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Abstract: Obesity in women of child-bearing age is a growing problem in developed and developing countries. Evidence from human studies indicates that maternal BMI correlates with offspring adiposity from an early age and predisposes to metabolic disease in later life. Thus the early life environment is an attractive target for intervention to improve public health. Animal models have been used to investigate the specific physiological outcomes and mechanisms of developmental programming that result from exposure to maternal obesity in utero. From this research, targeted intervention strategies can be designed. In this review we summarise recent progress in this field, with a focus on cardiometabolic disease and central control of appetite and behaviour. We highlight key factors that may mediate programming by maternal obesity, including leptin, insulin and ghrelin. Finally, we explore potential lifestyle and pharmacological interventions in humans and the current state of evidence from animal models.

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Dr. Lique Coolen
By email

23 June 2015

Dear Dr. Coolen,

We thank you for forwarding the requested revisions of our submitted manuscript **"Developmental programming by maternal obesity in 2015: outcomes, mechanisms and potential interventions"** for inclusion in the Hormones & Behaviour Special Issue *"SBN invited contributions to the second joint SBN and ICN meeting, 2014"*. We have addressed the reviewer's comments and include a full description in the response to reviewer.

Please find the revised manuscript and associated documents uploaded via the Elsevier Editorial System. We confirm again that this manuscript has not been published nor submitted elsewhere.

Please do not hesitate to contact us using the details below for any further information.

Yours sincerely,

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Dear Sir/Madam,

We thank you for your review of our submitted manuscript **"Developmental programming by maternal obesity in 2015: outcomes, mechanisms and potential interventions"** for inclusion in the Hormones & Behaviour Special Issue *"SBN invited contributions to the second joint SBN and ICN meeting, 2014"*. Please find below your comments addressed point by point:

1. While the review discusses the strengths of animal models, it does not address the limitations of the models.

We agree that this would be a valuable addition to the review. A more complete discussion of the limitations and strengths of different species as models for developmental programming studies has been added in lines 76-101 to address this point.

2. Authors need to provide a comparison of the developmental ontogeny of organ system of relevance in animal models with humans. Inclusion of schematic comparing human and animal models being discussed would be helpful in this regard.

Although we agree schematics of the developmental ontogeny of organ systems of relevance in animal models with humans would be helpful, we feel that inclusion of this would be a whole review in itself. It of course differs for different organ systems and even within one organ system different components of it differ. We therefore believe that this is too big a task to incorporate within the context of the current review. We have added comments in specific sections (as described in response to point 3) where differences may be particularly relevant so that the reader is at least aware of this complexity.

3. Authors need to emphasize the importance of choosing models that are appropriate in terms of the organ system of translational relevance. For instance if differentiation of organ systems occur postnatally in given species as opposed to prenatally in humans, the mediation can also involve effects via the mother in case of humans as opposed to direct effect in the animal models. These caveats need to be addressed.

As we have discussed above, a thorough comparison of the developmental ontogenies of key organs in humans and the common animal models used in programming studies would be a welcome addition to the literature. However, we feel that this is beyond the scope of this review. We recognise that exploration of these issues would improve this review and to address this we have added discussion of the developmental timings for relevant organs and systems throughout the

review, with a particular focus on the limitations of translating mechanistic studies in rodents to designing interventions in humans. In addition, discussion of the merits of different animal models and their relevance as models for specific tissues is included. Namely, additions have been made in lines 76-101, 288-291, 295-297, 332-339, 360-364 and 381.

4. In addition to dietary and exercise interventions authors should discuss briefly potential effects of pharmacological interventions (e.g. insulin sensitizing agents) on offspring health.

We concur that this would be a helpful addition to the review and as such a section discussing the current trials using metformin, an insulin sensitizer, has been added (lines 410-428).

Minor comments:

Line 84: Sentence is incomplete

It is not clear to us how the sentence (now in line 108) is incomplete and we would welcome further clarification here.

Line 218 - ventromedial hypothalamus has been previously abbreviated to VMH.

This has been amended.

Please do not hesitate to contact us using the details below for any further information.

Yours sincerely,

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Developmental programming by maternal obesity in 2015: outcomes, mechanisms and potential interventions

Authors: *Naomi C. Penfold, Susan E. Ozanne*

Highlights

- Leptin is a potential mediator of cardiovascular programming by maternal obesity.
- Insulin contributes to development of central control of glucose homeostasis.
- Ghrelin has neurodevelopmental actions in the rodent hypothalamus.
- Maternal obesity affects neural mechanisms of reward, motivation and learning.
- Dietary, exercise and pharmacological interventions aim to improve maternal metabolic state.

Developmental programming by maternal obesity in 2015: outcomes, mechanisms and potential interventions

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Abstract

Obesity in women of child-bearing age is a growing problem in developed and developing countries. Evidence from human studies indicates that maternal BMI correlates with offspring adiposity from an early age and predisposes to metabolic disease in later life. Thus the early life environment is an attractive target for intervention to improve public health. Animal models have been used to investigate the specific physiological outcomes and mechanisms of developmental programming that result from exposure to maternal obesity in utero. From this research, targeted intervention strategies can be designed. In this review we summarise recent progress in this field, with a focus on cardiometabolic disease and central control of appetite and behaviour. We highlight key factors that may mediate programming by maternal obesity, including leptin, insulin and ghrelin. Finally, we explore potential lifestyle and pharmacological interventions in humans and the current state of evidence from animal models.

Keywords

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Appetite;
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Intervention;
Obesity

Introduction

The importance of normal fetal growth was first highlighted by associations between low birth weight and the increased risk of heart disease and type 2 diabetes in adulthood (Barker et al., 1989; Hales et al., 1991). Subsequent studies of maternal under-nutrition and, more recently, maternal over-nutrition have demonstrated that the maternal nutritional environment and fetal and neonatal growth, collectively known as the first 1000 days of life, are key determinants of health in the next generation (de Rooij et al., 2006; Lumey and Stein, 1997; Ravelli et al., 1999; Ravelli et al., 1976). In humans, maternal obesity is associated with low and high birth weight (Cedergren, 2004; Gaudet et al., 2014) and increased risk of obesity and metabolic dysfunction in the offspring both in childhood (Boney et al., 2005; Whitaker, 2004) as well as in adulthood (Brisbois et al., 2012; Cooper et al., 2010). Maternal obesity is also associated with increased risk of offspring cardiovascular disease (Drake and Reynolds, 2010), type 2 diabetes (Berends and Ozanne, 2012) and neurodevelopmental and psychiatric disorders, including ADHD, autism, schizophrenia and mood disorders (Mehta et al., 2014; Rodriguez, 2010).

