From conception to infancy: clinical relevant strategies on child obesity development

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Running Title: Early Risk Factors for child obesity

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Abstract

Maternal lifestyle during pregnancy and early nutrition and environment of their offspring’s are considered relevant factors for childhood obesity preventative efforts. There are several models for the prediction of childhood overweight and obesity, but most of them have not been externally validated and the factors considered differ greatly among studies since the outcomes are predicted at different ages. The objective of the current review is to examine and interpret the knowledge on the early determinants of childhood obesity development in order to provide relevant strategies for daily clinical work. For this purpose, we have evaluated all the identified prenatal and postnatal factors potentially associated to child adiposity from conception up to the end of the second year of life. Actions to be considered are promoting healthy nutrition and healthy weight status at reproductive age and during pregnancy and monitoring carefully infant growth in order to detect early excessive weight gain. Pediatricians and other health care professionals should provide proper scientific individual nutritional advice to families to counteract excessive adiposity in the offspring. Based on systematic reviews, original papers and scientific reports we provide information to help setting up public health strategies to prevent childhood overweight and obesity.

Key words: Prenatal, postnatal, risk factors, child obesity, programming, pregnancy
Introduction

Obesity at school age is highly prevalent in both developed and developing countries and it is associated with several health complications not only during childhood but also later in life. Both prenatal and early postnatal factors are associated with the development of infant adiposity.\textsuperscript{1-2} Childhood obesity determinants should be modified as early as possible, since adiposity may be perpetuated leading to obesity during adolescence, adulthood and the next generations.\textsuperscript{3}

Based on systematic reviews, original papers and scientific reports, the aim of this article is to analyze and interpret the knowledge on the determinants of childhood obesity development in order to provide relevant strategies for daily clinical work, from conception up to the end of the second year. The information on this paper should be relevant for health care providers (national institutions, private health insurance companies) and professionals (gynecologists, pediatricians, endocrinologists, general practitioners, nutritionists, nurses and midwives, etc…) to be able to help setting up public health strategies to prevent childhood obesity.

Secular trends on child obesity and risk factors

The elevated prevalence of overweight and obesity in developed and developing countries has been described as a global pandemic. The rise in overweight and obesity prevalence in youths in the last four decades has been dramatic, and it could lead to a future decline in life expectancy. Moreover, the appearance of obesity is occurring at progressively younger ages, and this is of great concern from a public health perspective due to the tracking of childhood obesity, and to the strong relationship between the number of years lived with obesity and the risk of cardiovascular disease mortality and
all-cause mortality. Thus, nowadays, overweight and obesity cause more deaths worldwide than underweight (www.who.int/dietphysicalactivity/childhood/en/).

In children under five years, De Onis et al. reported that the prevalence of overweight (i.e., weight for height > 2 SDs above the median World Health Organization (WHO) standards) or obesity (i.e., weight for height > 3 SDs above the median WHO standards) was 6.7% in 2010 (about 43 millions). The reported prevalence of overweight/obesity in developed countries was 11.7% in developed countries and 6.1% in developing countries, respectively (Figure 1). Importantly, the majority of the young children with overweight or obesity lived in developing countries (34.7 million), specifically more than half of them in Asia. Thus, it was observed that there was a higher increase in the prevalence of overweight/obesity prevalence over the 1900-2010 period in developing (64.9%), than in developed (48.1%) countries.

In children and adolescents aged 5 to 19 years old, the prevalence of overweight and obesity has also risen significantly in the last four decades (www.who.int/gho/ncd/risk_factors/overweight_obesity/overweight_adolescents/en/), increasing the number of children and adolescents with obesity tenfold from 1975 to 2016. Likewise, from 1975 to 2016 the prevalence of obesity (body mass index BMI-for-age > 2 SD above WHO growth reference median) increased from 1% to 7% (BMI-for-age > 1 SD above WHO growth reference median) (Figure 2). In 2016, more than 124 million children and adolescents had obesity and the global prevalence of overweight and obesity was 18%, nearly one in five youth between 5 and 19 years old. Overweight and obesity rates showed remarkable increases worldwide since 1975, with 27.1% of children in developed and 23.4% in developing countries being overweight/obese in 2016 compared to 11.6% and 5.5% in 1975, respectively (Figure 2). In developing countries, there are continued increases of overweight and obesity
trends. In economically advanced countries, a recent overall flattening of trends has been recently observed; however, the burden of obesity in childhood is disproportionately affecting to low socioeconomic groups in these countries. Since 2000 it has been reported that differences in childhood overweight and obesity are widening between high and low socioeconomic position groups. Thus, it seems that the plateau in obesity trend is being experienced by children and adolescents from high socioeconomic background, while the prevalence continues increasing in lower socioeconomic groups.

In parallel with the increase of overweight and obesity prevalence in childhood, besides lifestyle factors, several prenatal and early postnatal factors that are associated with the development of infant adiposity such as prematurity and low birth weight, gestational diabetes, excess body mass gain during gestation, infant formula feeding, etc. have also raised their incidence in the last decades. Interestingly, the rise in the incidence of these perinatal risk factors have also been more pronounced in the developing than in developed countries.

For example, the global burden of prematurity (delivery < 37 weeks) is epidemic worldwide and it is increasing in most countries and regions (Figure 3). Thus, the global increase in pre-term birth rate from 1990 to 2010 was 14.7%. In 2010, the global prevalence of prematurity was 11.1% (14.9 million pre-term births per year), ranging from 5% in Northern Europe to 12.3% in sub-Saharan Africa and 13.3% in Southern Asia. Rates were higher in low income (11.8%) and lower-middle income (11.3%) countries, than in upper-middle (9.4%) and high-income (9.3%) countries. Overall, 60% of all preterm births (9 million of pre-term birth per year) occur in low-income and high fertility counties in sub-Saharan Africa and South Asia. The United States has a high
incidence of preterm births (9.62% of pre-term births in 2015) accounting for 42% of all pre-term births among high-income countries.

Being small for gestational age (SGA, defined as birthweight below the 10th centile of birth weight by sex for a specific completed gestational age of a given reference population), even in infants born at term, has also been related to excess adiposity\textsuperscript{11} and its incidence is very high worldwide. The Child Health Epidemiology Reference Group including 14 birth cohorts reported that in 2012 one in five infants were born SGA.\textsuperscript{12} In 2010, in 138 countries of low and middle income areas,\textsuperscript{13} it was estimated that globally 32.4 million infants were born SGA in low- and middle-income countries (27% of live births), and among them 29.7 million were born at term (≥37 weeks) and 10.6 million were born at term and low birthweight (<2500g). Importantly, two thirds of SGA infants were born in Asia; specifically, the highest rates of SGA were observed in South Asia (nearly one in two babies are SGA).

The prevalence of gestational diabetes mellitus (GDM) has also raised in the last decades.\textsuperscript{14} Several studies reported that GDM rates increased by 16 to 127% between 1995 and 2005, although the different screening method and diagnosis criteria make difficult to have a clear picture. The rise in GDM rates might also contribute to the increasing trend of the prevalence of obesity and diabetes in the offspring. In addition, mothers with GDM seem to end predominant breastfeeding earlier than mothers without GDM.\textsuperscript{15} A recent systematic review and meta-analyses in Eastern and Southeastern Asia estimated that the prevalence of GDM was globally of 10.1% of pregnant women and that in lower- and middle-income countries was 64% higher than in their high-income counterparts.\textsuperscript{16}

**Prenatal factors and child obesity**
Pre-pregnancy maternal BMI and Gestational weight gain

Maternal pre-pregnancy BMI and gestational weight gain were both positively and independently associated with neonatal and infant adiposity (Table 1). Normal and overweight women may be more physiologically sensitive to the effects of high gestational weight gain than those with obesity.\textsuperscript{17-19} Early and mid-pregnancy gestational weight gain, which primarily represents increased maternal fat rather than the weight of the fetus, may be causally linked to offspring adiposity through the increased availability of maternal fuels.\textsuperscript{20-21} Healthcare providers should pay particular attention to the BMI status of women at reproductive age, and where appropriate, advices for improving their diet, lifestyle and physical activity.

