Early life programming of health and disease: the long-term consequences of obesity in pregnancy: a narrative review

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Abstract

The prevalence of overweight and obesity is rising in all parts of the world and among young women it presents a very clear danger during pregnancy. Women who are overweight or who gain excessive weight during pregnancy are at greater risk of complications in pregnancy and labour, and are more likely to lose their child to stillbirth, or themselves die during pregnancy. This narrative review considers the evidence that in addition to increasing risk of poor pregnancy outcomes, obesity has the capacity to programme fetuses to be at greater risk of cardiometabolic disorders later in life. An extensive body of evidence from prospective and retrospective cohorts, and record linkage studies demonstrates associations of maternal obesity and/or gestational diabetes with cardiovascular disease, type-1 and type-2 diabetes. Studies in animals suggest that these associations are

underpinned by adaptations that occur in fetal life, which remodel the structures of major organs including the brain, kidney and pancreas.

As exposure to maternal obesity during fetal development also programmes a greater risk of obesity in later life, there is a risk of a transgenerational cycle of obesity and related disorders becoming established. Without significant investment in strategies to break such a cycle, the public health implications of the current rise in maternal obesity could last for a century or more. Maintaining healthy weight prior to and during pregnancy, and following guidance on breast feeding and complementary feeding may reduce the risk of poor health for infants exposed to obesity during fetal life.

The long-term consequences of obesity in pregnancy

The determinants of health and disease

The last 30-40 years have seen a profound change in our understanding of relationships between lifestyle and chronic disease. Recognition that lifestyle factors could modulate risk of non-communicable disease arose from the seminal works by Doll and Peto on tobacco smoking and cancer[1] and the elucidation of relationships between dietary fat, cholesterol concentrations and the contribution of LDL cholesterol to atherosclerosis[2,3]. Following on from this recognition came the now well-established view that risk is heavily determined by the interaction of lifestyle factors and the genotype. The phrase, "genes load the gun but the environment pulls the trigger", is widely quoted[4], after having been coined by Judith

Stern, a nutritionist from the University of California. The research that will be described in this review adds another layer to our understanding of the lifestyle-disease relationship and, as will be discussed, it is perhaps more accurate to say that genes load the gun, early life factors take aim and the environment pulls the trigger.

Figure 1 shows how different elements of broad human biology establish risk of disease at any stage of life. The contribution of genetics is strongest in the earlier years and a high proportion of non-communicable disease in infants and children will have a strong genetic component. The influence of lifestyle (smoking, diet, alcohol, socioeconomic status, occupational exposures and behaviours) gets stronger as we age, but will always be modified by the underlying genotype. However, the phenotype also plays a critical role. Whereas 'genotype' describes the information encoded by DNA, 'phenotype' refers to the traits the individual has when the genotype is expressed. The translation of the genotype to phenotype will be modified by epigenetic factors (tags on DNA and histone proteins which modulate gene expression in response to a range of factors, including the environment), and the environment encountered during fetal and infant development. It is helpful to regard health and disease status at any stage of life as being the product of cumulative gene-environment interactions at all previous stages of life[5]. The outcomes of such interactions at one stage of life will establish the phenotypic traits which determine how future interactions progress. This could be regarded as a lifecourse approach to understanding disease, or to stretch Stern's gun analogy further, we might say that the

aiming of the weapon prior to the environmental trigger that causes detriment, becomes more focused with aging.

As early development, particularly during the phase of life when organogenesis irreversibly establishes tissue structures, is a contributing factor to disease risk many decades later, exploring the relationship between maternal nutritional status in pregnancy and infant development is of great interest. Whilst there is an extensive body of evidence considering how maternal undernutrition can 'programme' later disease[6], the major nutritional concern in contemporary society relates to overweight and obesity. Figure 2 shows recent trends in overweight and obesity for adult women and infants aged 2-4 years. The marked rise in prevalence in both groups is striking, and the impact of widespread overweight among women of childbearing age upon the health of future generations is yet to be fully evaluated. The aim of this review is to discuss the evidence that links early life events to disease in later life and consider observations that indicate that maternal obesity is a key driver of non-communicable disease in the next generation. In the review the focus will be primarily on epidemiological associations between early life and later disease, but findings from experimental animal studies will be described as a means of illustrating the mechanisms the likely mechanistic links.

Maternal obesity and pregnancy outcomes

The risks associated with obesity in pregnancy manifest during the pregnancy itself, although this review will focus on the later impacts on the health of individuals who experienced maternal obesity during fetal development. Maternal weight status is an important determinant of pregnancy outcomes for both mothers and babies, and also of obstetric complications[8]. Overweight, obesity and excessive gestational weight gain are all risk factors for poor outcomes. Optimal gestational weight gain is dependent on weight status going into pregnancy. Whilst women of ideal weight pre-pregnancy may gain up to 16 kg across pregnancy, for those who are obese, a gain over 9kg would be considered excessive[9].

Obesity and excessive weight gain increase the risk of miscarriage[10] and stillbirth[11]. Obesity also increases risk of maternal death by up to 2-fold, relative to ideal weight women, depending on the severity of the obesity[12]. Overweight, obesity and excessive weight gain increase risk of all obstetric complications ranging from relatively minor gastrointestinal disturbances[13] through to the more severe hypertensive disorders[14] and gestational diabetes[15] (GDM). It is estimated that obesity increases the risk of pre-eclampsia by between 2- and 2.5-fold[16] and as the clinical response to this condition is to deliver the baby early, obesity becomes a key risk factor for preterm delivery. The association between obesity and gestational diabetes increases risk of macrosomia and injury to infants during delivery[17]. Obesity and excessive gestational weight gain also increase the risk of complications in labour. Spontaneous initiation of sustained labour is impaired, making induction more common in women with a BMI >30kg/m^2 [18]. Interventions, including instrumented delivery

and caesarean section are more frequent in pregnancies complicated by maternal obesity[19,20].

The early life origins of health and disease

The starting point for this review was the idea that lifelong risk of non-communicable disease is a product of interactions between genetic and epigenetic factors with the environment at all stages of life. Disease risk at any given point in life is partly determined by prior (epi)genetic-environment interactions. The impact of such interactions during fetal development is particularly significant and exposures to adverse environments during this phase of life are said to programme later disease risk. In this context 'programming' refers to permanent, irreversible adaptations to the environment, which compromise capacity to maintain normal metabolic and physiological function with ageing[6].

The embryos of all animal species begin development with the potential to develop and grow at a rate and to a form, that is determined by the genotype inherited from both parents. The expression of that genetic potential will lead to an achieved phenotype (Figure 3), which includes all aspects of anatomy, physiology, metabolism and endocrine functions, and hence the balance between health and disease. The early life programming concept is based on the contribution of modifying factors which alter the expression of the genotype and hence the achieved phenotype. Modifying influences on development will change the achieved phenotype at the level of individual organs, systems, tissues and even specific cell types by altering rates of cell division and differentiation. These changes will determine the

number of cells and types of cells within a tissue and hence it's resilience and homeostatic responses to physiological and metabolic challenges from the environment (dietary surplus or deficit, infection, trauma)[6]. Ultimately the establishment of the phenotype from the genotype is never complete and it continues to change throughout life, but tissues are at their most plastic during the phases of organogenesis and maturation which, in humans, occur before birth. In this way exposure to environmental factors establishes the functional lifespan of each organ, meaning the length of time over which it can maintain normal function and the capacity to withstand further adverse conditions. Beyond this functional lifespan each tissue will decline in function and disease will develop.