The prevalence of overweight and obesity has soared in the last 30 years globally (Ng et al., 2014). Worryingly, the number of children classified as overweight or obese has increased 150% worldwide in this timeframe (Ng et al., 2014) and the rate of obesity in women of child-bearing age is still rising (Fisher et al., 2013). Whilst genetic factors that predispose to obesity in an obesogenic environment, have likely contributed to the current global obesity epidemic, the short timescale of this increase implicates non-genetic factors including the impact of the intrauterine and neonatal environment on adult health and disease (McAllister et al., 2009). It is vital that we understand the mechanisms underlying such developmental programming of disease by maternal obesity in order to develop effective interventions to help mitigate the current rise in obesity, cardiovascular and metabolic disease as well as mental health disorders. Bariatric surgery to induce weight loss lowers the risk of gestational diabetes mellitus (GDM), fetal macrosomia and the rate of obesity in the offspring as well as improving offspring insulin sensitivity, demonstrating that improving the maternal metabolic

state prior to pregnancy is an effective intervention that improves the health of both mother and child (Kral et al., 2006; Shai et al., 2014; Smith et al., 2009). However, bariatric surgery is intrusive, high-risk, costly and can cause nutrient deficiency, the latter of which led to severe neural defects in some children conceived very soon after surgery (Pelizzo et al., 2014). A clearer understanding of the mechanisms mediating the increased risk of metabolic disease in offspring of obese women is required in order to develop less intrusive, better targeted interventions. This review will explore recent progress made in the understanding of the developmental programming by maternal obesity and potential avenues for intervention.

Animal models have revealed mechanisms underlying programming by maternal obesity

Animal studies have confirmed that maternal obesity programs metabolic syndrome-like outcomes in the offspring including impaired insulin action and glucose homeostasis (Martin-Gronert et al., 2010; Samuelsson et al., 2008; Shankar et al., 2010; Shelley et al., 2009), hypertension and cardiovascular dysfunction (Blackmore et al., 2014; Fernandez-Twinn et al., 2012; Samuelsson et al., 2008), as well as increased adiposity (Bayol et al., 2008; Samuelsson et al., 2008; Song et al., 2015) and an increased susceptibility to diet-induced obesity (DIO) (Bayol et al., 2007; Howie et al., 2009; Kirk et al., 2009; Nivoit et al., 2009; Samuelsson et al., 2008; Shankar et al., 2008; Torrens et al., 2012). The choice of animal model is often a compromise between practicality of the research and translatability to humans. Whilst non-human primates (NHPs) share the closest resemblance to human developmental trajectories and pregnancies, they have a long gestation length and time to maturity of the offspring, leading to high research costs. Sheep and pigs are used due to their similarities in placental structure and function to humans, whilst rabbits are a medium-sized mammal with intermediary similarities and differences to humans. These larger mammals are conducive to repeated sampling of blood and tissue, allowing for longitudinal studies and within-subject analysis. Models with larger litter sizes, such as pigs and rodents, allow for the easier

investigation of sex differences in programming. Rodent models have been used extensively due to their short gestation (three weeks) and maturity intervals (five weeks to puberty) and the ease with which to generate a well-powered experiment of animals of ages across the lifecourse. Furthermore, they enable genetic engineering to elucidate mechanisms. A disadvantage is that these smaller mammals are limited to one sampling point, precluding true longitudinal analysis. In addition, there are several differences in developmental timings of key tissues between rodents and humans. An overarching observation is that the third trimester in humans is roughly equivalent to the first postnatal weeks in the rodent. Notably adipose tissue develops from early in gestation in humans whereas subcutaneous and visceral depots develop from late gestation and early postnatal life, respectively, in rodents (Rosen and Spiegelman, 2014). Cardiomyocyte proliferation and growth is mostly complete by birth in the human and sheep (Morrison et al., 2007), whereas cardiomyocyte division ends at postnatal day 3 to 4 in the rat, with growth occurring over the first two weeks of life (Li et al., 1996). In addition, the development of key intra-hypothalamic connections occurs during the second postnatal week in rodents but these connections are established by birth in humans and NHPs ((Bouret, 2012; Coupe and Bouret, 2013; Liu et al., 2013). The choice of animal model will affect the translatability of the results, however the outcomes seen in these models often recapitulate phenotypes reported in humans, signifying the validity of the use of a range of animals to investigate the mechanisms underlying developmental programming.

Insulin and glucose homeostasis

Maternal obesity programs offspring adiposity, decreased glucose tolerance and impaired insulin sensitivity (Fernandez-Twinn et al., 2012; Samuelsson et al., 2008; Yan et al., 2011). The mechanisms underlying programming of insulin resistance and glucose homeostasis by maternal obesity include alterations in peripheral insulin signalling and insulin secretion [reviewed in (Berends and Ozanne, 2012) and (Duque-Guimaraes and Ozanne, 2013)]. Adult offspring exposed to maternal obesity are hyperinsulinaemic and have alterations in the expression of key insulin signalling and glucose

handling molecules in skeletal muscle, liver and adipose tissue that indicate a predisposition for insulin resistance and impaired glucose tolerance (Martin-Gronert et al., 2010; Nicholas et al., 2013a; Rattanatray et al., 2010; Shelley et al., 2009; Yan et al., 2011). At least some of the programming of insulin signalling protein expression appears to occur through post-transcriptional mechanisms via changes in microRNA (miR-) levels. Maternal obesity at conception in sheep increases hepatic miR-29b, miR-130 and miR-107 levels (Nicholas et al., 2013b). Increased miR-126 expression in adipose tissue of mice exposed to maternal obesity is associated with down-regulated expression of target genes involved in insulin signalling including insulin receptor substrate 1 (IRS-1) (Fernandez-Twinn et al., 2014). These programmed changes in IRS-1 and miR-126 were maintained following differentiation of pre-adipocytes *in vitro*, indicating that maternal obesity programs altered insulin signalling in the offspring adipose tissue in a cell-autonomous fashion.

