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Preface

An epidemic of obesity already at a young age is being observed in most societies around the world. The level of fatness of a child or an adolescent at which morbidity acutely and/or later in life increases is determined on an individual basis. However, overall obesity substantially increases the risk of subsequent morbidity. The definition and diagnosis of obesity in children and adolescents are difficult and controversial. In children and adolescents the degree of body fat mass depends upon ethnic background, gender, developmental stage and age. Waist circumference, skinfold thickness and body mass index are the most useful noninvasive clinical measures to define obesity. Waist circumference and waist-to-hip ratio are helpful to assess upper body fat deposition but do not provide for measuring visceral = intra-abdominal fat accumulation. Direct measurements of body fat content, e.g. hydrodensitometry, bioimpedance, or DEXA are useful tools in scientific studies. However, body mass index (BMI) (weight in kilograms divided by the square of the height in meters) is easy to calculate and is correlated sufficiently with direct measures of fatness. Recently, it has been proposed that the adult body mass index (BMI) cut-off points (25 and 30 kg/m^2) should be related to BMI percentiles in children and adolescents to provide for cut-off points at younger ages. Accordingly, age and gender specific BMI values for 2–18 years corresponding to BMI values of 25 and 30 kg/m^2 at 18 years of age have been published.

Projected obesity rates for obesity (BMI $\geq$30 kg/m^2) in the adult population of the United States are 30% for the year 2015 and over 40% for the year 2025. The Bogalusa heart study found that 22% of the children surveyed in 1990 had

a body mass index greater than the 85th percentile established in a similar survey conducted in 1980. There was little change in the cohorts of children with a BMI less than the 50th percentile. In contrast, there was a large increase in BMI in the cohorts with a BMI greater than the 50th percentile. In summary, over time, obese children have a tendency towards even more excessive weight. It has become clear that childhood obesity has reached epidemic proportions in all industrialized countries around the world. The current age-adjusted prevalence may be as high as 20–30% in some populations. For example, data from a nationally representative sample of 2,630 English children in 1999 show that the frequency of overweight ranged from 22% at age 6 years to 31% at age 15 years and that of obesity ranged from 10% at age 6 years and 17% at age 15 years.

The genetic basis of obesity has been elucidated to some extent through the discovery of leptin, the ob gene product, and the increasing knowledge on the role of neuropeptides such as for example proopiomelanocorticotropin (POMC), the orexins, neuropeptide Y (NPY) and the melanocyte concentrating hormone and its receptors (MSH and MCR). Environmental/exogenous factors largely contribute to the development of a high degree of body fatness early in life. Twin studies suggest that approximately 50% of the tendency towards obesity is inherited. Exogenous factors such as overconsumption of fat-rich diets, the excessive use of modern media and in particular television viewing and lack of physical activity (sedentary life style) heavily contribute to the development of obesity particularly in childhood and adolescence. In fact, four cross-sectional studies from national samples in the United States demonstrated a statistically significant correlation between adiposity and television viewing among children. 8- to 18-year-old children and adolescents spend an average of about 4.5 h per day watching television and videotapes and playing video games. Those demographic groups at highest risk for obesity, such as African-Americans and Latinos and children from families with low income, tend to watch even more television than other US children. In addition, socioeconomic factors as such may heavily contribute to the development of obesity of children and adolescents: in one recent study, teenagers in families with low income were significantly more likely to be overweight than children and adolescents in families with high income. Nutrition and diet early in infancy is thought to influence growth rate and body fatness beyond infancy. Whether obesity is mainly caused by excess energy intake or a reduction in energy expenditure or physical activity is unclear. Some authors have suggested that intrauterine growth retardation actually predisposes for the development of obesity and syndrome X later in life. However, the evidence for fat patterning resulting from differences in fetal or early postnatal nutrition is still open to question.

There are numerous disorders including a number of endocrine disorders (Cushing's syndrome, hypothyroidism etc.) and genetic syndromes (Prader-Labhard-Willi syndrome, Bardet-Biedl syndrome, Cohen syndrome, etc.) that can present with obesity at a very young age. A simple diagnostic algorithm allows for the differentiation between primary or secondary obesity. Among the most common sequelae of obesity in the adolescent are hypertension, dyslipidemia, back pain and psychosocial problems. The definition of obesity in childhood and adolescence is not easy. However, BMI is now generally accepted to be used to define obesity in children and adolescents clinically. Only in preadolescent boys does BMI relate to muscle mass as well and has to be used for the definition of fat mass with great caution. An increased risk of death from cardiovascular disease in adults has been found in subjects whose BMI had been greater than the 75th percentile as adolescents. Therapeutic strategies include psychological and family therapy, lifestyle/behavior modification and nutrition education. The role of regular exercise and exercise programs is emphasized. Surgical procedures and drugs used in adult obesity are still not generally recommended for obese adolescents.

Obesity is the most common chronic disorder in the industrialized societies. Its impact on individual lives as well as on health economics has to be recognized by physicians and the public alike: Obesity at a young age is a major burden for the economy. The annual economic costs due to medical expenses and lost income as a result of complications of adult obesity is estimated to be as high as approximately 70 billion dollars in the USA. At least another 30 billion dollars are thought to be spent on diet foods, products and programs to lose weight. If one is to calculate the prospective costs of obesity forms that have started at an early age, the prospective financial costs are even higher. On the other hand, sales and profits of the obesity treatment industry have already reached an enormous sum. Therefore, obesity in childhood and adolescence has already become a major factor in health care planning systems and within the health care industry as such. However, in addition to the prospect of diminished health, obese people are often stigmatized both socially and in the workplace. This fact also contributes to the economic cost of obesity albeit in an unknown and almost incalculable way.

This book aims to increase physicians' knowledge and understanding of obesity in childhood and adolescence as well as to further public awareness of the health burden and economic dimension of obesity at a young age. Several chapters deliver insight into the basic understanding of which factors contribute or prevent the development of overweight and obesity in young people. Other contributions provide tools for the clinician to manage the care of the child and adolescent with overweight/obesity. In addition, knowledge from the latest scientific studies on the molecular biology of obesity is also presented.