The association of maternal weight status with child adiposity does not only appear pre-pregnancy, but also after delivery. The best example to study the effects of obesity fetal metabolic programming in humans is considering perinatal and child outcomes differences between siblings born from mothers with obesity, before and after gastrointestinal bypass surgery. Children born after maternal surgery presented lower prevalence of macrosomia (1.8 vs. 14.8\%), and severe obesity at adolescence than their siblings born before surgery (11 vs 35\%).\textsuperscript{22-23}

Moreover, pre-pregnancy BMI and gestational weight gain both were associated with the child BMI Z score at age 4 years among siblings ($\beta = 0.09$ units: 0.08, 0.11; and $\beta = 0.07$ units 0.04-0.11);\textsuperscript{24} however, fixed effects models that account for familial factors resulted in null associations for both factors.\textsuperscript{24} In another prospective cohort of 146,894 participants, maternal weight gain (postnatal weight minus weight at the first antenatal clinic assessment) was associated with later offspring BMI at 18 years in siblings from women with overweight and obesity (0.06; 95\% CI: 0.01, 0.12) per 1-kg greater gestational weight gain, but not in normal-weight mothers (0.00; 95\% CI: -0.02, 0.02).\textsuperscript{25}
These results support certain intra-utero obesity programming in humans even considering the confounding factors potentially involved.

The increase in the pre-gestational BMI between the first and second pregnancy was also associated with greater risk of large for gestational age babies in a Swedish cohort with 151,025 participants. These results also support a causal relationship between the risk of maternal overweight and obesity with adverse results on obesity in the children.26

*Pregnant women should be supported to have an adequate gestational weight gain for a healthy pregnancy and be informed that even more important is to start the pregnancy with a BMI in the normal range (18.5 to 24.9 kg/m2).*

**Paternal obesity**

Paternal BMI has also been associated with childhood BMI (Table 1). In a systematic review,27 limited evidences for this association was reported, since three studies provided a direct comparison of parent-offspring associations, with a statistically stronger maternal influence found only in one cohort.28 Further large studies published after such systematic review, have confirmed that maternal BMI was stronger predictor of childhood obesity than paternal BMI.29-30 In addition, other studies with maternal (after pregnancy) and paternal measurements obtained on the date closest to the infant’s birth or at the age of child recruitment also corroborate the different association between parents.31-32

*Father’s BMI is also associated with childhood obesity.*

**Gestational diabetes**
A recent meta-analysis, including 35 papers and over 24,000 infants, reported that infants of mothers with gestational diabetes have 62 g greater fat mass (95% CI: 29 to 94, p = 0.0002) than infants of mothers without GDM.\(^3\) The effect was higher in boys than in girls. There was no effect attenuation after adjustment for maternal BMI. Moreover, in a sibling study including 248,293 families,\(^4\) BMI of men whose mothers had gestational diabetes was on average 0.94 kg/m\(^2\) (0.35 to 1.52) greater than in their brothers born before their mother was diagnosed with diabetes.

According to a recent Cochrane meta-analysis, exposure to the lifestyle intervention during gestational diabetes decreases birthweight, macrosomia and neonatal fat mass compared with the control group (mean difference in neonatal fat mass -37.30 g, 95% CI -63.97 to -10.63; one trial, 958 infants; low-quality evidence). During childhood, there was no clear evidence of a difference between groups for BMI \(\geq\) 85th percentile (RR 0.91, 95% CI 0.75 to 1.11; three trials, 767 children; I\(^2\) = 4%; moderate-quality evidence).\(^5\)

*It is important to screen gestational diabetes and paediatricians have to be informed on its diagnosis since these children may develop early metabolic disturbances and impaired growth and development.*

**Maternal Malnutrition and obesity risk in the offspring**

Poor maternal nutrition during gestation is an important determinant of both, undernutrition in childhood and obesity and related comorbidities in adulthood.\(^3\) The consequences of insufficient nutrition during gestation have been examined in several famine-based studies.

Findings from the Dutch Famine Birth Cohort Study and the Great Chinese Famine showed that exposure to famine in early gestation resulted in higher rates of overweight
and obesity in exposed than in non-exposed women. In contrast, the Leningrad Siege study did not find any relationship between famine exposure during pregnancy and obesity risk. The Biafran famine study observed higher overweight rates in individuals exposed to foetal/infancy undernutrition, but it was not possible to separate the famine effects in foetal and infancy periods. Maternal malnutrition, including both maternal underweight and obesity, is common in low-income women in developing countries due to inadequate nutrition in a period in which nutrient requirements are increased.

Undernutrition should be avoided during pregnancy

Maternal smoking during pregnancy

According to a systematic review, including 84,563 children from 14 observational studies, children who were exposed to smoking in utero are at increased risk for developing overweight (pooled adjusted odds ratio (OR) 1.50, 95% CI: 1.36, 1.65) at age 3-33 years), compared to non-exposed children. In a cross-sectional study in 3-10 year-old Portuguese children (n=17,509), a positive association of maternal smoking during pregnancy with adiposity measures was also shown. A meta-analysis including 17 studies, showed that prenatal maternal smoking was consistently associated with future offspring overweight/obesity. Therefore, maternal smoking has been identified as a risk factor for the development of obesity.

Maternal smoking should be avoided

Alcohol consumption during pregnancy

To our knowledge there are no studies in humans investigating the possible effect of alcohol consumption during pregnancy and the later development of overweight/obesity
in the offspring. Most studies focus on the impact of alcohol exposure on offspring
developmental delay, cognitive impairment and on neurological and neuropsychological
effects. In an animal experiment, Dobson et al. observed that chronic prenatal ethanol
exposure increased whole-body adiposity and pancreatic adiposity in guinea pig
offspring. Exposed guinea pigs were growth restricted at birth and exhibited higher
catch-up growth within the first week of postnatal life.

There is no idea of a concrete mechanism; since alcohol exposure leads to disturbed
lipid metabolism, reduction in birthweight and a subsequent higher catch-up growth,
there could be also an indirect relation to a higher risk of the development of later
obesity.

No alcohol should be consumed during pregnancy

Diet during pregnancy

The long-term consequences of adopting a ‘healthy’ or prudent diet in pregnancy on the
body composition of the offspring are yet to be determined. In a cohort study with 5717
mother-child pairs, maternal diet during pregnancy was not associated with offspring
adiposity at 10 y; there was some evidence of associations with offspring fat mass, but
effect sizes were negligible. Diet based on low-fat meats and dairy products, whole
grains, fruit, vegetables and fish, reduced maternal lipid levels but the effects on birth
weight were contradictory

Concerning macronutrients, in 1,410 pregnant women, maternal high fat diet during
pregnancy was significantly associated with neonatal fat mass. However, maternal fat
and protein intakes were not consistently associated with infant BMI peak and
childhood BMI. In the generation R study, higher protein intake during pregnancy is
associated with a higher fat-free mass in children at the age of 6 years, but not with their
fat mass. Moreover, low maternal plasma n-3 and high n-6 polyunsaturated fatty acid concentrations during pregnancy were also associated to higher obesity risk in girls at ages 2 to 7 years, and higher body fat and abdominal fat in childhood at 6 years. These results suggest the convenience to consume polyunsaturated fats during pregnancy.

High glycemic index diet along pregnancy is associated with a higher prevalence of large-for-gestational age. Consistently, increased odds of overweight/obesity in offspring at 5 and 6 years were found in large cohort studies in mothers with higher intakes of sugar during pregnancy. These results were also supported by the GUSTO study, as a 25-g (~100-kcal) increase in maternal carbohydrate intake (mainly sugar) was associated with a 0.01/mo (95% CI: 0.0003, 0.01/mo), higher pre-peak velocity and a 0.04 (95% CI: 0.01, 0.08) higher BMI peak at ages 2-4 years.

