

Prenatal and Postnatal Development of Obesity: Primary Prevention Trials and Observational Studies

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Introduction

Since Barker et al. [1] presented the fetal origins hypothesis in 1989 introducing the concept of the developmental origins of chronic diseases, the interest in this early life period has increased dramatically. What has been observed from developmental biologists for many years became relevant for disease-related research in clinical medicine, epidemiology, pediatrics, and nutrition research. Many scientists began to study the effects of external and internal exposures of the fetus or newborn on later health-related outcomes. Initially, cardiovascular diseases (CVDs) were the main focus of research. Today, a vast amount of studies has documented relations between fetal and/or early life experiences and later risk for CVD, cancer, diabetes and other chronic diseases. As overweight and obesity and their health consequences began to emerge as epidemic-like problems, the spectrum of research was extended to study the potential role of prenatal and early postnatal exposures on these outcomes. Due to unique periods of cellular differentiation and development, the early life period is considered to be particularly vulnerable for obesity development [2]. It has been suggested that developmental plasticity allows the fetus to adjust to environmental influences thereby adapting to the current, but also to the predicted postnatal situation. As elaborated in reviews by Gluckman et al. [3], later disease risk, which also includes the risk of obesity, appears to depend on the degree of match between the environment predicted during the developmental phase and the actual later environment.

Among the potential environmental exposures, nutrition is considered to play the most critical role in influencing placental and fetal growth, including

adipose tissue [4]. However, this specific field of obesity development provides comparably little human data, and long-term studies to support the role of nutritional influences in early life on adolescent or adult obesity are scarce. The aim of this presentation is to give a broad overview of the current status of research on the relation between early nutritional exposures and human obesity development as can be derived from studies in humans.

To date, the vast majority of studies on prenatal and early postnatal nutritional factors influencing later obesity are animal experiments, mostly in rats and sheep. These studies have documented that critical periods during fetal and neonatal development exist, when nutritional influences are able to exert long-lasting effects on body weight development [5, 6]. However, the described effects and mechanisms derived from these studies are only to a limited extent applicable to humans. Therefore, studies with human data are necessary to evaluate the relevance of the findings for the human species, and to substantiate the available observational, epidemiological data. Obviously, such studies are difficult to conduct, and ethical and practical restrictions lead to a body of evidence which has to rely mainly on observational studies or on disease-oriented clinical trials.

A further drawback is the very long time needed in human studies to prospectively evaluate the effect of early nutritional exposures on adult overweight or obesity. Therefore, only a few retrospective cohort data exist, characterized by very limited detail on exposure and outcome assessment. Other human studies work with intermediate outcomes such as birth weight or childhood body mass or obesity. Nevertheless, these studies provide useful insights.

Many studies approach the topic of obesity development with samples of small-for-gestational-age children, intrauterine growth retardation, or diabetic mothers. These specific clinical situations make it difficult to judge the impact of nutritional factors on 'normal growth'. Consequently, the impact of nutritional exposures on birth weight and adiposity need to be interpreted with caution. For reasons of clarity and relevance for this overview, studies with children appropriate for gestational age are mainly considered, as well as studies among well-nourished and healthy pregnant women. In order to structure this overview, it appears useful to partition the complex theme into three main topics: (1) birth weight and later weight; (2) prenatal nutritional exposures and later weight, and (3) early postnatal nutrition and later weight.

Background

Maternal nutrition, and partly influenced by it, the metabolic and hormonal intrauterine environment, may strongly influence the amount, metabolic activity and endocrine sensitivity of adipose tissue in the offspring [2], thereby possibly influencing the development of obesity in childhood and/or adulthood. The fetal supply, which determines fetal growth, results from a

complex maternal-fetal supply line. It involves maternal food intake, absorption, metabolism, health and hormonal status, as well as maternal nutrient partitioning and placental functioning. Consequently, maternal nutrition may lead to long-lasting effects via prenatal programming. The term 'programming' subsumes the diverse developmental adaptations to a stress or stimulus in a sensitive period of development evoked by nutritional and/or endocrine influences. This process can lead to permanent changes in organ structure and size, altered cell number, hormonal set points and altered gene expression, among others. These changes may predispose to metabolic and endocrine diseases later in life. Dietary restriction, macronutrient amount and composition, as well as micronutrient intake or status have been considered as potentially relevant prenatal exposures in this context. An important feature of programming is the observation that it may vary depending on the developmental period of the fetus or neonate, and on the species.