The range of factors known to have a programming effect on the developing fetus is known to be broad (Figure 3). Inevitably most factors are maternally derived as the intrauterine environment is where the fetal genotype encounters stimuli from the outside world, but there is an emerging body of evidence that suggests paternal factors carried by semen may also have programming potential. Most attention has focused on the influence of maternal nutritional status, and in particular undernutrition. The way in which that is signalled to the embryo and fetus is complex and nutritional status is, in itself, a product of both maternal intakes, nutrient demands and stores.

The first compelling evidence that early life events could programme disease in adulthood was derived from ecological and retrospective cohort studies. Comparing the geographical distributions of place of birth and cause of death among more than 2 million individuals who

died in England and Wales suggested a strong influence of the former upon risk of coronary heart disease in the 1970s[21]. Similarly, the distribution of death from coronary heart disease mapped closed onto the distribution of infant death in the 1920s[22]. This suggested that deprivation in early life was related to subsequent disease and cause of death and that this relationship persisted even when people moved to more affluent parts of the country. Further studies found strong associations between anthropometry at birth and risk of disease in adult life. Across cohorts in many countries, including the UK, Sweden, USA and India, it was noted that lower weight at birth (but still within the normal range) was associated with higher risk of blood pressure in adulthood, type 2 diabetes, insulin resistance and death from coronary heart disease[23-28]. These observations were particularly robust for type 2 diabetes and meta-analysis suggested a 25% greater risk of adult diabetes with every 1kg lower weight at birth[29].

Other indices of infant anthropometry at birth were also found to be associated with risk of ill-health in childhood and adult life. A larger head circumference, for example, was associated with greater risk of atopic wheezing in primary school age children[30]. Thinness at birth, measured as the ponderal index (weight/length^3) was found to associate with risk of type 2 diabetes as an adult[31], and a smaller abdominal circumference was associated with cardiovascular disease[32]. Collectively these observations led to the theory that factors which constitute an adverse environment for fetal development, result in irreversible changes to how organs and tissues develop, effectively programming their lifelong function and risk of non-communicable disease for the exposed individual. The extremes of anthropometric

indices at birth are the immediate indicator that the maternal environment has constrained genetic potential for growth. In keeping with the idea that risk of disease at any stage of life is the product of cumulative exposures to adverse factors at earlier stages, more complex analyses of retrospective cohorts showed interactions between fetal and adult factors. Risk of insulin resistance in 50-year-old men and women was greatest in those who were born thin (low ponderal index) but had higher body mass index as adults[33]. Finnish women born in the 1920s and 30s were more likely to develop coronary heart disease if they were of low birthweight and gained weight more rapidly up to the age of 9 years[34]. Similarly, the interaction of early life factors with the genotype is evident from observational data. Associations between common single nucleotide polymorphisms (gene variants) and disease were only manifested in individuals of lower birthweight in a cohort of Finnish adults[35,36].

The originators of the programming hypothesis postulated that the principle driver of early life programming was maternal undernutrition, as evidence suggested that birth anthropometry was determined by maternal nutritional status and because at the time the participants in the retrospective cohorts were conceived and born (early 20th Century), undernutrition was considerably more common than overnutrition, overweight and obesity. Reinforcement of the nutritional programming hypothesis came from follow-up studies of individuals conceived or born during the Dutch Famine of 1944-1945. At the end of World War Two, Nazi blockade of food supplies to western Holland resulted in 6 months of famine conditions. Adults who were conceived at this time were more likely to develop obesity,

196 type 2 diabetes and coronary heart disease than those born just before or just after the
197 famine[37,38]. Undernutrition at different stages of fetal development had differential effects
198 on disease in adult life. Exposure to famine in early gestation was associated with greater
199 risk of coronary heart disease, schizophrenia and depression, whilst exposure at any stage of
200 gestation was associated with type-2 diabetes[37]. Similarly fetal exposure to the Great
201 Chinese Famine of the 1950s was associated with greater risk of ischemic heart disease and
202 stroke, non-alcoholic fatty liver disease and type 2 diabetes[39-41] but not left atrial
203 enlargement[42].
204
205 There are different ways of viewing the relationship between anthropometry at birth and
206 disease in adult life. Nobody would view being born small as being a direct cause of non-
207 communicable disease. Lower weight or thinness at birth are merely indicators of risk. There
208 are three main schools of thought about what the observed relationship means. The
209 simplest view is that the association represents a trade-off in fetal life. Adverse conditions in
210 pregnancy due to undernutrition or other maternal stressors either result in death of the
211 embryo or fetus, or the conceptus survives through adaptations of tissue structures[6]. These
212 adaptations become permanent as they occur during organogenesis, and are subsequently
213 disadvantageous to the adult (Figure 4). Others have considered the persistence of what
214 appears to be maladaptation through evolution and have proposed that the when the fetus
215 adapts to the prevailing environment encountered by it's mother it develops characteristics
216 which prepare it for the continuation of that environment after birth. Disease risk will only
217 develop if conditions improve [43,44]. For example, conditions of undernutrition would be

218 better responded to if an individual were programmed in fetal life to be more energetically
219 efficient. However, if in future the individual lives in an environment where nutrition is
220 plentiful, then they would be more likely to become obese. The third viewpoint is that the
221 birth anthropometry-later disease association is an indication that there are genetic variants
222 that mediate both fetal growth restriction and non-communicable disease[45]. For example,
223 Warrington and colleagues[46] reported on genome wide association analysis of maternal and
224 offspring genotypes, birthweight and cardiometabolic disease in a population of more than
225 200,000 individuals. The analysis found 190 independent association signals indicating that
226 the fetal genotype determined both birthweight and adult blood pressure. This would
227 discount any involvement of maternal nutritional status or other putative programming
228 factors.
229
230 The fetal programming hypothesis is also open to criticism because so much of the
231 supporting evidence is dependent upon retrospective analysis of data gathered for other
232 purposes. Studies which attempt to link indicators of the fetal environment with outcomes
233 that manifest more than five decades later are inevitably vulnerable to confounding factors
234 which cannot be fully controlled for in statistical analysis[6,50]. In most studies except those
235 which have involved follow up of the wartime and other famines, there is no direct measure
236 of maternal nutritional status and much is inferred from birth anthropometry as an
237 imperfect proxy of undernutrition. A number of prospective cohort studies[47-49] have been
238 established to investigate the maternal nutrition relationship with offspring health, but all of

these are still many decades away from yielding useful observations that can adequately confirm or refute the hypothesis.

Given the counter-arguments to the nutritional programming hypothesis it has been important to assess the biological plausibility of the concept using experimental animal models. These have been able to demonstrate direct programming responses to manipulation of maternal diet, in the absence of genetic variation. Tests of the maternal diet-disease relationship have shown that the concept holds true, with a high degree of confidence. Programming through maternal undernutrition has been shown in a wide range of mammalian species including pigs, sheep, guinea pigs, mice and rats[50]. In genetically in-bred rodents restriction of maternal food intake, induction of iron deficiency and feeding a low protein diet in pregnancy impair fetal growth, disrupt placentation, lead to defects of glucose homeostasis, increase blood pressure and impair renal function in adult offspring, whose lifespans are reduced[51]. Studies of non-human primates also demonstrate that maternal undernutrition in pregnancy adversely programmes physiological and metabolic function in the exposed offspring[52]. Critically, the animal studies have shown that maternal undernutrition can programme later disease without any effect on birthweight. This undermines the argument that epidemiological evidence of programming explained by genetic variants that influence both fetal growth and long-term cardiometabolic functions[45].