According to a recent Cochrane review, there is very low-quality evidence from five trials to suggest a possible reduction in gestational diabetes risk for women receiving dietary advice during pregnancy, although a meta-analysis did not exclude this possibility. In obese women without gestational diabetes, diet and physical activity based interventions during pregnancy may reduce gestational weight gain and lower the odds of caesarean section as well as the risk of delivering a baby weighing above the 90th centile for gestational age and sex.

Intervention studies in obese pregnant women using low glycemic index diet and/or lifestyle interventions reduced some skinfolds thickness but not all in the baby at early stages and produced a sustained improvement in maternal diet at 6 months postpartum. Nevertheless, we should wait for the results on child adiposity at older ages. Since alterations in maternal/placental function occur in the first trimester of pregnancy prior to when most intervention trials are initiated, this could have limited the effect of such
RCTs. Thus, intervention studies from early pregnancy should be desirable, although we should be cautious and wait for the postnatal and childhood effects of such studies. Prenatal care providers counselling has great success meeting gestational weight gain targets. Lifestyle interventions are an acceptable approach although future studies should examine their efficacy.

Pregnant women should be advice not to exceed the recommended amount of free sugars intake (10% of energy) and to consume polyunsaturated fat (omega 3).

Physical activity during pregnancy

Just 15% of pregnant women follow the current recommendations on 30 min or more of aerobic exercise of moderate intensity during pregnancy. A recent Cochrane systematic review and meta-analyses reported that interventions based on diet, exercise, or both, reduced the risk of excessive gestational weight gain on average by 20%, but without major effects on the risk of infant macrosomia. Other recent meta-analyses, reported that leisure physical activity reduced significantly the risk to lower LGA babies (RR 0.51; 0.30-0.87). High levels of physical activity before pregnancy or in early pregnancy are also clearly associated with a significantly lower risk of developing GDM, which is a risk factor for further offspring obesity. In a cohort with 2.033 subjects, maternal exercise >3 times per week reduced the risk of macrosomia.

Concerning the effect of maternal physical activity on childhood obesity, to our knowledge, only 4 small studies (n=23 to 104) have raised the possibility of small inverse associations. However, in a cohort with 802 mother-child pairs, higher physical activity before and during mid-pregnancy, were not associated with lower adiposity in children at 7-10 years old. Thus, the existing evidence of long-term benefits on childhood adiposity outcomes later in life are scarce.
Despite there is no consistent association between maternal physical activity during pregnancy and childhood obesity, in absence of contraindications pregnant women should be advice to be physically active.

Antibiotics during pregnancy

Over the past 30 years, first trimester use of prescription drugs increased >60%. In 2010, 94% of pregnant women took at least one medication during pregnancy, and 82% did in the first trimester, among these medications, antibiotics were within the top 20 most frequently used, amoxicillin being top of the list. Maternal antibiotic use has been associated with changes in infant birth weight, and higher birth weights were reported among infants born to antibiotic users. Mor and colleagues showed that prenatal exposure to antibiotics was associated with a 26-29% increased prevalence of overweight and obesity at school age, after adjusting for confounding factors. Prenatal exposure to antibiotics may affect the postnatal metabolism by altering the composition of the “pioneer” microbiota. Prenatal exposure to antibiotics may also differentially alter methylation at regulatory regions of imprinted genes and somatic epigenetic changes may occur. We recommend the use of antibiotics only after identification of bacterial infection during pregnancy, in order to avoid obesity associated disbiosis.

Delivery and post-natal factors

Type of delivery

Growing amount of literature suggests that caesarean birth is associated with higher risk of overweight and obesity in offspring. Mueller et al. found that independent of
prenatal antibiotics, pre-gravid BMI, and birth weight, caesarean birth was associated with 46% higher risk of obesity in offspring at 7 years. While Li et al.\textsuperscript{82} in a meta-analysis concluded that caesarean birth was associated with 33%, 24% and 50% greater odds of overweight/obesity in children, adolescents and adults, respectively. Mounting evidence suggests that caesarean birth – obesity association might be attributable to surgically delivered newborns bypassing the bacterial inoculum of the vaginal canal at birth. In fact, Dominguez-Bello et al.\textsuperscript{85} showed that the microbiota of vaginally delivered neonates resembled the vaginal microflora of their own mother, whereas the microflora of neonates born by caesarean birth resembled that of the mother skin. Therefore, stools of caesarean birth delivered children have lower counts of \textit{bifidobacteria} and higher counts of \textit{Clostridium difficile} than vaginally delivered children.\textsuperscript{86} The gut microbiota exerts important functions in regulating energy balance and may contribute to the development of obesity.\textsuperscript{87} Of note is that furtherly, there are other early life factors that can influence intestinal microbiota composition such as infant feeding practices or antibiotic therapy.\textsuperscript{88}

\textit{Caesarean delivery should be strictly limited to medical indications}

**Body weight at birth and later obesity risk**

A large number of studies reported that there is a J-shaped or U-shaped relationships between weight at birth and adult BMI, with a higher prevalence of adult obesity occurring in individuals whose body weight at birth was either low or high\textsuperscript{89-90} Babies born with either low birth weight (<2500g)\textsuperscript{91} or high birth weight (>4000g)\textsuperscript{92} are at a higher risk of developing later obesity through different mechanisms.

**Low birth weight and later obesity**
BMI is often used as a proxy of obesity because it shows strong correlations with total adiposity, but BMI also reflects fat free mass (FFM) that would be protective for chronic diseases but does not account for body fat distribution. The relationship between high birth weight and lean mass (LM) or FFM has been consistently observed in children. Small body weight at birth, programs smaller proportions of LM later in life, and also the number of muscle fibres may be determined up to birth. As abdominal fat deposition, and in particular visceral adiposity, carries increased cardio-metabolic risk, it has been hypothesized that low birth weight may increase the susceptibility to cardiovascular diseases and type 2 diabetes, by programming higher abdominal/visceral fat deposition. Overall, there is consistent evidence of an inverse relationships between birth weight and the subscapular to triceps skinfolds ratio, while the associations with waist circumference or waist to hip ratio, were inconclusive. Studies that used more robust techniques to assess abdominal fat content or visceral and subcutaneous abdominal adiposity such as DXA, magnetic resonance imaging (MRI) and ultrasonography (US), also observed mixed results (Table 2). Overall, studies performed with paediatric populations showed inverse associations of birth weight with visceral, subcutaneous or abdominal adiposity, though non-significant and U-shaped relationships have also been reported (Table 2). It is worth noting, however, that inclusion criteria (born at term or including also pre-term participants, including or excluding macrosomic newborns, adjusting or not birth weight with gestational age, etc.) and applied birth weight cut-off points and definitions (SGA, intrauterine growth restriction (IUGR), etc.) of the mentioned studies were very heterogeneous and do not allow firm conclusions.

High birth weight and later obesity
A meta-analysis reported newborns >4000g are at increased risk of later obesity, whereas low (<2500g) and normal body weight at birth (2500g-4000g) were not related to obesity risk. Offspring of women with obesity are also significantly heavier, had higher fat mass at birth and are at higher risk of later obesity. In a retrospective large cohort study of children from low-income families (N=8,494), maternal obesity increased twofold the likelihood of being large for gestational age and the risk of obesity in children aged 2-4 years old.

*Healthcare during pregnancy should support strategies to ensure normal birth weight.*

**Breast feeding**

Several meta-analyses have reported that breastfeeding reduced the risk of obesity, whereas other studies found no effect at all. In the first year of life, body mass gain is usually slower in breastfed, than in formula fed infants. In other study, exclusive breastfeeding for six months reduced the effect of both birth weight and early growth on adiposity in pre-school children. A study performed with children born SGA observed that faster early growth by a nutrient-enriched diet was associated with adiposity at 5-8 years of age as compared with either standard formula or breastfeeding. Crume et al. observed that breastfeeding for at least six months reduced the adverse effect of exposure to diabetes in utero on abdominal adiposity in children. The AVON study, found that breastfeeding was associated with lower BMI and blood pressure even after adjusting for socioeconomic status. Also Wang et al., examined the effects of breastfeeding on childhood obesity from 24 months through 11 years of age and found that breastfeeding at 1 month reduced risk for childhood obesity
by 36%. The same authors reported that breastfeeding duration, more than six months (vs never) was associated with a decreased risk for childhood obesity by 42%. However, the Promotion of Breastfeeding Intervention Trial (PROBIT), which is one of the largest studies conducted on human lactation with 17,046 mother-child pairs, in a recent secondary analysis on a 16 year follow-up, showed that increasing the duration and exclusivity of breastfeeding was not associated with lowered adolescent obesity risk or blood pressure.