In addition to peripheral insulin signalling, recent evidence suggests that the central control of glucose homeostasis is vulnerable to the hyperinsulinaemic obese maternal environment. Genetically-induced maternal hyperinsulinaemia and insulin resistance is associated with disrupted glucose homeostasis and hyperinsulinaemia in male wild-type offspring despite normal body weight and glycaemia in the mother (Isganaitis et al., 2014). Furthermore, a recent study demonstrated that genetic abrogation of insulin signalling specifically in pro-opiomelanocortin (POMC) neurons of offspring exposed to a maternal high-fat diet (HFD) restores POMC innervation of pre-autonomic paraventricular nucleus (PVH) neurons and normalises the impaired glucose tolerance otherwise seen (Vogt et al., 2014). This is associated with an improvement in pancreatic beta cell glucose-stimulated insulin secretion and parasympathetic innervation of beta cells.

Maternal hyperinsulinaemia with insulin resistance might program altered offspring development via the concomitant maternal hyperglycaemia, since insulin does not cross the placenta whereas glucose does (Dabelea, 2007). In humans, impaired glucose tolerance during pregnancy is often associated with increased birth weight and increased risk of childhood obesity (Catalano et al., 2003; Cottrell and Ozanne, 2007; Hillier et al., 2007; Liu et al., 2014; Plagemann et al., 2002). Treating GDM

mothers to lower their blood glucose reduces this risk, particularly in male offspring (Bahado-Singh et al., 2012; Gillman et al., 2010). In a recent study in mice, genetically-induced maternal hyperglycaemia is associated with increased body weight and impaired glucose tolerance in wild-type male offspring (Nadif et al., 2015). Therefore control of glycaemia during pregnancy is not only important for maternal health but also for the long term health of the offspring.

Cardiovascular system

Hypertension and cardiac hypertrophy are common phenotypes observed in offspring exposed to maternal obesity (Fernandez-Twinn et al., 2012; Samuelsson et al., 2008). Studies in rabbits and rats have suggested that changes in sympathetic tone may be an important mediator of these effects. Maternal HFD in rabbits increases renal sympathetic nerve activity in the offspring (Prior et al., 2014). Likewise studies suggest that maternal obesity in rats induces hypertension in the offspring via increased sympathetic drive in early development (Samuelsson et al., 2010), which may be mediated by altered early life leptin signalling.

Leptin action in the nucleus of the solitary tract (NTS) and the ventromedial nucleus of the hypothalamus (VMH) increases sympathetic outflow via the renal nerve (Li et al., 2013; Mark et al., 2009; Marsh et al., 2003). Umbilical cord leptin levels are elevated in obese pregnancies (Ferretti et al., 2014; Karakosta et al., 2013; Walsh et al., 2014) and neonatal circulating leptin is elevated in offspring of obese mice (Samuelsson et al., 2008). Therefore, early life hyperleptinaemia may drive sympathetic hyperstimulation in the developing renal-cardiovascular system, leading to hypertension and cardiovascular dysfunction in adulthood (Briffa et al., 2014). Indeed, neonatal leptin administration in rats results in cardiac hypertrophy and dysfunction in adulthood (Marques et al., 2014b). In addition, rat offspring exposed to maternal obesity show an exaggerated hypertensive response to peripheral leptin administration in adulthood (Samuelsson et al., 2010). This is unlikely to be due to impaired central leptin signalling, as maternal obesity-mediated programming of leptin resistance is hypothalamic nuclei-specific (Kirk et al., 2009) and diet-induced obesity in adulthood

does not impair central leptin-mediated sympathetic activity via the renal nerve (Rahmouni et al., 2005). Therefore it has been postulated that the hyperleptinaemia seen in adult offspring of maternal obesity animal models drives the accompanying hypertension via the concomitant increase in central activation of the sympathetic nervous system (Samuelsson et al., 2010; Simonds et al., 2014). Notably, it has recently been shown that the increased risk of hypertension in obese individuals is dependent on functional leptin signalling (Simonds et al., 2014).

Our studies in a mouse model of maternal DIO have shown that male offspring of obese dams display cardiac hypertrophy associated with hyperinsulinaemia and increased oxidative stress prior to a change in body weight or adiposity, indicating that the programming of increased risk of cardiovascular disease is independent from mechanisms relating to obesity (Blackmore et al., 2014; Fernandez-Twinn et al., 2012). Furthermore, frank cardiac dysfunction with increased sympathetic dominance akin to the early stages of heart failure is evident in these mice by young adulthood (Blackmore et al., 2014). This dysfunction may relate to pathological cardiac hypertrophy and cardiac stress as early as weaning. Oxidative stress, inflammation and epigenetic mechanisms may all be involved in the programming of cardiovascular dysfunction by maternal obesity (Blackmore and Ozanne, 2013, 2014). Given that obesity itself increases the risk of heart disease, cardiac dysfunction may be exaggerated in high-fat-fed offspring exposed to maternal obesity. Indeed, the combination of maternal HFD and post-weaning exposure to HFD culminates in reduced vasorelaxation in both mice and non-human primates (Fan et al., 2013; Torrens et al., 2012), with increased oxidative stress in the femoral arteries of adult male offspring (Torrens et al., 2012).

In summary, early life exposure to hyperleptinaemia as a consequence of maternal obesity may drive increased sympathetic tone leading to hypertension and accelerate the onset of cardiac hypertrophy and heart failure.