The editors would like to extend their great gratitude and appreciation to the authors who are all world authorities in their field. To have worked with them has made this project both a joy and a success. In addition, the understanding, great care and enthusiasm with which the publisher, Dr. Thomas Karger and his team have accompanied and supported this book is gratefully acknowledged.

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Defining Childhood Obesity

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General Definition of Obesity

Obesity is generally defined as the abnormal or excessive accumulation of fat in adipose tissue to the extent that health may be impaired [1]. Measuring the level of adipose tissue and determining when it is likely to affect health is not an easy task. Quantification of adipose tissue mass can be achieved by a number of laboratory methods including underwater body density measurement and body fat content estimated by the dual-energy X-ray absorptiometer (DEXA). In addition, the development of new techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT), has provided researchers with opportunities to describe human adiposity in more detail [2, 3]. However, most of these methods require costly equipment meaning that their use is limited to clinical research setting.

In large-scale population surveys and clinical/public health screening, an index of body weight adjusted for stature is commonly used as a surrogate for body fat content [4, 5]. These indices are defined as different combinations of weight and height, such as weight divided by height or are defined as weight expressed as a percentage of mean weight for a given height and sex [6]. The most widely used is Quetelet's index, better known as body mass index (BMI), which is body weight (kg) divided by height squared (m^2). This index has been shown to correlate weakly with height and strongly with body fatness in adults [4, 7].

Although the correlation between BMI and body fat adjusted for height is high ($r = 0.82–0.91$) in adults [8], BMI fails to distinguish between lean body mass and fat. Thus, the relationship between BMI and body fatness varies according to body composition and proportions [9]. For instance, the percentage of body fat mass is higher in females than in males with a similar BMI.

In addition, body fatness has been shown to vary by age both before adulthood and with ageing. Any age-related change in height has an influence on BMI as well.

Determining the weight status and level of adiposity in children and adolescents is even more problematical. This is a stage of rapid growth and development. During growth in childhood and adolescence, not only does height increase but body composition changes as well, thus classification of obesity according to a single measure is difficult. In addition, international or regional weight status standards for children and adolescents may be less reliable as the age of onset of puberty and its associated physical changes often varies between different countries, ethnic groups or cultures [1].

Methods for Identifying Obesity in Children

In defining obesity in children and adolescents we are attempting to identify those with excessive adiposity. However, the ability to accurately estimate level of body fatness is only one of the criteria necessary for an effective measure of obesity. Power et al. [10] suggest that of equal importance is the simplicity of the measure, the cost, ease of use and acceptability to the subject. It must also be well documented with published reference values. None of the major approaches to defining childhood and adolescent obesity outlined below meets all these criteria.

Anthropometric Measures

Anthropometric measures are the most commonly used method for defining overweight and obesity in children and adolescents. However, to date, there has been no consistency in the way that these have been applied.

Relative Weight for Height and Age

Many countries have developed growth reference charts by performing cross-sectional studies in a large number of children from birth into adulthood. This has allowed the construction of charts that indicate the normal changes in weight and height that would be seen in both girls and boys at different ages. The spread of variation in growth patterns is usually indicated by fitting growth curves and then defining percentiles on these charts. Those whose measurements fall within very low percentiles of weight for age are seen as underweight and those within the top percentiles of weight for age as overweight and obese.

Childhood and adolescent obesity has typically been defined in terms of relative weight for height and age. In this approach, cut-off points for overweight and underweight are defined as a set percentage above or below the standard weight for a given height in the individual's age and sex group.

The standard weight is usually determined as the mean or median determined from a reference distribution for the population.

A variety of cut-off points have been proposed with the most commonly used approach classifies obesity as 120% or more of the standard (median) weight for sex, height and age. Other classification systems use certain percentiles in the reference growth curves to define weight status with the 85th percentile commonly used as the cut-off point for overweight and 97th percentile for obesity. A more sophisticated and precise measure of weight status involves calculating the Z (or standard deviation) score by subtracting the reference value from the measured weight and dividing by the standard deviation of the reference population. A Z score of +2 or more (i.e. 2 SD above the median) is usually taken to indicate obesity. Because this approach provides a comparable measure of weight status which is continuous and not influenced by age and gender it is often used in research projects where means and standard deviations of the relative weight need to be calculated for a group. However, it is difficult to calculate without the assistance of a computer and a more difficult concept for lay people to interpret.

Defining obesity in terms of relative weight for height and age provides a simple assessment process but it has a number of limitations regardless of the way that cut-off points are defined. It is based on the concept that a certain level of deviation from the median or reference population weight defines obesity regardless of whether the median changes. This limits its use in monitoring and surveillance as the reference curves are likely to vary between countries and may change over time within one country. Consequently, this approach does not result in an increase in the prevalence of obesity, although the mean weight in a height, age and sex group of the reference population increases. In addition, it is arbitrary and has not been associated with any objective measure of obesity-related health outcome in children and adolescents.

Body Mass Index for Age

Body Mass index is a ratio of the body weight in kilograms divided by the square of the height in meters. It has been shown to be a good indicator of adiposity in adults and there is a wide body of evidence which links increasing BMI to increased risk of morbidity and mortality in adults.

Although the relationship between BMI and adiposity is not as tight in children as it is in adults it still appears to be a useful tool for identifying overweight and obese children. The correlation between BMI and fat mass determined by DEXA was found to vary widely from 0.5 to 0.85 [11–13]. However, the false-positive rate was very low indicating that whilst it might identify some overweight children as normal weight there is a low likelihood that children would be misclassified as overweight [14]. As with adults, the relationship

between BMI and adiposity in children and adolescents will vary in those at the extremes of height and muscularity.

Although BMI for age has been identified as a useful measure of adiposity in children and adolescents its value in defining overweight and obesity has been limited by the lack of standard reference values. Only a small number of countries have defined reference growth charts, which include BMI for age percentiles. Cut-off points are defined in much the same way as they are for relative weight for height for age. Most countries have chosen to nominate the 85th and 95th percentiles of BMI for age and gender to define overweight and obesity, although there is still some support for the use of BMI for age Z scores.