As in humans, the adverse effects of maternal undernutrition upon offspring tend to develop with aging. For example, rats exposed to low protein diets during fetal life can

maintain normal renal function until they are 9 months old (about 40% of lifespan) but thereafter function declines more rapidly than in control rats and many males subject to maternal protein restriction die due to renal failure[53,54]. The same animals exhibit enhanced homeostatic responses to glucose loads as young adults but at 18 months old are insulin resistant, whilst control animals rarely show this impairment[55,56]. Consistent with the lifecourse view of health and disease, responses to nutritional challenges in adult life are modified by the fetal nutritional experience. Rats whose mothers were severely food restricted in pregnancy have an exaggerated response to a hypercaloric diet as adults, becoming more obese and metabolically impaired than offspring of mothers who were fed their normal diet[57]. Genetically modified mice with a diet-dependent pre-disposition to coronary heart disease had a greater atherogenic response to a high cholesterol diet if exposed to maternal protein restriction in utero[58].

Maternal obesity and the programming of disease

In investigating the associations between maternal undernutrition and programming of disease, experimental animal studies proved to be a useful follow up to the epidemiological observations, critically demonstrating the biological plausibility of the programming hypothesis and generating data relating to possible programming mechanisms. When considering possible links between exposure to maternal obesity and disease in adult life, the animal studies came largely before any amassing of compelling epidemiological evidence.

Obesity can be difficult to induce in experimental animal species as rodents, in particular, are better able than humans to regulate their energy balance[59]. Rats and mice are the species of choice for experimental models, and many studies rely on feeding diets high in fat and sugar to increase adiposity. Studies of this nature have shown that obesity in pregnancy can programme glucose intolerance, dyslipidaemia and elevated blood pressure in offspring[60]. However, these experiments may be confounded by the fact that the offspring are exposed directly to these diets in addition to the maternal adiposity during fetal development and the suckling period. To modify the maternal diets to increase fat and sugar content inevitably reduces intake of protein and micronutrients and this is known to have a programming impact in itself[50]. It is important to appreciate that these diets are provided to animals as a homogenous, pelleted foodstuff and ingesting high quantities of sucrose or specific fatty acids may be directly responsible for programming effects through their bioactivity, rather than the interpretation that the effects are due to maternal obesity[59].

An alternative approach has been to induce obesity using cafeteria feeding. This involves rats being offered a constantly changing array of highly palatable human foods in addition to their baseline (low energy) rodent feed[59, 61-64]. Once obesity is established the rats can be transferred to their lower energy food, or maintained on the cafeteria diet for pregnancy, and offspring can be kept with their mothers or cross-fostered to mothers with a different dietary or weight status. In this way the effects of obesity during pregnancy and lactation can be studied independently of direct dietary effects. This approach has shown that maternal obesity can programme brain development and behaviour, adiposity and glucose homeostasis in offspring[63-66]. Rats exposed to cafeteria diet in utero have an enhanced

preference for high sugar and high fat foods when they are adults. In non-human primates maternal obesity has similar effects to what is observed in rodents. In young Japanese macaques the offspring of obese mothers fed a Western style diet exhibited impaired insulin sensitivity in muscle even before they were weaned[67]. Hypersecretion of insulin by pancreatic islets of young macaques exposed to this Western diet in utero suggests that there is a programmed dysfunction of glucose metabolism which will deteriorate with ageing[68].

In humans it is well recognised that there is a strong genetic component to obesity. Individuals with one or two obese parents are more likely to be obese themselves and the heritability of an obese phenotype has been estimated to be as high as 70%. Whitaker *et al.*,[69] reported that the risk of obesity with one obese parent was doubled, but interestingly the relationship was stronger where it was the mother who was obese. Such observations do not only reflect genetic influences, as children will generally share their environment with their parents and hence experience the same dietary and behavioural drivers of excessive fat deposition. Exploration of a possible programming basis for this was initially stuck on the idea that low birthweight was a driver of later disease, as discussed earlier in this review. Studies showed that birth anthropometry was predictive of later obesity. A longitudinal follow up of the 1956 UK Birth Cohort found a J-shaped relationship between birthweight and BMI in 33-year-old men and this appeared to be heavily driven by maternal but not paternal weight[70]. A Finnish study found that risk of abdominal obesity was greater in young adults who had been born small-for-gestational age[71]. Generally the evidence supported the

view that obesity in adolescence and adulthood was predicted either by low birth weight or being a large baby at birth[72]. These observations of indirect relationships between early life exposures, with birthweight as a proxy are however, somewhat obsolete given there are more recent reports of direct associations between maternal BMI and adverse health indicators and outcomes in offspring.

The Growing Up Today study has followed up approximately 15000 children of women who participated in the well-characterised US Nurses Health Study[73]. When followed up in adolescence those who had been exposed to GDM during fetal development were more likely to be overweight. The analysis indicated an independent influence of maternal BMI in this relationship[73]. If mothers maintained a healthy weight before pregnancy and engaged in a healthy dietary pattern, 150 minutes or more of moderate/vigorous exercise and avoided smoking, then their children were less likely to be obese between 9 and 14 years[74]. Maternal BMI between 18.5 and 24.9 kg/m^2 was associated with a lower risk of childhood obesity (OR 0.44, 95%CI 0.39-0.50 relative to higher BMI range) and maternal BMI was the strongest predictor of childhood weight outcomes. Other studies have similarly indicated that adiposity is greater in children whose mothers were living with obesity[75-77]. A follow up of Thai 19-22 year olds found a 25% greater risk of obesity for every 1 kg/m2 increase in maternal BMI. The risk of offspring obesity among the children of mothers with BMI in the obese range was 17-fold higher than in children of mothers of ideal weight[78].

Of far greater significance are the observations that maternal obesity has a long-term impact on metabolic function and disease outcomes. Some of these have been derived from record linkage studies of very large populations. Follow up of 2.23 million Swedish births between 1992 and 2016 found that diagnosis of cardiovascular disease between the ages of 1 and 25 years was more likely in those whose mothers had been obese in pregnancy, than it was in those whose mothers had been of ideal weight[79]. The risk was graded so that whilst those whose mothers had BMI between 30 and 34.9 kg/m^2 were 16% more likely to have cardiovascular disease, this increased to 2.51-fold if maternal BMI was over 40 kg/m^2. Tan *et al.*,[77] found that elevated cardiovascular disease risk factors (raised blood pressure, dyslipidaemia) were present in 13-year-old children of mothers who were overweight or obese relative to children of mothers of ideal weight. Follow up of Finnish men and women born between 1934 and 1944 found that those whose mothers had had a BMI greater than 28 kg/m^2 in pregnancy were at greater risk of cardiovascular disease. Men were more prone to coronary heart disease and women to stroke[80]. Reynolds *et al.*,[81] showed that among 37709 34-61-year-olds, all cause mortality was greater in those whose mothers had been obese than in those whose mothers had been of idea weight. Offspring of mothers with BMI>30kg/m^2 were also more likely to have had a hospital admission with cardiovascular disease (OR 1.29, 95% CI 1.06-1.57).

