

# Role Of Nutrients In Promoting Adiposity Development

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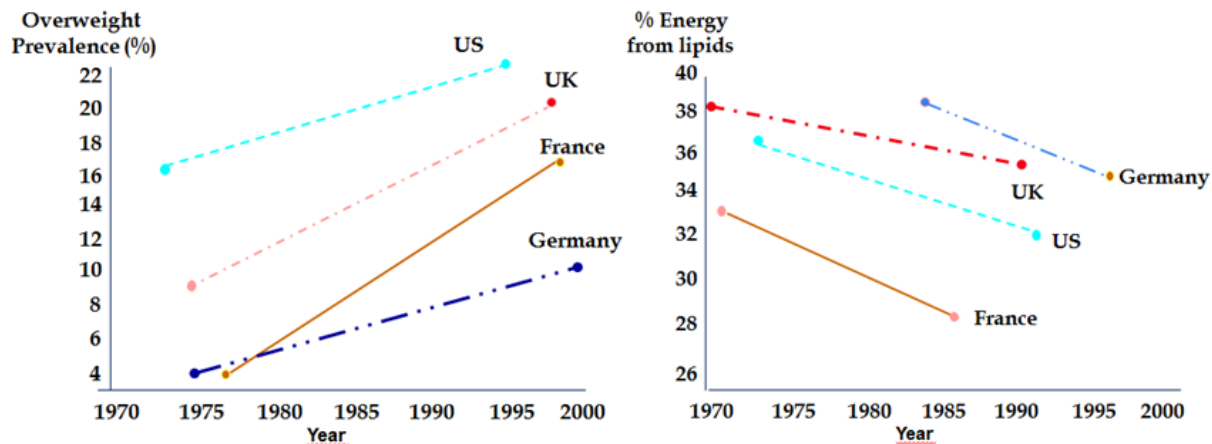
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The identification of risk factors is the key to prevention, however, until recently evidence on risk factors for childhood obesity was limited (1). The first studies were mainly cross sectional, and failed to identify associations between the child behaviour and the constitution of obesity. More recently, awareness is increasing for the importance of the environment in early life (2, 3). The early adiposity rebound recorded in most obese subjects suggests that factors promoting body fat development have operated early in life (4). Particularly, early nutrition can exert long-lasting influence on health. Birth weight, growth velocity and trajectories seem to be highly sensitive to the nutritional conditions present during pregnancy and in the first years of life. Good nutritional practices at later ages can limit or enhance metabolic risks, but the important role of early life environment may explain the difficulty to identify risk factors from studies conducted at later ages. The associations between nutrition at the different periods of life and the risk of overweight will be presented here.

## **Context Of The Obesity Epidemic**

Since several decades, childhood overweight was steeply increasing (5-8), but during the last 10 to 15 years, a plateau or even a decline in prevalence rates is reported in many industrialized countries (9-11). However, the problem remains important, because the prevalence of childhood obesity is still high in many countries.

While prevalence of childhood obesity was increasing, energy intake was decreasing (12). These time trends were reported in children and adolescents but also in young children (13-16). Fat intake was falling and the percentage of total energy derived from protein was rising, but no consistent trends appeared for CHO (12). Data from 2-19 year old children in NHANES I to NHANES III between 1971-1974 and 1988-1994 showed that fat intake was decreasing in all age ranges. In 2-5 year old children, energy from fat decreased from 36.2 to 32.8% between the two periods (13). Energy intakes in 1.5-2.5 year old English children fell from 1264 to 1045 kcal/day between 1967 and 1993 (14). Over the same period the percentage of energy from protein rose, the percentage from fat fell and the percentage from CHO stayed the same. Data from 2 to 18 year old German children of the DONALD study showed that fat intake decreased from 39.5 in 1986 to 36% in 2000, and this trend appeared as early as in the age range of 2-3 years (15). In 10 month old French children fat intake was 33% in 1973 (17) and 28% in 1986 (4). During the same period, in 2 year old children, fat intake decreased from 36.5 to 32.0% and protein intake increased from 14.5 to 17 % (16). Time trends in prevalence of obesity and in lipid intakes are presented Figure 1.



