Genetic factors are predominant for the spontaneous evolution of the body mass index (BMI), but only environmental events are able to modify the BMI curve

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Programming towards Childhood Obesity by Patrick Tounian

Key insights

Childhood obesity can be considered a programmed disease in which several genetic and/or in utero mechanisms play a role. Constitutional susceptibility is predominantly a genetic predisposition. For example, it is likely that the growth curves of obese children are programmed at a higher level than their nonobese counterparts. Further research into gene-gene interactions and a focus on the respective contribution between genetic contribution and lifestyle in determining individual weight are needed.

Current knowledge

An obesogenic environment can be considered the trigger, not the primary cause, of childhood obesity. Common obesity is polygenic with no observable simple Mendelian inheritance. The discovery of rare monogenic forms of obesity and obesity-linked mutations means any preconceived notions that obesity represents an issue with no biological basis can be dispelled. Adipostat, programmed BMI curves, and some environmental factors induce the programming towards childhood obesity. An improved understanding of the key molecular and genetic mechanisms that regulate body weight should help find the 'missing links' in the question of heritability and susceptibility.

Practical implications

Providers need to recognize that treatment requires a substantial motivation to fight against the programming and that childhood obesity is not simply the result of inappropriate habits. Moreover, prevention strategies should focus only on those children with a constitutional susceptibility to become obese under the pressure of an obesogenic environment.

Recommended reading

Loos RJ: Recent progress in the genetics of common obesity. *Br J Clin Pharmacol* 2009;68:811–829.

Schematic: programming towards childhood obesity and interdependent challenges (see text for details).

Programming towards Childhood Obesity

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Key Messages

- In an obesogenic environment, research suggests that a network of genes and gene-gene interactions are mainly responsible for childhood obesity and its predisposition, acting by altering either the central body weight regulatory system or hypothalamic appetite control. The exact roles of these genes and/or 'gene dosage' effects need to be understood.
- Future investigations should focus on the respective contributions between genetic programming and lifestyle factors in developing childhood obesity. Clinical management should target only those children at risk and their families instead of the current, less promising strategies at population level.

Key Words

Childhood obesity · Genetic predisposition · Obesity programming

Abstract

There is now considerable evidence that a constitutional susceptibility to fat gain is necessary for children to become obese under the pressure of an obesogenic environment; this is the programming towards obesity. The role of genetics in this programming is dominant. Besides the rare monogenic recessive forms of obesity secondary to mutations in genes involved in the hypothalamic appetite control path-

ways, obesity linked to mutations in melanocortin 3 and 4 receptors are more frequent due to their dominant mode of transmission. Predisposition to common obesity is polygenic and involves a network of genes; nevertheless, more research is required to elucidate their exact role. Fetal and perhaps early postnatal programming is also possible. Under- and overnutrition, diabetes, and maternal smoking during pregnancy were shown to promote later obesity and may affect the central body weight regulatory system during fetal development. The role of early postnatal factors such as formula-feeding rather than breastfeeding, excess in n-6 polyunsaturated fatty acids or protein intakes, and excessive weight gain early in life is more questionable and needs further investigation. Taking into consideration that childhood obesity is a programmed disease should modify its clinical management. Childhood obesity should no longer be considered as the result of inappropriate eating habits and/or excessive inactivity in order to relieve the obese children's discrimination and their parents' guilt. Since treatment of obese children requires a substantial motivation to continuously fight against the programmed excessive drive to eat, it seems wiser to wait for children to be old enough, thus more motivated, to initiate energy restriction. Moreover, with the great majority of children being not predisposed to obesity, prevention strategies should not be addressed to the whole pediatric population but targeted to those children at risk. Improvement of knowledge on programming towards obesity is essential to develop more promising therapeutic and preventive approaches.

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Introduction

During the last decades, the increased availability of palatable food and the conditions of decreased physical activity (motorization/sedentary games) dramatically increased the prevalence of childhood obesity in industrialized countries. More recently, occurrence of this obesogenic environment in developing nations led to a rapid increase in the prevalence of childhood obesity in urban regions, whereas a lot of children still suffer from under-nutrition in rural regions of the same countries [1].