As BMI for age relies on reference growth curves, this definition of overweight and obesity suffers from many of the same limitations as relative weight for height and age. As yet there have been no studies that have demonstrated that BMI for age is associated with the development of immediate and longer-term ill health. In addition, changes in the median and BMI distribution within the reference curves will influence how children and adolescents are defined as obese regardless of their absolute level of fatness.

A workshop organized by the International Obesity Task Force (IOTF) in 1997 concluded that some of these limitations could be overcome by developing a set of BMI percentile curves based on an international reference population and by defining cut-off points in relation to the percentiles that equates to a BMI of 25 kg/m^2 and a BMI of 30 kg/m^2 in adults. In doing so, the cut-off points for overweight and obesity are defined on the basis of a BMI percentile which has been associated with excessive risk of ill health in adulthood rather than being dependent on the median BMI value [15]. This approach was the basis of a set of international cut-off points published by Cole et al. [16], which are discussed later.

Additional Weight-for-Height Ratios

A range of ratios using weight and height, in addition to relative weight and BMI, have been proposed as methods for defining adiposity in children. The ponderal index (also known as Rohrer index) is defined as weight in kg divided by the cube of the height in meters and is sometimes used to define weight status in infants. The conicity index [17], defined as waist circumference/(0.109 $\times$ square root of height/weight), is also occasionally used in young children. These indices are not in common use and reflect relative leg length, body frame size, lean body mass as well as fatness [9].

Skinfold Thickness

Measurement of the skinfold thickness at various sites on the body has been used for many years to indicate both inadequate and excessive adiposity

in children. A skinfold thickness measures the amount of subcutaneous fat but an equation developed from the combination of measurements at defined sites provides a reliable estimate of total adiposity [18]. In addition, skinfold measurements taken at just the triceps by trained operators were shown to correlate well with estimates of total adiposity from DEXA in US children [13] and measurements of abdominal skinfolds also correlated highly with estimates of intra-abdominal adiposity obtained from CT or MRI scans [19]. The ratio of subscapular to triceps skinfold thickness has also been shown to be a good predictor of a centralized fat distribution [20].

Skinfold thickness is a cheap and relatively simple measure to perform, although skinfolds may be difficult to be measured in obese subjects. In addition, its reproducibility both for a single observer on the same subject and for different observers vary greatly. Skinfold thickness also appears to vary with race. The lack of growth charts for skinfold thickness or skinfold ratio limits its use for defining childhood obesity and as yet there are no clear associations between skinfold measures and risk of metabolic disease [10].

Waist Circumference

Waist circumference is now accepted as a reasonable guide to the level of intra-abdominal fat and has a clear association with the risk of metabolic disease in adults [1]. Its meaning and use in children is less certain. However, recent studies have indicated that waist circumference correlates well with the level of truncal fat and that this is also associated with markers of cardiovascular risk [21]. Waist circumference also appears to track through childhood and adolescence into adulthood [22].

Waist circumference is cheap, easy to assess and has a relatively low intra- and inter-observer variability. However, at present the work linking waist circumference to ill health in children is still very limited and there have been no cut-off points defined. In addition, waist circumference is only a measure of abdominal rather than total adiposity and so is not useful on its own as an indicator of obesity.

Other Circumferences and Ratios

In adults, the most commonly used circumferences for assessing body fat distribution have been waist, hip and thigh. These sites have been measured also in children, but the significance of these measurements and the ratios derived from them in relation to adiposity is not clear in childhood. In addition, no growth charts are available.

In addition, mid-upper arm circumference has been used to monitor underweight in pre-school children. It might also be a useful measure for assessing fatness during later childhood [10].

Skinfold thickness and arm circumference served as a basis for equations, which were developed in France to assess body composition in children. In this development, triceps skinfold thickness together with upper arm circumference were used to calculate fat and muscle areas and to produce equations, which were validated against magnetic resonance imaging (MRI). The authors concluded that as a result, upper arm fat area estimates and upper arm muscle area are simple and accurate indexes to assess body composition. French reference values are available from 1 month to 17 years of age [23].

In a US study, the relationships of intra-abdominal adipose tissue (IAAT) and subcutaneous abdominal adipose tissue (SAAT) with body composition and anthropometry were examined by using dual energy X-ray absorptiometry (DEXA), skinfolds and circumferences in Caucasian and African-American pre-pubertal children. IAAT and SAAT were found to be predictable from a series of regression equations both with and without the availability of DEXA. For example, the optimal approach for estimating SAAT was from waist circumference, subscabular skinfold and height, which explained 92% of the variation. Abdominal skinfold, subscapular skinfold and ethnicity explained 80% of the variance in IAAT [22].

Measures of Body Composition

A number of techniques have been developed for estimating body composition, total body fat stores and fat distribution. Because of the need for expensive equipment or highly specialized staff, their use is usually restricted to research or tertiary care centers. Estimates of adiposity from these techniques has been used in the past for defining obesity in children but the absence of any standards, the cost and inconvenience of measures negates their value as a measure of obesity. However, because they produce more reliable estimates of body fat stores they may be used to help validate more practical anthropometric measures. Body composition measurements are described elsewhere in this publication.

Current Practices for Definitions

Body mass index (BMI) has now been accepted as the most appropriate and useful measure of relative adiposity in adults and the World Health Organization has set out a universal system of classification to identify those adults overweight or obese. However, a range of measurement and classification systems still persist in the assessment of children with relative weight for height and age remaining the most widely used measure of adiposity in children but BMI for age appears to be often applied in adolescents. There is a growing

consensus that BMI for age should be applied to the assessment of weight status in children of all age but much confusion remains about how to choose an appropriate reference population and how to select appropriate cut-off points for defining a child as overweight or obese.

Current WHO Definitions

The current recommendations from the World Health Organization for defining overweight and obesity in children and adolescents highlights the complexity of the current situation. WHO recommends that weight-for-height Z-scores are used as definition for obesity in children aged 10 years or less. In adolescents (aged 10–19 years), WHO defines at risk of overweight as an age-sex-specific BMI greater than the 85th percentile of the reference population. Both these definitions require the use of growth standards or references and since the late 1970s, WHO has proposed the development of new international growth reference curves and BMI reference curves [24]. The WHO international reference curves for children and infants aged less than 5 years has been in development for a number of years, but as yet these have not been published.