Exposure to maternal obesity is associated with metabolic dysfunction. Boney and colleagues[82] reported that 11-year-old children were at increased risk of developing the metabolic syndrome if born to mothers living with obesity. Similarly elevated risk of insulin

370 resistance was observable in young men and, to a lesser extent, women if their mothers
371 were obese[76], whilst Bucci *et al*.,[83] reported muscular insulin sensitivity was impaired in frail
372 elderly men (average age 72 years) whose mothers had been obese. Follow up of men and
373 women born in Helsinki in the 1930s and 40s demonstrated that women whose mothers
374 were of higher BMI were at greater risk of developing type-2 diabetes as adults[80]. In the
375 same way, record linkage of 118201 Aberdeen births (1950-2011) to the Scottish diabetes
376 register revealed that offspring of overweight (OR 1.39, 95%CI 1.06-1.83) and obese (OR 3.8,
377 95%CI 2.33-5.06) mothers were at markedly elevated risk of type-2 diabetes[84]. There is also
378 evidence that maternal obesity increases the risk of type-1 diabetes as among more than 1.26
379 million Swedish children born between 1992 and 2004, obesity in pregnancy predicted a
380 type-1 diabetes diagnosis (OR 1.33, 95%CI 1.2-1.48)[85]. Similarly, analysis of data relating to the
381 births of children who were subsequently hospitalised with type-1 diabetes found that
382 maternal BMI>30 kg/m2 was a significant risk factor (IR 1.29 95%CI 1.01-1.64)[86]. To some
383 extent this relationship could be explained by the association of maternal obesity with
384 higher birthweight as there is an association between higher weight at birth and type-1
385 diabetes[87]. Alternatively it may be that maternal obesity is a driver of autoimmune damage
386 to the infant pancreas. Analysis of blood markers of islet autoimmunity in neonates found
387 that maternal obesity and gestational weight gain over 15 kg were associated with an
388 autoimmune profile[88], although other studies have not confirmed this observation[89]. Other
389 studies suggest that maternal obesity may programme renal development and function[90]
390 and asthma[91].
391

A number of studies are suggestive of programming effects of maternal obesity and/or obesogenic diets on appetite and food preferences in humans. A preference for a higher carbohydrate intake was observed in adult men, whose mothers were obese in pregnancy[92]. Follow-ups of the Avon Longitudinal Study of Parents and Children found that at age 10 years, dietary choices were strongly related to those of mothers pre-pregnancy. There was no evidence of any paternal influence on children's food choice, and the relationship between childhood feeding and mother's postnatal behaviours was less marked. This supports the idea that appetite regulation is programmed in utero[93]. In the same cohort, unhealthy maternal behaviours including consumption of 'junk' food in pregnancy was associated with fat mass in 15-year-old children, again with no paternal influence[94]. Wardle and colleagues[95] found that among lean children with overweight or obese parents, there was a higher preference for fatty foods in taste tests and an 'overeating eating style. Whilst the study did not split the cohort dependent on whether the mothers or fathers were obese, the average BMI of the mothers in the study was 36 kg/m^2, whilst it was only 29 kg/m^2 for the fathers. The data add to the view that maternal obesity determines offspring feeding behaviour in humans, as it does in experimental animals[66,96,97].

Mechanistic perspectives on programming by obesity

Many putative mechanisms have been suggested to explain how maternal nutritional status during pregnancy can programme disease risk in the exposed offspring. For any programming to take place there needs to be some signal, or signals, of the maternal

environment to the fetus. This signal then has to be recognized and elicit a response. There is a lot of debate about the process of recognition to initiate the response, with many researchers suggesting that maternal nutritional status elicits changes to the fetal epigenome and thereby sets in train long-term physiological adaptations, but the evidence for this is, as yet, not wholly convincing. The nature of the response to the maternal environment is somewhat easier to determine and one of the simplest mechanisms that can explain how variation in maternal nutritional status (including obesity) brings about changes in fetal anatomy and physiology involves the process of tissue remodelling. This rests on the idea that changes to the numbers of cells or the type of cells present within a tissue will reshape the morphology of that tissue and could have profound effects upon organ function[6].

All organs and tissues are derived from small populations of embryonic progenitor cell lines, which go through waves of rapid cell proliferation and differentiation to achieve their development before parturition. An adverse maternal environment during these critical periods can effectively prevent formation of an optimal number of specialized structures- remodelling the genetically determined pattern- and limit the functional capacity of the mature organ. There is extensive evidence from animal studies of maternal undernutrition which demonstrates remodelling takes place in response to adverse conditions in a range of organs, including the kidneys, brain and pancreas[98-100] This remodelling appears to underpin fetal programming of renal disease, appetite regulation and impaired metabolic regulation. Whilst harder to demonstrate in humans, there is evidence of associations between low

436 birthweight and renal structure[101-103]. The evidence base for tissue remodelling in response
437 to maternal obesity is more limited but in rodents there is evidence that offspring of obese
438 mothers fed a cafeteria diet prior to pregnancy also have altered renal structure (lower
439 nephron number, Akyol and Langley-Evans, unpublished data). Interestingly, ultrasound
440 examination of the kidneys of infants who mothers were obese indigenous Australians,
441 indicated that they had lower kidney volume, consistent with having been remodelled[90].
442
443 Modifying the numbers and types of cells present within a tissue will have a range of
444 consequences and the knock-on effects on metabolic and physiological regulation will
445 establish a predisposition for non-communicable disease. This will not manifest as disease in
446 childhood, instead being revealed when the individual undergoes metabolic or physiological
447 challenge, or as tissue functions naturally deteriorate with age. Alterations to the profile of
448 cell types present within a tissue may also modify the capacity of a tissue to produce or
449 respond to hormones, alter gene expression or interfere with cell signaling pathways. Some
450 of these changes may have very localized effects, simply impacting upon the function of a
451 particular tissue, but others could disrupt regulation throughout the body. The
452 epidemiological evidence that points to an association between maternal obesity and later
453 disease in humans is well matched with the evidence from animal studies, and both point to
454 disruption of metabolic regulation at the whole-body level. As shown in Figure 5, this may
455 result from remodeling of multiple tissues. Remodeling of adipose tissue so that there are
456 fewer cells may underpin the observed propensity for offspring of women with high BMI to
457 become obese as adipose tissue dysfunction impacts both the storage capacity of the tissue

458 and regulation of metabolism by adipokines. Insulin resistance and the reported type-1 and
459 type-2 diabetes in individuals exposed to obesity in fetal life could be explained by
460 pancreatic remodeling and programming of liver structure could contribute to a number of
461 metabolic anomalies including the dyslipidaemia reported by Tan *et al*.,[77]. Remodeling of the
462 hypothalamus has been reported as an outcome of maternal protein restriction in rats. If the
463 tissue were also sensitive to maternal obesity, then the impact on whole-body homeostasis
464 could be profound. Evidence from rodent studies suggests maternal obesity during lactation
465 does have an impact on hippocampal and hypothalamic neurotransmitter production, with
466 consequent effects on behaviour and feeding[65.66.104]. The observations that men who had
467 obese mothers have a greater preference for carbohydrates[92] and that children's food
468 preferences follow their mother's pre-pregnancy behaviours but not their father's[93], may
469 indicate that the same mechanisms could operate in humans.
470
471 Tissue remodelling provides a route through which the adverse developmental environment
472 of maternal obesity can programme offspring health, but does not explain how the fetal
473 tissues receive signals of that environment. Whatever the programming stimulus or insult is,
474 there is little doubt that it is mediated via the placenta. As shown in Figure 6, the placenta is
475 not a passive facilitator of movement of oxygen, substrates and metabolic waste products
476 between maternal and fetal compartments. It is a metabolically active tissue which
477 generates substrates for the fetus and is a source of hormones and growth factors. All
478 signals between mother and fetus are subject to modulation by placental activity.
479

The impact of maternal obesity on placentation is demonstrated by the greater risk of pre-eclampsia[105] in obese women. In pre-eclampsia, inflammatory processes and oxidative injury leads to arterial dysfunction and breakdown of transport capacity[106]. It seems likely that the condition is the extreme endpoint of damaging impacts of maternal obesity on placental integrity and function. This is likely to have adverse programming effects on fetal development. Histopathological analyses of placentas from obese women show evidence of inflammatory processes and under-perfusion, even in the absence of pre-eclampsia[107]. As early as the first trimester, obesity alters the expression of cell cycle regulatory genes in the placenta, which may impact on further placental growth and development and the capacity to maintain function at later stages of pregnancy[108]. Among the hormones secreted by the placenta are leptin and adiponectin. These adipokines influence the development of adipose tissue in the fetus. Leptin also modulates the formation of the homeostatic endocrine axes in the fetal brain. Measurements of adipokine concentrations in cord blood at birth has shown elevated concentrations with maternal obesity[109].