Ectopic lipid deposition

Maternal obesity programs increased adiposity and adipose tissue function in the offspring via alterations in adipocyte morphology and signalling (Alfaradhi and Ozanne, 2011; Benkalfat et al., 2011; Murabayashi et al., 2013) as well as changes in food intake. As well as increased adiposity, ectopic lipid deposition has also been observed in the liver and pancreas of offspring exposed to maternal obesity (Alfaradhi et al., 2014; Oben et al., 2010a; Oben et al., 2010b), in association with altered hepatic mRNA and protein expression profiles indicative of increased lipogenesis (Bruce et al., 2009), elevated markers of oxidative damage (Alfaradhi et al., 2014; Bringhenti et al., 2014; Torrens et al., 2012), inflammation, fibrosis and increased sympathetic nervous system activation (Oben et al., 2010a). These results provide evidence for an increased risk of non-alcoholic fatty liver and pancreas diseases (NAFLD and NAFPD, respectively) in offspring of obese mothers, a pathology which commonly occurs in obesity when the normal capacity of white adipose tissue for lipid storage has been exceeded. Recent evidence from a mouse model of maternal DIO suggests that the predisposition for NAFPD in high-fat-fed offspring is associated with a programmed shift in the cellular circadian clock (Carter et al., 2014). Perturbation in internal biological rhythms is a recent addition to the list of offspring physiologies affected by maternal nutrition (Martin-Gronert and Ozanne, 2013) and represents an exciting avenue for investigation, given the new understanding of circadian biology in health and disease (Bailey et al., 2014).

Interestingly, recent evidence from a swine model of maternal obesity suggests that increased risk of liver disease can be programmed transgenerationally, since early postnatal increases in adiposity and markers of pediatric liver disease are found in male piglets of obese grandmothers (Gonzalez-Bulnes et al., 2014).

Central control of food intake: programming the hypothalamus

The increased incidence of offspring obesity is frequently associated with hyperphagia in maternal over-nutrition models (Bayol et al., 2007; Kirk et al., 2009; Long et al., 2011; Nivoit et al., 2009;

212 Samuelsson et al., 2008). This increased caloric intake is accompanied by alterations in hypothalamic
213 expression of key neuropeptides, their receptors and molecules involved in signalling by peripheral
214 factors (Chen and Morris, 2009; Chen et al., 2009; Ferezou-Viala et al., 2007; Gupta et al., 2009;
215 Morris and Chen, 2009; Page et al., 2009) as well as altered hypothalamic development (Chang et al.,
216 2008; Kirk et al., 2009). Alterations in gene expression may be due to epigenetic alterations such as
217 changes in DNA methylation within the gene promoters, as observed in offspring exposed to early
218 life over-nutrition (Plagemann et al., 2009; Plagemann et al., 2010). The impaired development of
219 hypothalamic circuitry in rodents is likely due to alterations in the hormonal environment in early
220 postnatal life. Insulin has been implicated in the programming of hypothalamic circuits in response
221 to maternal diabetes and maternal over-nutrition (Steculorum et al., 2013; Vogt et al., 2014).
222 Maternal hypoinsulinaemic hyperglycaemia increases the ratio of orexigenic neurons to anorexigenic
223 neurons in the neonatal arcuate nucleus (Arc) (Franke et al., 2005; Steculorum and Bouret, 2011b)
224 and impairs Arc-PVH Agouti-related peptide (AgRP) and POMC projections (Steculorum and Bouret,
225 2011b). These changes are associated with elevated circulating glucose, insulin and leptin in the
226 neonate and central leptin resistance, hyperphagia and obesity in adult life (Steculorum and Bouret,
227 2011b). In addition, maternal over-nutrition can alter the timing, amplitude of, and response to the
228 postnatal surge in neonatal leptin concentrations that is critical for the development of
229 hypothalamic circuitry (Ahima et al., 1998; Bouret et al., 2004a; Long et al., 2011; Toste et al., 2006).
230 Leptin promotes neurite outgrowth from the Arc during neonatal life (Bouret et al., 2012; Bouret et
231 al., 2004b) and abnormal neonatal leptin signalling impairs the formation of the Arc-derived
232 hypothalamic projections (Attig et al., 2008; Delahaye et al., 2008; Yura et al., 2005). It has recently
233 emerged that ghrelin also contributes to the early life programming of obesity. Neonatal ghrelin
234 administration increases Arc neuronal number and increases the ratio of orexigenic to anorexigenic
235 gene expression (Steculorum and Bouret, 2011a). Chronic postnatal ghrelin impairs the formation of
236 Arc projections in association with metabolic dysfunction and impaired leptin sensitivity in
237 adulthood (Steculorum et al., 2015). Neonatal over-nutrition, by reducing litter size and thus

238 increasing access to the mother's milk, predisposes offspring to hyperphagia and obesity in
239 adulthood (Collden et al., 2015; Plagemann et al., 1999). This is associated with decreased serum
240 ghrelin in neonates, due to a loss of the normal up-regulation of ghrelin mRNA in the neonatal
241 stomach, and with abrogation of ghrelin-induced gene expression in the Arc, potentially due to
242 impaired transport of ghrelin into the ventromedial hypothalamus (Collden et al., 2015). Impairment
243 of central ghrelin action in neonates increases Arc projection density and leads to obesity,
244 hyperglycaemia and impaired leptin sensitivity in adulthood (Steculorum et al., 2015).
245 Thus alteration of central insulin, leptin and ghrelin signalling in neonates exposed to maternal
246 obesity, with insulin resistance, hyperglycaemia and hyperleptinaemia, may underlie the
247 programming of altered hypothalamic development and subsequent metabolic dysfunction in the
248 adult offspring.
249

250 ### *Maternal obesity predisposes to diet-induced obesity: the role of the reward system*