This indicates that excessive weight gain only occurs in children who are living in a high-risk environment favoring obesity, with only a minority of children being concerned. Indeed, there is now considerable evidence that a constitutional susceptibility to fat gain is necessary to become obese under the pressure of an obesogenic environment [2–4]. In other words, only children programmed to develop obesity are at risk; abundant food availability or inactivity have no effect on nonpredisposed children. The obesogenic environment is therefore a trigger but not the primal cause of obesity; it just allows the phenotypic expression in children programmed to become overweight.

The purpose of this paper is to review all the mechanisms programming a child towards obesity. The primary is genetic predisposition to obesity, but other early possible programming factors occurring in utero or during the first months of life are also discussed. Finally, in view of these data, erroneous opinions about the origin of childhood obesity are brushed aside and relevant clinical practice deduced (fig. 1).

Evidence for the Need of a Constitutional Susceptibility to Become Obese

The increases in body weight in healthy children follow well-established curves included in specific charts, despite large daily energy mismatches. This process, which maintains a constant increase in body weight within a narrow and individualized range, is known as adipostat. Probably through peripheral adiposity signals [5], particularly leptin and ghrelin, the hypothalamus coordinates adaptive responses to energy imbalances via reciprocal alterations in appetite and energy expenditure in order to maintain a standard increase in body weight. Clearly, all these processes which control the body weight of humans and program the children's increase in body weight mainly rely upon genetics [6].

It is likely that the increase in body weight in obese children is also programmed, but at a higher level than

Fig. 1. Schematic representing the concepts regarding childhood obesity. The cone filter represents the requirement for a genetic predisposition. For children that are not genetically predisposed, inactivity or abundant food availability will have no effect on the risk of developing clinical obesity during childhood.

their non-obese counterparts. This hypothesis is more plausible than a dysregulation of their adipostat inducing an excess weight gain when the children eat more than they expend. Indeed, when obese children try to lose weight, their adipostat actively resists by stimulating appetite [7] and reducing energy expenditure [8] in order to maintain the elevated body weight. In obese children, this programmed, elevated weight gain is also mainly influenced by genes.

In a systematic review of studies in twins and adopted children, Silventoinen et al. [3] demonstrated that genetic factors have a much stronger effect than environmental factors on the evolution of body mass index (BMI) in children up to the age of 18 years. Interestingly, if environmental factors did moderately affect BMI variation in childhood, their effect disappeared in adolescence from 13 years of age. This suggests that parents may influence the BMI evolution of their children during the first decade of their life, but BMI curve takes back its programmed evolution when adolescents are less dependent on their relatives to eat and move.

The predominant genetic influence on BMI evolution persists until adulthood. Stunkard et al. [9] demonstrated that the intrapair correlation of the values for BMI at 21 years of age was similar in identical twins either reared apart (in a different environment) or together (in the same environment), and 2.5- to 5-fold higher in monozygotic twins than in dizygotic twin pairs. In a longitudinal

Fig. 2. Oversimplified illustration of hypothalamic leptin-melanocortin signaling pathways. MSH: α -Melanocyte-stimulating hormone; SIM-1: single-minded homologue 1.

cohort study, a strong correlation was found between parents' BMI and the BMI of their offspring in both childhood (11 years) and midadulthood (44–45 years) [10]. These associations were not affected by adjustment for a wide range of lifestyle factors. Again, these studies demonstrate that BMI evolution is strongly influenced by the genetic background of each subject for many decades, while the effect of environmental factors is much less important.

The programming of the BMI curve in children does not mean that the evolution towards obesity is ineluctable. Both energy restriction and increased physical activity can contain or limit the programmed weight gain, even early in life. Genetic factors are predominant for the spontaneous evolution of BMI, but only environmental events are able to modify the BMI curve. However, these behavioral changes do not alter the previous programming of the weight gain curve, which remains identical because adipostat continuously resists to weight loss by stimulating appetite and reducing energy expenditure. This is the likely explanation for the failure of traditional obesity treatment.