At present, WHO recommends the use of height and weight reference data for populations produced by the National Center for Health Statistics (NCHS). The original NCHS/Centers for Disease Control (CDC) growth curves were formulated in 1975 by combining growth data from four sources in order to serve as a reference for the United States (US). WHO adopted this NCHS/CDC reference as the international reference in 1978. The original height and weight distributions were slightly modified in 1980 when a software version of the reference curves was developed by CDC. However, the WHO committee has drawn attention to several technical and biological problems with this reference particularly as there are currently large variations in the feeding patterns and rate of growth across different countries.

Part of the problem with definitions of childhood and adolescence based on existing reference charts is that these were developed to assess the growth of children and adolescents with a focus on identifying failure to thrive and inadequate nutrition. At the time of their development the problems of undernutrition were far more prevalent than those of overnutrition. With the major shift in the weight status of children and adolescents throughout the world towards overnutrition, extrapolating standard growth charts to define children and adolescents with excessive adiposity may not be appropriate.

A Strong Influence of the US Determination

The difficulty and expense of large longitudinal studies following the growth of children over time has meant that there are few countries that have their own standard growth curves and as a consequence many countries rely on

data and definitions set by the US. The influence of the original NCHS definitions and reference cut-off points derived from NHANES data has been strong, since several studies also outside the US have applied this reference in their national dataset to assess the prevalence of obesity. Although other international approaches exist and the US has since developed newer methods for defining weight status in children, the NCHS reference is still in use throughout the world.

In the early 1990s, an expert committee recommended obesity to be classified in the US on the basis of the BMI distribution in the reference population, with the 85th percentile being the cut-off point for at risk of overweight and the 95th percentile for overweight [11]. In an attempt to avoid reference percentile being determined from a population which is already too heavy, a reference population was produced from children and adolescents studied by the US National Center for Health Statistics (NCHS) in early 1970s [25].

Recent Proposals for Definitions

National Approaches

United States

The Centers for Disease Control and Prevention (CDC) has recently developed new growth charts, which include an age- and sex-specific BMI reference for children and adolescents aged from 2 to 20 years of age (fig. 1, 2). These charts also include a sex-specific weight-for-height reference for children aged 2–6 years. Data from five national health surveys carried out between 1963 and 1993 together with five supplementary sources of data serve as the reference population for developing for these curves.

Each of the CDC BMI-for-age gender-specific charts contains a series of curved lines indicating specific percentiles. Healthcare professionals use the following established percentile cut-off points to identify underweight and overweight in children. Based on the specific percentiles, the definitions for children being underweight, at risk of overweight or overweight are as follows:

Underweight	BMI-for-age $<$5th percentile
At risk of overweight	BMI-for-age 85th to $<$95th percentile
Overweight	BMI-for-age $\geq$95th percentile

The terminology of at risk of overweight and overweight (which in adults equates to overweight and obesity) is in line with the terms used by WHO to the weight status of adolescents as defined by their BMI for age curves.

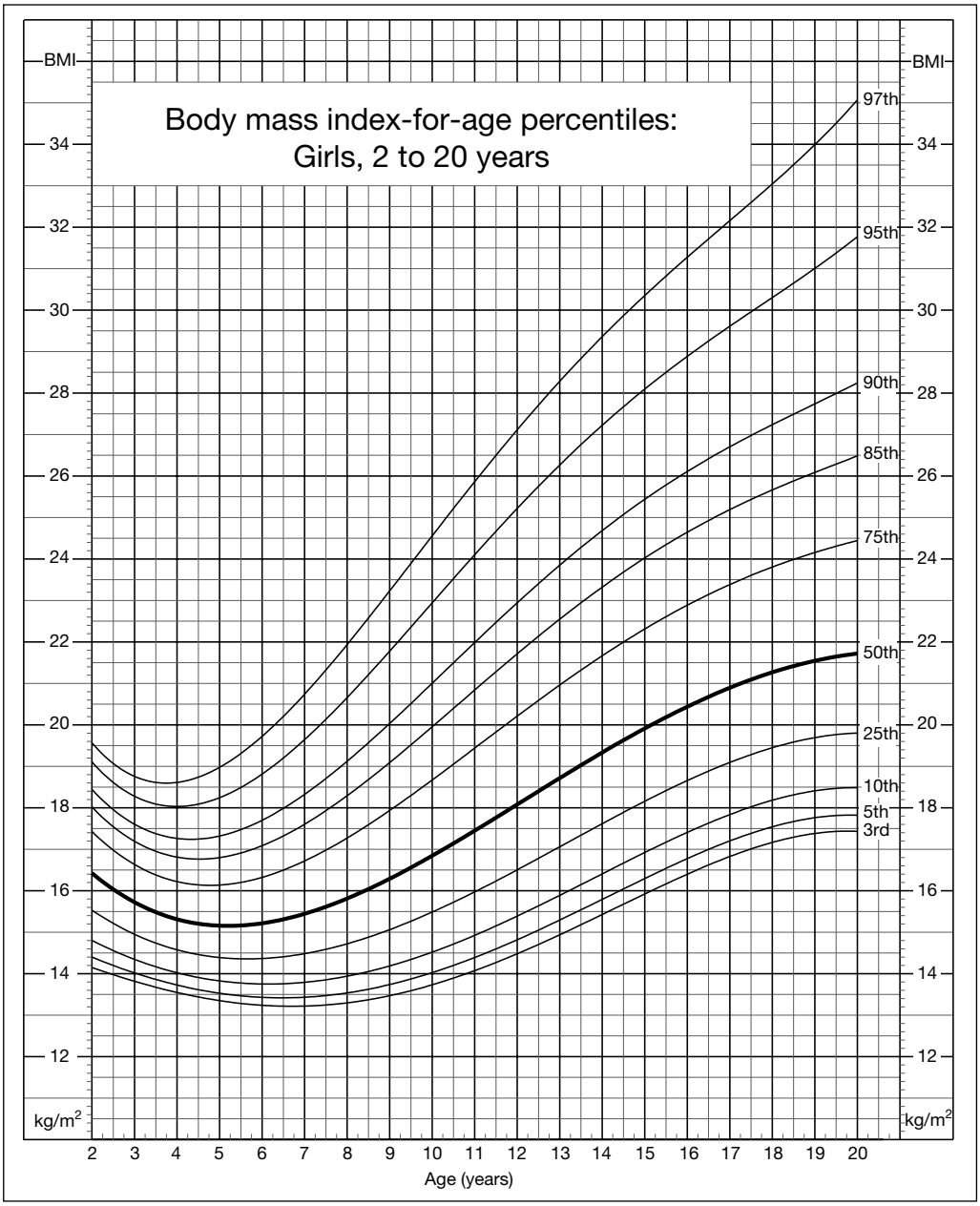

Fig. 1. CDC growth charts from the United States: BMI for age percentiles for girls aged 2–20 years. Source: The Centers for Disease Control and Prevention, 2000.

