Impact of Maternal Obesity on Long-Term Health Outcomes

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Differences in nutritional experience during limited, sensitive periods in early life, both before and after birth, can program a person's development, metabolism, and health for the future. Epidemiological studies, animal models, and clinical intervention trials provide ample evidence for long-term programming effects of nutritional and metabolic factors during these sensitive periods that affect health, well-being, and performance up to adulthood and old age.

The term programming was introduced into the scientific literature by Günther Dörner in 1975, based on the analysis of data from both experimental and clinical studies.[1] The concept received broader attention when David Barker and colleagues published retrospective epidemiological studies documenting associations of weight at birth and at age 1 year, respectively, with the risks of hypertension, diabetes, and coronary heart disease in adulthood.[2] These observations raised the hypothesis that maternal and fetal malnutrition during pregnancy induce both fetal growth restriction and increased later disease risk. More recent data also suggest that fetal overnutrition as a consequence of maternal obesity, diabetes during gestation, and certain dietary habits increase health risks for the offspring.[3] Moreover, postnatal growth and nutrition, and in particular accelerated weight gain in early childhood, appear to induce adverse effects on long-term health and well-being.

Obesity before and during pregnancy is common in many populations around the world. In the USA one in three women aged 20–39 years is obese, with a body mass index (BMI) >30 kg/m^2.[4] A very high obesity prevalence also is found in the Middle East, Australia, and some European countries.[5] Moreover, obesity rapidly increases in many newly industrialized and even in low-income countries. Health risks for pregnant women are markedly higher with obesity, eg, spontaneous 1st-trimester and recurrent miscarriage, cardiac disease, preeclampsia, dysfunctional labor, gestational diabetes, thromboembolism, cesarean section, postcesarean wound infection, postpartum hemorrhage, overall severe morbidity, and maternal deaths. A recent review in the UK found about half of maternal mortality associated with pregnancy overweight and obesity.[6] Also, infants of obese mothers carry increased risks including stillbirth and neonatal death, prematurity, congenital abnormalities, and lower breastfeeding rates and duration.

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Furthermore, maternal obesity can have severe long-term consequences for the offspring. The fuel-mediated hypothesis stipulates that an enhanced transplacental supply of glucose and fatty acids, along with elevated insulin levels, induces increased fetal growth, birthweight, and neonatal adiposity, along with adverse long-term effects on later health.[7] Hyperglycemia during pregnancy was found to be associated with increased neonatal adiposity, which predicts later BMI and body fat content.[8] Body weight gain prior to pregnancy, prepregnancy BMI, and gestational weight gain are all associated with infant birth weight, which predicts later obesity risk.[9,10] Many observational studies also have associated maternal BMI with the offspring obesity risk in childhood and adulthood.[11-13] These associations could reflect programming effects of the intrauterine environment, but also shared genetic factors, familial lifestyles, and socioeconomic factors, as well as other shared factors. A few studies have compared the association of offspring BMI with both maternal and paternal overweight and obesity, with closer associations with maternal BMI in some but not all studies.[14,15] Some evidence for causality arises from documented effects of bariatric surgery, with lower health risks in children born after surgery than in those born before surgery,[16] as well as from randomized controlled trials comparing the effects of routine care vs treatment of gestational diabetes on children.[17,18]

Maternal obesity may also program long-term child health through its adverse effects on intention to breastfeed, breastfeeding initiation, and breastfeeding duration. In a large cross-sectional survey of more than 9000 children participating in the obligatory school health examination in Bavaria, Germany, we found a much higher prevalence of obesity among children who had never been breastfed (4.5%) than in previously breastfed children (2.8%), with an inverse dose-response effect between the duration of breastfeeding and the prevalence of later obesity.[19] The protective effect of breastfeeding was not attributable to differences in social class or lifestyle. After adjusting for potential confounding factors, breastfeeding remained a significant protective factor against the development of obesity (OR 0.75, 95% CI 0.57–0.98) and overweight (0.79; 0.68–0.93) (Fig 1). Again, there was a clear dose-response relationship between breastfeeding duration and later risk of overweight and obesity, respectively.

Breastfeeding reduces overweight and obesity at school age in >9,000 Bavarian Children

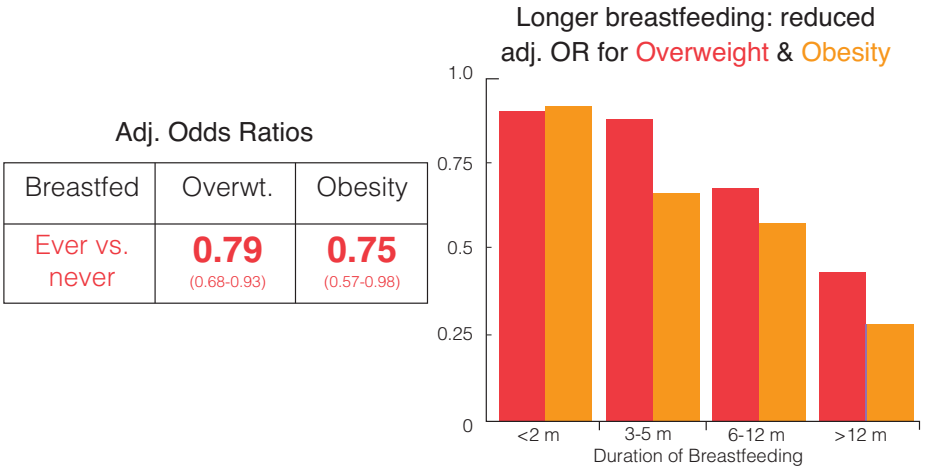

Fig 1. After adjusting for possible confounders, breastfeeding remained a significant protective factor against the development of overweight and obesity.[19]