Genetics of Childhood Obesity

Strong lines of evidence support the contention that individual differences in the predisposition to weight gain rely in a personal genetic profile. In contrast to the monogenic forms of obesity which are both rare and severe, common obesity is polygenic with no observable simple Mendelian inheritance, and its expression re-

quires the pressure of an obesogenic environment. It is interesting to observe that whatever the origin of the obesity, most of the genes involved regulate food intake and energy balance.

Rare Monogenic Recessive Forms of Obesity

At least 200 cases of human obesity have been associated with homozygous forms of a single gene mutation [11]. In affected subjects, obesity develops since the genetic alterations impede key steps in the hypothalamic leptin (LEP)-melanocortin signaling pathways that regulate food intake and, to a lesser extent, energy expenditure [11]. The most well-known mutations affect LEP itself or its receptor (LEPR), proopiomelanocortin (POMC) and pro-hormone convertase subtilisin/kexin type 1 (PCSK1). These peptides are included in pathways which generate the anorectic peptide α -melanocyte-stimulating hormone, which exerts its effect through its binding to melanocortin 3 (MC3R) and melanocortin 4 (MC4R) receptors (fig. 2). Mutations in human genes coding for LEP [12], LEPR [13], POMC [14], and PCSK1 [15] lead to early-onset obesity (table 1). Patients show a rapid and dramatic increase in weight, as illustrated by the weight curve of LEPR-deficient subjects (fig. 3). Beside a frequent impulsive pattern of eating behavior and food seeking disorder, patients suffering these rare monogenic forms of obesity are also characterized by the presence of associated phenotypes like endocrine dysfunctions or impaired pubertal development (table 1). To date, only the congenital leptin deficiency, affecting only 13 children in the world, can be treated. In these patients, leptin replacement with recombinant human leptin leads to the disappearance of the obsessive hunger resulting in a rapid weight loss, and the normalization of the pubertal development [16].

The discovery of these mutations has allowed the unraveling of the central mechanisms that regulate body weight and dispelled the preconceived notion that obesity represents an individual defect with no biological basis.

More recently, mutations in 3 genes involved in the neural development have proved to underlie rare monogenic obesity: single-minded homologue 1 [17], neurotrophic tyrosine kinase receptor type 2 [18] and brain-derived neurotrophic factor (BDNF) [19]. These genes are all involved in the functioning of the hypothalamus and alterations in the nucleotide sequence trigger hyperphagia. BDNF mutations were originally identified as a cause of rare monogenic obesity, but they revealed with time to be frequent enough to account for a non-negligible proportion of common obesity cases [19]. Further studies are necessary to confirm it.

Table 1. Monogenic forms of childhood obesity

Gene	Mode of transmission	Obesity	Associated phenotypes
LEP	recessive	severe	gonadotropic and thyrotropic insufficiency
LEPR	recessive	severe	gonadotropic, thyrotropic and somatotropic insufficiency
POMC	recessive	severe	ACTH insufficiency, mild hypothyroidism and ginger hairs if the mutation leads to the absence of POMC production
PCSK1	recessive	severe	gonadotropic and ACTH insufficiency, hypoglycemia
MC4R	dominant	common	none
MC3R	dominant	common	none

ACTH = Adrenocorticotrophic hormone.

MC4R-Linked Obesity

Due to its dominant mode of transmission, MC4R-linked obesity is the most prevalent form of monogenic obesity identified to date. It represents approximately 2–3% of childhood obesity with >90 different mutations throughout the gene described in different populations [11]. The penetrance of the disease is usually incomplete and clinical expression variable. This suggests an additional implication of the environment and other modulating genetic factors explaining why some carriers of the mutation are lean [20].