251 Studies in rodents have demonstrated that offspring exposed to maternal obesity and/or HFD during
252 gestation and lactation are predisposed to a greater increase in adiposity and metabolic
253 dysregulation than those from control dams when the offspring themselves are challenged with a
254 HFD after weaning (Benkalfat et al., 2011; Howie et al., 2009; Page et al., 2009; Parente et al., 2008;
255 Rajia et al., 2010). Post-weaning exposure to a HFD further alters hypothalamic mRNA and protein
256 expression (Page et al., 2009; Rajia et al., 2010), which may mediate the increased caloric intake and
257 drive the increased adiposity. Alternatively, the increased propensity for DIO in offspring of obese
258 mothers may be mediated via programmed dysregulation of the central mechanisms involved in
259 palatable food intake: namely the mesocorticolimbic dopamine pathway from the ventral tegmental
260 area (VTA) to the nucleus accumbens (NAcc). Dopaminergic signalling in the NAcc is thought to
261 control incentive salience, or the motivated "wanting" of palatable foods, whilst opioidergic inputs
262 onto the same pathway are thought to signal the pleasure associated with eating tasty foods and so

influence food preferences or the “liking” of palatable foods (Blum et al., 2012; Egecioglu et al., 2011; Volkow et al., 2011). Connections between the reward system and the hypothalamus are critical for the regulation of reward-related feeding (Dietrich et al., 2012; Leinninger et al., 2011). In humans and rodents, reward signalling is altered in obesity (Batterink et al., 2010; Burger and Stice, 2011; Finger et al., 2012; Johnson and Kenny, 2010; Shin and Berthoud, 2011; Stoeckel et al., 2008), due at least in part to chronic HFD-mediated epigenetic dysregulation of key dopaminergic and opioidergic signalling molecules (Vucetic et al., 2012; Vucetic et al., 2011). In addition, dysregulated reward signalling may predispose to diet-induced obesity (Blum et al., 2014; Volkow et al., 2008). Thus, the central reward system may be vulnerable to early life exposure to maternal obesity and programmed alterations may underlie the increased propensity for obesity when offspring are exposed to a highly palatable diet in adulthood.

Indeed, in animal models of maternal HFD or obesity, offspring consume more high-fat and high-sugar foods than controls (Bayol et al., 2007; Bocarsly et al., 2012; Ong and Muhlhausler, 2011, 2014; Tamashiro et al., 2009; Walker et al., 2008). This may be due to an increased preference for these macronutrients (Vucetic et al., 2010) but is not associated with altered orosensory stimulation by their taste (Treesukosol et al., 2014). Whilst food preferences can be programmed by maternal nutrition (reviewed in (Gugusheff et al., 2014), maternal obesity is also associated with altered motivation for palatable foods in multiple rodent models (Grissom et al., 2014b; Naef et al., 2011; Rodriguez et al., 2012). The programmed increases in preference for fat and sugar and altered motivation to work for such foods are associated with changes in dopaminergic tone (Naef et al., 2011; Naef et al., 2013) as well as in expression of key dopaminergic and opioidergic signalling genes (Naef et al., 2011; Ong and Muhlhausler, 2011; Vucetic et al., 2010), with evidence for epigenetic regulation at some loci (Grissom et al., 2014a; Vucetic et al., 2010). In fact, maternal obesity at conception is sufficient to program opioid dysregulation in the offspring (Grissom et al., 2014c). Therefore, maternal obesity may predispose the offspring to DIO via programmed changes in the mesocorticolimbic reward pathway. Importantly, the mesocorticolimbic dopamine pathway

develops *in utero* in rodents with VTA efferents innervating the accumbens and cortex by birth (Hu et al., 2004). Therefore, investigations into the *in utero* programming of the reward system may more readily translate from mouse to man than for some other systems.

Programming learning and memory: leptin and the hippocampus

Offspring exposed to maternal obesity are slower to acquire an executive function task, in which they demonstrate greater impulsivity but no difference in attention (Grissom et al., 2014b). The hippocampus mediates learning and develops perinatally in both humans and rodents (Semple et al., 2013). In rodents, an important period of synaptogenesis and dendritic spine formation in the developing hippocampus coincides with the peak of the postnatal leptin surge in rodents, which is significant as leptin induces excitatory synaptogenesis and promotes dendritic spine formation in the adult hippocampus (Dhar et al., 2014a; Dhar et al., 2014b). Leptin also potentiates GABAergic transmission in postsynaptic CA3 pyramidal cells from the hippocampi of newborn rats (Guimond et al., 2014). The basal activity of these cells is reduced in leptin-deficient mice, as is a marker of presynaptic GABA synthesis, indicating that leptin signalling is critical for GABAergic transmission in the developing hippocampus (Guimond et al., 2014). In addition, chronic leptin treatment during the first two postnatal weeks alters the expression of genes involved in NMDA signalling and synaptic machinery and reduces long-term potentiation in pre-weaning rats (Walker et al., 2007). A similar phenotype is observed in hyperleptinaemic neonates exposed to maternal HFD from late gestation through lactation (Walker et al., 2008). As such, altered leptin signalling in early life may impair the formation of synapses and dendritic spines and thus the maturation of the hippocampus, which may underpin the reported impaired cognition, learning and memory in later life and predisposition for psychopathologies and obesity (Valleau and Sullivan, 2014).

In addition, the programming of obesity and psychiatric disorders by maternal obesity has been attributed to increased maternal-fetal inflammatory signalling (Bolton and Bilbo, 2014; Marques et

al., 2014a). It has recently been shown that the impairment in Arc-PVH neuropeptide Y (NPY) projections seen in mice exposed to maternal DIO may be due to increased fetal exposure to the inflammatory cytokine interleukin-6 (IL-6) (Sanders et al., 2014). Maternal IL-6 is also increased mid-gestation in mothers with GDM and inversely correlates with birth weight and glucose tolerance (Hassiakos et al., 2015). In fact, the correlation between GDM and IL-6 levels is so strong that circulating IL-6 alone can predict GDM status. In addition, maternal obesity is associated with increased levels of inflammatory cytokines (Challier et al., 2008; Kepczynska et al., 2013; Kim et al., 2014), of which IL-6 is associated with increased risk of obesity in the offspring (Dahlgren et al., 2001; Smith et al., 2007). Therefore, inflammatory cytokines are also candidate programming mediators in the early life programming of central dysfunction by maternal obesity**.**

Candidate programming mechanisms and factors in maternal obesity

Potential molecular mediators of the programming of cardiometabolic disease and central neuroendocrine pathways by maternal obesity have been highlighted by recent mechanistic studies. Identification of the key programming factors is vital for the development of rational intervention strategies. It is also important to understand the key windows for intervention: do we aim to intervene before or during pregnancy and/or during early postnatal life? Should interventions target maternal diet, maternal obesity or both?