In addition to environmental influences, genetic factors are also considered to be important contributors. Studies with monozygotic twins have indicated that intra-pair differences between twins are to some extent influenced by the fetal environment and by birth weight. Body height appears to be influenced more strongly by birth size than adult body mass index (BMI) [7]. However, the relative importance of genetic and environmental factors remains unknown, although it appears to change with age [8].

During recent years, a considerable number of reviews about pre- and postnatal programming have summarized different aspects of maternal nutrition, fetal growth, and body weight. Table 1 presents selected publications for further reading.

Discussion

Topic 1: Birth Weight and Later Weight

Birth weight has become the most frequently used indicator of fetal growth in human studies trying to link prenatal influences to later disease-related events including obesity. However, several caveats need to be considered when interpreting these data. Although many prenatal influences are thought to affect fetal size and thereby birth weight, prenatal programming may occur in the absence of changes in fetal size. Different growth patterns may result in the same birth weight, so that the potential effect of intra-uterine growth patterns and their respective potential effect on later weight development cannot be accounted for.

Birth weight is related to birth length and gestational age, which in many studies were not taken into account. Parental body size is another important determinant of offspring size, e.g. maternal size is closely linked to birth size for preventing labor obstruction, which is often not considered when data on

Table 1. Selected reviews addressing aspects of pre- and postnatal programming of obesity

Title	Author, year	Reference number
Timing of nutrient restriction and programming of fetal adipose tissue development	Symonds et al., 2004	2
Life-long echoes – a critical analysis of the developmental origins of disease model	Gluckman et al., 2005	3
The influence of birth weight and intrauterine environment on adiposity and fat distribution in later life	Rogers, 2003	9
Micronutrients and fetal growth	Fall et al., 2003	21
Breast-feeding and childhood obesity – a systematic review	Arenz et al., 2004	27
The developmental origins of adult disease	Barker, 2004	33
Critical periods in human growth and their relationship to diseases of aging	Cameron and Demerath, 2002	34
Fetal origins of obesity	Oken and Gillman, 2003	35
Early nutrition and leptin concentrations later in life	Singhal et al., 2002	36
Maternal nutrition and fetal development	Wu et al., 2004	37
Obesity epidemic in India: intrauterine origins?	Yajnik, 2004	38
Early nutrition and later adiposity	Martorell et al., 2001	39

birth weight are related to adult body mass. Also, other relevant factors such as maternal smoking and socioeconomic status were frequently not taken into account. Furthermore, the relation between birth weight and adult weight is affected by trans-generational effects, as it has been observed that offspring birth weight is related to the mother's birth weight [8]. Finally, birth weight may be differentially related to additional facets of body mass, that is to lean and fat body mass and to body fat distribution.

The relation between birth weight and later BMI was analyzed in numerous studies [for a comprehensive review see, 9], and was described to be linear, j- or u-shaped. Taking the above-mentioned caveats into account, it has to be stated that although a positive association appears to exist, a definitive answer about the shape of that relation as well as the causes remains to be elucidated (fig. 1). Recent data indicate, however, that birth weight displays a more complex relation to adult BMI, body fat distribution and fat mass. For example, low birth weight in combination with rapid infant growth appears to increase the likelihood of obesity and/or central obesity in adulthood. Others suggest that birth weight is related to adult height and weight, but not to adult BMI.

The discussion on this issue would also be advanced by separating both the upper and lower extremes of the birth weight distribution, e.g. low birth

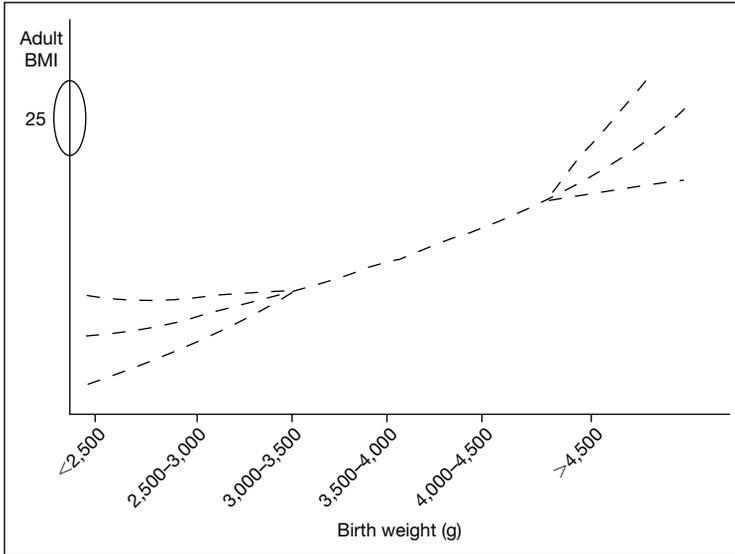


Fig. 1. Potential relation between birth weight and adult BMI.