In contrast to rare monogenic recessive forms of obesity, even a meticulous clinical analysis does not easily detect obesity stemming from MC4R mutations because of a lack of obvious associated phenotypes (table 1). In heterozygous MC4R mutation carriers, the onset and magnitude of obesity vary and are related to the severity of the functional alteration caused by the mutation. In most cases, children show an early-onset obesity in parallel with increased linear growth, especially in the first 5 years of life, but do not appear to be taller in adulthood [21, 22]. Obese children carrying MC4R mutations have a marked hyperphagia that decreases with age, but no specific trend to binge eating [23]. The metabolic rate is not decreased [23]. The patients do not suffer associated endocrine disorders [20–22]. The only physiological alterations, both reported in UK children [22], were an in-

Fig. 3. BMI curves of 2 homozygous null leptin receptor mutants (LepR 1 and 2), 1 homozygous null melanocortin 4 receptor patient (null MC4R), 6 heterozygous (heterozygous MC4R) and 40 non-mutated obese controls. The reference curves are the standard French percentile curves [derived from ref. 11].

crease in bone mineral density, which may be explained, at least partially, by a decrease in bone resorption and fasting hyperinsulinemia [24].

Homozygous carriers of the MC4R mutation are very rare. Four carriers of homozygous null mutations in the gene receptor have been found [22, 25, 26]. The carriers display a very early onset of severe obesity, the weight gain being not associated with additional related phenotypes.

Numerous experiments have been conducted to highlight the functional abnormalities underlying the part played by MC4R mutations in the genesis of the associated obesity (fig. 4). Mutations can result in a varied panel of alterations: abnormal MC4R membrane expression, impaired agonist response, alterations in the basal tonic

Fig. 4. MC4R-linked obesity is the most prevalent form of monogenic obesity identified to date. Functional abnormalities are depicted. a = Abnormal MC4R expression or impaired agonist response (satiety); b = alteration in the basal tonic activity of the receptor; c = disruption in the intracellular transport of proteins by cytosolic retention (e.g. BDNF). MSH = α -Melanocyte-stimulating hormone.

activity of the receptor, or a disruption in the intracellular transport of this protein by cytosolic retention. The latter has been described for the majority of MC4R mutations [27] and explains the impaired response to agonists.

A new direct line of research on the genetic determinants of childhood obesity has been drawn lately, with the discovery of genetic variants in MC3R (table 1). MC3R, another receptor activated with POMC-derived peptides, has an important complementary role in the regulation of energy homeostasis next to MC4R. Common variants are associated with pediatric obesity due to a greater energy intake but not diminished energy expenditure [28]. Recently, several rare mutations with functional alterations proved to be associated with severe obesity in children [29, 30]. Further epidemiological and functional research regarding the importance of MC3R mutations would shed light on the importance of MC3R mutants and potential combined effects with other genes in severe early-onset obesity.

In conclusion, childhood obesity linked to mutations in MC4R, and probably MC3R as well, resembles common forms of early-onset obesity and stands between exceptional forms of recessive monogenic obesity with complete penetrance and the polygenic forms of common obesity.

Polygenic Forms of Common Obesity

For the last 15 years, the numerous studies that have been carried out to delineate the architecture of genetic predisposition to common obesity has led to the discovery

of a network of genes involved and gene-gene interactions, being as sophisticated as brain circuitry. However, their role remains to be elucidated. The fact that, in contrast to monogenic obesity, each mutation leads to a variant that brings only a susceptibility and requires the presence of other variants plus an obesogenic environment to determine a phenotype, makes the discovery a harsh task. Chronologically, the identification of susceptibility genes has, first, been based on genetic epidemiological approaches, i.e. genome-wide linkage and candidate gene association studies. In recent years, significant progress has been made through genome-wide association studies that provide more accurate genomic locations for obesity-related genes and has allowed confirming or ruling out the implication of variants suggested by first generation approaches.

Family-based genome-wide linkage scans examine whether genetic markers, located at different loci along the whole genome, cosegregate with a disease or a trait across generations. Linkage results had identified promising candidate genes such as GAD2 (glutamate decarboxylase 2) at the origin of the γ -aminobutyric acid that upregulates food intake, ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1), which plays a part in brain insulin sensing, and SLC6A14 (solute carrier family 6 membrane 14), a tryptophan transporter implicated in appetite regulation [31]. Linkage analyses succeed when variants are common and exert a rather strong effect. The failure to replicate associations at many loci in the studies suggests that the variants have only a small genetic effect when taken alone [32].