In utero exposure to maternal obesity is an important target for intervention. It is important to note here the differences in placental biology and developmental timings between rodents, the key model for mechanistic studies, and humans. Rodent placentae structure and blood flow differ from human placentae, however mice have been used successfully to model intra-uterine growth restriction (Gonzalez-Bulnes and Astiz, 2015). Sheep and pig models are more common in investigations into placental biology and intrauterine development, due to their closer resemblance to human placental morphology but also the ability to insert catheters into the maternal and fetal circulation in order to monitor placental transfer over time *in vivo* (Barry and Anthony, 2008).

Maternal obesity during pregnancy may impair fetal nutrition via placental adaptations (Tarrade et al., 2015). Indeed placentae from obese women transport less maternal taurine, a critical beta-amino acid involved in placental development and fetal growth (Ditchfield et al., 2014) and have higher levels of oxidative stress and impaired mitochondrial respiration (Hastie and Lappas, 2014; Mele et al., 2014). In addition, maternal DIO in mice is associated with decreased placental mTOR signalling, which may contribute to the decreased fetal:placental weight ratio in late gestation via altered amino acid transport (Lager et al., 2014). Conversely maternal high-fat feeding, whether accompanied by obesity or not, is associated with fetal overgrowth and up-regulation of glucose and amino acid transport across the placenta (Jones et al., 2009; Sferruzzi-Perri et al., 2013). Thus, fetal growth may be altered in maternal obesity due to alterations in placental function.

In addition, altered maternal intake of vital micronutrients in maternal obesity may contribute to offspring epigenetic programming. Dietary intake of key methyl donors varies seasonally in certain populations such as those in the Gambia where the timing of pregnancy in relation to the seasons is associated with permanent alterations in DNA methylation at key loci in the offspring (Dominguez-Salas et al., 2014). This provides some of the earliest evidence for the impact of human maternal methyl donor dietary intake during pregnancy on life-long epigenetic programming in the offspring. In rodents, maternal dietary supplementation with methyl donors ameliorates the increased body weight gain in offspring of obese dams (Carlin et al., 2013; Cordero et al., 2014) and restores fat preference to control levels in association with normalisation of the methylation status at promoter regions of key genes involved in the central reward system (Carlin et al., 2013).

The early postnatal life and the lactation period is another target for intervention. Rodents experience fluctuations in hormonal levels during the first three weeks of life that have been implicated in the development and maturation of key hypothalamic circuitry (Bouret, 2013). Whilst this is different to human development, early postnatal life in humans is also considered to be a vital time for the maturation of the brain and adipose tissue. As such, exposure to maternal obesity during lactation is a factor in offspring health, with one potential mediator being alterations in

366 breast milk lipid content. In both humans and rodents, over-nutrition and accelerated growth during
367 the neonatal period is associated with increased adiposity in later life (Plagemann et al., 2012). The
368 combination of maternal obesity and HFD consumption reduces breast milk lipids, whilst HFD
369 consumption during lactation alone increases them (Rolls et al., 1986). Breast milk lipid content is
370 decreased in HFD-fed obese dams during lactation compared to HFD-fed control dams, due to
371 impaired mammary fatty acid synthesis (Saben et al., 2014). In a maternal DIO rat model, breast milk
372 levels of triglycerides are elevated but free fatty acids are decreased early in lactation and increased
373 in the latter stages (Kirk et al., 2009).
374 As discussed above, maternal obesity during pregnancy and lactation is associated with elevated
375 maternal circulating leptin, insulin, glucose and inflammatory cytokines, all of which have been
376 linked to cardiometabolic dysfunction in the offspring. Exposure to these maternal factors both *in*
377 *utero* and during early postnatal life can alter offspring development. As such, interventions should
378 aim to target women planning to conceive or soon after pregnancy is confirmed. Ensuring
379 appropriate maternal dietary nutrition, improving the metabolic status of obese women in order to
380 normalise hormonal levels, ameliorate inflammation and improve placental sufficiency, and
381 optimizing infant growth and nutrition in the neonatal period are key aims of intervention.
382

383 ## Interventions to improve outcomes of offspring exposed to maternal obesity

384 Improving women's metabolic health at the time when they are trying to reproduce is an attractive
385 target, since it would benefit the health of both mother and child and only a temporary
386 improvement in maternal health could improve public health for generations. Notably, dietary and
387 lifestyle advice has been shown to be effective in overweight and obese pregnant women (Dodd et
388 al., 2014).
389 Rodent models of maternal obesity have been used to study the effectiveness of dietary and
390 exercise interventions in the mother on offspring metabolic and behavioural phenotype, due to the
391 ability to enforce exercise and easily control diets in these species. Dietary intervention from before

pregnancy or during lactation normalises the increased adiposity and circulating leptin, insulin and triglycerides in weanling offspring, rescues the altered motivation and hyperphagia and partially normalises glucose homeostasis and adipocyte morphology in adulthood (Bayol et al., 2007; Rodriguez et al., 2012; Zambrano et al., 2010). In addition, maternal dietary intervention rescues the increased anxiety and altered social behaviours in female offspring of maternal DIO mice in association with amelioration of central inflammation in these offspring (Kang et al., 2014). However, the same reversal is not seen in male offspring. Voluntary exercise before and during pregnancy in lean dams improves glucose homeostasis in the offspring (Carter et al., 2012; Carter et al., 2013) and prevents hyperleptinaemia (Laker et al., 2014; Vega et al., 2013). This may be due to the reduction in levels of maternal circulating triglycerides, glucose, insulin, cholesterol, oxidative stress and corticosterone (Vega et al., 2013).

Randomised controlled trials (RCTs) are now being used to investigate whether the same improvements can be seen in obese human pregnancies. A low glycaemic index (GI) diet during pregnancy has been shown to increase weight loss from pre-pregnancy to three months after birth in overweight women and thus may minimise gestational weight gain (Horan et al., 2014). Current RCTs are addressing the effect of exercise alone (Sagedal et al., 2013; Seneviratne et al., 2014) or in combination with dietary intervention (Briley et al., 2014) to improve health outcomes in overweight and obese mothers and their children.