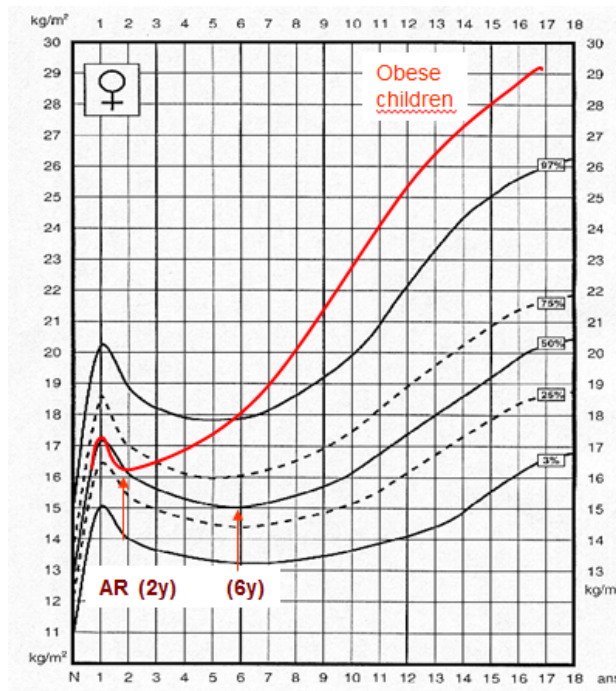
**Figure 1:** Time trend in the prevalence of overweight\* from 1970 to 2000 in 6 to 14 year old children in the US (5), UK (6), Germany (7) and France (8) and time trend in the percentage of energy provided by lipids in 1 to 2 year old children in the US (13), UK (14), Germany (15) and France (16). Trends in overweight prevalence and fat intakes go in opposite directions.

\* Overweight is defined according to IOTF criteria except for the US which use the 85<sup>th</sup> centile of the CDC references.

Falls in energy intake are likely to be associated with decreasing energy expenditure, particularly decreasing physical activity. However, this association seems less likely to account for falling energy intakes in very young as opposed to older children. Decreasing energy intake may relate to changes in the composition of the diet. Low fat foods reduce the energy density of diets and thus reduce total energy intake. In addition, low fat-high protein diets can reduce energy intake as young children prefer flavours associated with high dietary fat and because of the high satiating power of protein (12).

## Early Nutrition And Later Health

There is increasing evidence that early nutrition has an impact on adult health. During the period of “plasticity” which takes place from foetal life until 2 years of age (the “1000 days”), adequate nutrition is essential for the prevention of adult diseases (18). The early adiposity rebound (4) recorded in almost all obese subjects (19, 20) suggests that factors promoting body fat development have operated early in life (Figure 2).



**Figure 2** - Critical period of the development of obesity: the early adiposity rebound (AR) recorded in obese children (2 years) as compared with 6 years in average, suggests that determinants of later obesity have operated very early in life (after Péneau et al. (20)).

Increasing stature (4, 21) and earlier adiposity rebound (4, 22) over the last decades also suggest that secular trends of overweight may be more strongly associated with early feeding practices than with nutritional intakes at older ages.

The diet of young children is characterized by high protein and low fat contents (4, 21, 23, 24). By the age of 1 year, infant consume ~4g protein/kg body weight (16% of total energy) and ~28% energy from lipids (21). Protein intake represents 3 to 4 times international requirements (24). Protein intake reaches 20% of energy in 1 year old Italian children (25). Fat intake (% energy) was 33% in US toddlers (26) showing that many children had intakes below recommendations (27). Paradoxically, fat intake increases with age (4), while it should be high in infancy and decrease thereafter. This imbalance in protein and fat intakes is attributable to excessive consumption of animal products, particularly low fat dairy products (24). This nutrient composition of the diet is in sharp contrast with the composition of breast milk which has low protein (7%) and high fat (55%) contents (23, 27). A high protein diet can have deleterious consequences by stimulating growth (28, 29) which is a risk factor for later obesity (30). Lipids constitute the main energy source in infants whose energy needs are particularly elevated. They also are important structural components of neural and other body tissues (23, 27).