In candidate gene association studies, polymorphisms in genes known to code for proteins involved in the regulation of energy balance in animal models or human monogenic obesity are tested for association with obesity-related traits at the population level. Among the genes tested, polymorphisms in *LEP* and *LEPR* as well as different variants known to play a role in feeding behavior (*PCSK1*, *POMC*, or *BDNF*), neural signaling, e.g. cannabinoid receptor (*CNR1*), dopamine receptor (*DRD2*), or serotonin receptor (*2C HTR2C*), or function (*SLC6A4*) have been shown to be associated with obesity or predictive of BMI [31]. Interestingly, rare polymorphisms in *MC4R* have been quite consistently associated with a protective effect against obesity [33]. Candidate gene studies have provided suggestive evidence that multiple genes are involved in the predisposition to obesity. However, these genes were supported by data from grossly underpowered studies; thus, replication in large-scale studies and meta-analytical approaches could not conclude a definitive effect for most of the variants cited previously [31].

Genome-wide association studies have revolutionized the field of genetic epidemiology since they screen the whole genome at a very high resolution (hundreds of thousands of genetic variants). Thus, they make it possible to identify precisely those genetic variants robustly linked to obesity while they have relatively small effect sizes. So far, around 20 loci consistently associated with obesity-related traits have been discovered in adults [34]. In children, the most important locus was discovered in the fat mass and the obesity-associated gene *FTO*. *FTO* variants are associated with increased weight and ponderal index already at 2 weeks of age [35]. *FTO* is widely expressed in the brain, especially in the hypothalamic nuclei involved in regulating energy balance. Children who carry the risk allele display increased food intake and sometimes binge eating episodes with a preference for energy-dense food [36] as well as a decreased satiety [37]. Among all the other genes discovered, most of them act through effects in the central nervous system, although effects in other tissues for some of these genes remain possible [34]. The next step for all of these novel genes is to clarify the biological role of each variant in obesity.

More recently, a great deal of excitement has developed relating to a newly discovered genomic variability due to a variation in gene copy number. Copy number variation, or CNV, is defined as a variation from one person to the next in the number of copies (deletion, insertion, or du-

plication) of a given gene. This 'gene dosage' effect creates a risk for a disease, or confers protection from it. So far, several common obesity CNVs have been identified in extremely obese children. They consisted of deletions in a genomic region covering olfactory receptor genes. However, the author concluded that the association with obesity was too small to substantially contribute to the genetic basis of early onset of obesity [38]. Conversely, again in severely obese children, children harboring a rare large deletion in a chromosomal region encompassing the *SH2B1* gene, which is known to be involved in leptin and insulin signaling, exhibited hyperphagia and severe insulin resistance with mental retardation [39]. Finally, CNVs (deletions or duplications) in 8 loci proved to contribute to genetic susceptibility of common childhood obesity [40]. The research on the part played by CNVs in the genesis of childhood obesity is expanding rapidly. Since gene variants explain only a small proportion of the overall heritability, there is hope that CNVs will prove to contribute to the missing heritability.

The refining of methodological approaches, the use of large-scale cohorts with standardized phenotypes and the development of more accurate specific statistical tools will certainly enlighten the involvement of unsuspected loci and specify the role played by those already identified, especially in terms of gene-gene interactions. Moreover, pinpointing the respective contribution of genetic predisposition and lifestyle in determining individual weight is definitely the task to focus on. The findings to come will certainly increase our insights in the regulation of energy balance in humans and, hopefully, also provide new avenues for effective treatment and prevention since they will rely on the genetic profile of children at risk.

Epigenetics refers to processes that induce heritable changes in gene expression without altering the gene sequence.

Early Programming in Childhood Obesity

Some observations suggest that the fetal and early postnatal environments may play a role in favoring the occurrence of overweight or obesity later in life (table 2). These early determinants of future obesity represent constitutive factors which are not inscribed in the genetic patrimony and, generally, not transmitted across generations. Most of them are certainly still to be discovered. An epigenetic origin is probably involved [41]. Epigenetics refers to processes that induce heritable changes in gene expression without altering the gene sequence. They con-

sist mainly of DNA methylation and modifications of the histones around which DNA winds.