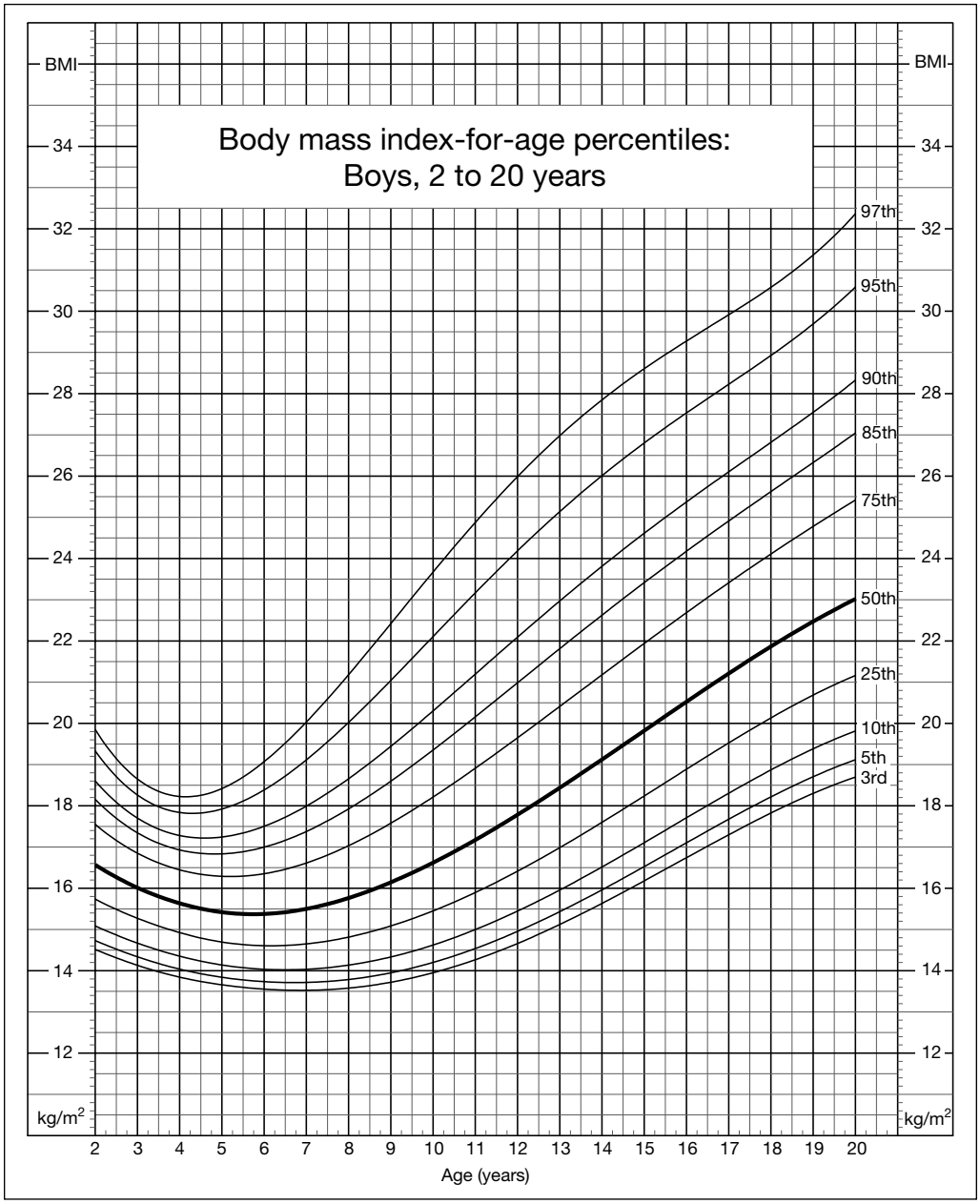

Fig. 2. CDC growth charts from the United States: BMI for age percentiles for boys aged 2–20 years. Source: The Centers for Disease Control and Prevention, 2000.

Other Countries

In addition to the US, some other countries have quite recently developed their own BMI-for-age reference charts. To date, such charts based on the local data have been produced for example in the United Kingdom [26], the Netherlands [27], Italy [28], France [29], Sweden [30] and Hong Kong, China [31]. Cut-off points for BMI used to define those children and adolescents with a weight problem have varied considerably in different countries [32], with the cut-off points of the 85th and 95th percentiles being the most commonly used [1].

Australia recently set a working definition of childhood obesity and has just released a set of National Clinical Guidelines for Weight Control and Obesity Management in Children and Adolescents [33]. The document proposes that BMI should be used as the standard measure of overweight and obesity from 2- to 18-year-olds in Australia. It suggests:

- The international reference developed by Cole et al. [16] should be used in population and clinical research.
- BMI for age percentile charts should be used in clinical and non-healthcare settings, with a BMI above the 85th percentile indicative of overweight and BMI above the 95th percentile indicative of obesity (it notes that these definitions are arbitrary and that amore appropriate definition is needed).
- That local standards for BMI and waist circumference should be developed but in the intervening period that the CDC BMI percentile charts are used.

