

## **Abstract**

The idea that nutrition in early life (such as before conception, during pregnancy and in infancy) can influence, or programme, long-term health, known as the 'Developmental Origins of Health and Disease Hypothesis', has generated great scientific interest. This concept is particularly relevant for the development of obesity and its complications, arguably the most important public health issue of the 21<sup>st</sup> century worldwide. The concept is strongly supported by evidence from animal studies, both observational and experimental (randomised) studies in humans, and is highly relevant for population health in both low-income and high-income countries. For instance, optimising nutrition in pregnancy (both in terms of under-nutrition and over-nutrition) and preventing too fast infant weight gain have been shown to reduce the risk of future obesity. Proposed mechanisms have included effects of early nutrition on the epigenome, hormones such as insulin, and regulation of appetite, that effect long-term risk of obesity. Although further data from experimental studies is required to support a causal link between early nutrition and future adiposity, the developmental origins hypothesis is already changing health policy and practice globally. The present review considers the evidence for the developmental origins of obesity, the mechanisms involved, and the implications for public health.

(200 words)

**Key words:** Obesity, programming, development, infant growth, breast-feeding

At the simplest level obesity can be regarded as a cumulative dysregulation of energy balance as a result of environmental and genetic contributing factors [1]. However, it is now increasingly apparent that treatment of obesity by simply addressing energy balance often yields disappointing results [1, 2]. Hence there is greater emphasis on prevention and particularly on the role nutrition in early life on prevention of future obesity and its complications [1, 2] – the so called ‘Developmental Origins of Health and Disease Hypothesis’ [3]. This concept, that nutrition during a brief window in development (such as before conception, during pregnancy and in infancy) can influence, or programme [4], later health is strongly supported by animal studies, evidence in humans from both high-income [5] and low-income countries [6-9], and has led to calls for changes in UK government policy [2]. The present review considers the evidence specifically for the developmental origins of obesity, the mechanisms involved, and the implications for public health, focusing where possible on experimental (randomised) studies in humans.

### **Historical Perspective**

One of the first demonstrations that early nutrition could affect long-term body size was by McCance in the 1960’s (as previously reviewed [5]). He showed that rats raised in small litters, and therefore overfed early in postnatal life (prior to weaning), were larger in adulthood. In humans, one of the first studies to suggest a long-term impact of early nutrition was from Eid in 1970 who showed that faster weight gain in the first 6 weeks of life increased the risk of obesity 6-8 years later [5]. This concept of early nutrition influencing later health was formally defined by Lucas as ‘*programming*’, -the process by which ‘a stimulus or insult during a critical or sensitive window in development produces long-term changes in the structure or function of the organism’ [4].

Some of the earliest evidence for programming was obtained in the late 1980’s. Analysis of historical health records from Hertfordshire found independent associations between birthweight and weight at 1 year with later risk of cardiovascular disease (CVD) [10].

Explanatory models based on this largely centred on fetal growth retardation, and included: (i) adverse effects of reduced fetal growth and nutrition on later CVD ('fetal origins of adult disease hypothesis') [11, 12]; (ii) the concept that a particular genotype can give rise to different physiological and structural outcomes depending on the environment during development ('developmental plasticity') [13]; (iii) that prior adaptive programming of phenotype to the early environment may be deleterious to later health if mismatched with subsequent environment [14]; (e.g. growth-retarded newborns adapted to a low nutrient intake in utero, might then be at risk in an environment with excess nutrient availability) - the 'thrifty phenotype' hypothesis [15] for programming of insulin resistance and obesity is an example of this; and (iv) the concept that genes which predispose to low birthweight may also predispose to later CVD [16], a possibility confirmed in more recent genome-wide analyses [17].

In 2004, research in nutritional programming moved back from fetal nutrition to the early postnatal period. Singhal and Lucas published the 'unifying postnatal growth acceleration hypothesis' [18], proposing that slower early postnatal growth as a consequence of lower nutrient intake could (i) explain the beneficial effects of breast-feeding for CVD (breast-fed infants are relatively undernourished and grow more slowly than those fed formula); and (ii) could unify the postnatal and fetal origins hypotheses, since a fetus born small for gestational age (SGA) may show postnatal catch-up growth, known to be deleterious in many animal species [19, 20].