In addition to changes in the expression and release of endocrine signals, obesity impacts on fatty acid metabolism in the placenta. Altered expression of transcription factors and regulatory genes, including peroxisome proliferator activated receptor gamma coactivator 1 and carnitine palmitoyltransferase 1_{alpha} will impact on both lipid and carbohydrate metabolism and has been observed alongside elevated LDL-cholesterol and lower HDL-cholesterol concentrations in cord blood of fetuses exposed to maternal obesity[110]. Similarly, the observation that expression of genes that regulate placental cholesterol transport is

related to maternal BMI, suggests that cholesterol handling is disrupted by maternal obesity[111]. This may promote atherogenesis in the placental vessels (associated with pre-eclampsia) and disrupt steroid hormone production. Obesity impacts upon fatty acid transport by the placenta and promotes an inflammatory response[112]. The capacity of the placenta to store fatty acids is limited with obesity, resulting in greater mobilisation into the fetal compartment[113].

Clues to the mechanism of programming by maternal obesity may be gained from studies of GDM, as the long-term health of offspring exposed to GDM are largely the same as observed with maternal obesity, although obesity can occur without GDM and vice versa. As early as 2 years of age, GDM offspring exhibit markedly greater risk of obesity[114] and this persists into childhood[115-117]. Dabelea and colleagues[118] followed up sibling pairs where one of the pair had been exposed to GDM and the other had not. Among people in their early 20's, those who had experienced GDM in fetal life had a BMI on average 2.6 kg/m2 greater than unexposed siblings[118]. Alongside greater risk of obesity, offspring of GDM-affected pregnancies are at greater risk of metabolic disorders. Damm *et al*.,[119] reported a 2-fold greater risk of obesity in adults exposed to GDM in utero, accompanied by an 8-fold greater risk of pre-diabetes and diabetes than in the background population. The adverse effects of exposure to GDM may be much broader, with, for example, reports of greater prevalence of psychiatric disorders in adults whose mothers had the condition in pregnancy[120].

A simple explanation of how GDM and possibly maternal obesity provide the insult which programmes long-term consequences for the exposed offspring, is that an excess of energy substrates reaches the fetal compartment. The conventional wisdom is that this is the cause of macrosomia in GDM pregnancies, as the fetus is hyperinsulinaemic and the insulin resistance of the mother drives glucose and lipids across the placenta[8]. However, this is an over-simplification as, like obesity, GDM has a broad impact on the placenta which will bring other factors into play. Widespread morphological changes including hypervascularisation and an increase in placental size and thickness are proposed to be a compensatory response to GDM which will preserve placental perfusion[121]. There is also an increase in placental inflammation[122]. Several defects of placental metabolism and function have been reported with GDM, including a reduction in iron transport[123] and changes to lipid metabolism[124]. With GDM the placenta accumulates elevated concentrations of saturated fatty acids, with reduced transport of mono- and polyunsaturated fatty acids to the fetus[124].

Whilst it is clear that the basic mechanisms which drive programming of health and disease by maternal obesity involve signalling across the placenta and a fetal tissue response at the level of gene and protein expression, the precise nature of the maternal signal and the fetal response in humans remain unknown. Identifying the mechanism is a high priority as without this understanding, any intervention to prevent the long-term consequences of maternal obesity will remain solely dependent upon health education and behaviour change strategies. Experience suggests that these have limited efficacy at the population level.

Implications for the future

The global obesity crisis will have profound consequences for the health of populations for decades to come. Obesity in adults is well recognised as a modifiable risk factor for type-2 diabetes, cardiovascular disease and many types of cancer. The evidence presented above would also suggest that the increasing numbers of individuals exposed to maternal overweight and obesity are themselves at greater risk of becoming obese and the associated cardiometabolic disorders. They will, in turn, be exposing their children to obesity in utero. There is a significant risk that a transgenerational cycle of obesity will be, or has already been, established (Figure 7). Such a cycle would have consequences for public health over a century or more unless effective means can be found to break it. Importantly, as obesity rates increase most rapidly in the populations of the global south, there is a risk of an explosion of metabolic disease on an unimaginable scale in nations ill-equipped to deal with it.

Breaking such a cycle is a public health challenge of colossal complexity. The mode of intervention must be multifactorial, comprising locally tailored, culturally sensitive community education, widespread screening for pre-disease and investment in preventive health services. In short, a global shift in food cultures and living environments is necessary. Achieving this is unlikely, but as the global focus moves towards sustainability there may be opportunities to make inroads. The timing of interventions to break the transgenerational obesity cycle also needs to be considered in a more holistic manner. It is simple to think that the antenatal period is the key window for intervention. Limiting gestational weight gain

and promoting a return to pre-pregnancy weight in the post-partum period will have many benefits. Pregnancy is perceived as a teachable moment when women are more open to public health messages and willing to make lifestyle changes[8, 125], but numerous large-scale trials show limited efficacy of, and high resistance to pregnancy-focused interventions[126, 127]. The most effective approaches to managing weight gain in pregnancy appear to rely on more personalised interventions that are supported by eHealth packages and health professionals that have received appropriate training[8,128,129]. Midwives, in particular, can find it difficult to engage with women about excess weight gain[130,131] but may find it useful to have an understanding of the transgenerational consequences of antenatal obesity as they frame their conversations with women.

Recommendations on antenatal weight management are heavily focused on women making changes to diet and lifestyle before they conceive[8]. For women with extreme obesity this might involve bariatric surgery and a number of studies demonstrate that women who achieve large weight loss through surgery have healthy pregnancies with reduced risk of complications and good outcomes[132-134]. There is an emerging literature on the effects this weight loss may have on the long-term health of babies born after weight loss. Smith and colleagues compared siblings whose mothers had undergone bariatric surgery, examining health indices in those born before and after the surgery[135]. Individuals born after weight loss surgery were born with lower birthweight and were markedly less likely to be obese than their siblings born before the surgery. There was also evidence of better insulin sensitivity, lower concentrations of inflammatory markers and adipokine concentrations that were more consistent with metabolic health[135]. However, the study only considered 49

589 sibling pairs and the ages of the subjects varied widely (2.6 to 26 years of age). The
590 systematic review of Dunford and Sangster concluded that pre-pregnancy weight loss
591 results in lower body fatness and improved insulin sensitivity in children born after weight
592 loss compared to before, and suggested that changes to DNA methylation may play a role in
593 this[136]. A study of 31 sibling pairs noted differential DNA methylation of genes associated
594 with insulin receptor signalling and type-2 diabetes risk[137]. However, as the study was small
595 and the significance of methylation differences in whole blood samples is debatable,
596 inferring a mechanism of programming from this is premature. It is hopeful, however, that
597 action to address weight problems before pregnancy can prevent maternal programming of
598 adverse health in the developing fetus. A number of trials are now underway to address the
599 impact of major weight loss on long-term health and wellbeing[138,139].
600
601 Just as health at any stage of life is dependent upon the outcomes of gene-environment
602 interactions at all preceding life stages, there are also opportunities to intervene and break
603 the programmed trajectory during childhood. The literature that explores the tracking of
604 obesity from childhood to adulthood indicates that the obese child is not predestined to
605 become an obese adult, although obesity in adolescence does appear to track strongly to
606 the adult years[140, 141]. This highlights that the childhood years are a key time to address
607 overweight and obesity that may have been programmed in utero. Importantly the evidence
608 shows that early intervention to reverse excessive weight in childhood removes any residual
609 metabolic risk, so the obese child who becomes a lean adult is at no cardiometabolic
610 disadvantage[140, 141].