The causal effect of breastfeeding has been also questioned recently by Smithers, Kramer and Lynch. They have taken insights from different study designs and looked specifically on the effect of breastfeeding on obesity. Their conclusion is that considering the evidence from several different study designs including randomized clinical trials, systematic reviews and meta-analyses, breastfeeding have no effect on obesity.

Early life risk factors coexist, are clustered or interact among them. For example, in women with obesity, excess gestational weight gain and shorter duration of breastfeeding are more common than in normal-weight women; SGA infants are more frequently fed with formula than AGA or LGA children; rapid growth is more common in SGA or pre-term children, etc. Robinson et al. in children aged 4 and 6 years observed the cumulative effect of five early risk factors (maternal obesity, excess gestational weight gain, smoking in pregnancy, short duration of breastfeeding and low maternal vitamin D status) on the risk of obesity and observed that the relative risk of being overweight/obese in children having four or more risk factors was 3.99 at 4 years and 4.65 at 6 years, compared with those who had none.

Breastfeeding has a lot of other advantages which makes it clear that we definitely recommend breastfeeding. In a Lancet Series paper the panel of authors conclude
“Human breastmilk is therefore not only a perfect adapted nutritional supply for the infant, but possibly the most specific personalised medicine that he or she is likely to receive, given at a time when gene expression is being fine-tuned for life. This is an opportunity for health imprinting that should not be missed”.125

Despite the inconclusive effect of breastfeeding on reducing obesity risk later in life, breastfeeding should be promoted due to its many positive and beneficial effects.

Formula feeding

One major question regarding infant formula is the protein content. A recent systematic review addressed the effects of infant formulas and follow-on formulas with different protein concentrations on infants’ and children’s growth, body composition and the risk of overweight and obesity later in life but the effect was uncertain.126 Only one large trial assessed the effect on BMI showing that a low-protein formula may reduce BMI and the risk of obesity at 6 years of age.127

In a recent trial, comparing formulae containing 1.8 or 2.7 g protein/100 kcal, anthropometric parameters in the low-protein group were lower compared with the high-protein group, and the differences were significant for head circumference from 2 to 60 months, body weight at 4 and 6 months and length at 9, 12 and 36 months of age. However, no significant differences in body composition were observed between these two groups at any age.128

Many studies indicate that infants of mothers with or without obesity who were fed traditional (high-protein) formulas gain more rapidly weight than breast fed infants.129 A new experimental low-protein (1.61-1.65 g protein/100 kcal) formula for infants between 3 and 12 months of age was recently tested in two trials.130 The weight is lower between 4 and 12 months of age and still the weight gain is not inferior to the WHO
growth standards curves. Also, biomarkers of protein metabolism were closer to breastfed infants.

Socha et al.\textsuperscript{131} also examined the growth in the first 2 years of life in 1,138 infants who were randomly assigned to receive follow-on formulas with low protein (1.77 g protein/100 kcal). They found that amino acids, IGF-1 and C-peptide increased significantly even in the low protein formula milk compared with the breastfeed group. Hormones like IGF-1 have impact on BMI, timing of adiposity rebound and body fat percentage later in life.\textsuperscript{131} Marked elevation in branched-chain amino-acid levels with high-protein intakes appears to contribute to increased insulin levels confirming the effect on obesity by high-protein formulas.\textsuperscript{132}

*High protein infant formulas should be avoided because they induce childhood obesity.*

**Rapid infant growth and obesity risk**

Rapid growth and excessive body mass gain in the two first years of life has been associated with increased risk for later obesity in high income industrialized countries.\textsuperscript{111,133-134} In low-middle income countries, in contrast, infant growth rate seems to predict subsequent FFM or height.\textsuperscript{135-140}

Baird et al.\textsuperscript{141} in a systematic review observed that the relative risks of obesity in infants growing more rapidly in the first year compared to those who grew more slowly ranged from 1.06 to 5.70. Monteiro and Victora\textsuperscript{142} in a systematic review also concluded that rapid growth during the first year of life is related to subsequent obesity in the life course.

The effect of early growth in more concrete periods of infancy on later body composition has also been examined. Particularly, studies have focused on the first six months of life in which body mass gain is primarily gain in FM, while FFM increases
preferentially after this age. In 3 years old children, Ejlerskov et al.\textsuperscript{97} observed that rapid weight gain from birth to 5 months (>0.67 z-score) was associated with higher FM, but not FFM, measured by bioelectrical impedance. In adolescents, high body mass gain from birth to 3 months was related to higher overall and truncal body fat percent assessed by DXA.\textsuperscript{143} In 4 to 20 years old youths, Chomtho et al.\textsuperscript{144} found that rapid weight gain in the first 6 months of infancy, but not in the second half of infancy, was the most strongly related to higher total and central adiposity as measured by the 4-component model. In 6 to 11 years old children, each 100g/month increase in body mass and FM gain from birth to 8 months was related to fivefold and eightfold odds for subsequent overweight/obesity, respectively.\textsuperscript{145}

It is worth noting that in certain population groups, such as SGA, intrauterine growth restriction or pre-term infants, rapid weight gain or catch-up growth may be beneficial in terms of morbidity and mortality in the short term, but increase the risk of chronic diseases later in life. Strategies focused on post-natal nutrition to maintain modest catch-up growth in SGA children would be effective. Likewise, Lei et al.\textsuperscript{146} examined 1,957 infants whose birth weight was below the 10th percentile from birth to 7 years, aiming to identify an optimal growth trajectory for term SGA children. The authors observed that SGA children with a fast post-natal catch up growth in the first months of life (up to 30th percentile), but modest thereafter to reach the 50th percentile at 7 years old, did not have an increased risk of adverse outcomes.

By other hand, after the first year of life when the adipose tissue is growing, there is a slimming of the child until about 6 years of age. Then the adipose tissue starts to increase relatively again and this is named as the adiposity rebound.\textsuperscript{147} A very early adiposity rebound is considered a determinant of obesity at further ages.\textsuperscript{148-149}

*Excessive weight gain during the first two years should be avoided.*
Macronutrients intake during infancy

Protein intake

Some observational studies have investigated the potential relationship between early intake of a high protein diet and the development of obesity. A consistently high protein intake at the ages of 12 and 18–24 months was independently related to a higher mean BMI-z score and % body fat at the age of 7 years and a higher risk of having a BMI or % body fat above the 75th percentile at that age. Moreover, an observational study in Danish infants followed-up until the age of 10 years showed that protein intake at 9 months of age was positively associated with height and weight but not with BMI or percentage of body fat at 10 years of age.

In twins followed-up until the age of 5 years, total energy from proteins was associated with higher BMI and weight, but not height between 21 months and 5 years. Substituting % energy from fat or carbohydrate for % energy from protein was associated with decreases in BMI and weight. Protein intake was associated with increased odds of overweight or obesity at 3 years, but not at 5 years.

In the Generation R cohort, 10 g per day higher total protein intake at 1 year of age was associated with a 0.05 higher BMI z-score at age 6. This association was fully driven by a higher FMI (0.06 z-score). The associations of protein intake with FMI were stronger in girls than in boys, stronger among children who had catch-up growth in the first year of life stronger for intake of animal protein than protein from vegetable sources.