## Early Protein Intake

- *Early protein intake and body fat development*

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Two decades ago, the French ELANCE longitudinal study showed that high protein intake at the age of 2 years was associated with an early adiposity rebound, a high body mass index (BMI) and high skinfold thickness at the age of 8 years (31). The positive relationship recorded between early protein intake and later body weight was confirmed in most studies (4), for example in Italy (32), Island (33) or Germany (34).

High protein intake seems to particularly affect growth patterns. The beneficial effect of human milk against obesity can in part be explained by its low protein content as breast feeding practice is associated with a delayed adiposity rebound (35). In a multicenter European study, healthy formula-fed infants were randomly assigned to receive cow milk-based infant and follow-on formula with lower or higher protein contents for the first year and compared with exclusively breastfed children (36). The high protein group had significantly higher weight gain and higher BMI level at 12 and 24 years. The low-protein group had a growth pattern that did not differ from the breast fed control group suggesting an advantage of avoiding protein excess. Later on, the study showed that infant formula with a lower protein content reduced BMI and obesity risk at 6 years of age (37).

Not only the quantity, but also the quality of proteins seems to play a role in the association between early intakes and later fatness. The longitudinal DONALD study showed that the protein sources that are mostly responsible for the association with adiposity are dairy products (34). Proteins from meats or cereals do not seem to contribute significantly to this effect. Consistently, high amounts of dairy products, but not of meat were associated with an early adiposity rebound (38).

- *Early protein intake and hormonal status*

High plasma insulin like growth factor-1 (IGF1) concentrations and reduced growth hormone (GH) secretion are characteristic features of children with simple obesity (39). High protein intake stimulates IGF1 and growth (28, 40). This effect is beneficial in the context of poor nutrition, but can be detrimental when high protein intake promotes excessive growth in the context of adequate nutrition. The influence of excessive protein intake can explain the typical characteristics of obese children who have rapid growth, early puberty and high lean body mass (41). High IGF1 levels could stimulate protein synthesis and cell proliferation. As IGF1 promotes the differentiation of preadipocytes into adipocytes (42) high protein intakes might induce hyperplasia in adipose tissue. The early increase in adipocyte number reported in obese children (41) might explain their early adiposity rebound. In addition, high protein intakes may lead to lower GH levels, reduced lipolysis and the development and maintenance of fat stores (12).

Here again, this effect depends on the protein source. High intakes of milk, but not meat, increase IGF1 contributing to accelerated growth (43).

## Early fat intake

### - *Early fat intake and body fat development*

Whereas high fat intake is often postulated as being a major contributor to obesity, no convincing evidence supports that link during the childhood years (1, 44). Indeed fat intakes are particularly recommended in early childhood when energy requirements are very high. Moreover, negative associations were found between fat intake and body weight status (13, 45), but these associations were attributed to underreporting and other study bias.

Recently, the ELANCE two-decade prospective study showed that early low fat intake was associated with high adult body fat and serum leptin concentration (46). Similar associations were reported in the context of undernutrition. Low birth weight (47) and stunting (48) are associated with later risk of obesity (Table 1).

**Table 1:** *Consequences of early nutritional deficit in different contexts: a common mechanism?*

- Low birth weight: « The thrifty phenotype hypothesis » (47)
- Poor early nutrition in developing countries: « Stunting » (48)
- Early fat restrictions (↓energy density): «The low fat programming » (46)

--> ↑ Obesity and metabolic diseases

A “low fat programming” was proposed (46) suggesting that fat restrictions may activate adaptive metabolism to prevent underweight, thus increasing the susceptibility to develop overweight and metabolic diseases in subjects exposed to high energy dense foods later in life. This transition from low to high intakes was termed the “mismatch” concept (49).

Besides the impact of dietary fat restrictions or excess on the energy balance at all ages, the nature of fatty acids may also play a role in the development of obesity. Experimental evidence suggests that polyunsaturated fatty acids of the omega-6 series (omega-6 PUFA ) may promote both adipogenesis in vitro and adipose tissue development in vivo in rodents during the gestation/lactation period. In western countries, the increasing incidence of obesity has coincided with the gradual increase of omega-6 PUFA, suggesting that the two may be causally related (50).

