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

Elvira Larqué[1], Idoia Labayen[2], Carl E Flodmark[3], Inge Lissau[3,4,] Sarah Czernin[5], Luis A Moreno[6], Angelo Pietrobelli[7] and Kurt Widhalm[5]*

[1]Department of Physiology. University of Murcia, Murcia, Spain; [2]Institute for Innovation & Sustainable Development in Food Chain (IS-FOOD) and Department of Health Sciences, Public University of Navarra, 31008 Pamplona, Spain; [3]Childhood Obesity Unit, Department of Pediatrics, University Hospital Malmo, Sweden; [4]Clinical Research Unit, University Hospital Copenhagen, Hvidovre, Denmark; [5]Division Nutrition and Metabolism, Department of Pediatrics, Medical University of Vienna, Austria; [6] GENUD (Growth, Exercise, Nutrition and Devlopment) research group, Instituto Agroalimentario de Aragón (IA2), Instituto de Investigación Sanitaria Aragón (IIS Aragón) and Centro de Investigación Biomédica en Red Fisiopatología de la Obesidad y Nutrición (CIBEROBN), Universidad de Zaragoza, Zaragoza, Spain; [7]Pediatric Unit, Verona University Medical School, Verona, Italy.

Running Title: Early Risk Factors for child obesity

*Corresponding author

Prof. Luis A Moreno

Facultad de Ciencias de la Salud

Universidad de Zaragoza

C/ Domingo Miral s/n

50009 Zaragoza Spain

Phone: +34976761000 (ext. 4457)

Fax: +34976761752

E-mail: lmoreno@unizar.es

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.[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.[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.[4] 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.[5] 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.[5]

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.[6] 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[7]; 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.[8]

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[9] 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[10] 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[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.[12] In 2010, in 138 countries of low and middle income areas,[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.[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.[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.[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[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.[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%).[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 (β = 0.09 units: 0.08, 0.11; and β = 0.07 units 0.04-0.11);[24] however, fixed effects models that account for familial factors resulted in null associations for both factors.[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).[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.[33] 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, [34] BMI of men whose mothers had gestational diabetes was on average 0.94 kg/m² (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 ≥ 85th percentile (RR 0.91, 95% CI 0.75 to 1.11; three trials, 767 children; I2 = 4%; moderate-quality evidence). [35]

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 [36-37]. In contrast, the Leningrad Siege study did not find any relationship between famine exposure during pregnancy and obesity risk.[38] 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.[39] 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.[40-41]

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.[42] 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.[43] A meta-analysis including 17 studies, showed that prenatal maternal smoking was consistently associated with future offspring overweight/obesity.[44] 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.[45] 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.[46] 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[47-48]

Concerning macronutrients, in 1.410 pregnant women, maternal high fat diet during pregnancy was significantly associated with neonatal fat mass. [49]However, maternal fat and protein intakes were not consistently associated with infant BMI peak and childhood BMI.[50] 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.[51] 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,[52] and higher body fat and abdominal fat in childhood at 6 years .[51] 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.[53] 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[54-55]. 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.[50]

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,[56] although a meta-analysis did not exclude this possibility.[57] 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.[57-60]

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.[60-62] 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.[63] 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.[64] Lifestyle interventions are an acceptable approach although future studies should examine their efficacy.[65]

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 [66-67]. 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.[68] Other recent meta-analyses, reported that leisure physical activity reduced significantly the risk to lower LGA babies (RR 0.51; 0.30-0.87).[69] High levels of physical activity before pregnancy or in early pregnancy are also clearly associated with a significantly lower risk of developing GDM,[69-70] 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.[71] 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.[72-75] 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.[76] 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%.[77] 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.[78] Maternal antibiotic use has been associated with changes in infant birth weight, and higher birth weights were reported among infants born to antibiotic users.[79] 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.[80] Prenatal exposure to antibiotics may affect the postnatal metabolism by altering the composition of the “pioneer” microbiota.[81] Prenatal exposure to antibiotics may also differentially alter methylation at regulatory regions of imprinted genes and somatic epigenetic changes may occur.[78]

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.[82-83] Mueller et al.[84] 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.[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.[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 *bifidobacteria* and higher counts of *Clostridium difficile* than vaginally delivered children.[86] The gut microbioma exerts important functions in regulating energy balance and may contribute to the development of obesity.[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.[88]

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[89-90] Babies born with either low birth weight (<2500g)[91] or high birth weight (>4000g)[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.[93-94] The relationship between high birth weight and lean mass (LM) or FFM has been consistently observed in children,[95-97] 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.[98-99]

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,[100] while the associations with waist circumference or waist to hip ratio, were inconclusive.[101] 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,[102] subcutaneous[102] or abdominal adiposity,[95,103-105] though non-significant[106] and U-shaped relationships[107] 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.[108] Offspring of women with obesity are also significantly heavier, had higher fat mass at birth and are at higher risk of later obesity.[109] 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.[110]

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,[111-113] whereas other studies found not effect at all.[114] In the first year of life, body mass gain is usually slower in breastfed, than in formula fed infants.[115]

It has been reported that breastfeeding for at least three months reduced the adverse effect of low birth weight on abdominal adiposity in adolescents.[116] In other study, exclusive breastfeeding for six months reduced the effect of both birth weight and early growth on adiposity in pre-school children.[97] 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.[117] Crume et al.[118] 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.[119] Also Wang et al.[120], 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%.[120] 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,[121] 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.[122]

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.[123]

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.[124] 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.[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.[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.[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.[111,133-134] In low-middle income countries, in contrast, infant growth rate seems to predict subsequent FFM or height.[135-140]

Baird et al.[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[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.[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.[143] In 4 to 20 years old youths, Chomtho et al.[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.[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.[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.[147] A very early adiposity rebound is considered a determinant of obesity at further ages.[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.[150] 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.[151]

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.[152]

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.[153]

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.[154] 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.[155]

Analyses of studies with limited number of subjects found positive, [156] no association or even an inverse association.[157] 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)[158], but not at 6 years.[159] 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.,[160] 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 assessedafter 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.[161] 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.[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.[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.[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.[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.[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.[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,[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 (>7months) 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.[175] However, a systematic review regarding the optimal timing of complementary food is cited.[173] 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: $\beta = -0.10$; 95% CI:-0.16, -0.028), but not in white children. [176] 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.[177-181] 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).[182] 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.[183] 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 2374 Greek children aged 1-5 years, children spending > or =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

Ref	Study	N	Parental variable	Offspring age	Offspring Variable	Significant Effect	OR
McCloskey et al.[186]	Barwon Infant Study	1074	Maternal Pre-pregnancy BMI	Newborn	Birth weight	Yes	17.8g per kg/m^2 (95% CI: 6.6, 28.9)
					Newborn mean skin fold thickness	Yes	0.1mm per kg/m^2 (0.0, 0.1)
Jacota et al. [18]	EDEN Cohort	1069	Maternal Prepregnancy BMI	5-6 years	BMI z-score	No, just in thin mothers	
			GWG		BMI z-score	No, just in thin mothers	
Sorensen et al. [29]	Danish National Birth Cohort	30 655	Maternal Pre-pregnancy BMI	7 years	BMI Z-score		0.208 (0.196, 0.220)
			Paternal BMI		BMI Z-score		0.154 (0.143, 0.166)
Linares et al.[187]	Growth and Obesity Children Cohort Study	594	Matrenal Prepregnancy BMI	0-7 years	Adiposity Rebound	Yes	1.07 (1.02-1.11)
			GWG			No	No
Gaillard et al.[30]	Generation R	4 871	Maternal Pre-pregnancy	6 years	BMI	Yes	0.16 (0.13, 0.19)
					Total Fat Mass	Yes	0.03 (0.01, 0.05)

			BMI Paternal BMI		BMI Total Fat mass	Yes No	0.11 (0.09, 0.14) 0.01 (-0.01, 0.03)
Daraki et al.[188]	Rhea Study	618	Maternal Prepregnancy BMI >25 kg/m^2	4 years	BMI overweight & obesity Waist Circumference>90th Sum 4 skinfolds	Yes Yes Yes	1.83 (1.19, 2.81) 1.97 (1.11-3.49) 5.10 mm (2.49-7.71)
Leonard et al.[189]	National Longitudinal Survey of Youth	7 359	Excessive GWG	Birth 2-5 years 6-11 year 12-19 years	>4000 g Overweight Overweigh Overweight	Yes Yes Yes Yes	1.51 (1.23-1.86) 1.16 (1.02-1.32) 1.10 (1.02-1.19) 1.15 (1.06-1.24)
Castillo et al.[190]	Pelotas Study	3129	Maternal Prepregnancy BMI GWG	6 years	Fat Mass Fat Mass	Yes Yes	0.11 Kg Fat Mass per 1 kg/m2 maternal BMI 0.18% in Body fat % 0.08 Kg Fat Mass per 1 kg GWG increase 0.18% in Body fat %
Tan et al. 2015[191]		68	Prepregnancy BMI	12 years	BMI Fat mass	Yes	