International Approach for Definitions

IOTF Workshop

The purpose of the workshop on childhood obesity in 1997 was to establish a reasonable index with which adiposity or overweight in children and adolescents could be assessed worldwide. The participants concluded that, although BMI was not a perfect measure of obesity, it had been validated against more precise body fat assessments, and thus was the most appropriate basis for defining overweight and obesity in children and adolescents. In addition, they suggested that, as BMIs of 25 and 30 have internationally acceptance as appropriate cut-off points for adults, percentile values at different ages corresponding to those BMIs at age 20 years would serve as the absolute reference cut-off point throughout childhood and adolescence [15].

International Reference Population

Based on the proposal made by the workshop organized by IOTF, age and sex specific cut-off points for BMI for overweight and obesity in children were developed by using dataset specific centiles linked to adult cut-off points.

Data for this development were obtained from six large nationally presentative cross-sectional surveys on growth from Brazil, Great Britain, Hong Kong, the Netherlands, Singapore and the US. For each of the surveys, centile curves were drawn such that they passed through cut-off points of 25 for adult overweight and 30 for adult obesity at age of 18 years. Averaging the curves from different surveys provided the age- and sex-specific cut-off points for BMI for overweight and obesity from 2 to 18 years. These cut-off points were tabulated at exact half-year ages (table 1). The cut-off points are recommended for use in international comparisons of prevalence of overweight and obesity among children and adolescents but were not deemed appropriate for clinical assessment [16].

The publication of Cole et al. [16] has raised much discussion in the literature concerning the evidence base, rationale, and practical issues in relation to an international approach to defining childhood obesity [34–37]. In recent publications, the international cut-off points have been compared with national definitions and have produced mixed results. A study of children aged 7 years in the United Kingdom tested the sensitivity of the IOTF international BMI cut-off points and the current UK BMI curves at classifying children identified as having excessive adiposity by bioelectrical impedance analysis (BIA). The authors concluded that the existing UK definition produced a much higher sensitivity and specificity than the IOTF approach to defining childhood obesity, especially for boys [38]. Another UK study also compared these two definitions in children aged 4–11 years. Compared to the UK reference, the international cut-off points exaggerated the gender difference in the prevalence of overweight and obesity and resulted in lower estimates for the prevalence of obesity [39]. The prevalence of overweight was also lower using the IOTF definition in children aged 2–14 years in a US study, where this definition was compared with the revised CDC growth charts. However, the opposite was true in adolescents aged 15–19 years [40].

A recent French study used four different definitions based on body mass index to assess the nutritional status (obesity, overweight and thinness) of French children aged 7–9 years. The references used to define grades of nutritional status were: (1) the French BMI reference standard to define thinness and overweight (3rd and 97th percentiles, respectively); (2) the Must et al. [25] standard to define thinness, overweight and obesity (5th, 85th and 95th percentiles, respectively); (3) the IOTF cut-off points to define overweight and obesity, and (4) the revised CDC standards to define thinness, overweight and obesity (5th, 85th and 95th percentiles, respectively). According to these definitions, overweight affected 16, 24, 18 and 21% of children, respectively, whereas the prevalence of obesity was 9, 4 or 6% based on the three latter definitions. Although each definition produced wide variation in estimates of total overweight and obesity, little difference was observed between sexes [41].

Table 1. International cut-off points for body mass index for overweight and obesity by sex in children and adolescents aged between 2 and 18 years defined to pass through body mass index of 25 and 30 kg/m^2 at age 18

Age	Body mass index 25 kg/m^2		Body mass index 30 kg/m^2	
years	males	females	males	females
2	18.41	18.02	20.09	19.81
2.5	18.13	17.76	19.80	19.55
3	17.89	17.56	19.57	19.36
3.5	17.69	17.40	19.39	19.23
4	17.55	17.28	19.29	19.15
4.5	17.47	17.19	19.26	19.12
5	17.42	17.15	19.30	19.17
5.5	17.45	17.20	19.47	19.34
6	17.55	17.34	19.78	19.65
6.5	17.71	17.53	20.23	20.08
7	17.92	17.75	20.63	20.51
7.5	18.16	18.03	21.09	21.01
8	18.44	18.35	21.60	21.57
8.5	18.76	18.69	22.17	22.18
9	19.10	19.07	22.77	22.81
9.5	19.46	19.45	23.39	23.46
10	19.84	19.86	24.00	24.11
10.5	20.20	20.29	24.57	24.77
11	20.55	20.74	25.10	25.42
11.5	20.89	21.20	25.58	26.05
12	21.22	21.68	26.02	26.67
12.5	21.56	22.14	26.43	27.24
13	21.91	22.58	26.84	27.76
13.5	22.27	22.98	27.25	28.20
14	22.62	23.34	27.63	28.57
14.5	22.96	23.66	27.98	28.87
15	23.29	23.94	28.30	29.11
15.5	23.60	24.17	28.60	29.29
16	23.90	24.37	28.88	29.43
16.5	24.19	24.54	29.14	29.56
17	24.46	24.70	29.41	29.69
17.5	24.73	24.85	29.70	29.84
18	25.00	25.00	30.00	30.00

From Cole et al. [16].

Furthermore, Wang and Wang [42] compared different references (IOTF, WHO and CDC) for assessing child and adolescent overweight and obesity in different populations by using data from cross-sectional studies carried out in children aged 6–18 years from the US, Russia and China. In assessing overweight, there was good agreement between the reference standards in general, although they varied by sex-age groupings and countries. Overweight prevalence was twice as high in children (6–9 years) than in adolescents (10–18 years) in China and Russia, but was similar in the US. On the contrary, estimates of obesity prevalence using these three references varied substantially.

Definitions Not Dependent Upon a Reference Population

Currently used definitions of childhood overweight and obesity are all dependent upon generating some form of cut-off points from a reference growth curve. Even if a truly international reference growth curve could be developed the process still relies on identifying norms of body weight or circumference. However some recent studies have suggested that defining obesity in terms of biological endpoints rather than population distribution will overcome this limitation. In an Australian study, the percent body fat was calculated from the sum of four skinfolds, and was compared against levels of cholesterol and triglycerides [43]. Based on associations found, the authors concluded that a cut-off point of 30% body mass as fat for girls and 20% of boys aged 9 or 15 years appeared to be an appropriate standard for defining obesity. These results were in agreement with the findings from Bogalusa study in the US [44], which resulted in the cut-off points of 30% for girls and 25% for boys.