Under- or Overnutrition during Pregnancy

Studies of individuals exposed to famine in utero during World War II show that mothers who suffered famine periconceptually and in the first trimester of pregnancy gave birth to children with a normal weight at birth but exhibited increased risk of later obesity [42]. Conversely, in individuals whose mothers were exposed to famine during the last trimester of pregnancy the risk of obesity was absent [42]. The proposed mechanisms underlying this relationship are a dysfunction in the hypothalamic nuclei that control energy balance. It is hypothesized that undernutrition during central nervous system development (first months of gestation) generates a process favoring a better metabolic efficiency to compensate for the energetic deficit. This acquired energy-sparing system would lead to an excessive fat storage when enough food is available. The absence of an effect when mothers are deprived of food only during the last trimester could be explained by the fact that the development of the central body weight regulatory system was achieved when undernutrition occurred.

Prepregnancy obesity in mothers and gestational weight gain are also positively associated with obesity in offspring from childhood to adulthood [43]. This is likely to primarily reflect the genetic effect on obesity. However, maternal weight loss through bariatric surgery prevents transmission of obesity to children compared with the offspring of mothers who did not undergo the surgery and remained obese [44]. The mechanism underlying the relationship between the nutrition state of the mother and the predisposition to obesity in children still obviously needs to be elucidated. Epigenetic factors may be suggested since maternal intake of nutrients has been shown to alter the methylation of genes resulting in effects on fetal and offspring development [41].

Maternal Smoking during Pregnancy

Children whose mothers smoked during pregnancy are at elevated risk for becoming overweight from childhood to adulthood [45]. Mechanisms by which maternal smoking may program child weight are not yet well characterized. Since the association between maternal smoking and child overweight is independent of birth weight or fetal growth and postnatal weight gain, a more rapid postnatal weight gain as the cause of later obesity can be excluded [45]. Nicotine, which is transported across the placenta, may act at the fetal brain level during its devel-

opment by altering the control center of appetite. The resulting fetal programming may be responsible for further obesity through alterations in the control of food intake. The modified appetite control observed in offspring of mothers who smoked during pregnancy supports this hypothesis [46].

Gestational Diabetes

Gestational diabetes has been associated with an increased rate of offspring childhood obesity [47], although the risks seem to be small [48]. Confounding factors like maternal obesity or increased insulin resistance susceptibility which favor the occurrence of both gestational diabetes and familial obesity may explain this association, all the more so as the relationship is statistically small. Gestational diabetes would therefore be a trait of the familial predisposition to obesity and not the cause of offspring overweight.

It is, however, also possible that fetal exposure to maternal hyperglycemia results in fetal hyperinsulinemia, which in turn may alter the development of the body weight regulation center in the brain. Further obesity in offspring would therefore be the consequence of metabolic imprinting [49].

Elevated Birth Weight

A birth weight >4 kg is associated with an increased risk of obesity later in life [50]. However, this association is probably due to confounding factors owing to maternal characteristics, among them, maternal obesity is likely to be predominant [50]. Therefore, elevated birth weight should not be considered as a risk factor for further obesity.

Rapid Weight Gain Early in Life

Greater early infancy weight gain has been suggested to be an important risk factor to develop further obesity [51]. A direct relationship between the excessive weight gain early in life and the occurrence of later overweight raises concern about the relevance of weight catch-up of small-for-gestational-age neonates. These results also suggest new strategies to prevent obesity by limiting weight gain in early infancy [52].

However, it can be speculated whether this increased early weight gain was the cause of further obesity or if it was only an early expression of a genetic predisposition to obesity. Recent studies using robust genetic markers of obesity clearly demonstrated that early infancy weight gain represents the early phenotypic expression of the genetic factors that predispose to later obesity and not its

Table 2. Early programming in childhood obesity: summary of the possible constitutive factors