			GWG				
Aris et al.[192]	GUSTO Study	937	Maternal Pre-pregnancy BMI	0-3 years	Overweight	Yes	0.19 (0.10-0.27) Interaction with fasting glucose in lean mothers
Lin et al.[193]	GUSTO Study	937	Maternal Pre-pregnancy BMI GWG	0-2 years	Subescapular thickness	Yes	3.85% (2.16-5.57) for 1 SD 3.28% (1.75-4.84) for 1 SD
Starling et al.[21]	Colorado Prebirth cohort	8826	Maternal Prepregnancy BMI GWG	3days	Fat Mass Fat Mass	Yes Yes	5.2 g Fat Mass per 1 kg/m2 maternal BMI (3.5-6.9) 0.12% in Body fat % (0.08-0.16) 24 g Fat Mass per 0.1 kg/wk GWG (17.4-30.5) 0.55% in Body fat % (0.37-0.72)
Widen et al.[1]	Columbia Center for Children's Environmental health birth cohort study	323	Maternal Pre-pregnancy BMI Excesive GWG	7 years	BMI z-score % Fat BMI	Yes Yes Yes	0.44 (0.2-0.7) 2.2% (1.0-3.5) β = 2.21 (95% CI: 1.15, 3.26)
Gademan et al.[194]	ABCD Study	1727	Maternal Pre-pregnancy	5-6 years	BMI	Yes	0.10 (0.08-0.12) per 1 kg/m2 maternal BMI

			BMI		Fat% Risk for overweight	Yes Yes	0.21% (0.13-0.29) per 1 kg/m2 maternal BMI 1.15 (i.10-1.20)
Perng et al.[195]	VIVA Cohort	1090	Maternal Pre-pregnancy BMI	6-10 years	BMI Z-score Total Fat Trunk Fat	Yes Yes Yes	0.27 (0.21-0.32) per 5 kg/m2 maternal BMI 0.9 Kg (0.7-1.14) per 5 kg/m2 maternal BMI 0.39 kg (0.29-0.49) per 5 kg/m2 maternal BMI
Li et al.[196]		38539	Maternal Pre-pregnancy BMI Excesive GWG	0-12 months	Childhood overweight/obesity childhood overweight childhood obesity	Yes Yes	1.29 (1.23-1.36) 1.31 (1.23-1.40)
Chandler et al.[197]		47	Maternal Pre-pregnancy BMI	0-12 months	Fat mass	No	
Hinkle et al. [19]	Early Childhood Longitudinal Study	3600	Excessive GWG	5 years	BMI Z-score	Yes but in normal and overweight mothers	
Wright et al.[198]	ALSPAC		Parental obesity	7-11 years	Fat Z-score	Yes	
Tanvig et al.	Danish	366886	Maternal	Neonates	Birth weight	Yes	1 kg/m^2 Maternal BMI

[199]	Medical Birth Registry		Prepregnancy BMI		Birth Abdominal Circumference (AC)	Yes	associated with an increase in AC of 0.5 mm and an increase in birthweight of 14.2 g (13.9–14.5 g)
Kaar et al. [200]	EPOCH study	313	Maternal Prepregnancy BMI Maternal Pre-pregnancy BMI+excess GWG	10 year	BMI Waist circumference Subcutaneous fat visceral fat	Yes	0.13 (0.02, 0.253) 0.38 (0.10, 0.65) 3.49 (0.89, 6.08) 0.37 (0.004, 0.74) β = 1 unit increase in offspring parameter for every 1 kg/m2 increase in maternal pre-pregnancy 0.34 (0.25, 0.44) 0.83 (0.58, 1.08) 7.26 (4.90, 9.62) 0.72 (0.39, 1.06)-
Alberico et al.[201]		14 109	Maternal obesity Pre-pregnancy BMI GWG	Neonates	Macrosomia	Yes	1.7 (1.4-2.2) 1.9 (1.6-2.2)
Ziyab et al. [202]	Isle Wight Birth Cohort	1456	Maternal Prepregnancy Overweight	0-18 years	BMI trajectories	Yes	3.16 (1.52-6.58)
Ensenauer et al. [203]		6837	Excesive vs Adequate Gestational Weight Gain	5.8 years	Overweight Abdominal adiposity	YEs	1.57 (1.30-1.91) 1.39 (1.19-1.63)

Ode et al.[204]		97	Pre-preggnancy BMI	2wk-3 months	Fat mass	NO	
Fleten et al.[205]	Norwegian mother and child cohort	29 216	Maternal Pre-pregnancy BMI Paternal	3 years	BMI	Yes but modest No differences between parents	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).
Stuebe et al.[206]		1 250	Maternal Pre-preggnancy BMI	neonates	z-score Barth weight neonatal fat mass	Yes but glucose intolerance in the mothers	5-kg/m2maternal BMI increase 0.08 (0.04-0.12) 23.78 (12.19-35.38)
Lindberg et al.[207]	WINGS	471	Prepregnancy BMI>25 Prepregnancy BMI>30 GWG	5 and 8 years	Overweight/obesity	No No Yes	1.64 (1.01-2.66) at 5 year 1.73 (1.09-2.75) at 8 year
Fraser et al.[208]	UK prospective pregnancy cohort	5154	Pre-preggnancy BMI GWG >IOM	9 years	Adiposity per 1kg change in maternal pre-pregnancy weight Fat mass	Yes Yes	88g (77, 98) 1075g (773, 1378)

Crozier et al.[209]	Southampton Women's Survey	948	GWG >IOM	Birth	Fat mass	No	
				4 year		No	
				6 years		Yes	0.26 (0.07, 0.45)
Schack-Nielsen et al.[210]	Copenhangen Perinatal Cohort	4234	GWG	0-14 years	z-score BMI	Yes	0.011 (0.004-0.018) per 1 Kg increase in GWG
Lawlor et al.[211]			Maternal Pre-pregnancy BMI	9-11 years	Fat Mass Z-score	Yes	0.24 (0.22-0.26)
			Paternal Prepregnancy BMI		Fat Mass Z-score	Yes	0.13 (0.11-0.15)
Oken et al.[212]	Nurses's Helath Study II	11 994	GWG>IOM 1990	9 - 14 years	BMI Z-score	Yes	0.14 (0.09,0.18)
					Risk of obesity	Yes	1.42 (1.19-1.70)
Gale et al.[213]		216	Maernal Pre-pregnancy BMI	9 years	Fat mass index	YES	0.26 (0.04-0.48) per 1 SD maternal BMI
Oken et al.[214]	VIVA cohort	1 044	Adequate GWG	9 - 14 years	Risk of overweight	Yes	3.77 (1.38, 10.27)
			GWG>IOM 1990			Yes	4.35 (1.69-11.24)
Labayen et al.[215]	EYHS	1813	Maternal pre-gestaional BMI	9 and 15 years	Total Body Fat	Yes	0.588 (0.416 – 0.760)

			Paternal BMI			Yes	0.607 (0.386–0.827)
Lawlor et al. [28]	MUSP	3 340	Maternal Pre-pregnancy BMI Paternal	14 years	BMI	Yes Yes	0.362 SD (0.323, 0.402) per 1 SD maternal BMI 0.239 SD (0.197, 0.282) per 1SD paternal BMI

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.

Reference	Age	N	Study population	Exposure	Outcome measure	Method of measurement	Covariates	Relevant results
Garnett et al. [104]	7-8 years	255	Australian prepubertal children	BW s.d.s	Abdominal FM (% of total body fat)	DXA		Negative association $\beta=-0.18$; 9=0.009
Dolan et al.[105]	5-18 years	101	Multi-ethnic children and adolescents (USA)	BW for gestational age	Truncal FM	DXA	Race, age, sex, Tanner stage, current body weight	Negative association P=0.03
Labayen et al.[103]	13.5-17.5 years	284	Healthy caucasian adolescents (Spain)	BW (g)	Abdominal FMI (kg/m^2) in three regions	DXA	Age, sex, gestational age, breastfeeding, Tanner stage, PAL, SES,	Negative associations β from -0.067to -0.044 $P \leq 0.004$
Durmus et al.[216]	2 years	481	Children participating in a prospective cohort study in, the Netherlands	BW s.d.s	VFT SFT	US	Age (months), sex, breastfeeding and BMI	NS
Biosca et al.[95]	6-10 years	124	Healthy Caucasian children (Spain)	BW for gestational age: SGA AGA LGA	Abdominal FM in three regions and Truncal FM	DXA	Age, sex and height	SGA had higher Truncal (≈2%) and abdominal FM (3% to 4%) than AGA and LGA
Jaiswal et	6-13	442	Multi-ethnic	BW (kg)	VAT (cm^3)	MRI	Maternal pre-pregnant	Negative

al.[102]	years		children (USA)		SAAT (cm^3)		BMI, maternal smoking, education and income, current daily calorie intake and PAL and BMI	association with SAT β per 1 s.d.=-8.8; P=0.008
Stansfield et al.[107]	14-18 years	575	White and black adolescents (USA)	BW tertiles <3100g 3100g-3600g >3600g	VAT (cm^3)	MRI	Age, sex, race, Tanner stage, PAL, SES, BMI	U-shaped relation P=0.028
Kensara et al.[217]	64-72 years	32	Older Englishmen	BW (g) Low BW (<3.18 kg) *vs.* High BW (>3.86 kg)	Trunk to limb fat mass (TLFM)	DXA	Total FM, SES, PAL, smoking status	Low BW group had higher TLFM (.42 *vs.* 1.16; P = 0.005)
McNeely et al.[218]	34-56 years	91	White and Japanese American middle age adults (USA)	BW (g)	VAT SAAT	MRI	Age, sex, ethnicity, BMI	NS
Demerath et al.[219]	18-75 years	233	Adults born appropriate for gestational age, singletons (UK)	BW s.d.s	VAT SAAT	MRI	Gestational age, birth order, age, height, sex, infant feeding mode, educational level, smoking status, physical activity	NS
Rolfe Ede et al.[220]	30-55 years	1092	Adults from birth cohorts from 1950 to 1975 (UK)	BW (kg)	VFT	US	Age, sex, educational level, BMI	β=-0.07; P=0.01
Pilgaard et	18-24	116	Swedish healthy	BW s.d.s	VAT (vol %)	MRI	Sex	Negative

al.[221]	years		adult twins (58 pairs)		SAT (vol %)			associations Percent-wise impact per 1 s.d. VAT: -12.5, $P<0.05$ SAT:-10.3, $P<0.001$
Ronn et al.[222]	18-61	1473	Adult Inuit	BW: IUGR	VFT	US	Age, birthplace, family history of obesity, waist circumference	Increase (%) in VFT per kg increment in birth weight (95% CI): −4.1 (−7.3, −0.9) in men
Araujo de Franca et al.[223]	30 years	2663	Adults participating from 1982 in a birth cohort study (Brazil)	BW z-score IUGR	VFT SFT	US	Family income, maternal education, height and skin colour, maternal BMI before pregnancy, smoking in pregnancy, gestational age	Women with IUGR higher VFT (mean difference 0.7 cm, $P=0.01$) Men with IUGR lower SFT (mean difference: 0.2 cm, $P<0.001$)

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.