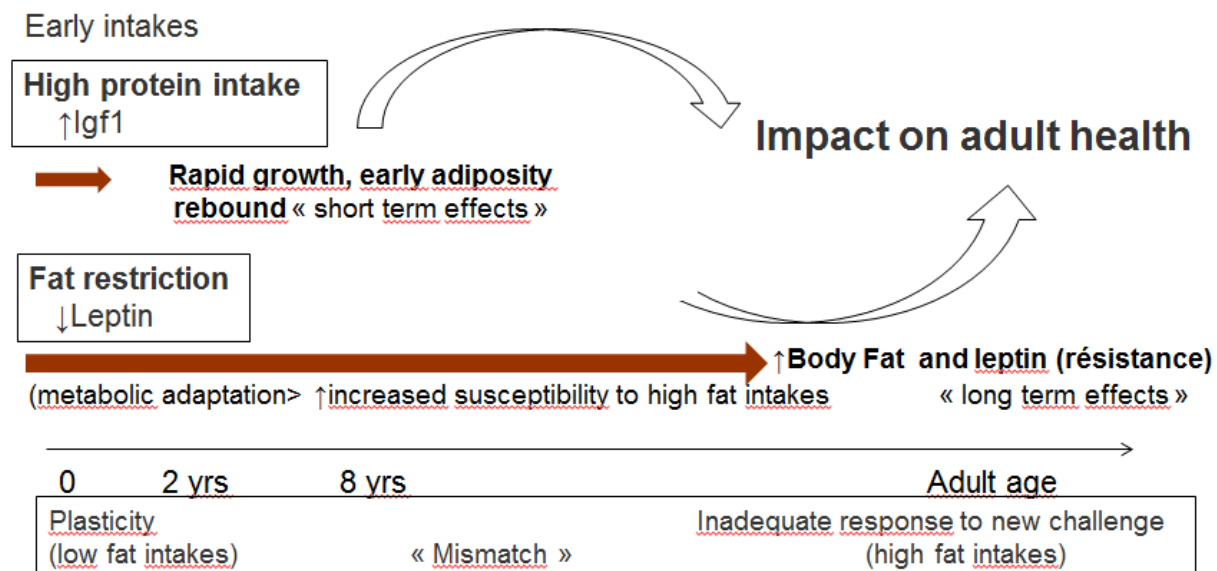
### - *Early fat intake and hormonal status*

The negative association of fat intake in early life with body fat and serum leptin concentration at adult age (46) suggests that leptin resistance could have been programmed by the early restriction of dietary fat.

Once again, more evidence for the association between early nutrition and later leptin resistance appears in the context of undernutrition. Leptin concentration is decreased in low birth weight babies (51), but increased in adults who were stunted (52) or had low birth weight (53). Similarly, low-fat intake may decrease serum leptin concentration in early life and programme compensatory metabolic responses affecting neural structures (54) leading to leptin resistance at adult age.

### Short and long term consequences of nutrient balance in early life

While the consequences of high protein intake in early life are evident as early as the first years of life (rapid growth, early adiposity rebound), by contrast, the consequences of dietary fat restrictions only appear at later ages. The rapid effects of high protein intakes can result from an immediate increase of IGF1 influencing growth directly while leptin resistance due to fat restriction could develop progressively during growth. These hypotheses on the short and long term consequences of high protein-low fat diets are presented Figure 3.



**Figure 3** - Programming of metabolic diseases by early high protein-low fat intakes: hypotheses on the short term (protein excess) and long term (fat restriction) consequences of the nutrient imbalance diet on growth and adult health.

### Stabilisation of the prevalence of obesity: a role of early nutrition?

Since the year 2000, stability or levelling off in the prevalence of obesity is now evident among children and adolescents in several parts of the world (9-11). Considering early life factors, some hypothesis can be proposed. During the period of the obesity epidemic, protein intake was steeply increasing and fat intake was decreasing (Figure 1). Since the end of the 90's, a clear change occurred. Protein intake decreases and fat intake increases (55, 56), or stopped decreasing (57). Unlike in the past, the composition

of the infant diet in the recent years is closer to the composition of human milk. In addition, breast feeding was recently increasing in several countries. These favourable changes in early nutritional intakes since the end of the 90's could partly explain the recent decreasing prevalence of childhood obesity.