High protein intake in infancy should be avoided because it is associated with childhood obesity.
Dietary Fat intake

There are few observational studies focused on dietary fat intake in children up to 2 years in relation to later BMI. A recent systematic review of systematic reviews reported that there is no conclusive evidence of a relationship between fat intake up to 3 years and childhood overweight/obesity. In 2014, a Cochrane review assessed the effects of fat intake in infancy on childhood outcomes but most of the children were older than 2 years and they are out of the scope of this review.

Analyses of studies with limited number of subjects found positive, no association or even an inverse association. However in the Generation R Study, with 2,927 children, a higher PUFA intake at 14 months was associated with a lower risk of preschool overweight at 4 years (OR: 0.77, 95% CI: 0.62, 0.96 per SD), but not at 6 years. This might suggest that the potential effects of fat intake is weaken after a longer follow-up period or that the adiposity rebound, which occurs around the age of 6 y obscured a possible inverse association between PUFA intake and body fat at this age specifically. In addition, Agostoni et al., who measured dietary intake at 1 and 5 years and BMI at 5 years in 147 children, observed that intakes of total fat, SFAs, MUFAs, or PUFAs at 1 or 5 y were not associated with BMI at 5 years.

The influence of low-saturated-fat counselling compared with no dietary counselling on cardio-metabolic health in >1000 children from ≥7 months was assessed after the age of 2 years, and up to 10 years; there were continuously fewer overweight girls in the intervention group than in the control group. Because the intervention consisted of dietary counselling, it is not certain whether the effects were caused by a low-saturated-fat diet or other effects of the long-term lifestyle advice.

There is no consistent association between total fat intake in infancy and obesity.
Free sugars intake

A higher total added sugar intake at 1 year was related to a lower BMI z-score at age 7 years. An increase in total added sugar during the second year of life tended to be associated with a higher BMI z-score, but no associations were found with % body fat.\textsuperscript{162}

Obesity prevalence at 6 years among children who consumed sugar sweetened beverages (SSB) during infancy was twice as high as that among non–SSB consumers (17.0\% vs 8.6\%). Adjusted odds ratio of obesity at 6 years was 71\% higher for any sugar sweetened beverage intake compared with no sugar sweetened beverage intake during infancy.\textsuperscript{163} In another study, higher juice intake at 1 year was associated with higher juice intake, SSB intake, and BMI z-score during early and mid-childhood.\textsuperscript{164}

*Free sugars should be limited during the first two years of life*

Supplementation with Pre- and pro-biotics

In adults with overweight/obesity prebiotics have been shown to decrease food intake and reduce body fat.\textsuperscript{165} In children with overweight and obesity a recent randomized controlled trial showed an improvement of subjective appetite ratings with prebiotic supplementation for 16 weeks.\textsuperscript{166} In older children the daily intake of 8g oligofructose enriched-inulin translated into reduced energy-intake in a breakfast buffet. These results are supported by a previous work of Cani et al.\textsuperscript{167} who showed in a pilot study that oligofructose supplementation increases satiety after breakfast and dinner and reduces hunger and prospective food consumption following diner. In a similar study, Liber and Szajewska,\textsuperscript{168} did not show any differences in body weight between the intervention and placebo group.
In animals, prebiotic oligofructose supplementation reduced energy intake, weight gain and fat mass; the impact of prebiotic intake on body composition in general and on gut microbiota was of greater magnitude than for probiotic intake (*Bifidobacterium animalis subsp. Lactis BB-12*). Intake of pre- and probiotics both individually and combined had a positive effect on glycemic control in obese rats.\(^{169}\)

*There are limited data to make a conclusion on pre- and probiotics early in life to reduce the risk of obesity.*

**Complementary feeding**

Regarding complementary feeding within the first two years of life, it is disappointing that there are more guidelines available, rather than scientific data and facts. Most of these guidelines agree on recommending exclusive or full breastfeeding for at least up to 6 months\(^{170-171}\) and to avoid both early (<4 months) and late (>7 months) introduction of gluten, which reduces the risk of celiac disease (CD).\(^{172}\) A report from 2016 on Nutritional interventions or exposures in infants and children aged up to 3 years and their effects on subsequent risk of overweight, obesity and body fat\(^{154}\) revealed 5 systematic reviews on various timings of complementary feeding introductions. Seven studies considered the association between complementary feeding and body composition, but only one study reported an increase in the percentage of body fat among children given complementary foods before 15 weeks of age.\(^{173}\) In a summary of 11 papers of which 4 focus on complementary feeding it is concluded that a high protein content might increase the risk of future obesity, but not a higher FM\(^{174}\) However, no sufficient data permits to underline any relationship between high protein intake and body composition matters.\(^{152}\) Available data did not find any association between protein intake in the second year of life and body fatness.
Furthermore, several studies without a meta-analysis summarized the present knowledge and also include partially the same papers as previous reviews. However, a systematic review regarding the optimal timing of complementary food is cited. This review indicates that there is no clear association between the timing of the introduction of complementary foods and childhood overweight or obesity, but some evidence suggests that very early introduction (at or before 4 months), rather than at 4–6 months, may increase the risk of childhood overweight. 

There is no consistent evidence of an association of the timing of introduction of complementary feeding with later overweight and obesity.

Sleep duration

In 1,338 children from 1 to 3 years old, higher adiposity was independently associated with shorter sleep duration in South Asian children (%BF: β = -0.10 ; 95% CI:-0.16, -0.028), but not in white children. However, in several cohort studies child's short sleep duration was associated with overweight/obesity and/or adiposity risk in children from 1.5 to 9 years old. In the ALSPAC cohort, among the eight factors in early life (3 years old) associated with an increased risk of obesity in childhood, short sleep duration (< 10.5 hours) at age 3 years was significantly associated with obesity (β=1.45, 95% CI: 1.10 to 1.89). Children below 2 years old have the opportunity to sleep during the day and this should be taken in account.

Despite these evidences, behavioural sleep strategies on 328 children (174 interventions) with parent-reported sleep problems at age 7-8 months delivered over one to three structured individual nurse consultations from 8 to 10 months, versus usual care were not successful to reduce BMI at 6 years. It is unclear whether the inverse
association between BMI and sleep is the cause or the consequence or disturbed
hormonal rhythm because obesity.

*Short sleep duration up to 2 years is associated with infant adiposity.*

**Screen activities**

The literature on screen time and obesity within the first 1,000 days of life is sparse. A
recent systematic review of observational studies on screen time use in children under 3
years of age showed that high screen time among infants and toddlers are correlated to
child BMI.\(^{184}\) In 2,374 Greek children aged 1-5 years, children spending \( \geq 2 \) h/day
watching television seem to have higher energy intake compared to children watching
TV less than 2 h/day, even after adjustment for potential confounders.\(^{185}\)

*The limited available information regarding obesity and screen time need further
investigation in this age group.*

**Conclusions**

There are enough evidences of early nutrition and environmental factors to affect
childhood obesity development (Figure 4). According with literature before pregnancy,
it is important to start gestation with maternal BMI in the normal range. During
pregnancy, women should achieve proper gestational weight gain, and to avoid
malnutrition, smoking, and free sugar intake higher than 10% energy. After birth and
during the first two years of life to avoid high protein intake, free sugars and excessive
weight gain.

Actions to be considered are promoting healthy nutrition and normal weight status at
reproductive age and during pregnancy, monitoring infant growth carefully in order to
detect excessive weight gain. Infants should consume a diversified diet during the first
two years of life.