611

612 Choices about infant feeding methods may represent the first point in the postnatal period
613 when the impact of being an obese mother may be ameliorated. Systematic reviews and
614 meta-analyses indicate that breastfeeding reduces the risk of childhood and adult obesity,
615 with exclusive breastfeeding and breastfeeding for a longer period (up to 12 months) having
616 greater benefits[142]. Horta and colleagues[143] showed that breastfeeding was protective
617 against overweight and obesity in both childhood (OR 0.74, 95%CI 0.68-0.79) and in adults
618 (OR 0.88 95%CI 0.82-0.94). The greater risk of overweight seen in formula fed infants could
619 result from the higher protein content of formula milks[144], but it is also clear that
620 breastfeeding brings advantages beyond just the milk composition. Demand-led feeding, for
621 example, will be associated with normal development of satiety pathways and appetite
622 regulation, and milk contains a range of non-nutrient components. These include the
623 appetite regulatory hormones leptin, adiponectin, resistin and ghrelin[145], which may play a
624 key role in establishment of appetite control in the infant hypothalamus[146].

625

626 Whilst breastfeeding may represent a means of compensating against exposure to obesity
627 in utero, little is known about how obesity changes the composition (nutrient and hormone)
628 of human milk and whether breastfeeding by an obese mother carries the same advantages
629 as reported for the full breastfeeding population. Studies in rodents have identified that
630 cafeteria feeding during lactation can programme offspring feeding and other behaviours,
631 suggesting that milk may carry adverse programming signals[65,66,104]. However the
632 immaturity of rat pups at birth makes them very different to human infants, so the same

633 milk-related cues may not apply in the development of the human infant brain. Human milk
634 is believed to be a highly dynamic food, with its composition changing according to stage of
635 development, in response to diet, time of day and even varying between breasts in the same
636 woman. However, much of the literature on milk composition is old and features poorly
637 designed, small studies and little is known about how milk composition varies in response to
638 acute changes in diet and what impact maternal adiposity may have. Leghi *et al*.,[147] reported
639 that concentrations of macronutrients in milk showed little variation over a 3 week period.
640 *Ward et al*.,[148] found considerable diurnal variation in composition. Acutely increasing
641 maternal fat consumption did not impact on macronutrients in milk over a 12-hour period,
642 whilst in contrast an increase in sugar intake resulted in a rapid increase in milk
643 triglycerides[148]. A lot more research is required to understand what sort of diet may be
644 optimal for the production of an anti-obesogenic milk profile by women and how this may
645 vary between women of ideal weight and those who are overweight.
646
647 The introduction of complementary foods (weaning) is another point in time where
648 decisions may have long-term benefits for further health. Timing of weaning is believed to
649 play an important role and, as described above, maintaining breastfeeding throughout the
650 process prolongs exposure to human milk and the associated beneficial factors. There is
651 evidence that very early introduction of solids (before 4 months) or delaying to beyond 6
652 months may increase risk of childhood overweight[149]. The inclusion of foods rich in protein
653 appears advantageous in terms of infant growth and body composition, but if used in
654 complementary feeding between 2 and 12 months, the risk of overweight in childhood is

655 increased[150]. There is a literature that considers feeding style during weaning, with some
656 researchers advocating that a baby-led weaning approach, rather than a parent-led spoon-
657 feeding approach, reduces risk of later obesity by allowing the infant to self-regulate intake
658 and programme the development of satiety centres in the hypothalamus, which are not
659 mature at birth. However, there is no significant evidence that there is a robust effect, and
660 baby-led weaned infants may in fact self-select a diet that is high in sugars[151-153].
661
662 To effectively meet the challenge of a transgenerational cycle of obesity and metabolic
663 disorders, a multifaceted approach will be necessary. This needs to target infants and
664 children to promote healthy eating and lifestyles; adolescents to reinforce those messages
665 before they become reproductively active; pregnant women to optimise nutrition, control
666 weight gain and prevent GDM and; the post-partum period to promote a return to pre-
667 pregnancy weight and facilitate long-term breastfeeding[154]. The emergence of evidence that
668 paternal factors can also programme cardiometabolic health in offspring via semen-related
669 factors, means that boys as well as girls need to be the focus of optimal health behaviours
670 for parenting[155,156]. The global increase in obesity among children and adults is a public
671 health concern with the potential to have consequences over many generations. The
672 growing understanding that excessive adiposity in pregnancy can threaten both the
673 immediate and long-term health outcomes for the developing fetus should act as a stimulus
674 for action across the world. Improving the nutrition and understanding of young people in
675 order to optimise their reproductive fitness will be a considerable challenge in the face of
676 other societal and population health issues, but should be regarded as a high priority.

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Figure legends

Figure 1 The underlying determinants of health and disease are complex and vary across the lifespan.

At all stages of life health status is a product of gene-environment interactions. In early life genetics plays a more important than in later life. Risk of disease at all stages of life is a product of the outcomes of gene-environment interactions at earlier stages.

Figure 2 The rising prevalence of obesity

A. Overweight and obesity among adult women in selected countries.
B. Overweight and obesity among children aged 2-4 years in selected countries.

Data from[7].

Aus- Australia, Can-Canada, Chn-China, Fra-France, Ger-Germany, Gre-Greece, UK-United Kingdom, USA-United States of America.

Figure 3 Maternal and paternal factors modify genetically determined developmental potential to determine the fetal genotype at birth.

Figure 4 Programming of disease in later life can be driven by both maternal under- and overnutrition.

Figure 5 Remodelling of the structures of specific tissues in fetal life may explain how maternal obesity programmes offspring adiposity and metabolic function.

Figure 6 The placenta must mediate the signal of maternal nutritional status to the fetus.