In addition, pharmacological studies are addressing the possibility of normalising the maternal metabolic and hormonal state with a view to improving offspring health. Metformin, an insulin sensitiser, has been trialled as an alternative to insulin treatment for gestational diabetes, with initial results indicating no affect on offspring blood pressure at 2 years of age in comparison to insulin treatment nor in maternal postpartum weight loss when compared to placebo (Battin et al., 2015; Refuerzo et al., 2015). There is currently a trial underway to test whether metformin administration during pregnancy in obese women will prevent macrosomia and this study will include investigation of materrnal factors, including insulin resistance, inflammation and adiposity, as well as fetal

adiposity (Chiswick et al., 2015). However, concerns have been raised as to the lack of long-term safety data in offspring exposed to metformin during gestation (Fantus, 2015). Animal models are invaluable to help address this issue. An initial study into the effects of metformin administration during pregnancy in a maternal obesity mouse model found that offspring from metformin-treated dams were protected from glucose intolerance and key gene expression changes in skeletal muscle (Tong et al., 2011). A more recently published study suggests that offspring from high-fat fed dams treated with metformin during pregnancy are protected against the exacerbated body weight gain upon exposure to a high fat diet in adulthood (Salomaki et al., 2014). However, this was not a model of maternal obesity and the number of litters studied was low. Additional investigations in rodent models are needed to understand the long-term effects of gestational exposure to metformin and to complement the human trials on short-term outcomes in obese pregnancies.

Further study in animal models is therefore required to inform the most effective timing and intensity of specific dietary and pharmacological interventions, including in altricial species to model intervention periods in line with human developmental timings (Nathanielsz et al., 2013).

Conclusion

In summary, recent animal studies of developmental programming by maternal obesity have advanced our understanding of the underlying mechanisms as well as further elucidated aspects of offspring physiology that contribute to their increased risk of obesity, cardiometabolic disease and mental health disorders. As the focus shifts towards designing interventions to curtail the developmental programming by maternal obesity, studies in both animals and humans are necessary to ensure safety, effectiveness and specificity.

Figure 1 legend

Figure 1: Maternal obesity programs obesity, cardiometabolic disease and neuropsychiatric disorders in the offspring. Maternal factors involved include hyperinsulinaemia, hyperglycaemia, hyperleptinaemia, hyperlipidaemia and impaired placental function. Common programming mechanisms in offspring tissues include oxidative stress, epigenetics and inflammation. Inflammation, insulin, leptin and ghrelin have all been implicated in brain development. The early life programming of brain circuits [HIP – hippocampus, HYP – hypothalamus, ML – mesolimbic pathway] may contribute to altered energy balance, motivated and other behaviours. Altered central control of the autonomic nervous system (ANS) may underlie cardiac and pancreatic phenotypes in the offspring. Programmed changes in adipose tissue, liver, pancreas and skeletal muscle function contribute to impaired glucose homeostasis. Overall, alterations in individual tissue function contribute to the increased risk of obesity, cardiometabolic disease and neuropsychiatric disorder in the offspring. Current strategies aim to ameliorate metabolic status of the obese mother via lifestyle or pharmacological interventions before conception or during pregnancy in order to normalise offspring phenotype.

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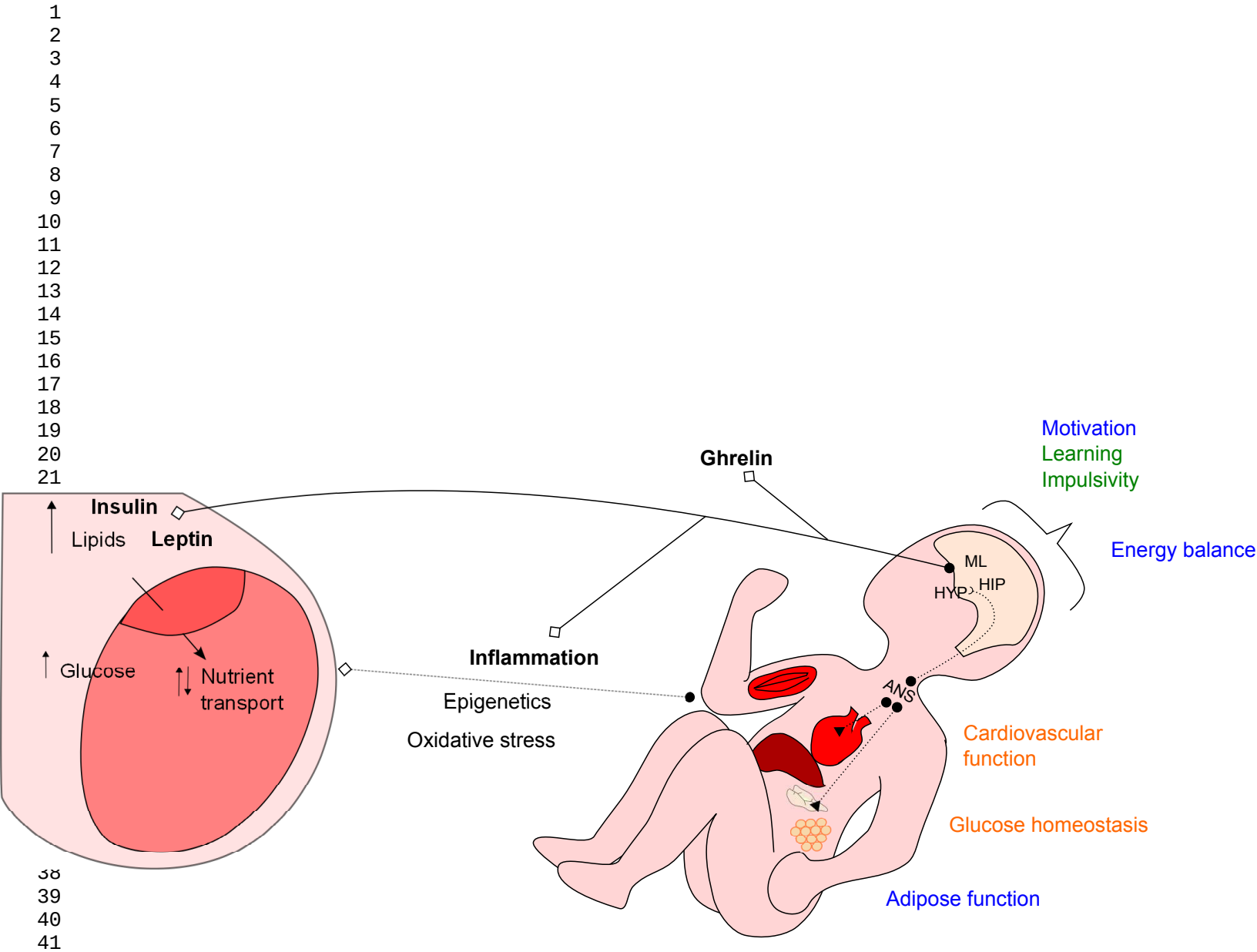
5-Figure(s)