Pediatricians and other health care professionals should provide proper scientific
individual nutritional advice to families. Society should support families/mothers to
keep infants within the normal range of weight development.
LEGENDS FOR FIGURES

Figure 1. Estimated prevalence of overweight and obesity (weight for height > 2 SDs above the median WHO standards) in young children (from 0 to 5 years old) in 1990 and 2010. Data source\(^5\)

Figure 2. Estimated prevalence of overweight and obesity (BMI-for-age > 1 SD above WHO growth reference median) in children and adolescents from 5 to 19 years old in 1975 and 2016. Data source: World Health Organization (http://www.who.int/gho/ncd/risk_factors/overweight_obesity/overweight_adolescents/en/). Countries were grouped using the same criterium of the NCD Risk Factor Collaboration.\(^6\)

Figure 3. Estimated prevalence of pre-term birth rate by regions for 1990 and 2010.\(^9\)

Figure 4. Relevant factors for childhood obesity preventative efforts.
Table 1. Parental pre-pregnancy BMI and/or gestational weight gain (GWG) associations with offspring adiposity

<table>
<thead>
<tr>
<th>Ref</th>
<th>Study</th>
<th>N</th>
<th>Parental variable</th>
<th>Offspring age</th>
<th>Offspring Variable</th>
<th>Significant Effect</th>
<th>OR</th>
</tr>
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<tbody>
<tr>
<td>McCloskey et al.186</td>
<td>Barwon Infant Study</td>
<td>1074</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>Newborn</td>
<td>Birth weight</td>
<td>Yes</td>
<td>17.8g per kg/m² (95% CI: 6.6, 28.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Newborn mean skin fold thickness</td>
<td>Yes</td>
<td>0.1mm per kg/m² (0.0, 0.1)</td>
</tr>
<tr>
<td>Sorensen et al. 29</td>
<td>Danish National Birth Cohort</td>
<td>30 655</td>
<td>Maternal Prepregnancy BMI</td>
<td>7 years</td>
<td>BMI Z-score</td>
<td>No, just in thin mothers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GWG</td>
<td></td>
<td>BMI Z-score</td>
<td>No, just in thin mothers</td>
<td></td>
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<tr>
<td>Linares et al. 187</td>
<td>Growth and Obesity Children Cohort Study</td>
<td>594</td>
<td>Maternal Prepregnancy BMI</td>
<td>0-7 years</td>
<td>Adiposity Rebound</td>
<td>Yes</td>
<td>1.07 (1.02-1.11)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>GWG</td>
<td></td>
<td></td>
<td>No</td>
<td>No</td>
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<tr>
<td>Gaillard et al. 30</td>
<td>Generation R</td>
<td>4 871</td>
<td>Maternal Pre-pregnancy</td>
<td>6 years</td>
<td>BMI</td>
<td>Yes</td>
<td>0.16 (0.13, 0.19)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total Fat Mass</td>
<td>Yes</td>
<td>0.03 (0.01, 0.05)</td>
</tr>
<tr>
<td>Study</td>
<td>Study Type</td>
<td>Sample Size</td>
<td>Maternal Prepregnancy BMI &gt;25 kg/m²</td>
<td>4 years</td>
<td>BMI overweight &amp; obesity</td>
<td>Waist Circumference &gt; 90th</td>
<td>Sum 4 skinfolds</td>
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<tr>
<td>Daraki et al. 188</td>
<td>Rhea Study</td>
<td>618</td>
<td>Maternal Prepregnancy</td>
<td>4 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Leonard et al. 189</td>
<td>National Longitudinal Survey of Youth</td>
<td>7359</td>
<td>Excessive GWG</td>
<td>&gt;4000 g</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Castillo et al. 190</td>
<td>Pelotas Study</td>
<td>3129</td>
<td>Maternal Prepregnancy</td>
<td>6 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Tan et al. 2015 191</td>
<td>Prepregnancy BMI</td>
<td>68</td>
<td></td>
<td>12 years</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Study (year)</td>
<td>Study (center)</td>
<td>Participants</td>
<td>GWG</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>0-3 years BMI</td>
<td>Overweight</td>
<td>Interaction with fasting glucose in lean mothers</td>
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<tr>
<td>Aris et al. 192</td>
<td>GUSTO Study</td>
<td>937</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>0-3 years</td>
<td>Overweight</td>
<td>Yes</td>
<td>0.19 (0.10-0.27) Interaction with fasting glucose in lean mothers</td>
</tr>
<tr>
<td>Lin et al. 193</td>
<td>GUSTO Study</td>
<td>937</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>0-2 years</td>
<td>Subescapular thickness</td>
<td>Yes</td>
<td>3.85% (2.16-5.57) for 1 SD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GWG</td>
<td></td>
<td></td>
<td></td>
<td>3.28% (1.75-4.84) for 1 SD</td>
</tr>
<tr>
<td>Starling et al. 21</td>
<td>Colorado Prebirth cohort</td>
<td>8826</td>
<td>Maternal Prepregnancy BMI</td>
<td>3days</td>
<td>Fat Mass</td>
<td>Yes</td>
<td>5.2 g Fat Mass per 1 kg/m2 maternal BMI (3.5-6.9) 0.12% in Body fat % (0.08-0.16)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>GWG</td>
<td></td>
<td></td>
<td></td>
<td>24 g Fat Mass per 0.1 kg/wk GWG (17.4-30.5) 0.55% in Body fat % (0.37-0.72)</td>
</tr>
<tr>
<td>Widen et al. 1</td>
<td>Columbia Center for Children’s Environmental health birth cohort study</td>
<td>323</td>
<td>Maternal Prepregnancy BMI</td>
<td>7 years</td>
<td>BMI z-score % Fat</td>
<td>Yes</td>
<td>0.44 (0.2-0.7) 2.2% (1.0-3.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Excessive GWG</td>
<td></td>
<td></td>
<td>Yes</td>
<td>$\beta = 2.21$ (95% CI: 1.15, 3.26)</td>
</tr>
<tr>
<td>Gademan et al. 194</td>
<td>ABCD Study</td>
<td>1727</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>5-6 years</td>
<td>BMI</td>
<td>Yes</td>
<td>0.10 (0.08-0.12) per 1 kg/m2 maternal BMI</td>
</tr>
<tr>
<td>Study</td>
<td>Cohort/Sample</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>Time Frame</td>
<td>Maternal BMI Z-score</td>
<td>Childhood overweight/obesity</td>
<td>Excessive GWG</td>
<td>Fat%</td>
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<tr>
<td>Perng et al.(^{195})</td>
<td>VIVA Cohort</td>
<td>1090</td>
<td>6-10 years</td>
<td>Yes</td>
<td>Yes</td>
<td>0.21% (0.13-0.29) per 1 kg/m² maternal BMI</td>
<td>1.15 (1.10-1.20)</td>
</tr>
<tr>
<td>Li et al.(^{196})</td>
<td></td>
<td>38539</td>
<td>0-12 months</td>
<td>Yes</td>
<td>Yes</td>
<td>0.27 (0.21-0.32) per 5 kg/m² maternal BMI</td>
<td>0.9 Kg (0.7-1.14) per 5 kg/m² maternal BMI</td>
</tr>
<tr>
<td>Chandler et al.(^{197})</td>
<td></td>
<td>47</td>
<td>0-12 months</td>
<td>No</td>
<td>No</td>
<td>1.29 (1.23-1.36)</td>
<td>1.31 (1.23-1.40)</td>
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<tr>
<td>Hinkle et al.(^{19})</td>
<td>Early Childhood Longitudinal Study</td>
<td>3600</td>
<td>5 years</td>
<td>BMI Z-score</td>
<td>Yes but in normal and overweight mothers</td>
<td></td>
<td></td>
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<tr>
<td>Wright et al.(^{198})</td>
<td>ALSPAC</td>
<td>Parental obesity</td>
<td>7-11 years</td>
<td>Fat Z-score</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Tanvig et al.(^{19})</td>
<td>Danish</td>
<td>366886</td>
<td>Maternal Neonates</td>
<td>Birth weight</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^{195}\) Perng et al., 2015; \(^{196}\) Li et al., 2015; \(^{197}\) Chandler et al., 2017; \(^{19}\) Hinkle et al., 2018; \(^{198}\) Wright et al., 2019; \(^{19}\) Tanvig et al., 2019.
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample Size</th>
<th>Maternal Exposure</th>
<th>Offspring Exposure</th>
<th>Effect Size</th>
<th>Reference</th>
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<tr>
<td>Kaar et al. 200</td>
<td>EPOCH study</td>
<td>313</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>Abdominal Circumference (AC)</td>
<td>Yes</td>
<td>1.7 (1.4-2.2)</td>
</tr>
<tr>
<td>Alberico et al. 201</td>
<td>14 109</td>
<td>Maternal obesity Pre-pregnancy BMI</td>
<td>Macrosomia</td>
<td>1.57 (1.30-1.91)</td>
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<tr>
<td>Ziyab et al. 202</td>
<td>Isle Wight Birth Cohort</td>
<td>1456</td>
<td>Maternal Prepregnancy Overweight</td>
<td>BMI trajectories</td>
<td>Yes</td>
<td>3.16 (1.52-6.58)</td>
</tr>
<tr>
<td>Ensenauer et al. 203</td>
<td>6837</td>
<td>Excessive vs Adequate Gestational Weight Gain</td>
<td>Overweight Abdominal adiposity</td>
<td>YEs</td>
<td>1.57 (1.30-1.91)</td>
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<tr>
<td>Study</td>
<td>Sample Size</td>
<td>Pre-pregnancy BMI</td>
<td>Follow-up Time</td>
<td>Outcome Measure</td>
<td>Findings</td>
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<tr>
<td>Ode et al.</td>
<td>97</td>
<td>Pre-pregnancy BMI</td>
<td>2wk-3 months</td>
<td>Fat mass</td>
<td>NO</td>
<td></td>
</tr>
<tr>
<td>Fleten et al.</td>
<td>29,216</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>3 years</td>
<td>BMI</td>
<td>Yes but modest</td>
<td></td>
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<tr>
<td>Stuebe et al.</td>
<td>1,250</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>Neonates</td>
<td>z-score Barth weight, neonatal fat mass</td>
<td>Yes but glucose intolerance in the mothers</td>
<td></td>
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<tr>
<td>Lindberg et al.</td>
<td>471</td>
<td>Prepregnancy BMI &gt;25, Prepregnancy BMI &gt;30</td>
<td>5 and 8 years</td>
<td>Overweight/obesity</td>
<td>No, No, Yes</td>
<td></td>
</tr>
<tr>
<td>Fraser et al.</td>
<td>5,154</td>
<td>Pre-pregnancy BMI</td>
<td>9 years</td>
<td>Adiposity per 1kg change in maternal pre-pregnancy weight, Fat mass</td>
<td>Yes, Yes</td>
<td></td>
</tr>
</tbody>
</table>