Since this early work, there has been an over-whelming accumulation of evidence to support the developmental origins of obesity. However, a key limitation of previous research has been the lack of *experimental* evidence to support a causal role of early nutrition in programming human health. Such trials have proved to be challenging because interventions have had limited effects on proxy measures of development (e.g. birthweight), and because of difficulties in following-up trial participants over many years. Nevertheless, as reviewed below, data from experimental human trials are

beginning to emerge and strongly support a causal link between early nutrition and long-term risk of obesity and its consequences.

## **Evidence from Epidemiological and Experimental Studies**

### *Intrauterine Influences –Undernutrition*

Although now regarded as a crude index of in-utero physiology and nutrition, most earlier work in nutritional programming focused on the association of birthweight with later obesity and its complications. This association has been replicated many times (including a systematic review of risk of type 2 diabetes in >150,000 individuals [21]) in both high-income [5] and low-income countries [7-9] and has led to the 'fetal undernutrition' hypothesis (as reviewed [22]). Consequently, nutritional interventions in pregnancy have been proposed to influence the development of obesity and CVD in the offspring.

However, although maternal supplementation in low-income populations (of micronutrients [23], or of energy and protein [24]), can reduce low birthweight, whether supplementation affects long-term health outcomes in the offspring remains uncertain and supported by only weak evidence [22]. For instance, a recent systematic review found that antenatal multiple micronutrient supplementation (compared to iron and folic acid) in low-income settings had no benefits for childhood survival, growth, body composition, blood pressure, respiratory or cognitive outcomes [25].

One possible explanation for the lack of a causal link between antenatal nutrition and long-term offspring health is that the critical window for nutritional programming is earlier and prior to conception. This hypothesis was tested in a recent trial of >6000 women from Mumbai who were randomly assigned to a low-micronutrient snack (control) or to a daily snack of green leafy vegetables, fruit and milk (intervention) given  $\geq 90$  days before conception and throughout pregnancy [26]. The intervention had no effect on birthweight, although there was a fall in the prevalence of gestational diabetes.

Although longer follow-up of infants in the Mumbai trial is required, currently, this study does not support a casual role for nutrition prior to conception or during pregnancy in influencing the risk of obesity in the offspring. Overall there is little experimental evidence to support the fetal undernutrition hypothesis [27].

#### *Intrauterine Influences -Overnutrition*

More recently, the focus in programming research has moved from studies of undernutrition, to studies of maternal over-nutrition and obesity, a huge global public health issue affecting >50% of women in many countries. The idea that maternal obesity (either pre-pregnancy or excessive weight gain during pregnancy) increases the risk of obesity and its complications in the offspring (summarised as the 'fetal over-nutrition' hypothesis [22]) is strongly supported by animal studies and observational studies in humans (as reviewed [22, 28, 29]). For example, a recent systematic review [29] identified consistent associations between increased adiposity in the offspring with maternal pre-pregnancy BMI (observed in 34/38 studies), gestational weight gain (19/21 studies), maternal diabetes mellitus (22/33 studies), delivery by caesarean section (6/11 studies), and a high birthweight (24/28 studies). The fetal over-nutrition hypothesis is further supported by the observation that infants of mothers who lose weight following bariatric surgery are at less risk of obesity compared to infants of the same mother born before surgery (a study design that controls for potential maternal confounding factors) [30]. However, similar strengths of associations for obesity between the mother and offspring as between fathers and offspring do not support the fetal over nutrition concept, raising the possibility that common lifestyle factors act within the family to increase risk of obesity in both the mother and her offspring [31]. Therefore whether there is casual link between maternal over-nutrition and childhood obesity remains uncertain.

A planned individual-patient meta-analysis of 7 dietary or lifestyle interventions in pregnancy could help resolve the role of maternal nutrition in predisposing to offspring adiposity [32]. Although, these intervention trials have shown consistent benefits of lifestyle interventions on maternal gestational weight gain and insulin resistance, few have found benefits for the offspring, other than a lower risk of birthweight above 4 kg (in 2 studies) [32]. However, the UK Pregnancies Better Eating and Activity trial in 1555 obese women reported a 0.26 SD lower scapular (but not triceps) skinfold thickness in infants in the intervention arm at age 5.9 months [33]. Whether this observation persists, and so supports a causal association between maternal nutrition/lifestyle and later childhood obesity requires further clarification.

### **Postnatal Influences**

Two recent systematic reviews have comprehensively compiled the evidence on the impact of infant nutrition on long-term risk of obesity and its complications [29, 34]. Hence, the current review will highlight only key concepts particularly in areas where experimental data is available.