Motivation
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Epigenetics
Oxidative stress
ANS
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Glucose homeostasis
Adipose function

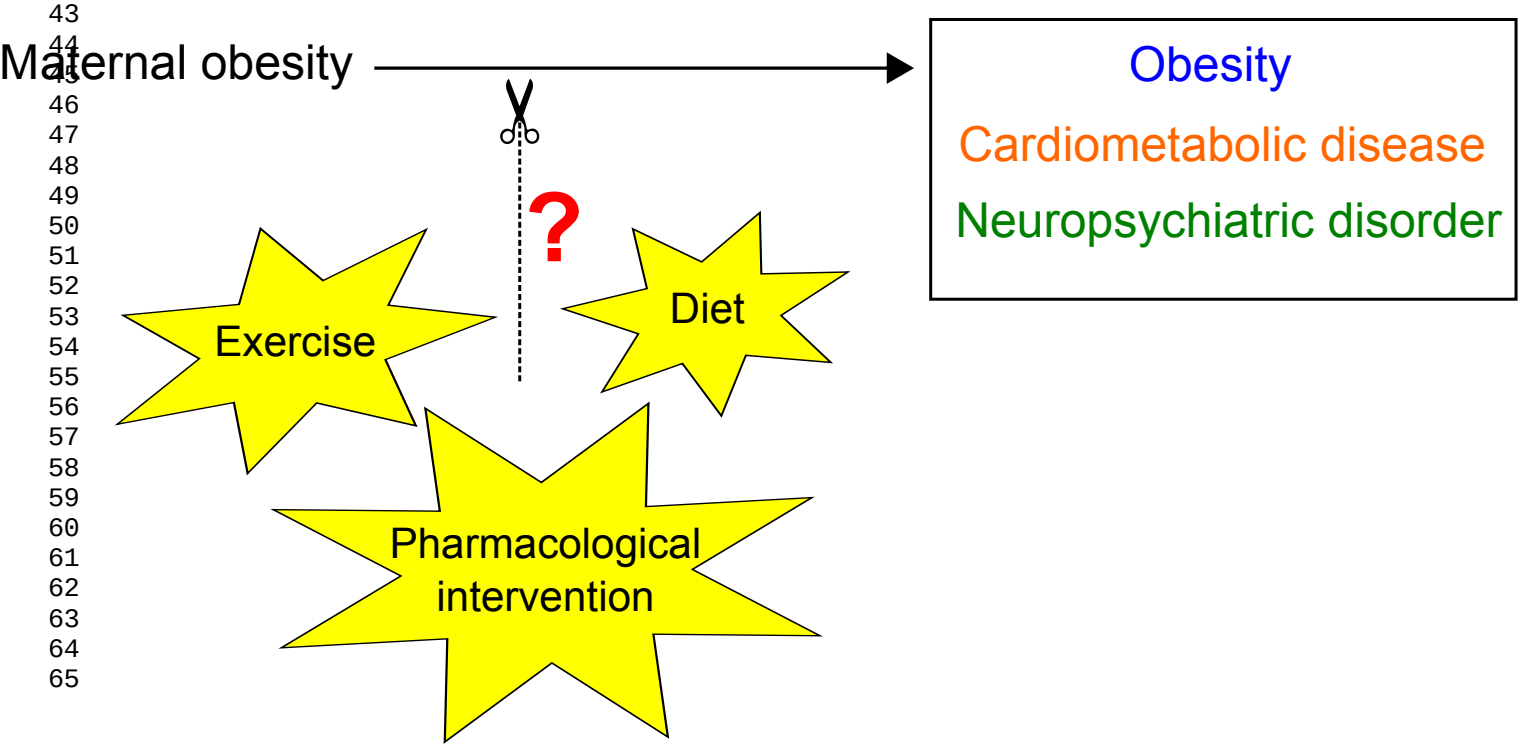
Maternal obesity
Obesity
Cardiometabolic disease
Neuropsychiatric disorder
?
Exercise
Diet
Pharmacological intervention

Figure 1: Maternal obesity programs obesity, cardiometabolic disease and neuropsychiatric disorders in the offspring. Maternal factors involved include hyperinsulinaemia, hyperglycaemia, hyperleptinaemia, hyperlipidaemia and impaired placental function. Common programming mechanisms in offspring tissues include oxidative stress, epigenetics and inflammation. Inflammation, insulin, leptin and ghrelin have all been implicated in brain development. The early life programming of brain circuits [HIP – hippocampus, HYP – hypothalamus, ML – mesolimbic pathway] may contribute to altered energy balance, motivated and other behaviours. Altered central control of the autonomic nervous system (ANS) may underlie cardiac and pancreatic phenotypes in the offspring. Programmed changes in adipose tissue, liver, pancreas and skeletal muscle function contribute to impaired glucose homeostasis. Overall, alterations in individual tissue function contribute to the increased risk of obesity, cardiometabolic disease and neuropsychiatric disorder in the offspring. Current strategies aim to ameliorate metabolic status of the obese mother via lifestyle or pharmacological interventions before conception or during pregnancy in order to normalise offspring phenotype.