weight (<2,500 g) and macrosomia (>4,000 g) from the rest. In both cases, pathophysiological factors might be operating (e.g. placental dysfunction, diabetes of the mother) which confound the relation birth weight and later weight. The evidence that children born with macrosomia are at increased risk of obesity is much stronger, partly explained by maternal diabetes or impaired glucose tolerance.

Given the previous findings that with increasing birth weight other outcomes such as CVD and diabetes appear to be reduced, this positive relation of birth weight with later weight and obesity status needs to be further elucidated. One school of thought about this paradoxical situation is the suggestion that body composition and/or body fat distribution might mediate this relation. As only very few studies have assessed a more detailed anthropometry beyond weight and height either at birth or later in life, respective data are less abundant. However, the available studies indicate that birth weight is more strongly related to later lean body mass than to fat mass (table 2). Later body fat distribution was also considered in its relation to birth weight. Here, the findings are rather inconsistent, partly due to heterogeneity in applied measures and subjects studied. While several studies observed that birth weight was positively related to waist circumference, no such findings were reported for waist-to-hip ratio or other measures of fat distribution. Overall, the interpretation of findings is hampered by methodological discussions about the pros and cons of controlling for attained BMI in these studies.

Table 2. Results of studies relating birth weight to subsequent body lean and fat body mass

Reference	Age years	Year of birth	n	Study population	Outcome measure	Adjustment for	Results
Phillips [10], 1995	47–55	1935–1943	217	Men and women, UK	BMI Muscle mass	/	Relation to BMI, n.s. Significant positive association with muscle mass
Kahn et al. [11], 2000	17–22		192	Men	Thigh muscle+ bone area, thigh subcutaneous fat area	Race, height	Thigh muscle+bone area bone area significantly associated with BW (regression coefficient 0.22, $p < 0.01$); Thigh subcutaneous fat area not associated with BW ($p > 0.05$)
Gale et al. [12], 2001	70–75		143	Men and women, UK	LBM FBM	Age, sex, height	Positive association, rises from 22.16 kg for BW; 3:3 <3.15–23.14 kg for BW >3.64 kg, $p < 0.0001$
Loos et al. [7], 2002	18–34	1964–1982	415	Female twins in Belgium (East Flanders)	LBM	GA, body mass	no association Positive association, increases from 42.4 kg for BW-GA z-score ≤ 1 to 44.1 kg if BW-GA z-score ≥ 1 ($p < 0.001$)
Loos et al. [7], 2002	18–34	1964–1982	388	Male twins in Belgium (East Flanders)	LBM	GA, body mass	LBM increased by 0.64 kg/kg increase in BW ($p = 0.01$)
Singhal et al. [13], 2003	mean 7.4		86	Male and female children in UK (Cambridge)	LBM FBM	Age, sex, socio-economic status, Tanner stage, physical activity, height squared	SD increase in BW = 0.9 – 1.4 kg more in fat free mass No association with fat mass
Sayer et al. [14], 2004	mean 64.3	1931–1939	737	Men in UK (Hertfordshire)	LBM, FBM BMI	Age, social class, smoking status, alcohol consumption, physical activity	Strong association of BW with LBM ($r = 0.27$), moderate association with BMI ($r = 0.13$), weak association with FBM ($r = 0.10$)

BMI = Body mass index (kg/m^2); BW = birth weight; GA = gestational age; FBM = fat body mass; LBM = lean body mass; n.s. = non-significant. Adapted from Rogers [9].

Associations between the considered measures disappear or change direction depending on whether attained BMI is adjusted for or not.

In summary, the relation between birth weight and adult BMI or obesity status is complex and not entirely understood so far. This complicates the interpretation of studies that use birth weight as a measure of fetal growth and prenatal nutritional influences respectively.