1230 *Figure 7 A transgenerational cycle of obesity and related disorders.*

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1233 *Figure 1*

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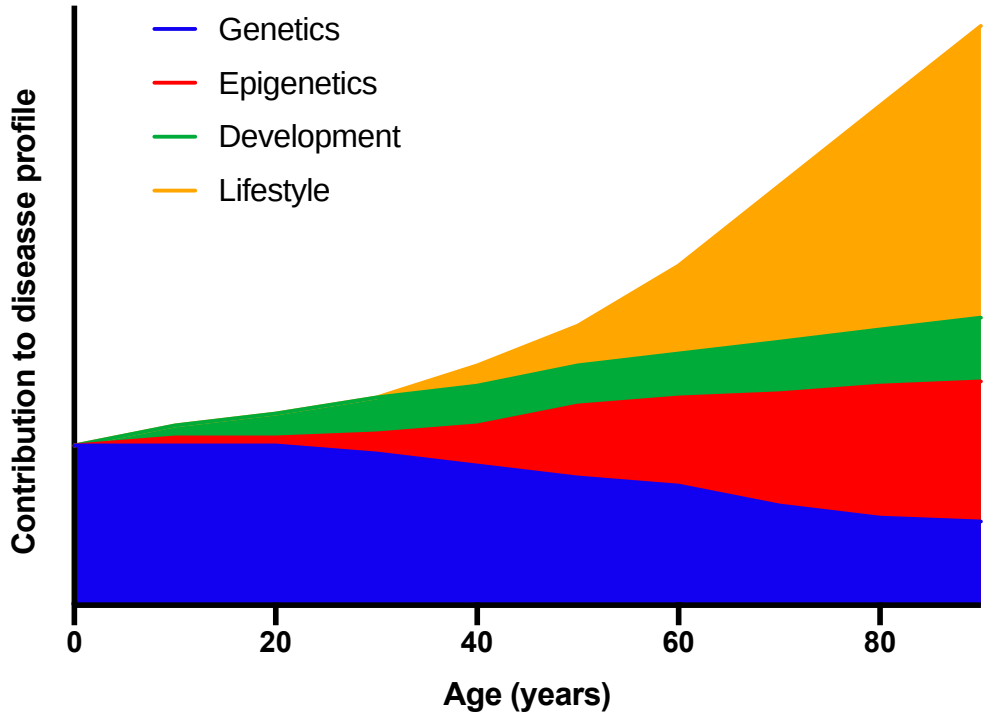

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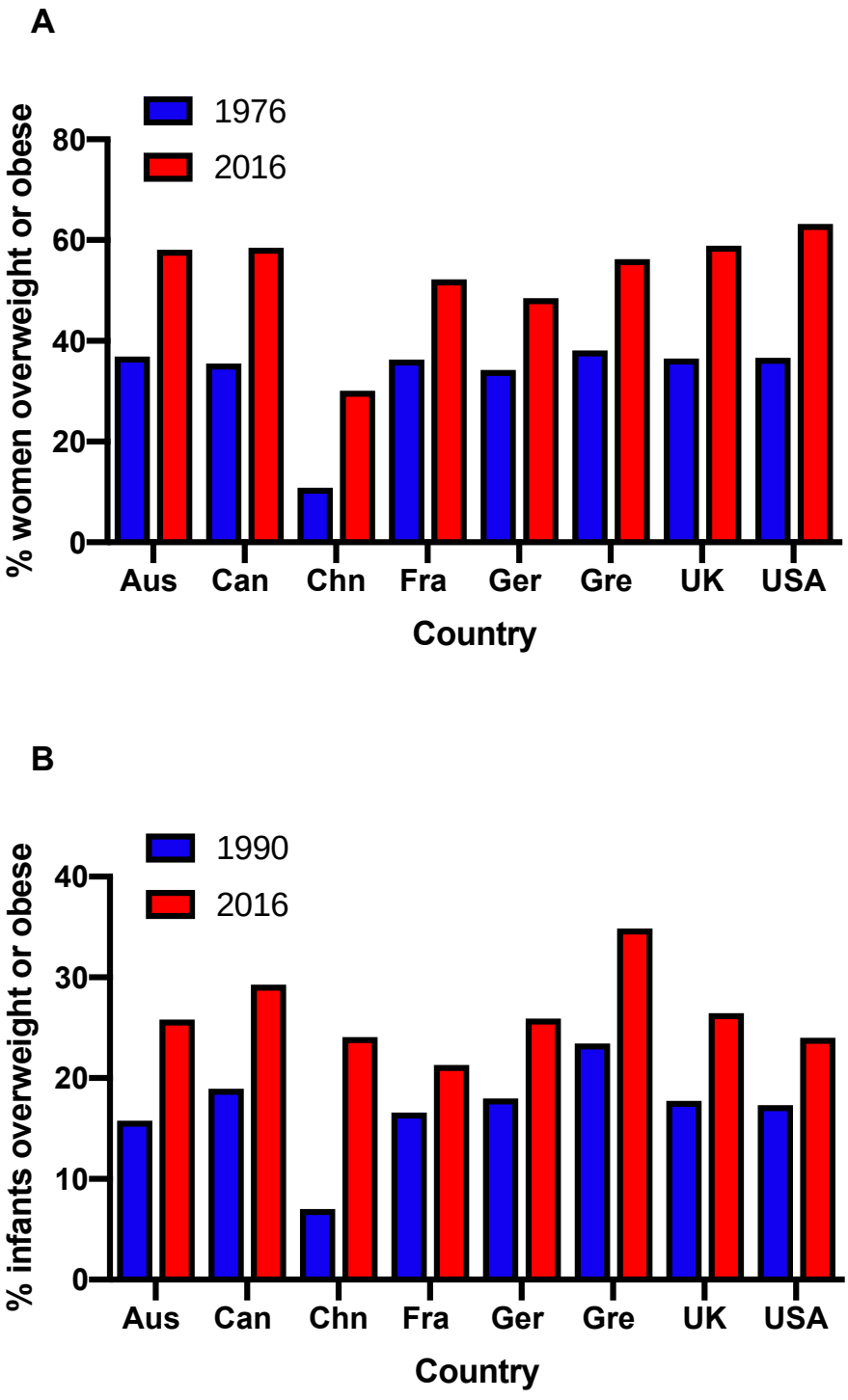

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1240 *Figure 2*

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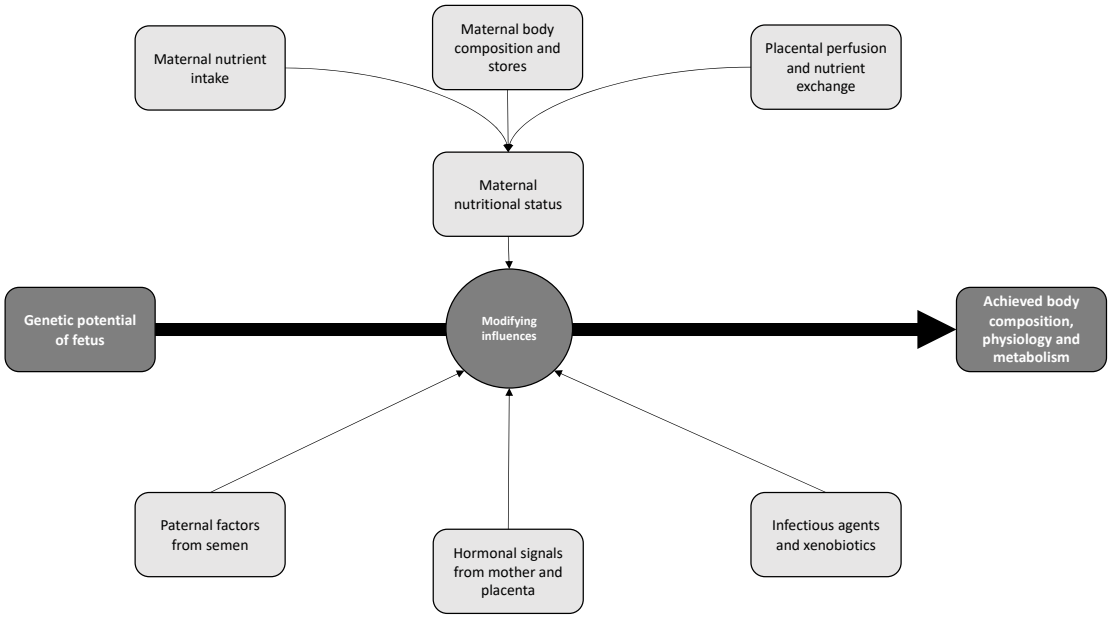
1242 *Figure 3*