A protective effect of breastfeeding also was found in several other studies, whereas some others found no benefit. However, systematic reviews and meta-analyses of cohort, case-control, or cross-sectional studies showed a modest but consistent protective effect of breastfeeding.[20,21]

The exploration of metabolic programming effects of maternal obesity on long-term health and on underlying mechanisms offers tremendous opportunities for early prevention of major health risks already during pregnancy, which could provide great benefits for promoting long-term health of the population. Because of the increasing public health importance and the transgenerational nature of the problem, obesity (more specifically, adiposity or body fat content) and associated disorders are the research focus of the new large multidisciplinary consortium *EarlyNutrition* supported by the European Commission's 7th Framework Programme with partners across Europe, the USA, and Australia (www.early-nutrition.org). *EarlyNutrition* will investigate the three principal hypotheses that are currently suggested to explain why early nutrition programs obesity and its comorbidities, ie, the fuel-mediated in utero hypothesis, the accelerated postnatal weight-gain hypothesis, and the mismatch hypothesis (Fig 2).

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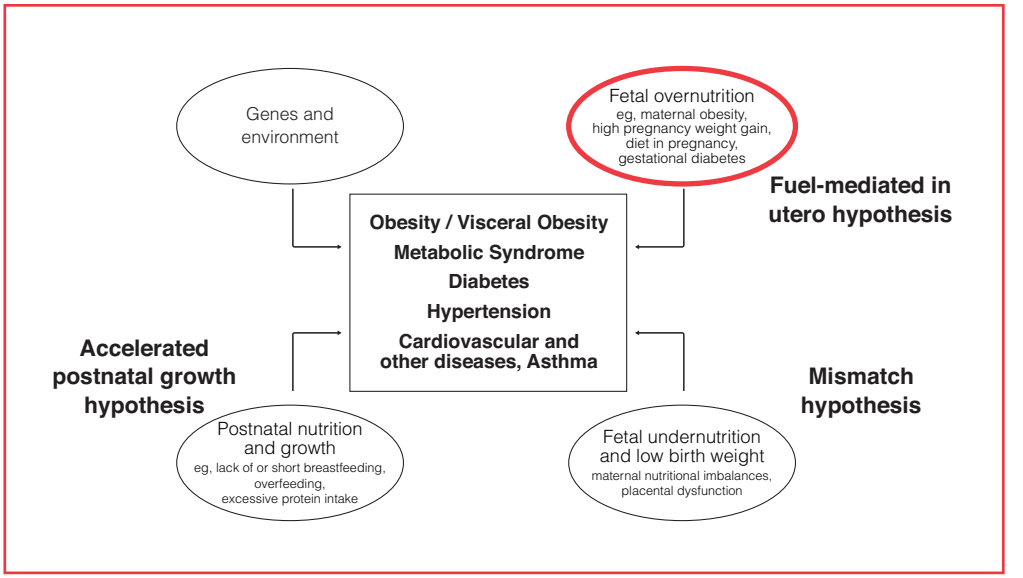

Fig 2. Key hypotheses linking early events and risk of obesity and other non-communicable diseases.[22]

The consortium will conduct experimental studies in animals, contemporary cohort studies, follow-up of existing randomized controlled trials (RCTs) in pregnant women and infants, as well as new RCTs with novel interventions. Through this integrated approach the roles of placental function, early fetal and postnatal growth patterns, the mother's prepregnancy nutritional status, pregnancy weight gain, physical activity, lifestyle, nutrition and fatty acid status, impaired maternal glucose tolerance, as well as the infant's early life nutrition and physical activity as determinants of the later health of the offspring will be explored. We aim to achieve better evidence for the impact of early metabolic programming on long-term health, well-being, and performance, with a focus on reduction of adiposity and associated disorders, characterization and validation of biomarkers for early growth patterns and later outcomes, and demonstration of effects of novel dietary interventions.

Below are several key conclusions:

- Obesity and hyperglycemia in pregnancy, and weight gain prior to pregnancy, are associated with adverse outcomes in many observational studies.
- Maternal bariatric surgery and treatment of gestational diabetes have reduced adverse outcomes in infancy.

- It appears prudent to aim at normalizing body weight in women of childbearing age prior to pregnancy, and to promote regular physical activity and a balanced health-promoting diet.
- Given the limited current level of evidence, better data are needed from contemporary, observational studies and particularly from randomized controlled intervention trials that explore effective behavioral, nutritional and other interventions, in order to inform policy and practice.
- In addition, further exploration of underlying mechanisms and of particularly susceptible subgroups is highly desirable.
- Timely progress in the field will be best achieved by close collaboration of public agencies, academia, industry, and small and medium enterprises. One example of such a collaboration is the European Commission FP7-funded collaborative research project *EarlyNutrition* (www.early-nutrition.org).

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Q & A

Q: You have shown that, in Denmark, birth weight is going up. Is this the result of better nutrition rather than increased obesity? Could it be that we cannot relate to those children who now have higher birth weights the same way that we did to previous generations?

Dr Koletzko: Birth weight is a very crude measure, and average birth weight is an even more crude measure. It does not allow us to really understand the complexity of the relationship. Increased mean birth weight can be a good thing if it means reduced early preterm births, intrauterine dystrophy, and small-for-gestational age births. Increased mean birth weight is less of a good thing if it means increased rate of macrosomia and neonatal adiposity increase. So we have to look at factors beyond mean birth weight in a population. In Denmark, the clear increase in large-for-gestational age babies is one of the key drivers of the increase of mean birth weight. We need to look into this in more detail.