Topic 2: Prenatal Nutritional Exposures

Most studies on prenatal nutritional exposures examined the effects on birth weight. Only very few data are available on later weight development. As nutritional exposures are a diverse group, they are considered separately.

Dietary Restriction during Gestation

Numerous animal studies indicate that the timing of maternal nutrient restriction plays a major role in determining fetal adipose tissue mass. Restrictions in early pregnancy (with later adequate intake) tend to increase adipose tissue deposition, whereas later restrictions decrease it [2]. Observational human data come from the Dutch famine of 1944–1945, and appear to confirm these results for humans. In this retrospective cohort study, the effect of the intrauterine exposure to a limited period of famine was assessed. An exposure to maternal malnutrition during early gestation (as compared to exposure in late gestation) was associated with higher BMI at age 19 in men [15], and with higher BMI and waist circumference in women only at age 50 [16]. Exposure to famine during mid and late pregnancy was associated with lower birth weight and birth length. Data from developing countries clearly show that protein/energy malnutrition of the mother is associated with intrauterine growth retardation. Prenatal growth retardation followed by infant catch-up growth was found to increase the risk of obesity. Low birth weight has also been described to be associated with a pattern of central fat accumulation.

An issue of increasing interest in industrialized countries is the dietary management of overweight/obese pregnant women. Three trials on energy/protein restriction in overweight women were reviewed in a Cochrane review [17]. A significant reduction in gestational weight gain was reported, whereas the results on birth weight were inconclusive, with one study reporting no effect and the other a significant reduction in birth weight. Data on later weight development of the offspring were not available.

With the increasing prevalence of obesity, dietary restraint during pregnancy might become another issue of concern. Restrained eating appears to negatively influence weight gain during pregnancy, however, data on this are scarce.

Maternal Food Intake

Very few studies in humans have reported on the effects of specific food items on fetal or postnatal weight development (except for alcohol consumption and abuse, aspects not considered here). Coffee and caffeine consumption were considered in several studies, but significant effects on birth weight, independent of smoking behavior, were not found. Fish intake and/or the intake of n-3 fatty acids were considered in several studies, mainly for their potential protection against preterm delivery. Both observational and experimental studies (with n-3 supplements) reported on fetal growth, as assessed by birth weight. These data partly indicate that with increasing intake of fish or n-3 fatty acids fetal growth increases. However, a very high level of intake was also shown to be associated with decreased birth size. Therefore, the effects of the nutritional factors might depend on the amount consumed.

Maternal Macronutrient and Energy Intake

The major focus in the area of macronutrients has been placed on protein intake. Animal studies indicate that high protein intake is associated with low birth weight, but data from human observational studies remain inconclusive [18]. Experimental human studies, summarized in a Cochrane review, were not able to demonstrate significant effects on birth weight or birth length. Considered exposures were advice to increase energy and protein intake, and a balanced energy/protein supplementation [17].

Recently, interest has increased in the role of carbohydrate intake, particularly in the role of the intensely discussed glycemic index. Again, results appear to be conflicting. While some studies found no influence of carbohydrate intake on birth weight, others have found some effects for the glycemic index, indicating that with an increasing glycemic index birth weight tends to increase and vice versa.

In light of the current obesity epidemic, energy intake during pregnancy and the associated pregnancy weight gain are of increasing interest. As in other studies, the relation between dietary energy intake and weight development remains difficult to ascertain. If, however, maternal weight status or pregnancy weight gain are used as indicators for maternal energy balance, more insights can be derived. For example, in a retrospective cohort study maternal obesity significantly increased the risk of obesity in children up to 4 years of age [19]. Maternal overweight was suggested to be the reason of increasing the rates for neonatal macrosomia [20], which is associated with an increased risk of obesity.

Micronutrients

A vast number of studies have dealt with the effects of single or combined micronutrient supplementation and a reduction in low birth weight, growth retardation or other adverse pregnancy outcomes, mainly in developing

countries. Recent reviews [21, 22] indicate that for some micronutrients evidence was sufficient to assume a positive effect on birth weight or a reduction in low birth weight infants. However, many trials were considered to be of inadequate design, so that final conclusions cannot be drawn at this stage. Only a few studies were dedicated to the effects of micronutrient intake among pregnant women from industrialized countries. In several Cochrane reviews of randomized controlled trials single nutrient supplementation was considered, but parameters of fetal growth were not their main endpoint. The presented results on birth weight did not indicate significant effects, except for calcium supplementation, which was reported to protect against low birth weight [23].