#### *Early Infancy*

The most widely researched area within nutritional programming is for the influence of breast-feeding on future obesity. Nine systematic reviews and 3 systematic reviews of systematic reviews have investigated this association and most have shown a consistent protective effect (13% lower risk of later obesity with breast-feeding) [34]. A longer duration of breast-feeding appears to have a more protective effect, but there is little evidence to support a benefit of exclusive versus partial breast-feeding [34]. However, despite the consistency of the evidence, these observational studies cannot rule out residual confounding or establish causation.

Clearly, randomised controlled trials (RCTs) of breast-feeding interventions have major ethical and logistical challenges. One such intervention, the Promotion of Breast-feeding

Intervention Trial (PROBIT) increased the duration of exclusive breast-feeding, but found no benefit for childhood adiposity (as reviewed [34]). However, this study was designed to investigate effects of duration of breast-feeding and exclusivity on later health and not any breast-feeding versus formula-feeding (especially early in infancy). Another RCT was in preterm infants, who were randomly assigned to donated, banked breast-milk or to infant formula given either as the sole diet or as a supplement to their mother's own milk [18]. In these studies, human-milk feeding compared to formula-feeding decreased major risk factors for CVD (leptin resistance, dyslipidaemia, high blood pressure, and insulin resistance) up to 16 years later [18]. Infants with the highest proportion of human milk intake had the greatest benefit, so supporting a dose-response effect.

How breast-feeding protects against later obesity is unknown, but research has focused on 4 main areas: i) differences in maternal behaviour (e.g. children who were breast-fed may be less prone to obesity because breast-feeding is more common in families that adopt healthier lifestyles; ii) differences in infant behaviour (breast-fed infants, by controlling the amount of milk they consume, may learn to better regulate their energy intake); iii) differences in composition of human milk compared to formula; and iv) differences in growth patterns between breast- and formula-fed infants [35]. Of these areas, there is little evidence to suggest that future obesity is influenced by behavioural differences between breast- and formula-fed infants, or by nutrients found in human milk, but absent from unmodified formulas (e.g. probiotics, non-digestible carbohydrates, or long chain polyunsaturated fatty acids [34]). However, there is consistent evidence that less postnatal growth acceleration (upward centile crossing) could partly explain the long-term cardiovascular advantages of breast-feeding [29].

Support for the growth acceleration concept has accumulated rapidly. The association between faster infant growth with later obesity and its cardiovascular complications has been seen in infants born at term, SGA, or pre-term; for both infant weight gain and linear growth; in infants breast- or formula-fed; for health outcomes in children and

adults; and in both high-income and low-income countries (including South Africa, Mexico, Brazil, China, Sri Lanka, and India) [5, 29]. The effects of growth acceleration on obesity have been seen in 45 of 46 studies [29], including an individual patient meta-analysis in 47,661 individuals (summarised in 5 systematic reviews, [5]). These effects appear to be most marked for central or visceral fat and are substantial, with the relative risk of obesity associated with faster infant weight gain estimated to range from 1.2 to as high as 5.7 [5].

Importantly, the growth acceleration hypothesis is strongly supported by evidence from experimental studies. The fact that formula-fed infants grow faster than those breast-fed (probably due to the higher protein content of formula) has provided an opportunity to test the growth acceleration hypothesis in RCTs using formulas of different protein concentration. For instance, term infants born SGA and randomly assigned to protein-enriched formulas had 3 mm Hg higher diastolic blood pressure at age 6–8 years, and, in 2 trials, 18–38% greater fat mass at age 5–8 years than controls [5]. Lower protein formulas (that result in slower infant weight gain) have been shown to reduce the later risk of obesity in 5 RCTs from both high-income and middle-income countries (as reviewed [5]). The largest study, the European clinical obesity trial, found that infants randomised in the first year of life to formulas with standard versus higher protein concentration had lower risk of obesity at age 2 and 6 years [36] and even lower pre-peritoneal fat mass, a key metabolic risk factor [37]. Interventions in the above trials were all in the first year (ranging from the first 2 weeks [18], to 1–12 months of age, [5]), but the most sensitive window for programming effects within the first year is unknown and an area of active research.

Although most RCTs have focused on formula-fed infants, the growth acceleration hypothesis is also likely to apply to infants predominantly breast-fed. For example, a RCT of a responsive feeding intervention that reduced over-feeding in both formula- and breast-fed infants (and hence led to slower growth in the first 6 months), also reduced



the risk of obesity at age 1 year [38]. Although longer follow-up is required, this trial supports the role of early over-feeding in programming obesity in breast-fed as well as formula-fed infants.