REFERENCES

1. Rugholm, S., *et al.* Stability of the association between birth weight and childhood overweight during the development of the obesity epidemic. *Obes Res* **13**, 2187-2194 (2005).
2. Graversen, L., *et al.* Stability of the associations between early life risk indicators and adolescent overweight over the evolving obesity epidemic. *PLoS One* **9**, e95314 (2014).
3. Black, R.E., *et al.* Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet* **382**, 427-451 (2013).
4. Abdullah, A., *et al.* The number of years lived with obesity and the risk of all-cause and cause-specific mortality. *Int J Epidemiol* **40**, 985-996 (2011).
5. de Onis, M., Blossner, M. & Borghi, E. Global prevalence and trends of overweight and obesity among preschool children. *Am J Clin Nutr* **92**, 1257-1264 (2010).
6. Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128.9 million children, adolescents, and adults. *Lancet* **390**, 2627-2642 (2017).
7. Ng, M., *et al.* Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* **384**, 766-781 (2014).
8. Chung, A., *et al.* Trends in child and adolescent obesity prevalence in economically advanced countries according to socioeconomic position: a systematic review. *Obes Rev* **17**, 276-295 (2016).
9. Blencowe, H., *et al.* National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. *Lancet* **379**, 2162-2172 (2012).
10. Harrison, M.S. & Goldenberg, R.L. Global burden of prematurity. *Semin Fetal Neonatal Med* **21**, 74-79 (2016).
11. Labayen, I., *et al.* Early life programming of abdominal adiposity in adolescents: The HELENA Study. *Diabetes Care* **32**, 2120-2122 (2009).
12. Lee, A.C., *et al.* Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21(st) standard: analysis of CHERG datasets. *BMJ* **358**, j3677 (2017).
13. Lee, A.C., *et al.* National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. *Lancet Glob Health* **1**, e26-36 (2013).
14. Ferrara, A. Increasing prevalence of gestational diabetes mellitus: a public health perspective. *Diabetes Care* **30 Suppl 2**, S141-146 (2007).
15. Baerug, A., *et al.* Recent gestational diabetes was associated with mothers stopping predominant breastfeeding earlier in a multi-ethnic population. *Acta Paediatr* **107**, 1028-1035 (2018).
16. Nguyen, C.L., Pham, N.M., Binns, C.W., Duong, D.V. & Lee, A.H. Prevalence of Gestational Diabetes Mellitus in Eastern and Southeastern Asia: A Systematic Review and Meta-Analysis. *J Diabetes Res* **2018**, 6536974 (2018).
17. Widen, E.M., *et al.* Gestational weight gain and obesity, adiposity and body size in African-American and Dominican children in the Bronx and Northern Manhattan. *Matern Child Nutr* **12**, 918-928 (2016).

18. Jacota, M., Forhan, A., Saldanha-Gomes, C., Charles, M.A. & Heude, B. Maternal weight prior and during pregnancy and offspring's BMI and adiposity at 5-6 years in the EDEN mother-child cohort. *Pediatr Obes* (2016).
19. Hinkle, S.N.*, et al.* Excess gestational weight gain is associated with child adiposity among mothers with normal and overweight prepregnancy weight status. *J Nutr* **142**, 1851-1858 (2012).
20. Hivert, M.F., Rifas-Shiman, S.L., Gillman, M.W. & Oken, E. Greater early and mid-pregnancy gestational weight gains are associated with excess adiposity in mid-childhood. *Obesity (Silver Spring)* **24**, 1546-1553 (2016).
21. Starling, A.P.*, et al.* Associations of maternal BMI and gestational weight gain with neonatal adiposity in the Healthy Start study. *Am J Clin Nutr* **101**, 302-309 (2015).
22. Kral, J.G.*, et al.* Large maternal weight loss from obesity surgery prevents transmission of obesity to children who were followed for 2 to 18 years. *Pediatrics* **118**, e1644-1649 (2006).
23. Smith, J.*, et al.* Effects of maternal surgical weight loss in mothers on intergenerational transmission of obesity. *J Clin Endocrinol Metab* **94**, 4275-4283 (2009).
24. Branum, A.M., Parker, J.D., Keim, S.A. & Schempf, A.H. Prepregnancy body mass index and gestational weight gain in relation to child body mass index among siblings. *Am J Epidemiol* **174**, 1159-1165 (2011).
25. Lawlor, D.A., Lichtenstein, P., Fraser, A. & Langstrom, N. Does maternal weight gain in pregnancy have long-term effects on offspring adiposity? A sibling study in a prospective cohort of 146,894 men from 136,050 families. *Am J Clin Nutr* **94**, 142-148 (2011).
26. Villamor, E. & Cnattingius, S. Interpregnancy weight change and risk of adverse pregnancy outcomes: a population-based study. *Lancet* **368**, 1164-1170 (2006).
27. Patro, B.*, et al.* Maternal and paternal body mass index and offspring obesity: a systematic review. *Ann Nutr Metab* **63**, 32-41 (2013).
28. Lawlor, D.A.*, et al.* Epidemiologic evidence for the fetal overnutrition hypothesis: findings from the mater-university study of pregnancy and its outcomes. *Am J Epidemiol* **165**, 418-424 (2007).
29. Sorensen, T.*, et al.* Comparison of associations of maternal peri-pregnancy and paternal anthropometrics with child anthropometrics from birth through age 7 y assessed in the Danish National Birth Cohort. *Am J Clin Nutr* **104**, 389-396 (2016).
30. Gaillard, R., Rifas-Shiman, S.L., Perng, W., Oken, E. & Gillman, M.W. Maternal inflammation during pregnancy and childhood adiposity. *Obesity (Silver Spring)* **24**, 1320-1327 (2016).
31. Linabery, A.M.*, et al.* Stronger influence of maternal than paternal obesity on infant and early childhood body mass index: the Fels Longitudinal Study. *Pediatr Obes* **8**, 159-169 (2013).
32. Whitaker, R.C., Deeks, C.M., Baughcum, A.E. & Specker, B.L. The relationship of childhood adiposity to parent body mass index and eating behavior. *Obes Res* **8**, 234-240 (2000).
33. Logan, K.M., Gale, C., Hyde, M.J., Santhakumaran, S. & Modi, N. Diabetes in pregnancy and infant adiposity: systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed* **102**, F65-F72 (2017).
34. Lawlor, D.A., Lichtenstein, P. & Langstrom, N. Association of maternal diabetes mellitus in pregnancy with offspring adiposity into early adulthood:

sibling study in a prospective cohort of 280,866 men from 248,293 families. *Circulation* **123**, 258-265 (2011).

35. Brown, J*., et al.* Lifestyle interventions for the treatment of women with gestational diabetes. *Cochrane Database Syst Rev* **5**, CD011970 (2017).
36. Ravelli, A.C., van Der Meulen, J.H., Osmond, C., Barker, D.J. & Bleker, O.P. Obesity at the age of 50 y in men and women exposed to famine prenatally. *Am J Clin Nutr* **70**, 811-816 (1999).
37. Wang, Y., Wang, X., Kong, Y., Zhang, J.H. & Zeng, Q. The Great Chinese Famine leads to shorter and overweight females in Chongqing Chinese population after 50 years. *Obesity (Silver Spring)* **18**, 588-592 (2010).
38. Stanner, S.A*., et al.* Does malnutrition in utero determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *Bmj* **315**, 1342-1348 (1997).
39. Hult, M*., et al.* Hypertension, diabetes and overweight: looming legacies of the Biafran famine. *PLoS One* **5**, e13582 (2010).
40. Bhutta, Z.A*., et al.* Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? *Lancet* **382**, 452-477 (2013).
41. Khan, M.N., Rahman, M.M., Shariff, A.A., Rahman, M.S. & Rahman, M.A. Maternal undernutrition and excessive body weight and risk of birth and health outcomes. *Archives of public health = Archives belges de sante publique* **75**, 12 (2017).
42. Oken, E., Levitan, E.B. & Gillman, M.W. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. *Int J Obes (Lond)* **32**, 201-210 (2008).
43. Li, L*., et al.* Maternal smoking in pregnancy association with childhood adiposity and blood pressure. *Pediatr Obes* **11**, 202-209 (2016).
44. Ino, T. Maternal smoking during pregnancy and offspring obesity: meta-analysis. *Pediatr Int* **52**, 94-99 (2010).
45. Dobson, C.C*., et al.* Chronic prenatal ethanol exposure increases adiposity and disrupts pancreatic morphology in adult guinea pig offspring. *Nutr Diabetes* **2**, e57 (2012).
46. Brion, M.J*., et al.* Maternal macronutrient and energy intakes in pregnancy and offspring intake at 10 y: exploring parental comparisons and prenatal effects. *Am J Clin Nutr* **91**, 748-756 (2010).
47. Khoury, J., Henriksen, T., Christophersen, B. & Tonstad, S. Effect of a cholesterol-lowering diet on maternal, cord, and neonatal lipids, and pregnancy outcome: a randomized clinical trial. *Am J Obstet Gynecol* **193**, 1292-1301 (2005).
48. Kinnunen, T.I*., et al.* Preventing excessive weight gain during pregnancy - a controlled trial in primary health care. *Eur J Clin Nutr* **61**, 884-891 (2007).
49. Shapiro, A.L*., et al.* Infant Adiposity is Independently Associated with a Maternal High Fat Diet but not Related to Niacin Intake: The Healthy Start Study. *Matern Child Health J* (2017).
50. Chen, L.W*., et al.* Associations of maternal macronutrient intake during pregnancy with infant BMI peak characteristics and childhood BMI. *Am J Clin Nutr* **105**, 705-713 (2017).
51. Vidakovic, A.J*., et al.* Maternal plasma PUFA concentrations during pregnancy and childhood adiposity: the Generation R Study. *Am J Clin Nutr* **103**, 1017-1025 (2016).