1-kg/m² maternal BMI was 0.04-kg/m² increase in offspring BMI (95% CI: 0.031, 0.039; P < 0.001).
1-kg/m² paternal BMI 0.05-kg/m² increase in offspring BMI (95% CI: 0.040, 0.051; P < 0.001).
5-km/m² maternal BMI increase 0.08 (0.04-0.12)
23.78 (12.19-35.38)
1.64 (1.01-2.66) at 5 year
1.73 (1.09-2.75) at 8 year
88g (77, 98)
1075g (773, 1378)
<table>
<thead>
<tr>
<th>Study References</th>
<th>Study</th>
<th>Sample Size</th>
<th>GWG vs. IOM</th>
<th>Time</th>
<th>Outcome Measure</th>
<th>Key Findings</th>
</tr>
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<tbody>
<tr>
<td>Crozier et al.209</td>
<td>Southampton Women’s Survey</td>
<td>948</td>
<td>GWG &gt; IOM</td>
<td>Birth 4 year 6 years</td>
<td>Fat mass</td>
<td>No No Yes</td>
</tr>
<tr>
<td>Schack-Nielsen et al.210</td>
<td>Copenhagen Perinatal Cohort</td>
<td>4234</td>
<td>GWG</td>
<td>0-14 years z-score BMI</td>
<td>Yes</td>
<td>0.011 (0.004-0.018) per 1 Kg increase in GWG</td>
</tr>
<tr>
<td>Lawlor et al.211</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>9-11 years</td>
<td>Fat Mass Z-score</td>
<td>Yes</td>
<td>0.24 (0.22-0.26)</td>
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<tr>
<td>Oken et al.212</td>
<td>Nurses’s Health Study II</td>
<td>11994</td>
<td>GWG&gt; IOM 1990</td>
<td>9 - 14 years BMI Z-score Risk of obesity</td>
<td>Yes Yes</td>
<td>0.14 (0.09,0.18) 1.42 (1.19-1.70)</td>
</tr>
<tr>
<td>Gale et al.213</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>216</td>
<td>9 years</td>
<td>Fat mass index YES</td>
<td></td>
<td>0.26 (0.04-0.48) per 1 SD maternal BMI</td>
</tr>
<tr>
<td>Oken et al.214</td>
<td>VIVA cohort</td>
<td>1044</td>
<td>Adequate GWG GWG&gt; IOM 1990</td>
<td>9 - 14 years Risk of overweight</td>
<td>Yes Yes</td>
<td>3.77 (1.38, 10.27) 4.35 (1.69-11.24)</td>
</tr>
<tr>
<td>Labayen et al.215</td>
<td>EYHS</td>
<td>1813</td>
<td>Maternal pre-gestaional BMI</td>
<td>9 and 15 years Total Body Fat</td>
<td>Yes</td>
<td>0.588 (0.416 – 0.760)</td>
</tr>
<tr>
<td>Study (Lawlor et al. 28)</td>
<td>Location (MUSP)</td>
<td>Sample Size</td>
<td>Maternal Pre-pregnancy BMI</td>
<td>Paternal BMI</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3340</td>
<td>14 years</td>
<td>BMI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Main results of studies relating body weight at birth to abdominal or visceral adiposity measured by dual-X-ray absorptiometry, magnetic resonance imaging or ultrasonography.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age</th>
<th>N</th>
<th>Study population</th>
<th>Exposure</th>
<th>Outcome measure</th>
<th>Method of measurement</th>
<th>Covariates</th>
<th>Relevant results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garnett et al. 104</td>
<td>7-8 years</td>
<td>255</td>
<td>Australian prepubertal children</td>
<td>BW s.d.s</td>
<td>Abdominal FM (% of total body fat)</td>
<td>DXA</td>
<td></td>
<td>Negative association β=-0.18; 9=0.009</td>
</tr>
<tr>
<td>Dolan et al. 105</td>
<td>5-18 years</td>
<td>101</td>
<td>Multi-ethnic children and adolescents (USA)</td>
<td>BW for gestational age</td>
<td>Truncal FM</td>
<td>DXA</td>
<td>Race, age, sex, Tanner stage, current body weight</td>
<td>Negative association P=0.03</td>
</tr>
<tr>
<td>Labayen et al. 103</td>
<td>13.5-17.5 years</td>
<td>284</td>
<td>Healthy caucasian adolescents (Spain)</td>
<td>BW (g)</td>
<td>Abdominal FMI (kg/m²) in three regions</td>
<td>DXA</td>
<td>Age, sex, gestational age, breastfeeding, Tanner stage, PAL, SES,</td>
<td>Negative associations β from -0.067 to 0.044 P≤0.004</td>
</tr>
<tr>
<td>Durmus et al. 216</td>
<td>2 years</td>
<td>481</td>
<td>Children participating in a prospective cohort study in, the Netherlands</td>
<td>BW s.d.s</td>
<td>VFT</td>
<td>US</td>
<td>Age (months), sex, breastfeeding and BMI</td>
<td>NS</td>
</tr>
<tr>
<td>Biosca et al. 95</td>
<td>6-10 years</td>
<td>124</td>
<td>Healthy Caucasian children (Spain)</td>
<td>BW for gestational age: SGA AGA LGA</td>
<td>Abdominal FM in three regions and Truncal FM</td>
<td>DXA</td>
<td>Age, sex and height</td>
<td>SGA had higher Truncal (~2%) and abdominal FM (3% to 4%) than AGA and LGA</td>
</tr>
<tr>
<td>Jaiswal et 6-13</td>
<td>442</td>
<td></td>
<td>Multi-ethnic</td>
<td>BW (kg)</td>
<td>VAT (cm³)</td>
<td>MRI</td>
<td>Maternal pre-pregnant</td>
<td>Negative</td>
</tr>
</tbody>
</table>
| Study | Age Range | Sample Size | Region/Population | BMI, Maternal Smoking, Education and Income, Current Daily Calorie Intake and PAL and BMI | Association with SAT
\( \beta \) per 1 s.d. | Additional Variables |
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stansfield et al.(^{107})</td>
<td>14-18 years</td>
<td>575 White and black adolescents (USA)</td>
<td>BW tertiles &lt;3100g 3100g-3600g &gt;3600g</td>
<td>SAT (cm(^3))  BMI, maternal smoking, education and income, current daily calorie intake and PAL and BMI</td>
<td>( \beta ) per 1 s.d.=-8.8; P=0.008</td>
<td>Age, sex, race, Tanner stage, PAL, SES, BMI U-shaped relation P=0.028</td>
</tr>
<tr>
<td>Kensara et al.(^{217})</td>
<td>64-72 years</td>
<td>32 Older Englishmen</td>
<td>BW (g) Low BW (&lt;3.18 kg) vs. High BW (&gt;3.86 kg)</td>
<td>VAT (cm(^3)) MRI</td>
<td>Total FM, SES, PAL, smoking status</td>
<td>Low BW group had higher TLFM (.42 vs. 1.16; P = 0.005)</td>
</tr>
<tr>
<td>McNeely et al.(^{218})</td>
<td>34-56 years</td>
<td>91 White and Japanese American middle age adults (USA)</td>
<td>BW (g)</td>
<td>VAT MRI</td>
<td>Age, sex, ethnicity, BMI</td>
<td>NS</td>
</tr>
<tr>
<td>Demerath et al.(^{219})</td>
<td>18-75 years</td>
<td>233 Adults born appropriate for gestational age, singletons (UK)</td>
<td>BW s.d.s</td>
<td>VAT MRI</td>
<td>Gestational age, birth order, age, height, sex, infant feeding mode, educational level, smoking status, physical activity</td>
<td>NS</td>
</tr>
<tr>
<td>Rolfe Ede et al.(^{220})</td>
<td>30-55 years</td>
<td>1092 Adults from birth cohorts from 1950 to 1975 (UK)</td>
<td>BW (kg)</td>
<td>VFT US</td>
<td>Age, sex, educational level, BMI</td>
<td>( \beta )=-0.07; P=0.01</td>
</tr>
<tr>
<td>Pilgaard et al.(^{221})</td>
<td>18-24 years</td>
<td>116 Swedish healthy</td>
<td>BW s.d.s</td>
<td>VAT (vol %) MRI</td>
<td>Sex</td>
<td>Negative</td>
</tr>
<tr>
<td>Study</td>
<td>Age</td>
<td>Sample Size</td>
<td>Sample Description</td>
<td>Assessment</td>
<td>Outcome</td>
<td>Results</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>-------------</td>
<td>--------------------</td>
<td>------------</td>
<td>---------</td>
<td>---------</td>
</tr>
</tbody>
</table>
| Ronn et al. 221               | 18-61| 1473        | Adult Inuit        | BW, IUGR  | VFT, US | VAT: -12.5, P<0.05  
SAT: -10.3, P<0.001  
Age, birthplace, family history of obesity, waist circumference |
| Araujo de Franca et al. 223   | 30   | 2663        | Adults participating from 1982 in a birth cohort study (Brazil) | BW z-score, IUGR | VFT, SFT | Women with IUGR higher VFT (mean difference: 0.7 cm, P=0.01)  
Men with IUGR lower SFT (mean difference: 0.2 cm, P<0.001)  
Family income, maternal education, height and skin colour, maternal BMI before pregnancy, smoking in pregnancy, gestational age |