### *Later Infancy*

The growth acceleration concept could also explain other aspects of the developmental origins of obesity hypothesis. For example, faster infant weight gain resulting from higher protein and energy intake, could explain the association between early introduction of complementary feeding (<4 months) with greater risk of later obesity [39]. Similarly, the association between an earlier age of adiposity rebound and future adiposity [40] may occur because an earlier age of adiposity rebound identifies children whose BMI centile is high and/or already crossing centiles upwards [41]. Finally, the association between a high protein intake in infants and toddlers (particularly from cow's milk) with later obesity may result, in part, from the growth promoting effects of protein [40, 42].

### **Mechanisms**

A detailed summary of mechanism for the developmental origins of obesity is beyond the scope of this review. However, as discussed previously [3, 7], most research has focused on genetic factors affecting both developmental markers (e.g. birthweight) and later health, the role of epigenetic changes [28], effects on gut microbiota, and programming effects on appetite and set-points for hormonal systems affecting appetite and metabolism [5,29,34].

The simplest explanation for associations between markers of early development and future obesity may be confounding by socio-economic or genetic factors. For example, the same genes that predispose to low birthweight may also predispose to CVD [16, 17]. Similarly, the same genes that promote faster infant weight gain may increase later obesity [43]. However, emerging experimental evidence, particularly for effects of early

postnatal nutrition, argues against this explanation [5] and therefore there is great interest in the mechanistic link between early nutrition and future obesity. For example, several associations have been reported between maternal obesity, epigenetic markers and later health outcomes, although whether these associations are causal is unknown [28]. Interestingly, in contrast to maternal obesity, there have been no epigenetic studies linking development factors in the first 2 years with later obesity [29]. Similarly, there are no consistent associations between environmental factors in the first 2 years, such as the gut microbiome, use of probiotics, and childhood sleep patterns [29,34], and future adiposity.

Mechanistic research investigating effects of postnatal growth rates on future obesity has focused particular on regulation of appetite [44]. For example, infants fed from a bottle are less able to regulate their milk intake than those fed directly from the breast (as reviewed [5]). Hormonal changes that drive these appetite effects could include effects of early protein intake (particularly branched chain amino-acids) in programming higher insulin-like growth factor-1 and insulin concentrations [5, 36]. However, there is little evidence for any causal mechanism in humans to explain the developmental origins of obesity.

### **Public Health Implications**

The strength of the evidence supporting the early life origins of obesity hypothesis has substantial implications for public health and is challenging established practices (as reviewed [5]). For maternal interventions before and during pregnancy, clearly, preventing both under- and over-nutrition has huge health benefits for the mother and her infant. Optimising nutrition during these critical windows in development, particular for micronutrients such as folic acid, iron, vitamin D, and iodine, is therefore a worthwhile public health aim in its own right. However, whether interventions during pregnancy can be used as a public health strategy to tackle the global epidemic of obesity and its complications is currently unknown.

For interventions in infancy, professional bodies such as the Scientific Advisory Committee on Nutrition, and Royal College of Paediatrics and Child Health in the UK, and the Institute of Medicine in the US have recognised the importance of patterns of early growth for development of future adiposity and its complications. Consequently, the WHO growth charts, based on slower growing breast-fed infants, have been widely adopted to help reduce the risk of over-feeding. Furthermore, promotion of catch-up growth by nutritional supplementation in healthy term infants born SGA is no longer recommended and health care professionals are aware of the importance of preventing both infant growth faltering and over-feeding (e.g. by practising responsive feeding) [5]. Finally, the increased risk of obesity associated with a high protein intake in early life has to lead to recommendations to restrict or reduce cow's milk intake in infants and toddlers [5] and to development of lower protein formulas which produce a pattern of growth more similar to the breast-fed infant [45]. The key public health message is that optimum nutrition of infants is more complex than simply 'more is better'.

### *Conclusion*

The idea that early nutrition can affect health throughout life has captured the imagination of the public and the scientific community. This concept is particularly relevant for the development of obesity and its complications, arguably the most important public health issue of the 21<sup>st</sup> century. Developing early life interventions for the prevention of long-term obesity, and understanding the mechanisms involved, must therefore be a high global priority.

### **Word Count**

3053

### **Conflicts of Interest**

None

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