects of maternal obesity and offspring postnatal high-fat diet to increase young adult offspring blood pressure to be additive[125]. Thus, maternal obesity and offspring obesity are able to independently promote hypertension.

The increase in offspring hypertension in response to maternal obesity may be, at least in part, due to the programming of altered vascular structure and function. Rat offspring of dams fed with a high-fat diet during pregnancy and lactation show alterations in aortic structure at 6 months of age with reduced aortic endothelial cell volume and smooth muscle cell number[158]. Structural changes in the offspring abdominal aorta have also been seen in non-human primate offspring of high-fat diet-fed mothers with increased intima media thickness compared to offspring of control mothers[159]. Rat offspring of obese dams also have abnormal aortic fatty acid composition[160], and increased aortic stiffness[158]. Furthermore, rodent offspring of high-fat diet-fed mothers have impaired endothelial-dependent vasodilation of the aorta[158], femoral[157,160,161] and mesenteric[73,162–164] arteries, as well as an enhanced femoral vasoconstrictor response to noradrenaline[161], and reduced mesenteric vasoconstrictor response to phenylephrine[163]. This may, at least in part, be due to impaired nitric oxide bioavailability[157] and thus impaired nitric oxide-dependent endothelial function[163].

Studies of maternal diet-induced obesity in rats have suggested that the hypertension observed in offspring of obese dams has a sympathetic origin, as analysis of heart rate viability indicated an increase in the sympathetic component of blood pressure regulation, while β-adrenergic blockage was shown to inhibit the hypertensive phenotype[156]. There was also altered responses to phenylephrine or sodium nitroprusside indicative of reduced baroreflex sensitivity[156]. Similarly, in mouse offspring of obese dams, observations of increased blood pressure without a difference in heart rate suggest a resetting of the arterial baroreflex to allow an elevated resting arterial blood pressure[125]. It is possible that programming of adult offspring hypertension is, at least in part, due to fetal and neonatal hyperleptinaemia affecting the development of hypothalamic neural circuits involved in blood pressure regulation[165]. Leptin is known to affect the development and function of neural circuits involved in the autonomic nervous system regulation of blood pressure in mice[166]. Furthermore, treatment of control-fed rat pups with exogenous leptin, mimicking the neonatal hyperleptinaemia seen in offspring of obese dams, increased offspring systolic blood pressure at 1 month of age with evidence of heightened sympathetic tone compared to saline-treated control offspring[167].

Evidence of offspring kidney dysfunction from human studies and animal models

With regards to kidney function, human studies have shown maternal obesity to be associated with congenital abnormalities of the kidney and urinary tract[168,169] and reduced late-gestational fetal kidney volume relative to fetal body weight[170]. As kidney volume is suggested as an approximate measure of renal nephron number[171], maternal adiposity may be associated with reduced fetal nephron count, which can potentially lead to nephron hyperfiltration in order to maintain renal function, and thus progressive kidney damage and the development of hypertension in later life[172]. Consistent with these observations, maternal obesity has been associated with increased risk of offspring developing childhood chronic kidney disease in a US-based cohort[169].

In contrast, a study in rats has shown that exposure to maternal obesity in the late-gestation fetus did not affect fetal kidney nephron number[173]. However, there was evidence for increased cellular stress, inflammation and apoptosis in the kidney of fetuses of obese dams compared to healthy controls[173]. Furthermore, late-

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gestation proteomic analysis of male fetal mouse kidneys from dams fed with a high-fat diet showed differential expression of proteins linked to transcription/translation, mitochondrial processes and membrane remodelling compared to offspring of controls[174].