52. Hakola, L.*, et al.* Maternal fatty acid intake during pregnancy and the development of childhood overweight: a birth cohort study. *Pediatr Obes* (2016).
53. Moses, R.G.*, et al.* Effect of a low-glycemic-index diet during pregnancy on obstetric outcomes. *Am J Clin Nutr* **84**, 807-812 (2006).
54. Murrin, C., Shrivastava, A. & Kelleher, C.C. Maternal macronutrient intake during pregnancy and 5 years postpartum and associations with child weight status aged five. *Eur J Clin Nutr* **67**, 670-679 (2013).
55. Jen, V.*, et al.* Mothers' intake of sugar-containing beverages during pregnancy and body composition of their children during childhood: the Generation R Study. *Am J Clin Nutr* **105**, 834-841 (2017).
56. Tieu, J., Shepherd, E., Middleton, P. & Crowther, C.A. Dietary advice interventions in pregnancy for preventing gestational diabetes mellitus. *Cochrane Database Syst Rev* **1**, CD006674 (2017).
57. Effect of diet and physical activity based interventions in pregnancy on gestational weight gain and pregnancy outcomes: meta-analysis of individual participant data from randomised trials. *BMJ* **358**, j3119 (2017).
58. Donnelly, J.M., Walsh, J.M., Byrne, J., Molloy, E.J. & McAuliffe, F.M. Impact of maternal diet on neonatal anthropometry: a randomized controlled trial. *Pediatr Obes* **10**, 52-56 (2015).
59. Poston, L.*, et al.* Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *Lancet Diabetes Endocrinol* **3**, 767-777 (2015).
60. Dodd, J.M.*, et al.* The effects of antenatal dietary and lifestyle advice for women who are overweight or obese on maternal diet and physical activity: the LIMIT randomised trial. *BMC Med* **12**, 161 (2014).
61. Patel, N.*, et al.* Infant adiposity following a randomised controlled trial of a behavioural intervention in obese pregnancy. *Int J Obes (Lond)* (2017).
62. Tanvig, M. Offspring body size and metabolic profile - effects of lifestyle intervention in obese pregnant women. *Dan Med J* **61**, B4893 (2014).
63. Catalano, P. & deMouzon, S.H. Maternal obesity and metabolic risk to the offspring: why lifestyle interventions may have not achieved the desired outcomes. *Int J Obes (Lond)* **39**, 642-649 (2015).
64. Yeo, S., Walker, J.S., Caughey, M.C., Ferraro, A.M. & Asafu-Adjei, J.K. What characteristics of nutrition and physical activity interventions are key to effectively reducing weight gain in obese or overweight pregnant women? A systematic review and meta-analysis. *Obes Rev* **18**, 385-399 (2017).
65. Lau, Y.*, et al.* Electronic-based lifestyle interventions in overweight or obese perinatal women: a systematic review and meta-analysis. *Obes Rev* (2017).
66. Gjestland, K., Bo, K., Owe, K.M. & Eberhard-Gran, M. Do pregnant women follow exercise guidelines? Prevalence data among 3482 women, and prediction of low-back pain, pelvic girdle pain and depression. *Br J Sports Med* **47**, 515-520 (2013).
67. Evenson, K.R., Savitz, D.A. & Huston, S.L. Leisure-time physical activity among pregnant women in the US. *Paediatr Perinat Epidemiol* **18**, 400-407 (2004).
68. Muktabhant, B., Lawrie, T.A., Lumbiganon, P. & Laopaiboon, M. Diet or exercise, or both, for preventing excessive weight gain in pregnancy. *Cochrane Database Syst Rev*, CD007145 (2015).

69. da Silva, S.G., Ricardo, L.I., Evenson, K.R. & Hallal, P.C. Leisure-Time Physical Activity in Pregnancy and Maternal-Child Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Cohort Studies. *Sports Med* **47**, 295-317 (2017).
70. Tobias, D.K., Zhang, C., van Dam, R.M., Bowers, K. & Hu, F.B. Physical activity before and during pregnancy and risk of gestational diabetes mellitus: a meta-analysis. *Diabetes Care* **34**, 223-229 (2011).
71. Owe, K.M., Nystad, W. & Bo, K. Association between regular exercise and excessive newborn birth weight. *Obstet Gynecol* **114**, 770-776 (2009).
72. Clapp, J.F., 3rd. Morphometric and neurodevelopmental outcome at age five years of the offspring of women who continued to exercise regularly throughout pregnancy. *J Pediatr* **129**, 856-863 (1996).
73. Clapp, J.F., 3rd, Simonian, S., Lopez, B., Appleby-Wineberg, S. & Harcar-Sevcik, R. The one-year morphometric and neurodevelopmental outcome of the offspring of women who continued to exercise regularly throughout pregnancy. *Am J Obstet Gynecol* **178**, 594-599 (1998).
74. Mattran, K., Mudd, L.M., Rudey, R.A. & Kelly, J.S. Leisure-time physical activity during pregnancy and offspring size at 18 to 24 months. *J Phys Act Health* **8**, 655-662 (2011).
75. Kong, K.L., Campbell, C., Wagner, K., Peterson, A. & Lanningham-Foster, L. Impact of a walking intervention during pregnancy on post-partum weight retention and infant anthropometric outcomes. *Journal of developmental origins of health and disease* **5**, 259-267 (2014).
76. Kong, K.L., Gillman, M.W., Rifas-Shiman, S.L. & Wen, X. Leisure time physical activity before and during mid-pregnancy and offspring adiposity in mid-childhood. *Pediatr Obes* **11**, 81-87 (2016).
77. Lupattelli, A*., et al.* Medication use in pregnancy: a cross-sectional, multinational web-based study. *BMJ Open* **4**, e004365 (2014).
78. Vidal, A.C*., et al.* Associations between antibiotic exposure during pregnancy, birth weight and aberrant methylation at imprinted genes among offspring. *Int J Obes (Lond)* **37**, 907-913 (2013).
79. Jepsen, P*., et al.* A population-based study of maternal use of amoxicillin and pregnancy outcome in Denmark. *Br J Clin Pharmacol* **55**, 216-221 (2003).
80. Mor, A*., et al.* Prenatal exposure to systemic antibacterials and overweight and obesity in Danish schoolchildren: a prevalence study. *Int J Obes (Lond)* **39**, 1450-1455 (2015).
81. Azad, M.B., Bridgman, S.L., Becker, A.B. & Kozyrskyj, A.L. Infant antibiotic exposure and the development of childhood overweight and central adiposity. *Int J Obes (Lond)* **38**, 1290-1298 (2014).
82. Li, H.T., Zhou, Y.B. & Liu, J.M. The impact of cesarean section on offspring overweight and obesity: a systematic review and meta-analysis. *Int J Obes (Lond)* **37**, 893-899 (2013).
83. Yuan, C*., et al.* Association Between Cesarean Birth and Risk of Obesity in Offspring in Childhood, Adolescence, and Early Adulthood. *JAMA Pediatr* **170**, e162385 (2016).
84. Mueller, N.T*., et al.* Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity. *Int J Obes (Lond)* **39**, 665-670 (2015).
85. Dominguez-Bello, M.G*., et al.* Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci U S A* **107**, 11971-11975 (2010).