Factors	Relevance to childhood obesity risk/etiology
<i>Fetal programming (i.e. maternal state during pregnancy)</i>	
Under- or overnutrition	Nutritional state of the mother may alter the methylation of genes, resulting in effects on fetal/offspring development in later life [41] Effects of exposure to undernutrition seen only in the first trimester of pregnancy [42] Maternal weight loss via bariatric surgery prevented transmission of obesity [44]
Smoking	Mechanisms not yet well characterized Data suggest children of mothers who smoked during pregnancy are at elevated risk for becoming overweight/obese [45]
Gestational diabetes	Several confounding factors exist (i.e. trait of familial predisposition) Associated with a small increase in the rate of childhood obesity risk [47, 48] Possible metabolic imprinting through exposure to maternal hyperglycemia, altering the development of regulatory centers in the brain [49]
<i>Early postnatal programming</i>	
Elevated weight at birth	>4 kg may be associated with an increased risk; however, confounding factors exist owing to maternal characteristics
Rapid weight gain	Not an issue in small-for-gestational-age neonates: genetic markers suggest rapid early infancy weight gain only represents a phenotypic expression and not an etiology [53] Elevated risk for later cardiovascular diseases or metabolic syndrome is more likely [54]
Feeding practices	Studies demonstrating the putative protective effects of breastfeeding against later obesity may have inherent bias or confounding factors [58] The role of excess intake of n-6 polyunsaturated fatty acids in lactating mothers [61] and the possible link between high protein intake in infancy and risk of later obesity [62–65] are inconclusive to date

etiology [53]. Therefore, rapid weight gain early in life should not be considered as a problem with regard to prevention of further obesity, particularly in small-for-gestational-age neonates. The risks for later cardiovascular diseases or metabolic syndrome seem, however, to be much more convincing [54].

Formula Feeding versus Breastfeeding

Prevention of later obesity is recognized as one of the multiple benefits of breastfeeding [55]. When compared to formula feeding, lower content of protein and energy, better control of the amount of milk consumed and lower growth during the first year of life are the main underlying mechanisms suggested to explain the protective effect of breastfeeding against later obesity [56].

However, the majority of the studies aimed at demonstrating that breastfeeding causes a reduction in risk of later obesity exhibit some serious bias. First of all, confounding factors such as socioeconomic status, ethnicity or paternal BMI are difficult to be taken into account in the statistical analyses and may therefore explain the re-

lationship between breastfeeding and protection against obesity. Moreover, for obvious ethical reasons, almost all trials are not randomized. It is well known that breastfeeding is more frequent in families with higher socioeconomic status in which the risk of obesity is reduced. Reducing the effect of this important confounding factor in the statistical analyses is insufficient to exclude the huge bias introduced by the absence of randomization. In one report, preterm babies were randomly assigned to receive banked breast milk or infant formula. There were no significant differences in body weight at follow-up and at 13–15 years of age [57]. For all these reasons, serious concerns arise about the putative protective effect of breastfeeding against later obesity [58]. More evidence is necessary to assess the potential role of breastfeeding in reducing later obesity development [56, 58].

Excess in n-6 Polyunsaturated Fatty Acid Intake

Animal studies have shown that an increase in the relative intake of n-6 to n-3 polyunsaturated fatty acids during pregnancy and lactation promotes adipose tissue

development in offspring, which in turn may augment the risk of later obesity [59]. Subsequently, some authors hypothesized that the dramatic increase during the last decades in n-6 polyunsaturated fatty acid intake in lactating mothers and infants may have contributed to the childhood obesity epidemic [60]. However, robust data from human studies are lacking to support this hypothesis [61]. Further studies are required to test the putative relationship between excess n-6 polyunsaturated fatty acid intake and later obesity.

Excess in Protein Intake

Higher protein intake in the first months of life was associated with increased body fatness later in childhood [62]. As a consequence, a link between protein intake in infancy and the risk of later obesity was suggested. A higher protein intake stimulates secretion of insulin-like growth factor 1, which in turn might induce adipose cell proliferation and consecutively increased adipose tissue. However, later studies did not confirm these results [63, 64].

To test the hypothesis that higher protein intake in infancy leads to more rapid weight gain and consecutively increases the risk of later obesity, a multicenter European study has been conducted [65]. More than 600 infants

were randomly assigned to receive formula with lower or higher protein contents for the first year of life. Preliminary results at 2 years showed a significantly increased BMI z-score in the lower protein formula group. However, the mean difference was so small between the groups (180 g for body weight and 2 mm for height) that even if the follow-up of the study could confirm the tendency observed at 2 years, the role of an excess protein intake early in life in the development of later obesity, if present, can indeed be considered as negligible.