Postnatally, studies in rodents have found that young offspring of dams fed with an obesogenic diet have impaired renal structure, function and inflammation[175]. This persists in adulthood with increased renal inflammation, oxidative stress and fibrosis[176–178], accompanied by markers of kidney dysfunction[158,178] in both the presence[178] and absence[158] of altered renal histology. A potential mechanism for the programming of offspring renal dysfunction is maternal obesity-induced depression of sirtuin 1 expression[179], a key regulator promoting lipid utilisation and suppressing lipogenesis. In an mouse model, both overexpression and administration of a sirtuin 1 activator were able to attenuate some, but not all, of the negative programming effects of maternal obesity in the offspring kidney[180]. Exposure to maternal obesity *in utero* may also lead to increased offspring susceptibility to subsequent renal injury, with enhanced offspring renal damage following streptozotocin-induced diabetes[177], as well as enhanced renal inflammation, fibrosis, glomerulosclerosis and kidney dysfunction in mouse and rat offspring challenged with a postnatal obesogenic diet[176,181,182].

Studies which have investigated offspring outcomes in both male and female offspring suggest there may be differences in the programming of offspring renal damage by maternal obesity[179,183], although there are some inconsistencies as to which sex is more vulnerable to adverse effects. For example, a rat model of maternal diet-induced obesity has shown increased renal lipid accumulation and more prominent renal fibrosis in male offspring[179], while in contrast another study has shown that maternal diet-induced obesity resulted in greater changes in the female rat offspring renal transcriptome, compared to males[183].

Overall maternal obesity has been shown to affect offspring renal and vascular function, predisposing offspring to increased risk of developing hypertension in later life (Fig. 1).

Exercise interventions in obese pregnancy

Evidence from human studies

With the significant body of evidence associating maternal obesity with adverse offspring cardiometabolic outcomes (Fig. 1), there is a clear need for the development of effective interventions in obese pregnancy to protect offspring health. In human subjects, intervention studies exploring the effects of exercise during overweight or obese pregnancy either alone[184–197] or combined with other lifestyle and dietary changes[198–221] have shown mixed and somewhat inconsistent success for the prevention of adverse maternal, pregnancy and neonatal outcomes.

In terms of maternal outcomes, gestational weight gain was shown to be reduced by exercise intervention in some studies[188,189,192,198,200,205,210,211,216,217,219–221], although not in others[184,185,193,197,199,207,215,218]. There is some evidence of reduced maternal adiposity[200] and post-partum weight retention[191,198,215] with exercise interventions during pregnancy, although this is not consistent across all studies[184,185]. A similar pattern is seen for incidence of gestational diabetes with evidence of reduced risk by intervention in some[185,188,194,208,214,221], but not all cohorts[189,192,196,200,205,207,209,210,213,215,217]. Physical activity interventions were also shown to promote improved maternal vascular function with decreased blood pressure reported in some[185,221], but not all[193,210] studies. Some studies also suggest that maternal exercise intervention promotes improved maternal cardiorespiratory fitness[184,189,190] and metabolic profiles[203], although results were again inconsistent[197,212].

Generally no effects of exercise interventions have been observed on birth weight or frequency of large for gestational age infants[184,186,189,192,193,195,197–200,210,215–219], although some studies did report reduced birth weight[188]. There is also, albeit inconsistent[186,191,197], evidence of reduced adiposity in neonates[206] and 6 month old infants[201], although this phenotype was lost by 3 years[204]. Analysis of cord blood metabolites has shown no difference in some studies[197,202], while others reported reduced cord leptin levels[206]. Few studies have considered the offspring cardiovascular system, however one study suggested that exercise intervention in maternal obesity does not affect newborn systolic or diastolic cardiac functional parameters[187], although there is evidence of reduced resting pulse rate in 3 year old offspring[204], which may indicate reduced cardiovascular risk.

The large variation in human intervention studies may be due to a combination of the different intervention protocols utilised, poor adherence to intervention programmes[184,187,195,215] and variations in factors such as population ethnicity. Furthermore, due to the time scales involved in follow-up studies, there is a severe lack of long-term offspring data for the effect of maternal exercise intervention in the context of obese pregnancy, with the oldest study to date following offspring up to 3 years of age[204]. Thus, animal models are an important tool to investigate the long-term effects of exercise interventions on offspring health, as well as underlying mechanisms.