86. Jakobsson, H.E., *et al.* Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut* **63**, 559-566 (2014).
87. Bouter, K.E., van Raalte, D.H., Groen, A.K. & Nieuwdorp, M. Role of the Gut Microbiome in the Pathogenesis of Obesity and Obesity-Related Metabolic Dysfunction. *Gastroenterology* (2017).
88. Penders, J., *et al.* Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* **118**, 511-521 (2006).
89. Yuan, Z.P., *et al.* Possible role of birth weight on general and central obesity in Chinese children and adolescents: a cross-sectional study. *Ann Epidemiol* **25**, 748-752 (2015).
90. Rogers, I. The influence of birthweight and intrauterine environment on adiposity and fat distribution in later life. *Int J Obes Relat Metab Disord* **27**, 755-777 (2003).
91. Rockenbach, G., *et al.* Sex-specific associations of birth weight with measures of adiposity in mid-to-late adulthood: the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). *Int J Obes (Lond)* **40**, 1286-1291 (2016).
92. Skilton, M.R., *et al.* High birth weight is associated with obesity and increased carotid wall thickness in young adults: the cardiovascular risk in young Finns study. *Arteriosclerosis, thrombosis, and vascular biology* **34**, 1064-1068 (2014).
93. Singhal, A., Wells, J., Cole, T.J., Fewtrell, M. & Lucas, A. Programming of lean body mass: a link between birth weight, obesity, and cardiovascular disease? *Am J Clin Nutr* **77**, 726-730 (2003).
94. Labayen, I., *et al.* Early programming of body composition and fat distribution in adolescents. *Journal of Nutrition* **136**, 147-152 (2006).
95. Biosca, M., *et al.* Central adiposity in children born small and large for gestational age. *Nutricion Hospitalaria* **26**, 971-976 (2011).
96. Fonseca, M.J., Severo, M., Correia, S. & Santos, A.C. Effect of birth weight and weight change during the first 96 h of life on childhood body composition--path analysis. *Int J Obes (Lond)* **39**, 579-585 (2015).
97. Ejlerskov, K.T., *et al.* The impact of early growth patterns and infant feeding on body composition at 3 years of age. *Br J Nutr* **114**, 316-327 (2015).
98. Patel, H.P., *et al.* Developmental influences, muscle morphology, and sarcopenia in community-dwelling older men. *The journals of gerontology. Series A, Biological sciences and medical sciences* **67**, 82-87 (2012).
99. Maltin, C.A., Delday, M.I., Sinclair, K.D., Steven, J. & Sneddon, A.A. Impact of manipulations of myogenesis in utero on the performance of adult skeletal muscle. *Reproduction (Cambridge, England)* **122**, 359-374 (2001).
100. Labayen, I., *et al.* Small birth weight and later body composition and fat distribution in adolescents: The AVENA Study. *Obesity* **16**, 1680-1686 (2008).
101. Araujo de Franca, G.V., Restrepo-Mendez, M.C., Loret de Mola, C. & Victora, C.G. Size at birth and abdominal adiposity in adults: a systematic review and meta-analysis. *Obes Rev* **15**, 77-91 (2014).
102. Jaiswal, M., *et al.* Is low birth weight associated with adiposity in contemporary U.S. youth? The Exploring Perinatal Outcomes among Children (EPOCH) Study. *Journal of developmental origins of health and disease* **3**, 166-172 (2012).
103. Labayen, I., *et al.* Early Life programming of Abdominal Adiposity in Adolescents: The HELENA Study. *Diabetes Care* **32**, 2120-2122 (2009).

104. Garnett, S.P.*, et al.* Abdominal fat and birth size in healthy prepubertal children. *Int J Obes Relat Metab Disord* **25**, 1667-1673 (2001).
105. Dolan, M.S., Sorkin, J.D. & Hoffman, D.J. Birth weight is inversely associated with central adipose tissue in healthy children and adolescents. *Obesity (Silver Spring)* **15**, 1600-1608 (2007).
106. Mook-Kanamori, D.O.*, et al.* Fetal and infant growth and the risk of obesity during early childhood: the Generation R Study. *European journal of endocrinology* **165**, 623-630 (2011).
107. Stansfield, B.K.*, et al.* Nonlinear Relationship between Birth Weight and Visceral Fat in Adolescents. *J Pediatr* **174**, 185-192 (2016).
108. Yu, Z.B.*, et al.* Birth weight and subsequent risk of obesity: a systematic review and meta-analysis. *Obes Rev* **12**, 525-542 (2011).
109. Catalano, P.M. & Shankar, K. Obesity and pregnancy: mechanisms of short term and long term adverse consequences for mother and child. *BMJ* **356**, j1 (2017).
110. Whitaker, R.C. Predicting preschooler obesity at birth: the role of maternal obesity in early pregnancy. *Pediatrics* **114**, e29-36 (2004).
111. Weng, S.F., Redsell, S.A., Swift, J.A., Yang, M. & Glazebrook, C.P. Systematic review and meta-analyses of risk factors for childhood overweight identifiable during infancy. *Arch Dis Child* **97**, 1019-1026 (2012).
112. Arenz, S., Ruckerl, R., Koletzko, B. & von Kries, R. Breast-feeding and childhood obesity--a systematic review. in *Int J Obes Relat Metab Disord*, Vol. 28 1247-1256 (England, 2004).
113. Owen, C.G., Martin, R.M., Whincup, P.H., Smith, G.D. & Cook, D.G. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. in *Pediatrics*, Vol. 115 1367-1377 (United States, 2005).
114. Martin, R.M.*, et al.* Effects of promoting longer-term and exclusive breastfeeding on adiposity and insulin-like growth factor-I at age 11.5 years: a randomized trial. *Jama* **309**, 1005-1013 (2013).
115. Rogers, S.L. & Blissett, J. Breastfeeding duration and its relation to weight gain, eating behaviours and positive maternal feeding practices in infancy. *Appetite* **108**, 399-406 (2017).
116. Labayen, I.*, et al.* Breastfeeding attenuates the effect of low birthweight on abdominal adiposity in adolescents: the HELENA study. *Maternal and Child Nutrition* **11**, 1036-1040 (2015).
117. Singhal, A.*, et al.* Nutrition in infancy and long-term risk of obesity: evidence from 2 randomized controlled trials. in *Am J Clin Nutr*, Vol. 92 1133-1144 (United States, 2010).
118. Crume, T.L.*, et al.* Long-term impact of neonatal breastfeeding on childhood adiposity and fat distribution among children exposed to diabetes in utero. *Diabetes Care* **34**, 641-645 (2011).
119. Brion, M.J.*, et al.* What are the causal effects of breastfeeding on IQ, obesity and blood pressure? Evidence from comparing high-income with middle-income cohorts. *Int J Epidemiol* **40**, 670-680 (2011).
120. Wang, L., Collins, C., Ratliff, M., Xie, B. & Wang, Y. Breastfeeding Reduces Childhood Obesity Risks. *Child Obes* **13**, 197-204 (2017).
121. Patel, R.*, et al.* Cohort profile: The promotion of breastfeeding intervention trial (PROBIT). *Int J Epidemiol* **43**, 679-690 (2014).
122. Martin, R.M.*, et al.* Effects of Promoting Long-term, Exclusive Breastfeeding on Adolescent Adiposity, Blood Pressure, and Growth Trajectories: A

Secondary Analysis of a Randomized Clinical Trial. *JAMA Pediatr*, e170698 (2017).
123. Smithers, L.G., Kramer, M.S. & Lynch, J.W. Effects of Breastfeeding on Obesity and Intelligence: Causal Insights From Different Study Designs. *JAMA Pediatr* **169**, 707-708 (2015).
124. Robinson, S.M.*, et al.* Modifiable early-life risk factors for childhood adiposity and overweight: an analysis of their combined impact and potential for prevention. *Am J Clin Nutr* **101**, 368-375 (2015).
125. Victora, C.G.*, et al.* Breastfeeding in the 21st century: epidemiology, mechanisms, and lifelong effect. *Lancet* **387**, 475-490 (2016).
126. Patro-Golab, B.*, et al.* Protein Concentration in Milk Formula, Growth, and Later Risk of Obesity: A Systematic Review. *J Nutr* **146**, 551-564 (2016).
127. Weber, M.*, et al.* Lower protein content in infant formula reduces BMI and obesity risk at school age: follow-up of a randomized trial. *Am J Clin Nutr* **99**, 1041-1051 (2014).
128. Putet, G.*, et al.* Effect of dietary protein on plasma insulin-like growth factor-1, growth, and body composition in healthy term infants: a randomised, double-blind, controlled trial (Early Protein and Obesity in Childhood (EPOCH) study). *Br J Nutr* **115**, 271-284 (2016).
129. Haschke, F.*, et al.* Postnatal High Protein Intake Can Contribute to Accelerated Weight Gain of Infants and Increased Obesity Risk. *Nestle Nutrition Institute workshop series* **85**, 101-109 (2016).
130. Ziegler, E.E.*, et al.* Adequacy of Infant Formula With Protein Content of 1.6 g/100 kcal for Infants Between 3 and 12 Months. *J Pediatr Gastroenterol Nutr* **61**, 596-603 (2015).
131. Socha, P.*, et al.* Milk protein intake, the metabolic-endocrine response, and growth in infancy: data from a randomized clinical trial. *Am J Clin Nutr* **94**, 1776S-1784S (2011).
132. Hellmuth, C.*, et al.* Effects of Early Nutrition on the Infant Metabolome. *Nestle Nutrition Institute workshop series* **85**, 89-100 (2016).
133. Ong, K.K. & Loos, R.J. Rapid infancy weight gain and subsequent obesity: systematic reviews and hopeful suggestions. *Acta Paediatr* **95**, 904-908 (2006).
134. Druet, C.*, et al.* Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. *Paediatr Perinat Epidemiol* **26**, 19-26 (2012).
135. Wells, J.C., Chomtho, S. & Fewtrell, M.S. Programming of body composition by early growth and nutrition. in *Proc Nutr Soc*, Vol. 66 423-434 (England, 2007).
136. Adair, L.S.*, et al.* Size at birth, weight gain in infancy and childhood, and adult blood pressure in 5 low- and middle-income-country cohorts: when does weight gain matter? *Am J Clin Nutr* **89**, 1383-1392 (2009).
137. Corvalan, C., Gregory, C.O., Ramirez-Zea, M., Martorell, R. & Stein, A.D. Size at birth, infant, early and later childhood growth and adult body composition: a prospective study in a stunted population. *Int J Epidemiol* **36**, 550-557 (2007).
138. Gonzalez, D.A., Nazmi, A. & Victora, C.G. Growth from birth to adulthood and abdominal obesity in a Brazilian birth cohort. *Int J Obes (Lond)* **34**, 195-202 (2010).
139. Wells, J.C., Hallal, P.C., Wright, A., Singhal, A. & Victora, C.G. Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. in *Int J Obes (Lond)*, Vol. 29 1192-1198 (Unknown, 2005).