A large prospective cohort study from the UK found only vitamin C intake in early pregnancy to be significantly related to birth weight, but the effect was very small. Maternal circulating nutrient concentrations were also assessed. Unexpectedly, high retinol concentrations were associated with reduced birth weight [24, 25]. A few other observational studies exist, but the sophistication of the dietary intake assessment or of data handling was often rather poor.

Topic 3: Early Postnatal Nutrition

Breastfeeding

The first observation indicating that breastfeeding might be related to childhood weight development was made in a case-control study published in 1981 [26]. Since then, numerous studies have investigated this relation, and some but not all of these have confirmed this finding. A recent meta-analysis, based on a systematic literature review, found a small but statistically significant protective effect of breastfeeding [27]. The pooled, adjusted effect estimate derived from 9 studies, including data from more than 69,000 children, indicated a 22% lower risk of childhood obesity among breastfed children compared to formula-fed children (fig. 2). The duration of breastfeeding, however, was not found to have an effect in all studies. Possible mechanistic explanations for the protective effect of breastfeeding include metabolic programming via hormonal and metabolic effects of nutritive and/or non-nutritive compounds in breast milk, energy and protein content, behavioral effects such as self-regulation of energy/food intake, but also residual confounding by parental characteristics [for further details see, 28].

The relation of breastfeeding to adult overweight/obesity was assessed in two prospective studies. A small study with 172 subjects found an increased body mass and fat mass among men (aged 32) who had been breastfed [29]. The much more powerful analysis of data from the British 1958 Birth Cohort, with BMI data from 9,287 subjects at age 33, indicated no significant relation to breastfeeding status when confounding variables were taken into account [30].

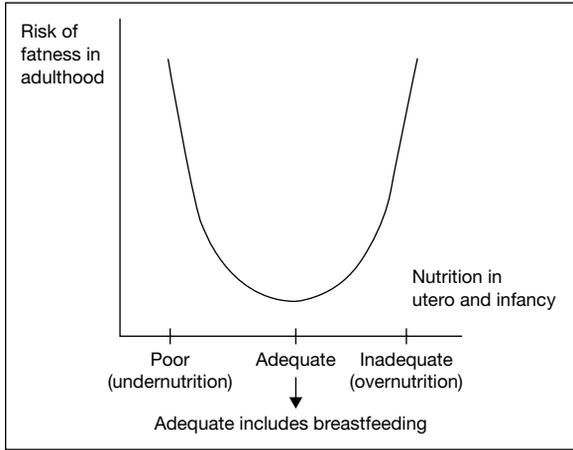


Fig. 2. Schematic description of the relation between nutrition in utero and infancy and its relation to the risk of adult body fatness. Adapted from Martorell et al. [39].

Protein Intake and Energy Intake

The different anthropometric development of breast- and bottle-fed children could be partly due to their difference in protein content. But also beyond breastfeeding, several studies found a positive association between protein intake in the first year of life and infant weight gain and later body mass development respectively. Others, however, could not support these findings so that an ultimate conclusion cannot be drawn at this stage. Similarly, among the few studies that looked at energy intake some found a positive relation with weight status in childhood [31], whereas other studies did not [32].

Conclusions

Because obesity is extremely difficult to treat, prevention is of paramount importance. Therefore, nutritional research is evaluating all critical periods of human obesity development during the life course, including the prenatal period, to identify appropriate and sound nutritional recommendations. Current developments, e.g. an increasing prevalence of overweight and obesity before and during pregnancy, inadequate weight gain in the majority of pregnancies, as well as restrained eating behavior during pregnancy, are additional challenges in this context. Overall, it appears that further data are needed to develop more elaborate recommendations for pregnant women, taking recent research findings into account. Adequate micronutrient intake to reduce low birth weight, and adequate macronutrient and energy intake to

avoid macrosomia may have considerable preventive potential (fig. 2). However, so far, no optimal nutritional recommendations can be made with respect to the long-lasting effects of maternal nutrition as a determinant of the developmental origin of obesity [3]. Similarly, nutritional influences during early postnatal life appear to bear some potential for obesity risk reduction, with the most extensive research support for a preventive effect of breast-feeding. For other recommendations, e.g. carbohydrate modification or energy restriction, an adequate data base is lacking.