BW: birth weight; DXA: Dual X-ray Absorptiometry; FM: fat mass; FMI: fat mass index; IUGR: intrauterine growth restriction; birth weight for gestational age and sex below the 10th centile; MRI: Magnetic Resonance Imaging; PAL: Physical activity level; SAAT: subcutaneous abdominal adipose tissue; SES: socioeconomic status; s.d.s: standard deviation score; SFT: Subcutaneous fat thickness; US: ultrasonography; VAT: visceral adipose tissue; VFT: Visceral fat thickness.
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   activity during pregnancy and offspring size at 18 to 24 months. *J Phys Act 

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   retention and infant anthropometric outcomes. *Journal of developmental origins 

   physical activity before and during mid-pregnancy and offspring adiposity in 

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   birth weight and aberrant methylation at imprinted genes among offspring. *Int J 

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Prevalence of overweight and obesity in children aged 0-5 years (%)

- Developed countries: 4.2% (2010) vs 6.1% (1990)
- Developing countries: 3.7% (2010) vs 7.9% (1990)
- Oceania: 2.9% (2010) vs 3.6% (1990)
- South America: 1.6% (2010) vs 8.0% (1990)
- Central America: 4.8% (2010) vs 7.2% (1990)
- Caribbean: 4.6% (2010) vs 6.9% (1990)
- Western Asia: 3.0% (2010) vs 4.6% (1990)
- Southeastern Asia: 2.1% (2010) vs 4.6% (1990)
- South Central Asia: 2.3% (2010) vs 3.6% (1990)
- Eastern Asia: 4.8% (2010) vs 6.2% (1990)
- Western Africa: 2.2% (2010) vs 6.4% (1990)
- Southern Africa: 6.4% (2010) vs 7.6% (1990)
- Middle Africa: 2.5% (2010) vs 8.7% (1990)
- Eastern Africa: 3.9% (2010) vs 6.7% (1990)
Prevalence of overweight and obesity in children and adolescents aged 5-19 years (%)

<table>
<thead>
<tr>
<th>Region</th>
<th>2016</th>
<th>1975</th>
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<td>Global</td>
<td>24.6</td>
<td>27.1</td>
</tr>
<tr>
<td>Developed countries</td>
<td>7.4</td>
<td>11.5</td>
</tr>
<tr>
<td>Developing countries</td>
<td>5.5</td>
<td>23.4</td>
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<tr>
<td>Andean Latin America</td>
<td>7.0</td>
<td>27.8</td>
</tr>
<tr>
<td>Southern Latin America</td>
<td>12.4</td>
<td>31.1</td>
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<tr>
<td>Central Latin America</td>
<td>7.7</td>
<td>30.0</td>
</tr>
<tr>
<td>Caribbean</td>
<td>6.6</td>
<td>29.8</td>
</tr>
<tr>
<td>Oceania</td>
<td>10.3</td>
<td>17.3</td>
</tr>
<tr>
<td>Southern Africa</td>
<td>1.1</td>
<td>31.8</td>
</tr>
<tr>
<td>Middle East and North Africa</td>
<td>8.7</td>
<td>12.5</td>
</tr>
<tr>
<td>East Africa</td>
<td>1.5</td>
<td>5.3</td>
</tr>
<tr>
<td>Subsaharian</td>
<td>1.2</td>
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<tr>
<td>Central Asia</td>
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<td>High-Income Asia Pacific</td>
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<td>South Asia</td>
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<td>East and Southeast Asia</td>
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<td>Eastern Europe</td>
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<td>Central and Eastern Europe</td>
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<td>South Western Europe</td>
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<tr>
<td>North Western Europe</td>
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<td>25.5</td>
</tr>
<tr>
<td>High-income English-speaking countries</td>
<td>16.9</td>
<td>34.9</td>
</tr>
</tbody>
</table>
Prevalence of preterm birth rates in 1990 and 2010 (%)

- Southern Latin America: 7.3 (2010), 8.4 (1990)
- Central Latin America: 8.8 (2010), 8.6 (1990)
- Eastern Europe: 6.2 (2010), 6.6 (1990)
- Central and Eastern Europe: 5.5 (2010), 7.4 (1990)
- South Western Europe: 5.5 (2010), 7 (1990)