Conclusions

Clearly some environmental factors seem to induce a fetal programming towards obesity (under- or overnutrition and maternal smoking during pregnancy, or gestational diabetes), but the putative role of postnatal factors in early obesity programming (formula feeding rather than breastfeeding, excess in n-6 polyunsaturated fatty acids or protein intakes) needs to be further explored. In any case, genetic programming towards childhood obesity appears to be much more relevant than early fetal or

postnatal programming. It can, however, be assumed that early environmental factors may accelerate the phenotypic expression of a genetic predisposition, explaining in part why children seem to become obese earlier in their lifetime than their parents [66].

Application to Childhood Obesity Management

According to the data presented above, we consider that childhood obesity is a programmed disease for which phenotypic expression needs an obesogenic environment. Psychological stress, drugs, brain tumors or brain damage due to sleep insufficiency have been shown to initiate excess weight gain in children. However, most of them act as a trigger in a predisposed child rather than an authentic cause. Considering that children become obese because they are programmed to, excess energy intake and inactivity should be regarded as a consequence of the disease and not its cause [67, 68]. Thus, childhood

obesity should not be considered as the result of either inappropriate eating habits or an abdication of parental responsibilities. Parents should not be blamed for the obesity of their children; nonetheless, their role in the outcome of the treatment of their children's obesity remains funda-

Clearly some environmental factors seem to induce a fetal programming towards obesity but the putative role of postnatal factors in early obesity programming needs to be further explored.

mental. Unfortunately, these notions are not common and most people still think the opposite, contributing to increasing the discrimination and the stigmatization of obese children and their parents. It is urgent to inform people about the real origin of childhood obesity in order to relieve the distress of obese children and their families.

The constitutional origin of pediatric obesity may also explain the usual unsuccessful long-term outcome of its treatment [69, 70]. Treatment of childhood obesity needs continuous energy restriction and/or increased physical activity to fight against the programmed BMI curve. Any slackening induces a quick and ineluctable return of BMI to its previously programmed curve. Maintaining a long-term energy restriction is all the more difficult since the adipostat resists weight loss by increasing appetite [7]. A substantial motivation is therefore necessary to resist to a programmed BMI curve. This probably explains the higher failure rate of obesity treatment in younger children [71]. Since the precocity of setting up the treatment is not a predictive factor of the long-term outcome [72, 73], it is not necessary to begin energy restriction as soon

as possible in children. Conversely, it is wiser to wait for the child to be enough motivated to start a diet, given the hunger induced by energy restriction is all the more hard to bear in young children. One should remember that whenever the treatment is initiated, it does not have any influence on the programming of the BMI curve [72, 73].

The dramatically disappointing results of prevention programs may also be due to the programming of childhood obesity [74, 75]. Indeed, these collective interventions aimed at preventing obesity are targeted at the whole pediatric population whereas only a minority of predisposed children is concerned. Moreover, this preventive approach may increase discrimination of obese children and induce eating behavioral disorders in the large number of non-predisposed children [74]. Since the majority of the children are not predisposed to obesity, prevention strategies should be targeted at children at risk. Children at risk of becoming obese are those with at least one obese parent and those who present an adiposity rebound before 6 years of age [76]. These at-risk children must be detected early in order to rapidly benefit from personalized intervention to prevent further fat gain. However, the efficacy of such tailored interventions remains to be demonstrated.

Conclusions

Considerable evidence is now available to support the existence of a programming towards childhood obesity, but the underlying mechanisms still remain to be explored. Clearly, the role of genetics dominates, but more research should be conducted to identify the genes involved. Fetal and perhaps early postnatal programming is also possible, but many studies are still required to confirm their contribution in pediatric obesity. Besides this programming, other factors such as viruses [77] or microbiota composition [78] may also be involved and need to be elucidated. In the future, improved knowledge on the pathophysiology of childhood obesity is absolutely essential to allow the development of more promising therapeutic and preventive approaches.

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