140. Sachdev, H.S., *et al.* Anthropometric indicators of body composition in young adults: relation to size at birth and serial measurements of body mass index in childhood in the New Delhi birth cohort. *Am J Clin Nutr* **82**, 456-466 (2005).
141. Baird, J., *et al.* Being big or growing fast: systematic review of size and growth in infancy and later obesity. *Bmj* **331**, 929 (2005).
142. Monteiro, P.O. & Victora, C.G. Rapid growth in infancy and childhood and obesity in later life--a systematic review. *Obes Rev* **6**, 143-154 (2005).
143. Kwon, S., Janz, K.F., Letuchy, E.M., Burns, T.L. & Levy, S.M. Association between body mass index percentile trajectories in infancy and adiposity in childhood and early adulthood. *Obesity (Silver Spring)* **25**, 166-171 (2017).
144. Chomtho, S., *et al.* Infant growth and later body composition: evidence from the 4-component model. *Am J Clin Nutr* **87**, 1776-1784 (2008).
145. Koontz, M.B., Gunzler, D.D., Presley, L. & Catalano, P.M. Longitudinal changes in infant body composition: association with childhood obesity. *Pediatr Obes* **9**, e141-144 (2014).
146. Lei, X., *et al.* The optimal postnatal growth trajectory for term small for gestational age babies: a prospective cohort study. *J Pediatr* **166**, 54-58 (2015).
147. Rolland-Cachera, M.F., *et al.* Adiposity rebound in children: a simple indicator for predicting obesity. *Am J Clin Nutr* **39**, 129-135 (1984).
148. Mo-Suwan, L., McNeil, E., Sangsupawanich, P., Chittchang, U. & Choprapawon, C. Adiposity rebound from three to six years of age was associated with a higher insulin resistance risk at eight-and-a-half years in a birth cohort study. *Acta Paediatr* **106**, 128-134 (2017).
149. Arisaka, O., Sairenchi, T., Ichikawa, G. & Koyama, S. Increase of body mass index (BMI) from 1.5 to 3 years of age augments the degree of insulin resistance corresponding to BMI at 12 years of age. *Journal of pediatric endocrinology & metabolism : JPEM* **30**, 455-457 (2017).
150. Gunther, A.L., Buyken, A.E. & Kroke, A. Protein intake during the period of complementary feeding and early childhood and the association with body mass index and percentage body fat at 7 y of age. *Am J Clin Nutr* **85**, 1626-1633 (2007).
151. Hoppe, C., Molgaard, C., Thomsen, B.L., Juul, A. & Michaelsen, K.F. Protein intake at 9 mo of age is associated with body size but not with body fat in 10-y-old Danish children. *Am J Clin Nutr* **79**, 494-501 (2004).
152. Pimpin, L., Jebb, S., Johnson, L., Wardle, J. & Ambrosini, G.L. Dietary protein intake is associated with body mass index and weight up to 5 y of age in a prospective cohort of twins. *Am J Clin Nutr* **103**, 389-397 (2016).
153. Voortman, T., *et al.* Protein intake in early childhood and body composition at the age of 6 years: The Generation R Study. *Int J Obes (Lond)* **40**, 1018-1025 (2016).
154. Patro-Golab, B., *et al.* 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: a systematic review of systematic reviews. *Obes Rev* **17**, 1245-1257 (2016).
155. Hooper, L., *et al.* Effects of total fat intake on body weight. *Cochrane Database Syst Rev*, CD011834 (2015).
156. Skinner, J.D., Bounds, W., Carruth, B.R., Morris, M. & Ziegler, P. Predictors of children's body mass index: a longitudinal study of diet and growth in children aged 2-8 y. *Int J Obes Relat Metab Disord* **28**, 476-482 (2004).

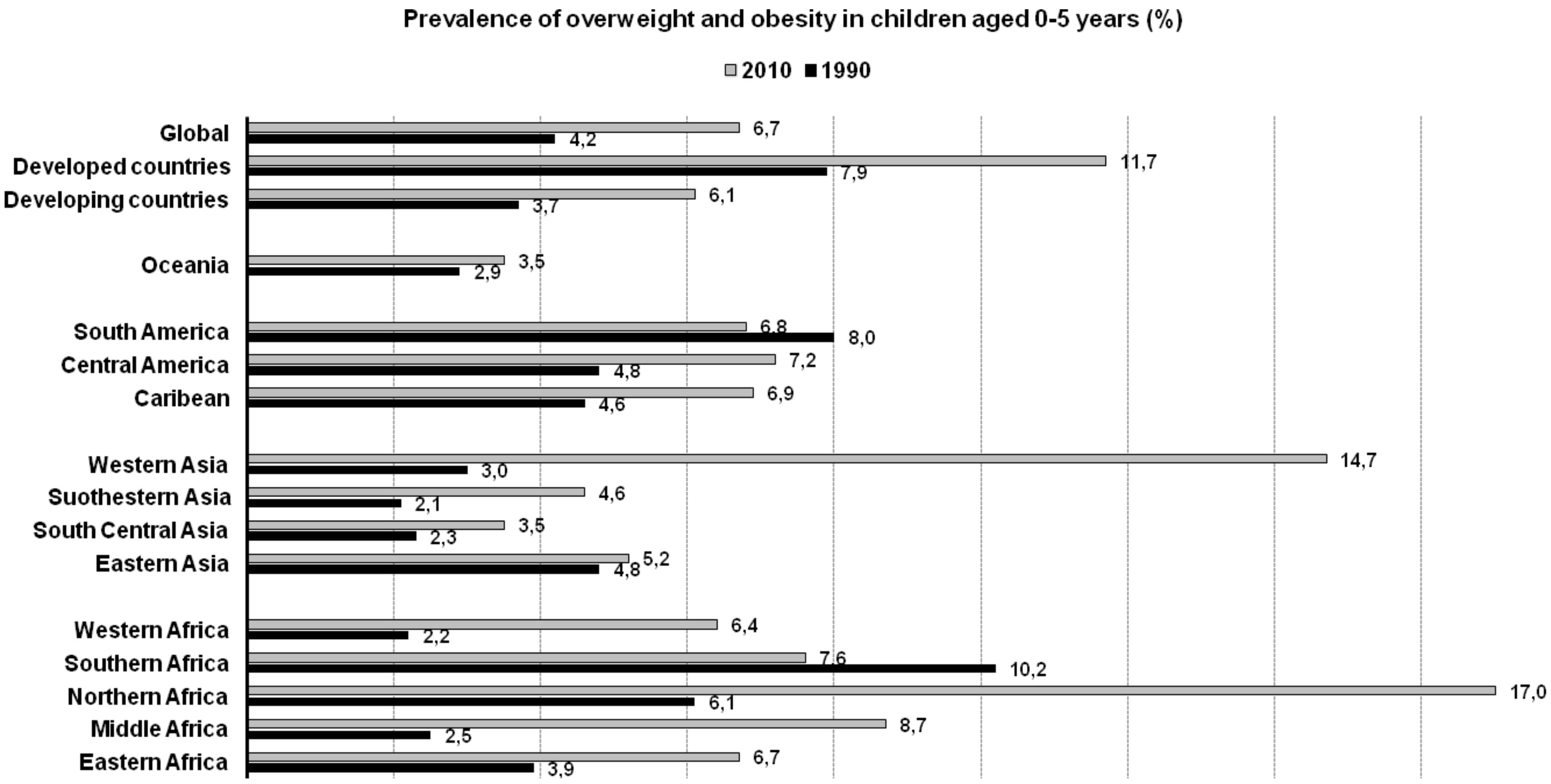
157. Rolland-Cachera, M.F., *et al.* Association of nutrition in early life with body fat and serum leptin at adult age. *Int J Obes (Lond)* **37**, 1116-1122 (2013).
158. Heppe, D.H., *et al.* Parental, fetal, and infant risk factors for preschool overweight: the Generation R Study. *Pediatr Res* **73**, 120-127 (2013).
159. Stroobant, W., *et al.* Intake of Different Types of Fatty Acids in Infancy Is Not Associated with Growth, Adiposity, or Cardiometabolic Health up to 6 Years of Age. *J Nutr* **147**, 413-420 (2017).
160. Agostoni, C., *et al.* Dietary fats and cholesterol in italian infants and children. *Am J Clin Nutr* **72**, 1384S-1391S (2000).
161. Hakanen, M., *et al.* Development of overweight in an atherosclerosis prevention trial starting in early childhood. The STRIP study. *Int J Obes (Lond)* **30**, 618-626 (2006).
162. Herbst, A., *et al.* Direction of associations between added sugar intake in early childhood and body mass index at age 7 years may depend on intake levels. *J Nutr* **141**, 1348-1354 (2011).
163. Pan, L., *et al.* A longitudinal analysis of sugar-sweetened beverage intake in infancy and obesity at 6 years. *Pediatrics* **134 Suppl 1**, S29-35 (2014).
164. Sonneville, K.R., *et al.* Juice and water intake in infancy and later beverage intake and adiposity: could juice be a gateway drink? *Obesity (Silver Spring)* **23**, 170-176 (2015).
165. Parnell, J.A. & Reimer, R.A. Weight loss during oligofructose supplementation is associated with decreased ghrelin and increased peptide YY in overweight and obese adults. *Am J Clin Nutr* **89**, 1751-1759 (2009).
166. Hume, M.P., Nicolucci, A.C. & Reimer, R.A. Prebiotic supplementation improves appetite control in children with overweight and obesity: a randomized controlled trial. *Am J Clin Nutr* **105**, 790-799 (2017).
167. Cani, P.D., Joly, E., Horsmans, Y. & Delzenne, N.M. Oligofructose promotes satiety in healthy human: a pilot study. *Eur J Clin Nutr* **60**, 567-572 (2006).
168. Liber, A. & Szajewska, H. Effect of oligofructose supplementation on body weight in overweight and obese children: a randomised, double-blind, placebo-controlled trial. *Br J Nutr* **112**, 2068-2074 (2014).
169. Bomhof, M.R., Saha, D.C., Reid, D.T., Paul, H.A. & Reimer, R.A. Combined effects of oligofructose and Bifidobacterium animalis on gut microbiota and glycemia in obese rats. *Obesity (Silver Spring)* **22**, 763-771 (2014).
170. Agostoni, C., *et al.* Complementary feeding: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* **46**, 99-110 (2008).
171. Organization, W.H. The Optimal Duration of Exclusive Breastfeeding: Report of an Expert Consultation. (Geneva, 2001).
172. Guandalini, S. Risk of celiac disease autoimmunity and timing of gluten introduction in the diet of infants at increased risk of disease. *J Pediatr Gastroenterol Nutr* **41**, 366-367 (2005).
173. Pearce, J., Taylor, M.A. & Langley-Evans, S.C. Timing of the introduction of complementary feeding and risk of childhood obesity: a systematic review. *Int J Obes (Lond)* **37**, 1295-1306 (2013).
174. Michaelsen, K.F., Larnkjaer, A., Larsson, M.W. & Molgaard, C. Early Nutrition and Its Effects on Growth, Body Composition and Later Obesity. *World review of nutrition and dietetics* **114**, 103-119 (2016).
175. Shalitin, S., Battelino, T. & Moreno, L.A. Obesity, Metabolic Syndrome and Nutrition. *World review of nutrition and dietetics* **114**, 21-49 (2016).