Another study from Taiwan utilized performance in a range of physical fitness tests as an outcome for determining BMI cut-off points appropriate for children aged 7–18 years. The relationship between BMI and performance of fitness tests was examined in 878,207 students participating in a nationwide fitness survey in Taiwan. They found a strong relationship between BMI and fitness level based on a composite score from four separate tests. When they excluded the unfit students (poorest quartile), the 85th and 95th BMI percentile values of the fitter students were in line with the adult cut-off points of 23 and 25 kg/m^2, which, according to the authors, have been recommended as the Asian criteria for overweight and obesity in adults [45].

Special Issues Concerning Universal Definitions

Ethnicity: Body Stature and Fat Content at Given BMI

Although BMI is generally accepted as a reasonable measure of body fatness, there is some, but not consistent evidence that the relationship between

BMI and adiposity is not constant throughout a population and may vary greatly between different ethnic groups both in adults [46, 47] and children [25, 48]. The reason for the different relationships between BMI and body fatness in different ethnic populations is not known. However, variation in relative subcutaneous fat distribution and in the relative proportions of the trunk and lower extremities to the height have been suggested to be potential causes of these differences and confounding factors in the use of the BMI as an index of adiposity [49]. For example, Asian adults have been shown to have relative shorter legs and slender body built (i.e. likely to have less muscle mass) than Caucasians [50]. As a result, for a given BMI Asians may have more fat [47, 50] and a higher risk for obesity-related diseases [51] than Caucasians. The resulting underestimation of obesity by applying international BMI standards has been reported, for example, among Chinese, Malays and Indians living in Singapore [52] as well as other Asian nationalities living in the US [53, 54]. Whether higher body fat at a lower BMI corresponds also with an increased risk of morbidity and mortality remains to be determined [50]. Furthermore, the implications in children and adolescents of these possible racial/ethnic differences in the relationship between the true proportion of body fat and BMI are even less clear than in adults. Two studies have reported that Caucasian children had higher body fatness for a given BMI than African American children [55, 56], whereas no differences in relation between BMI and body composition were found in European, Maori and Pacific Island children [57].

Ethnicity: Timing of a Growth Spurt and Sexual Maturation

Individuals and populations differ in the timing and tempo of the adolescent growth spurt (and sexual maturation), which may have an effect on the interpretation of BMI in childhood and adolescence. On average, the lower extremities experience maximum growth before maximum growth in the trunk, but the major increase in body mass is more coincident with growth of the trunk [7]. Individuals and populations vary not only in the timing of peak height velocity during the adolescent spurt but also in sexual maturation [58–60]. These events appear earlier in countries where individuals experience the longest life expectancies. For example, the age at menarche is among the lowest in many southern European countries as well as in Japan and China, whereas in Malaysia and South Korea sexual maturation seems to occur later [60].

Failure to account for population and individual differences in maturation status may lead to misclassification of adolescents who differ in rates of growth and maturation from the reference population, since fatness and BMI has been shown to be more closely associated with maturation stage than chronological age [61]. In a recent paper, the effect of adjusting for difference in timing of maturation when assessing the prevalence of adolescent overweight in different

populations was investigated. As a result of the maturity adjustment, the estimated prevalence of overweight increased in China and Russia, where girls mature later than the reference population (US NHANES I). The overall effects of adjustment, however, were quite small [62].

A combined effect of pubertal status and ethnicity on skeletal muscle mass and bone mass was examined in white, black and Asian children aged 6–18 years living in New York. The correlations between lean mass indicated by total body potassium (TBK) and bone size indicated by total body calcium (TBCa) were studied and TBK/TBCa was compared between sexes, pubertal stage groups and ethnic groups. TBK/TBCa decreased as body weight increased in prepuberal girls, and decreased as body weight and age increased in pubertal girls, but did not change with body weight or age in boys of any subgroup. No significant differences were found between whites and Asians [63].

Underweight and Stunting

The majority of studies examining whether BMI is a good indicator of fatness in children and adolescents have been carried out in populations living in developed countries. The value of BMI cut-off points for overweight has received less attention in malnourished populations in developing countries, where stunting and wasting are common. Some concerns have been raised about the ability of reference standards to detect both overweight and underweight with the same high level of sensitivity and specificity. The IOTF international definitions for childhood overweight and obesity [16] do not have equivalent cut-off points to define underweight, which limits their use in assessing weight status throughout the Asian region. However, the new CDC BMI-for-age charts do attempt to define underweight from the same reference curves using the 5th percentile as the cut-off point for underweight (see above).

Stunting and its effect on definitions of obesity is another key issue to consider. It is known that BMI is not a perfect measure in children, partly because it covaries with height [64]. In a recent study, the correlation between BMI and other indicators of fatness (skinfold thicknesses) were examined in rural Guatemalans. In this study, BMI was found to be a good indicator for overall fatness, but poor as an indicator for central fat. However, in stunted children BMIs were high despite small extremity skinfold thicknesses. The authors concluded that BMI alone should be interpreted with caution, since it may overestimate the prevalence of fatness in stunted children [65].

A paper by Popkin et al. [66] examined the relationship between stunting and overweight status for children aged 3–6 and 7–9 years in Russia, Brazil, and the Republic of South Africa and China. Using identical cut-off points for BMI, the prevalence of overweight in these countries ranged from 10.5 to 25.6% (based on the 85th percentile). Stunting was also common affecting 9.2–30.6%

of children in surveyed countries. These results showed a significant association of stunting with overweight status as well as with high weight-for-height in a variety of ethnic environmental and social backgrounds.

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Body Composition Measurements

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The term 'body composition' can have a different meaning depending on one's interest, scientific background, and experience. The simplest model of body composition divides body weight (Wt) into two compartments: fat mass (FM) and fat-free mass (FFM). There are more informative models that describe the elemental or chemical makeup of tissues, organs, or the whole body [1], as well as the physiological function and anatomical structure. A multi-level organizational model (fig. 1) has been used to show the relationship among the various models developed over the last 50 years [2, 3]. The model that is probably the most used is the one that partitions the FFM into its water, protein, mineral, and glycogen components. A number of non-invasive techniques have been developed for the in vivo assay of one or more of these components [4]. Direct assays of FM have only been possible for about the last 10 years. These are the development of the more sophisticated techniques of dual-energy X-ray absorptiometry (DXA), computed tomography (CT), and magnetic resonance imaging (MRI). Anthropometric techniques have also been used for many years to estimate body composition, but these techniques will not be the focus of this chapter. Instead, the following sections of this chapter describe the more common measures of body composition that are performed in children and adolescents, and how these can be used to assess body fatness.