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Discussion

Dr. Singhal: Do you really think that a 20% reduction in obesity with breastfeeding is a small effect, because I think that is a huge effect.

Dr. Kroke: I think it is a huge effect in childhood obesity but the effect on adult obesity remains to be quantified and it is going to be less than that.

Dr. Singhal: One of the things about the use of body mass index as an outcome is that it is influenced by both lean and fat mass. For example we have shown that birth weight correlates very closely with lean tissue mass but not with fat mass later in life. Do you think that this could explain some of the confounding factors that you see? Are there any data that have actually looked at lean and fat mass separately?

Dr. Kroke: Body mass index is clearly not a perfect indicator of body fatness and some, but few studies indicate that early life factors more strongly influence lean body mass than fat mass.

Dr. Hanson: In relation to the possible effect of breastfeeding on obesity I would like to ask you about two papers that seem to be related to this. One very recently was using siblings as controls and they did not see any effect of breastfeeding on obesity,

and the other one is a large American study showing that the effect was seen in Whites but not so-called Hispanics or Blacks. Why is that, genetic differences or what?

Dr. Kroke: I would argue that risk factors are always acting in concert with other risk factors so their relative importance might change with the presence of other risk factors. Differences between risk of obesity in Blacks and Whites might be present, so the relative importance of breastfeeding might change according to that.

Dr. Hanson: Could it be dietary habits between these so-called racial groups that differed or could it be other factors? Could their diets be different to an extent that they made a difference?

Dr. Kroke: You mean the maternal diet?

Dr. Hanson: The mothers diet, yes.

Dr. Kroke: Yes, that could be an explanation.

Dr. Lucas: As I mentioned this morning the original animal data on programming had all to do with postnatal nutrition and so did the primate data, and so did the first human data experiments that were started in the early 1980s. A hypothesis to test at that stage, which was raised by the animal data, was that it was postnatal nutrition that influences later obesity. The fetal theory came very much later and as you pointed out it has probably not come to very convincingly related birth weight and maternal nutrition. The real hypothesis to test was the data that came from original studies showing that early nutrition made a major difference to later weight, and the first primate studies which showed the late emergence of a program defect on body fatness. Now this is particularly important in the interpretation of the human data because if we go back to the 20% effects of breastfeeding on later obesity, we shouldn't assume that this is actually going to melt away, this could actually become greater with time, it could amplify in a sense that the primate model, the best animal model we have, showed that the effects of early nutrition didn't actually emerge until adolescence and adult life, most of which has not been covered by the human studies. So I don't think we should necessarily be pessimistic. What we have is a very good story that early growth is highly related to later obesity risk, observationally we know that breastfed babies grow more slowly, we know they have got a 20% increased risk of obesity on a meta-analysis, and we might predict amplification in adolescence and adulthood. So I would be slightly less negative about the field.

Dr. Kroke: I didn't mean to be negative, I just wanted to point out that there are so many studies out there which are really difficult to interpret and that do not give us information or answers on this prenatal phase. There are data but still we are lacking studies that really work with adult outcomes so it is rather speculative what we can give at the moment, and I think it is important to have some data with outcomes as a basis for recommendations.

Dr. Lucas: I agree we are not ready for that.

Dr. Cohen: With respect to the breastfeeding cohort, mothers that breastfeed through the first year of life, what were the differences, if any, in terms of different end points for beginning the introduction of solid foods, for example those mothers that may have started at 3 versus 6 months or later in terms of the breastfeeding children and obesity later in life? Were there any differences?

Dr. Kroke: I didn't look at that issue, I don't know.

Dr. Haschke: I agree with Dr. Lucas that, when it comes to breastfeeding and later obesity, all studies are observational, and most didn't have the relation between early feeding and later fatness in the primary outcome variable. So the design of those studies which have been analyzed in the meta-analysis differed but none of these studies was really designed to answer the question. The only study which had the goal to look at this was the Eurogrowth study which was done in 12 European cities. It went until 5 years of age, and there was definitely no effect of breastfeeding on body mass index until 5 years of age. However, there was always a significant impact of birth weight or

body mass index at birth or 1 month of age, and there was a significant impact of mid-parental body mass index, and once these two variables were in the equation everything else disappeared. The influence of breastfeeding was there until 12–18 months of age and it disappeared. When we analyzed the Eurogrowth study according to developed growth charts for breastfed infants as a subgroup it was only necessary to do this until 18 months of age. Then there was no difference between the two cohorts. At least there were 1,500 infants which were followed up so I would doubt whether the association is so clear.