176. Collings, P.J., *et al.* Sleep Duration and Adiposity in Early Childhood: Evidence for Bidirectional Associations from the Born in Bradford Study. *Sleep* **40**(2017).
177. Baird, J., *et al.* Duration of sleep at 3 years of age is associated with fat and fat-free mass at 4 years of age: the Southampton Women's Survey. *J Sleep Res* **25**, 412-418 (2016).
178. Cespedes, E.M., *et al.* Chronic insufficient sleep and diet quality: Contributors to childhood obesity. *Obesity (Silver Spring)* **24**, 184-190 (2016).
179. Taveras, E.M., Gillman, M.W., Pena, M.M., Redline, S. & Rifas-Shiman, S.L. Chronic sleep curtailment and adiposity. *Pediatrics* **133**, 1013-1022 (2014).
180. Bornhorst, C., *et al.* From sleep duration to childhood obesity--what are the pathways? *Eur J Pediatr* **171**, 1029-1038 (2012).
181. Diethelm, K., Bolzenius, K., Cheng, G., Remer, T. & Buyken, A.E. Longitudinal associations between reported sleep duration in early childhood and the development of body mass index, fat mass index and fat free mass index until age 7. *Int J Pediatr Obes* **6**, e114-123 (2011).
182. Reilly, J.J., *et al.* Early life risk factors for obesity in childhood: cohort study. *BMJ* **330**, 1357 (2005).
183. Wake, M., Price, A., Clifford, S., Ukoumunne, O.C. & Hiscock, H. Does an intervention that improves infant sleep also improve overweight at age 6? Follow-up of a randomised trial. *Arch Dis Child* **96**, 526-532 (2011).
184. Duch, H., Fisher, E.M., Ensari, I. & Harrington, A. Screen time use in children under 3 years old: a systematic review of correlates. *Int J Behav Nutr Phys Act* **10**, 102 (2013).
185. Manios, Y., *et al.* Television viewing and food habits in toddlers and preschoolers in Greece: the GENESIS study. *Eur J Pediatr* **168**, 801-808 (2009).
186. McCloskey, K., *et al.* The association between higher maternal pre-pregnancy body mass index and increased birth weight, adiposity and inflammation in the newborn. *Pediatr Obes* (2016).
187. Linares, J., *et al.* The effects of pre-pregnancy BMI and maternal factors on the timing of adiposity rebound in offspring. *Obesity (Silver Spring)* **24**, 1313-1319 (2016).
188. Daraki, V., *et al.* Metabolic profile in early pregnancy is associated with offspring adiposity at 4 years of age: the Rhea pregnancy cohort Crete, Greece. *PLoS One* **10**, e0126327 (2015).
189. Leonard, S.A., Petito, L.C., Rehkopf, D.H., Ritchie, L.D. & Abrams, B. Weight gain in pregnancy and child weight status from birth to adulthood in the United States. *Pediatr Obes* (2016).
190. Castillo, H., Santos, I.S. & Matijasevich, A. Relationship between maternal pre-pregnancy body mass index, gestational weight gain and childhood fatness at 6-7 years by air displacement plethysmography. *Matern Child Nutr* **11**, 606-617 (2015).
191. Tan, H.C., *et al.* Mother's pre-pregnancy BMI is an important determinant of adverse cardiometabolic risk in childhood. *Pediatr Diabetes* **16**, 419-426 (2015).
192. Aris, I.M., *et al.* Associations of gestational glycemia and prepregnancy adiposity with offspring growth and adiposity in an Asian population. *Am J Clin Nutr* **102**, 1104-1112 (2015).
193. Lin, X., *et al.* Ethnic Differences in Effects of Maternal Pre-Pregnancy and Pregnancy Adiposity on Offspring Size and Adiposity. *J Clin Endocrinol Metab* **100**, 3641-3650 (2015).

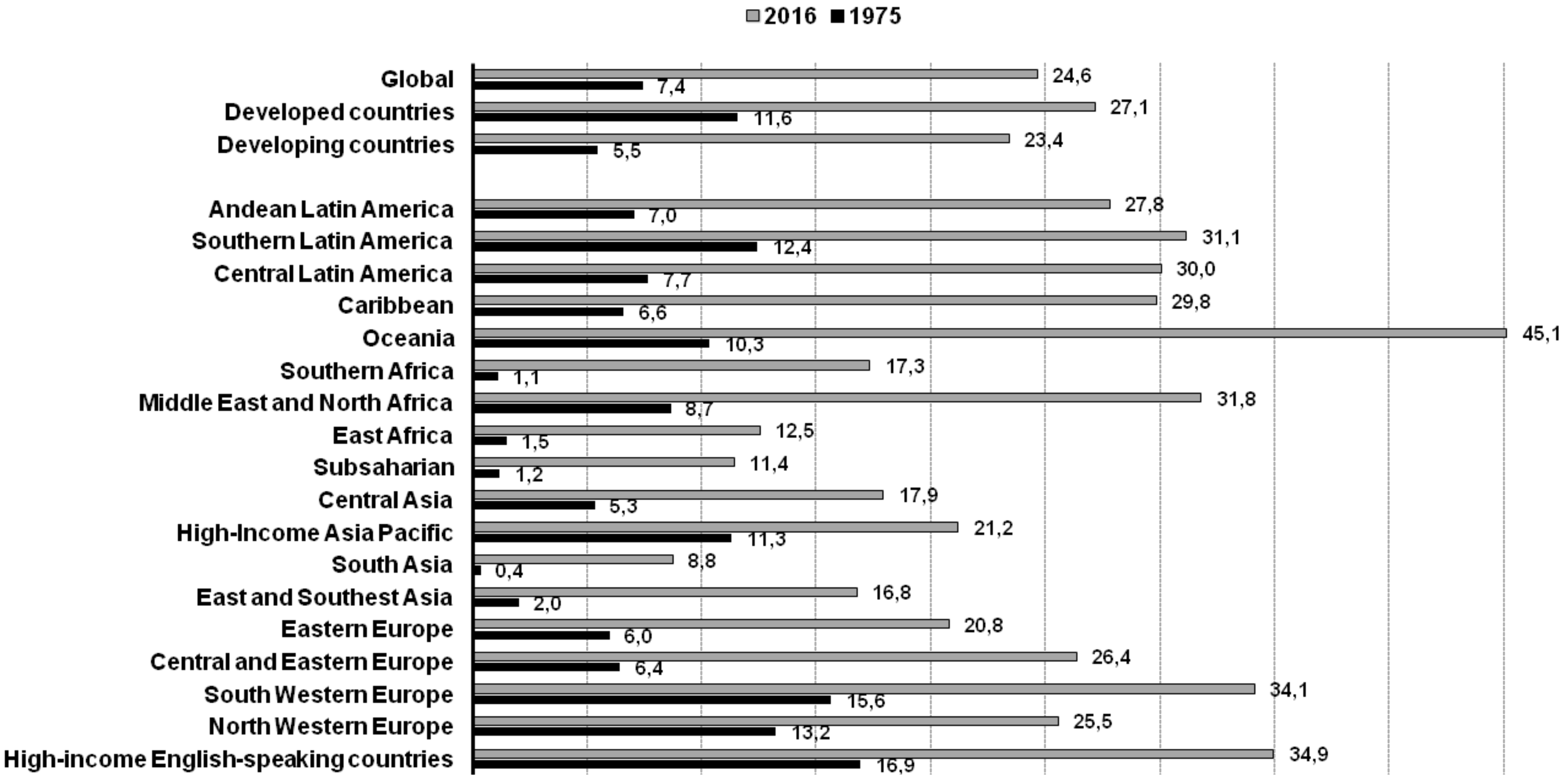
194. Gademan, M.G.*, et al.* Maternal prepregancy BMI and lipid profile during early pregnancy are independently associated with offspring's body composition at age 5-6 years: the ABCD study. *PLoS One* **9**, e94594 (2014).
195. Perng, W., Gillman, M.W., Mantzoros, C.S. & Oken, E. A prospective study of maternal prenatal weight and offspring cardiometabolic health in midchildhood. *Ann Epidemiol* **24**, 793-800 e791 (2014).
196. Li, N.*, et al.* Maternal prepregnancy body mass index and gestational weight gain on offspring overweight in early infancy. *PLoS One* **8**, e77809 (2013).
197. Chandler-Laney, P.C., Gower, B.A. & Fields, D.A. Gestational and early life influences on infant body composition at 1 year. *Obesity (Silver Spring)* **21**, 144-148 (2013).
198. Wright, C.M., Emmett, P.M., Ness, A.R., Reilly, J.J. & Sherriff, A. Tracking of obesity and body fatness through mid-childhood. *Arch Dis Child* **95**, 612-617 (2010).
199. Tanvig, M.*, et al.* Pregestational body mass index is related to neonatal abdominal circumference at birth--a Danish population-based study. *BJOG* **120**, 320-330 (2013).
200. Kaar, J.L.*, et al.* Maternal obesity, gestational weight gain, and offspring adiposity: the exploring perinatal outcomes among children study. *J Pediatr* **165**, 509-515 (2014).
201. Alberico, S.*, et al.* The role of gestational diabetes, pre-pregnancy body mass index and gestational weight gain on the risk of newborn macrosomia: results from a prospective multicentre study. *BMC Pregnancy Childbirth* **14**, 23 (2014).
202. Ziyab, A.H., Karmaus, W., Kurukulaaratchy, R.J., Zhang, H. & Arshad, S.H. Developmental trajectories of Body Mass Index from infancy to 18 years of age: prenatal determinants and health consequences. *J Epidemiol Community Health* **68**, 934-941 (2014).
203. Ensenauer, R.*, et al.* Effects of suboptimal or excessive gestational weight gain on childhood overweight and abdominal adiposity: results from a retrospective cohort study. *Int J Obes (Lond)* **37**, 505-512 (2013).
204. Ode, K.L., Gray, H.L., Ramel, S.E., Georgieff, M.K. & Demerath, E.W. Decelerated early growth in infants of overweight and obese mothers. *J Pediatr* **161**, 1028-1034 (2012).
205. Fleten, C.*, et al.* Parent-offspring body mass index associations in the Norwegian Mother and Child Cohort Study: a family-based approach to studying the role of the intrauterine environment in childhood adiposity. *Am J Epidemiol* **176**, 83-92 (2012).
206. Stuebe, A.M.*, et al.* Maternal BMI, glucose tolerance, and adverse pregnancy outcomes. *Am J Obstet Gynecol* **207**, 62 e61-67 (2012).
207. Lindberg, S.M., Adams, A.K. & Prince, R.J. Early predictors of obesity and cardiovascular risk among American Indian children. *Matern Child Health J* **16**, 1879-1886 (2012).
208. Fraser, A.*, et al.* Association of maternal weight gain in pregnancy with offspring obesity and metabolic and vascular traits in childhood. *Circulation* **121**, 2557-2564 (2010).
209. Crozier, S.R.*, et al.* Weight gain in pregnancy and childhood body composition: findings from the Southampton Women's Survey. *Am J Clin Nutr* **91**, 1745-1751 (2010).
210. Schack-Nielsen, L., Michaelsen, K.F., Gamborg, M., Mortensen, E.L. & Sorensen, T.I. Gestational weight gain in relation to offspring body mass index