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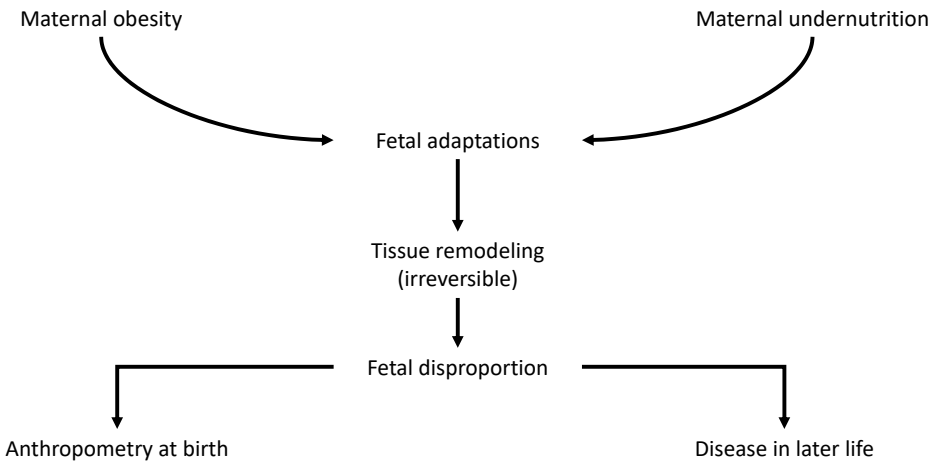

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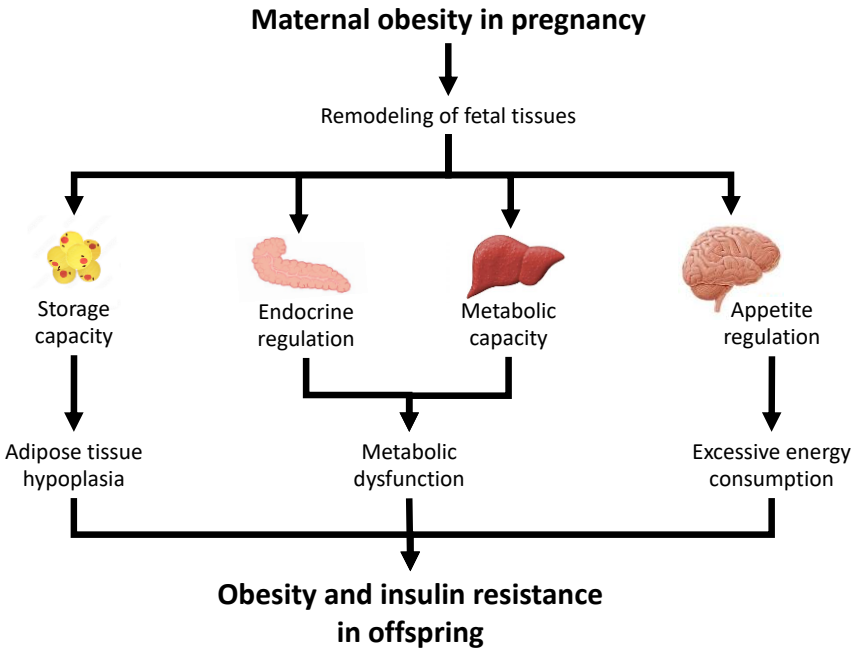

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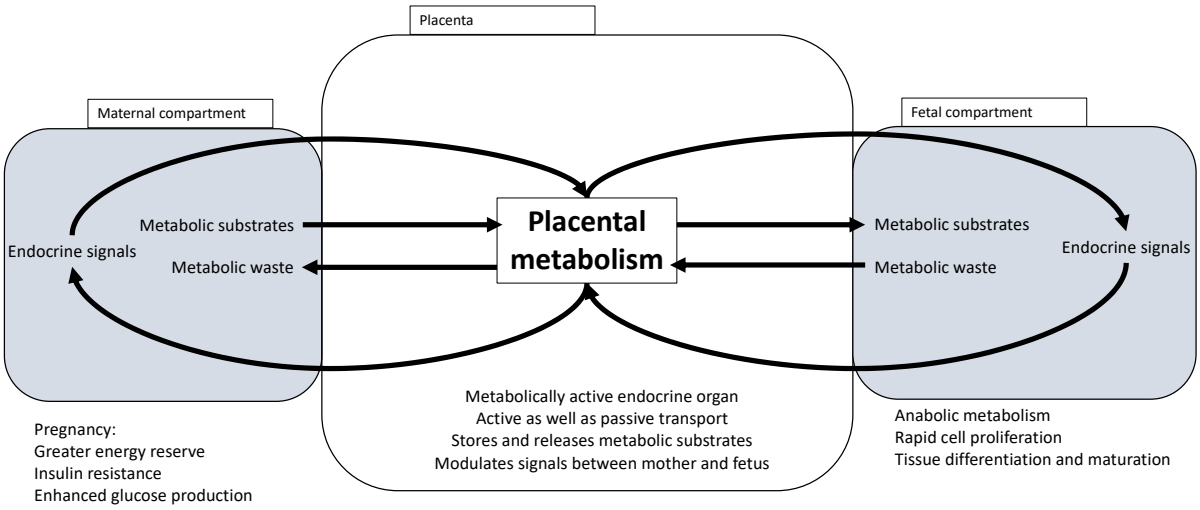
1250 *Figure 6*



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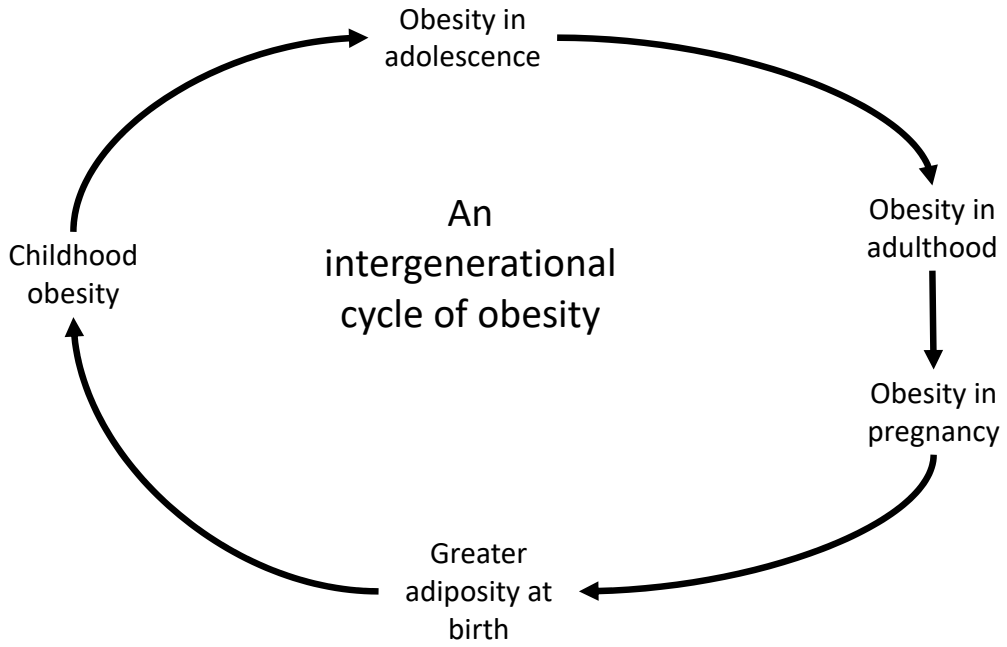

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