Dr. Steenhout: We know that infants from diabetic or obese mothers or from mothers who develop gestational diabetes are more at risk of developing obesity later in life. Have you found studies showing that, in those circumstances, breastfeeding is also protective? As those groups are at higher risk of developing obesity, probably they are also better subgroups to analyze the potential protective effect of breastfeeding. What is your opinion?

Dr. Kroke: I am actually not aware of any study that worked with diabetic mothers and then did a follow-up of breastfeeding or type of feeding later on. I would assume that if there is a potential effect of breastfeeding this also has to be found in children that are born macrosomic or that are born to diabetic mothers.

Dr. Sorensen: I really know very little about obesity but there is an anecdotal observation that my specialists tell me. When I ask them can we do something in the first year of life? Can we identify children in the first year of life, regardless of how they are fed, that are on the heavier weight side and will continue into obesity? Their observation is that some of those very chubby children, without any intervention, suddenly by age 1 or 2 become perfectly normal, and that is also a perception in the public and it makes it difficult to tell parents that their 6- or 8-month-old is way overweight. They say well, many children in our family were like this and they are fine. While others never stop being on the heavy side. This is totally anecdotal but I just would like to ask you if there is any basis to having two populations, two different ways of going on from very early onset overweight, some that are seen without any intervention and others that actually become obese children?

Dr. Kroke: I think this goes into the discussion that we had before on rapid growth and early childhood. There are children who grow fast in the first 1 or 2 years of life, crossing centiles, and remain like this, but there also seem to be children who are similarly fat but remain within their centiles and never cross the line to obesity. So yes, I think we could call them different populations, we know that the predictive value of this risk factor is never 100% so you have just a relative increase in risk of 30–40%; it never explains the entire observation. I think there are no means at the moment to differentiate population subgroups, let's say those with catch-up growth or rapid growth during childhood plus factor X and X and X, they have almost 90 or 100% probability of developing obesity whereas just having been fat during the period without these additional factors that does not have any effect. It could be a way to proceed and to try to do that.

Dr. Klisk: Just to follow up your comments. In the 1970s I know of at least one paper that implied that the weight of a child below 12 months of age had no correlation to their weight as an adult. That concept has become fixed in pediatrics for many years. I know there have been studies that have shown that this impact does persist. Have you found recent data that correlate infant weight to the ultimate adult weight?

Dr. Kroke: The most reliable data on that issue are weight at age 7 as being most predictive of adult BMI, not earlier weight, because there is so much going on in terms of changes that this does not seem to be as predictive as at age 7. But as I said, birth weight is also related to adult BMI, the question is just how strong that association is.

Dr. Klisk: I think this comes up frequently as a clinical issue. I tell the parents of infants who are rapidly gaining weight to start dieting or restricting during infancy if the infants are significantly above the 95th percentile for weight for height.

Dr. Maffeis: You said that there is a relationship between birth weight and BMI in childhood, but you also said that the BMI of the mother is able to negate the effect of birth weight. However, there are some data in the literature suggesting that the relationship between birth weight is maintained if you adjust for the BMI of the mother. Can you comment on this finding?

Dr. Kroke: There was just one study from the UK that said that the relation disappears if you adjust for maternal BMI, just to illustrate that there are many questions around this relation. I am not surprised that somebody else found just the opposite, it is just to make the point that we are clearly in a very vague association here that has been described.

Dr. Laron: Could you say something about the correlation between brain growth and body growth during early intervention, because we know that in utero it is the brain which is so sensitive and which is relatively larger than other parts of the body?

Dr. Kroke: Actually no, I am not an expert in brain and neural development.

Dr. Laron: Do the Cochrane reviews mention the influence of various nutrients on the brain versus other growing parts of the body?

Dr. Kroke: These studies mainly assessed pregnancy and birth-related clinical outcomes, so they don't even have something like head circumference available which one could use as a proxy for whatever is going on with the brain. Unfortunately there is nothing available, and in a very few cases only there is a follow-up of these children with this intervention. So I cannot give you an answer to that.