Evidence from animal models

Most studies of maternal exercise intervention in obese pregnancy have been carried out in rodent models. Although there is some variation in the nature of the intervention with different studies utilising voluntary or involuntary wheel running[48,222–230], treadmill running[128,231–235] or swimming[236], some consistent patterns have emerged in terms of maternal and offspring outcomes.

Rodent models have shown that exercise interventions can improve the maternal metabolic profile, including improvement of the impaired glucose tolerance, increased insulin concentrations and impaired insulin signalling usually seen in obese dams[222,231–233], although

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not maternal weight or adiposity[48,222,223,231,233]. Exercise intervention during obese rodent pregnancy can also partially prevent some aspects of increased oxidative stress in maternal tissues[222] and the placenta[231]. Furthermore, maternal exercise prevents obesity-induced increases in rodent placental lipid accumulation, inflammation and alterations in placental morphology to reduce vascularisation[231,232].

In the offspring, the elevated blood glucose and insulin levels seen in both male and female offspring of obese rodent dams can be improved in the pup[223] and adult offspring[48,222,225–228,231,234,236] by exercise intervention during pregnancy. Maternal exercise intervention is also protective against other adverse effects of maternal obesity in rats and mice, including preventing increased adiposity[225,234,236], cognitive impairment[229], dysregulation of hypothalamic gene expression[48], hepatic dysfunction and insulin resistance[226], epigenetic and transcriptional changes in skeletal muscle leading to impaired muscle oxidative capacity[223,227,228], increased inflammation[48] and β-cell dysfunction[230]. However, few studies have specifically investigated the effects of exercise intervention in obese pregnancy on offspring cardiovascular function[128]. In male mice it has been shown that maternal exercise prevents cardiac hypertrophy and dysfunction in offspring of obese dams, however there was no such protective effect seen on offspring vasculature with no reversal of increased systolic blood pressure or increased aortic diameter by maternal exercise intervention[128].

Some mouse studies have suggested that the positive effects of maternal exercise intervention on obese pregnancies may be mediated via improvement of maternal hyperinsulinaemia, which may be sufficient to prevent offspring hyperinsulinaemia[231], adipose tissue insulin resistance[231] and cardiac dysfunction[128]. However, as maternal exercise has not been shown to rescue the programming of offspring hypertension in rodents[128], other programming factors may also be involved. One candidate for the programming of hypertension is maternal hyperleptinaemia, as this is not corrected by maternal exercise in rodents[222,231].

Similar to the programming of the offspring cardiometabolic phenotype by maternal obesity discussed in previous sections, the effects of exercise intervention on early life also show some sexual dimorphism. Some studies have shown greater benefits to the more severely affected male rat pups[223], while in contrast, in weaning mouse offspring, maternal exercise intervention has been shown to be more effective in females, with female-specific improved metabolic characteristics[236]. However, in other mouse studies the degree of metabolic improvement conferred to adult offspring by maternal exercise appears similar for both sexes[225,226].

Thus, maternal exercise in obese pregnancy, while showing varied success in human trials, does appear to be an effective potential intervention to protect offspring from the long-term programming of cardiometabolic disease by maternal obesity. A greater number of high-quality human intervention studies, with better compliance and longer term follow-up, are required in order to validate these observations seen in animal models.

Conclusions

In conclusion, maternal obesity can programme offspring cardiometabolic disease, with the impact of maternal obesity beginning in early life, and persisting throughout adulthood. This includes the programming of increased offspring risk of adiposity, type 2 diabetes, cardiac dysfunction and hypertension (Fig. 1). Maternal exercise interventions have the potential to mitigate some, although not all, of the adverse effects of maternal obesity on offspring health. Thus alternative interventions, such as diet and antioxidant therapies[237], either alone or in combination, are also avenues of future potential research to prevent transmission of poor cardiometabolic health from mother to child.

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Conflict of Interest

None.

Authorship

S. E. O. conceived the review. I. I. drafted the manuscript and prepared the figure. S. E. O. and I. I. revised the manuscript.

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