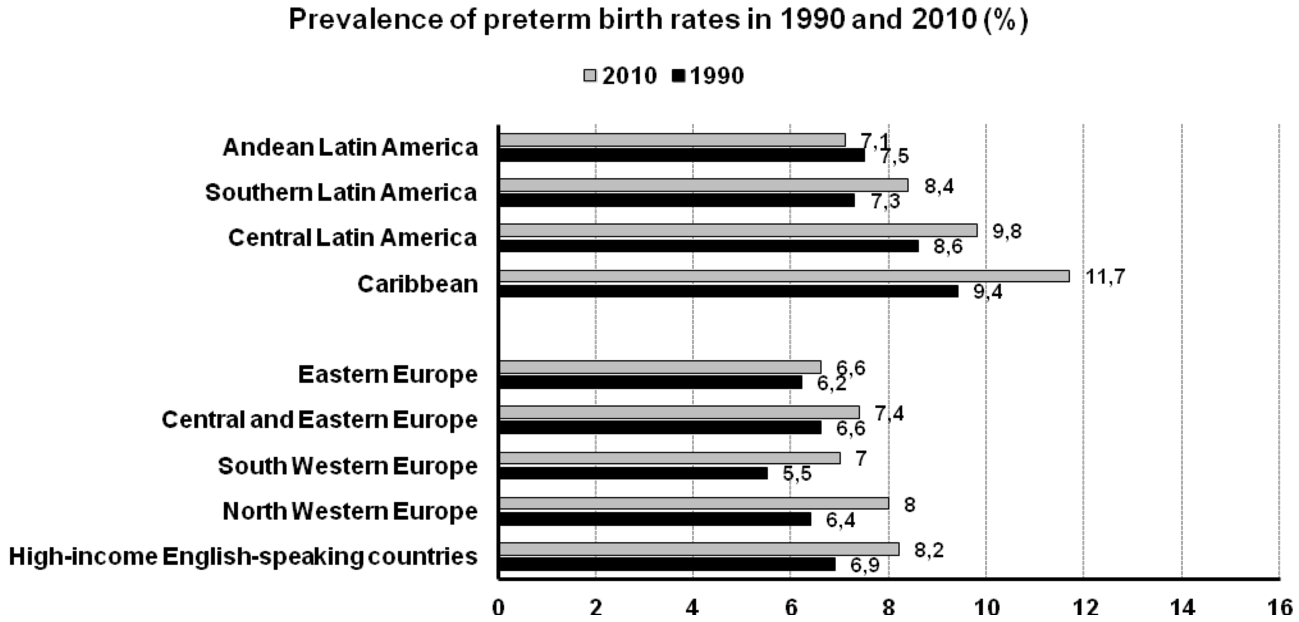
and obesity from infancy through adulthood. *Int J Obes (Lond)* **34**, 67-74 (2010).

211. Lawlor, D.A.*, et al.* Exploring the developmental overnutrition hypothesis using parental-offspring associations and FTO as an instrumental variable. *PLoS Med* **5**, e33 (2008).
212. Oken, E., Rifas-Shiman, S.L., Field, A.E., Frazier, A.L. & Gillman, M.W. Maternal gestational weight gain and offspring weight in adolescence. *Obstet Gynecol* **112**, 999-1006 (2008).
213. Gale, C.R.*, et al.* Maternal size in pregnancy and body composition in children. *J Clin Endocrinol Metab* **92**, 3904-3911 (2007).
214. Oken, E., Taveras, E.M., Kleinman, K.P., Rich-Edwards, J.W. & Gillman, M.W. Gestational weight gain and child adiposity at age 3 years. *Am J Obstet Gynecol* **196**, 322 e321-328 (2007).
215. Labayen, I.*, et al.* Intergenerational cardiovascular disease risk factors involve both maternal and paternal BMI. *Diabetes Care* **33**, 894-900 (2010).
216. Durmus, B.*, et al.* Growth in foetal life and infancy is associated with abdominal adiposity at the age of 2 years: the generation R study. *Clin Endocrinol (Oxf)* **72**, 633-640 (2010).
217. Kensara, O.A.*, et al.* Fetal programming of body composition: relation between birth weight and body composition measured with dual-energy X-ray absorptiometry and anthropometric methods in older Englishmen. *Am J Clin Nutr* **82**, 980-987 (2005).
218. McNeely, M.J., Fujimoto, W.Y., Leonetti, D.L., Tsai, E.C. & Boyko, E.J. The association between birth weight and visceral fat in middle-age adults. *Obesity (Silver Spring)* **15**, 816-819 (2007).
219. Demerath, E.W.*, et al.* Rapid postnatal weight gain and visceral adiposity in adulthood: the Fels Longitudinal Study. *Obesity (Silver Spring)* **17**, 2060-2066 (2009).
220. Rolfe Ede, L.*, et al.* Association between birth weight and visceral fat in adults. *Am J Clin Nutr* **92**, 347-352 (2010).
221. Pilgaard, K.*, et al.* Differential nongenetic impact of birth weight versus third-trimester growth velocity on glucose metabolism and magnetic resonance imaging abdominal obesity in young healthy twins. *J Clin Endocrinol Metab* **96**, 2835-2843 (2011).
222. Ronn, P.F.*, et al.* Birth weight and risk of adiposity among adult Inuit in Greenland. *PLoS One* **9**, e115976 (2014).
223. Araujo de Franca, G.V.*, et al.* Associations of birth weight, linear growth and relative weight gain throughout life with abdominal fat depots in adulthood: the 1982 Pelotas (Brazil) birth cohort study. *Int J Obes (Lond)* **40**, 14-21 (2016).


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

Prevalence of overweight and obesity in children and adolescents aged 5-19 years (%)




Prevalence of preterm birth rates in 1990 and 2010 (%)
2010
1990
Andean Latin America
7,1
7,5
Southern Latin America
8,4
7,3
Central Latin America
9,8
8,6
Caribbean
11,7
9,4
Eastern Europe
6,6
6,2
Central and Eastern Europe
7,4
6,6
South Western Europe
7
5,5
North Western Europe
8
6,4
High-income English-speaking countries
8,2
6,9
0
2
4
6
8
10
12
14
16