## **Nutrition And Obesity In Children And Adolescents**

Longitudinal studies have demonstrated the importance of early nutrition up to the ages of 2-3 years in promoting later obesity. The relationship between macronutrient intake and adiposity has been widely investigated in older children but studies failed to explain the development of obesity, probably due to some bias. Cross-sectional studies provide results from children who are already overweight and then do not reflect the real contribution of a specific nutrient to adiposity development. Diet assessment methods are unable to detect small different intake, data may be influenced by psychological or dieting aspects and finally energy intake and energy expenditure should be considered (58-60).

### **Carbohydrates, fibre and sugar-sweetened beverages**

#### *- Low glycemic index carbohydrates*

It has been proposed that the potential effects of nutrients on adiposity would not entirely depend on the amount consumed but on qualitative aspects, such as their physiological actions, would be relevant. High glycemic load (GL) diet has been suggested to be related to adiposity development, whereas low glycaemic index (GI) carbohydrates could be protective, but studies do not provide conclusive data (61). Buyken et al. (62) observed that dietary GI increased from 1990 to 2002, consistent with the trend in childhood obesity prevalence, but this study didn't demonstrate that either dietary GI, GL or added sugar intake could have significant influence on changes in body composition. In a study aimed at evaluating the association between dietary GI, BMI and body fat distribution in 3734 Italian school children (age range 6-11 years), GI was the only nutritional factor significantly associated with waist circumference. The risk of obesity was almost two-folds higher in the upper quartile compared to the lowest quartile of dietary GI (63).

#### *- Fibre*

Increased consumption of high-fibre foods was identified as one of the three lifestyle patterns related to lower odds of obesity (64). On the contrary high-fibre diets tend to be low in energy density and are associated with lower obesity risk. Dietary fibre increases satiety levels and may delay or decrease subsequent energy intake (65). In 2003 the WHO identified energy-dense diets and low fibre intake as important determinants of obesity, however, most of the evidence was based on studies in adults. Few longitudinal studies have examined the role of fibre on obesity risk in children or adolescents. The ALSPAC study confirmed that dietary pattern high in energy density and low in fibre at 5 and 7 years of age was associated with greater fat mass and increased risk of excess adiposity at 9 years (66).



## - *Sugar-sweetened beverages (SSB)*

Caloric intake from SSBs increased by 135% between 1977 and 2001. Particularly, 11-13 year old adolescents were reported to consume more SSBs than younger children and older adults (67, 68). Calories obtained from beverages appear to be sensed differently from similar energy ingested as solid food. Energy in beverages does not produce a decrease in the intake as solid food (69). Interest in the relationship between soft-drink consumption and obesity in children was stimulated by Ludwig (70) who showed that baseline soft-drink consumption predicted future weight gain. This early study has been supported by many other studies and meta-analyses. The risks of cardiovascular disease, obesity and metabolic syndrome have been related to consumption of sugar-sweetened beverages in several, but not all meta-analyses. The NHANES cross-sectional study demonstrated that increased beverage consumption was associated with an increase in the total energy intake of the preschool-aged children but not with their BMI (71). A recent study showed no association between SSBs and percent body fat ( $p=0.93$ ) from early childhood into adolescence in the Framingham Children's Study (72).

Two meta-analysis and randomized trials in children demonstrated a link between intake of SSBs and the risk of becoming overweight. Higher intakes were significantly associated with increased risk of being overweight (odds ratio 1.55, 95% confidence interval 1.32 to 1.82 (73-77). Higher BMI z-scores were strongly associated with the consumption of SSBs and high fat foods (HFFs). For each additional occurrence of SSB and HFF intake per day, BMI z-score increased by 0.015 U ( $P < 0.01$ ) and 0.014 U ( $P < 0.001$ ), respectively (78). Similar to what is seen among older children, children aged 2 to 5 years drinking SSB demonstrate both prospective and cross-sectional correlations with higher BMI z-score (79).

