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## Introduction

This evidence submission has been compiled jointly by researchers at the University of Cambridge who are experts in the fields of metabolic dysregulation (Susan Ozanne; Professor of Developmental Endocrinology, ORCID: 0000-0001-8753-5144) and maternal medicine (Catherine Aiken; Associate Professor in Maternal and Fetal Medicine, ORCID: 0000-0002-6510-5626). We have carried out scientific research in the field of early (fetal and neonatal) life nutrition and its long-term effects on cardio-metabolic health for 30 years and 20 years respectively. We both currently lead active research groups focussed on how nutrition during pregnancy (with a focus on obesity and gestational diabetes) impacts on the life-course health of children.

Below we provide an outline of key relevant scientific evidence regarding the influence of pre-and post-natal nutrition on the risk of subsequent obesity (topic 4 from the list of questions identified by the House of Lords Select Committee on Food, Diet and Obesity).

The evidence synopsis presented highlights key findings that illuminate the links between the early-life environment and subsequent obesity risk. For further discussion of the potential underlying mechanisms and detailed exploration of the surrounding literature, we direct interested parties to our recent invited review papers; [1,2], both published in the latter half of 2023.

## Evidence synthesis

(i) *Pre-Clinical Models*

It is established that mice born to mothers with diet-induced obesity have increased body weight and excess adiposity from early postnatal life onwards [3]. Studies suggest that hypothalamic leptin resistance in offspring may be programmed by exposure to maternal obesity during intrauterine development, thus establishing life-long reduced satiety and tendency towards over-eating [4].

Hypothalamic alterations, which can lead to increase food intake, and thus predispose to obesity in the long-term, have also been observed in other species in response to maternal high-fat diet during pregnancy. This paradigm is established in non-human primates, in whom highly-controlled randomised studies have been performed [5].

Our work has also demonstrated that mice exposed to maternal diet-induced obesity over-eat a high-fat diet compared to mice born to lean

mothers. These offspring remain more susceptible to excess eating and hence obesity throughout life as a result of disruption to the hypothalamic feeding pathways [6]. Importantly, the use of a mouse model for these experiments means that these effects can be demonstrated independent of familial genetics, which remains a complicating factor in human studies.

Our studies using a mouse model of nutritionally-induced low birth weight and accelerated early postnatal growth, add to the established body of work by clearly delineating the distinct impacts of the pre- and post- natal nutritional environment on obesity risk. Offspring exposed to under-nutrition in the womb followed by over-nutrition in the early post-natal period are highly susceptible to diet-induced obesity [7]. In contrast nutritionally-induced slow growth during lactation leads to protection from postnatal diet-induced obesity.

(ii) *Human studies*

Despite the clear advantages of animal models, in particular the ability to randomise to maternal diet and control for genetic differences, there are also distinct limitations in translating conclusions between species. Of necessity, much of the relevant data from human studies is observational and much can be learnt from opportunistic study of 'natural experiments', for example paired-sibling studies, where they occur.

Associations between maternal obesity, either before conception [8,9] or during pregnancy [10,11] , and the risk of childhood obesity are commonly observed in cohort studies. Observational studies suggest that maternal adherence to a 'Mediterranean diet' is associated with reduced BMI in mid-childhood [12].The phenomenon of 'catch-up' growth, the growth-restricted fetus that grows rapidly postnatally being at high risk of later adiposity, is also observed in human cohorts [13].

Although cohort studies support a link between maternal nutrition and childhood obesity, disentangling the specific impact of maternal nutrition from other key influences, including shared maternal and fetal genetics, and the impact of the post-natal family environment is challenging [14].

A key piece of evidence pointing towards an impact of maternal nutrition in pregnancy (independent of genetics) on the risk of later obesity, is that children born after maternal diagnosis of diabetes have a higher body mass index than siblings born from pregnancies in which no diabetes was diagnosed [15]. However, studies show inconsistent results regarding the risk of obesity in children born from pregnancies prior to maternal weight-loss surgery compared to their siblings born after maternal weight loss [16,17]. Time to conception following surgery is a confounding factor in such studies with increased small for gestational age infants likely observed when conception occurs soon after surgery.

*Nutritional interventions to alter childhood obesity risk*
As regards antenatal interventions, observational data suggests that maternal prenatal vitamin supplementation is not effective in reducing childhood obesity risk [18]. Similarly, a systematic review of clinical trials of n-3 LCPFA supplementation in pregnancy or lactation suggests no significant benefit [19]. A recent individual-patient level meta-analysis including data from 6 original trials of combined diet/lifestyle antenatal interventions in women who were overweight or obese showed no effect on childhood BMI [20]. Very few randomised trials of post-natal nutritional interventions are available, however a trial of small-for-gestational age infants randomised at birth to either control formula or nutrient-enriched formula showed that the nutrient-enriched formula fed group had increased fat mass later in childhood [21].

**Evidence synopsis**
Available evidence from both animal models and human cohorts suggests a significant impact of both pre- and postnatal nutrition on later risk of obesity, which is interactive. In particular, the phenomenon of catch-up growth (restricted prenatal growth followed by accelerated postnatal growth) is observed associated with increased risk of obesity in both human and animal studies. There is currently a lack of interventions shown to be effective to mitigate this risk in human populations, and more research is urgently needed in this area.

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*1 April 2024*