A recently published meta-analysis of randomized clinical trials commissioned by the World Health Organization found that decreased intake of added sugar significantly reduced body weight (0.80 kg, 95% confidence interval (CI) 0.39-1.21;  $P < 0.001$ ), whereas increased sugar intake led to a comparable weight increase (0.75 kg, 0.30-1.19;  $P = 0.001$ ) (80). A parallel meta-analysis of cohort studies also found that higher intake of SSBs among children was associated with 55% (95% CI 32-82%) higher risk of being overweight or obese compared with those with lower intake (81).

Another aspect is represented by high dietary sodium intake which is positively associated with fluid consumption and predicts SSB consumption in consumers of SSBs. The high dietary sodium intake of children and adolescents may contribute to a greater consumption of SSBs, identifying a possible link between dietary sodium intake and excess energy intake thus contributing to obesity risk (82).

## **Fats**

Western diet is an example of high energy-dense diet: high in fat and low in fibre. Experimental research provides clear evidence that energy-dense diets affect innate appetite control and are associated with greater energy consumption (83). Fats are also less satiating relative to other macronutrients, although this may be modified by the energy density of high-fat foods (84). Evidence supporting dietary fat in the development of obesity beyond its contribution to energy intake is inconclusive (85) although intervention studies demonstrate that reductions in fat intake can result in weight loss (86). The ALSPAC

study demonstrated that diets high in energy density and fat increase the risk of excess adiposity in school children (87). Several cross-sectional studies have shown a higher intake of fat and a lower intake of carbohydrates in obese patients as compared to normal weight children (88), but in other studies, however, no evidence of an association between percentage macronutrient intake and BMI or waist circumference and development of obesity was found (45, 89,90).

As previously evoked polyunsaturated fatty acids of the omega-6 series seems to promote adipose tissue development and changes in fatty acid composition of ingested fats over the last decades may have been important determinants in the increasing prevalence of childhood overweight and obesity (50). The role of polyunsaturated fatty acids was confirmed in a study on macronutrient composition of the diet in 5.5 to 18.8 year old Spanish children. No difference was recorded between cases and controls, except for polyunsaturated fatty acids (PUFA) intake, which was significantly associated with obesity (91).

## **Proteins**

As in early life, children's and adolescent's diet is characterized by a higher protein intake than recommended (25). A systematic review of the literature on protein intake from 0 to 18 years of age (92) found convincing evidence that higher protein intake before the age of 2 years was associated with increased growth and higher subsequent BMI but found limited-inconclusive evidence that protein intake during childhood and adolescence was associated with later risk of overweight. Günther et al. (34), using data from the DONALD study, identified not only 12 months but also 5-6 years as a critical period at which higher total and animal, but not vegetable, protein intakes were positively related to body fatness at 7 years. In a prospective cohort study, Skinner (93) showed that mean protein (14 E%) and fat intakes recorded between 2 and 8 years were positive predictors of BMI at 8 years. A study conducted in 7-12 year old French children suggested that high protein intake was specifically associated with an android body fat pattern (94). The Bogalusa Heart Study examined dietary intakes in 10-year-old American children (95) and found that children with the highest indices of obesity ingested significantly more protein.

## **Conclusion**

Obesity is a slowly evolving condition. There is increasing evidence that early life environment has an impact on adult health. Studies showing associations between high protein or low fat intakes in early life and later overweight have highlighted the inadequate nutrient balance of the infant diet in industrialized countries. Protein intake represents about 3-4 times the protein needs and fat intake is remarkably low, contrasting with the high fat-low protein content of human milk and with official recommendations that fat intake should not be restricted before the age of 3 years. Paradoxically, fat intake increases with age, while it should be high in infancy and decrease thereafter. An imbalanced diet in early life may program adaptive metabolism that can become detrimental when environmental conditions will change at later ages. There is less evidence for the associations between food intake and obesity in studies conducted in school age children and adolescents. Evidence suggests that the imbalanced diet in early life may have contributed to the childhood obesity epidemic. The different impact of nutrition in early life or in later

childhood on future health, stresses the importance of providing nutritional intakes adapted to the child's metabolic needs at the various stages of growth.

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In the early 80's she published the first BMI growth charts and developed the concept of "Adiposity rebound" predicting the risk of obesity. She conducted several studies on nutrition and growth and showed that high protein and low fat intakes in early life were associated with an increased risk of developing later overweight.

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