Body Volume and Density Measurements

One of the earliest non-invasive methods for the measurement of body composition in humans, which is still in use today, is based on body volume or density. To some, this approach has become a reference method, comparable with those based on chemical analysis. The information that is needed is the

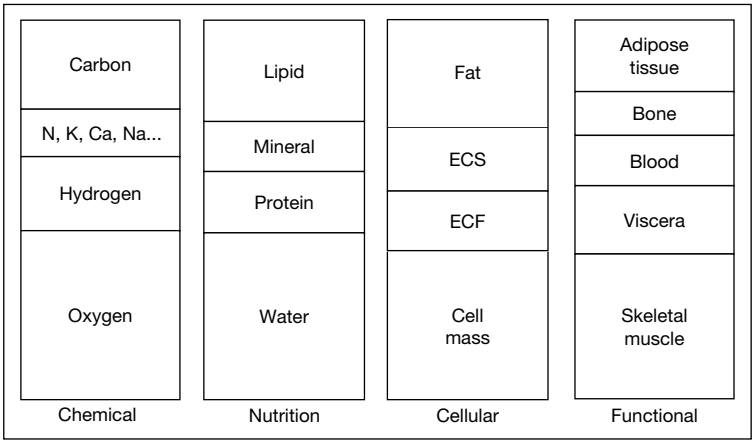

Fig. 1. Multi-level model of body composition. Modified from Wang et al. [2, 3].

density of the whole body, FFM, and FM. An accurate measurement of a subject's body weight (Wt) is relatively easy to achieve; the measurement of body volume (Vol_{TB}) is more challenging. The classic technique, called underwater weighing (UWW), requires that a subject's body weight is measured while the subject is totally submerged underwater, and has exhaled as much of the air from their lungs as possible. The basic 2-C equations are: Wt = FFM + FM and $Vol_{TB} = Vol_{FFM} + Vol_{FM}$. Combining these two equations, the following classic UWW relationship between body fatness (%FM) and density (ρ_{TB}) can be easily obtained:

$$\%FM = 100 \times \left[\frac{k_1}{\rho_{TB}} + k_2 \right]$$

where the constants (k_1, k_2) are determined by the values for ρ_{FM} and ρ_{FFM} [5, 6]. Density of fat can be assumed to be relatively constant independent of age, whereas the density of FFM can change with age or disease, reflecting the proportions of water, protein, and mineral. During childhood and adolescents, the density of FFM is not constant, thus age-specific values (table 1) are needed for this method [7].

The density of FFM may also be altered by disease or medications. Changes in the hydration of the FFM are the most significant, since body water is the major contributor to the total FFM. To overcome this limitation, the basic 2-C model can be expanded to three compartments (3-C), where both ρ_{TB} and total body water (TBW) must be measured. Likewise the model can be expanded

Table 1. Constants used in the two-compartment UWW technique for estimating body fatness in children and adolescents*

Age group years	Males		Females	
	k_1	k_2	k_1	k_2
5–6	5.43	5.03	5.53	5.14
7–8	5.38	4.97	5.43	5.03
9–10	5.30	4.89	5.35	4.95
11–12	5.23	4.81	5.25	4.84
13–14	5.07	4.64	5.12	4.69
15–16	5.03	4.59	5.07	4.64
17–18	4.95	4.50	5.05	4.62
Young adults				
	4.95	4.50	Siri et al. [5]	
	4.57	4.142	Brozek et al. [6]	

*Younger age groups also provided by Lohman [7].

to four compartments (4-C) if the body's mineral content is also known. The difficulty with the 4-C approach is that three separate measurements are required, which defeats the original concept of a single, rather simple, measurement of only body volume. For short-term longitudinal studies, where the body's mineral content (mainly in bone) does not change significantly or the hydration of the FFM is relatively constant, the 2-C model is more than adequate for the assessment of body fatness.

Air-displacement plethysmography (ADP) offers an alternative method for the measurement of body volume or density [7, 8]. Only one ADP instrument (BODPOD, Life Measurements Inc., Concord, Calif., USA) is commercially available. An advantage of this technique is that the subject does not have to be submerged underwater, although they do need to wear a tight-fitting bathing suit and cap to cover hair on their head. The technique is based on Boyle's Law and Poisson's Law for gases, which is basically that pressure × volume in a closed chamber is constant if temperature does not change significantly. For the measurement procedure, the subject sits on a bench in a small chamber (about the size of a telephone booth) that is connected to a reference chamber by a diaphragm. When the door is closed, the diaphragm is oscillated at a low frequency, and the pressure different between the subject's chamber and the reference chamber (fixed volume) is measured. Corrections are needed to account

for breathing (heated moist air coming from the lungs) and the isothermal air in contact with the subject's skin and body hair. Estimates of body volume using ADP and UWW have been shown to be highly correlated and virtually interchangeable for healthy adults [8]. More studies with children are needed, but it is reasonable to expect a similar conclusion will be reached.

Body Water and Potassium Measurements

As noted previously, the most basic 2-C body composition model assumed body Wt is the sum of the FM and FFM compartments. The direct measurement of FM is difficult. Thus, the approach has been to measure some property of the FFM compartment, and to derive the estimate for FM as difference between body weight (Wt) and FFM. The two techniques that are the most often used to estimate FFM are the measurements of total body water (TBW) and total body potassium (TBK). The simple equations for body fatness are:

$$\%\mathrm{FM}_{\mathrm{TBW}} = 100 \times \left[\mathrm{Wt} - \frac{\mathrm{TBW}}{k_3} \right]$$

$$\%\mathrm{FM}_{\mathrm{TBK}} = 100 \times \left[\mathrm{Wt} - \frac{\mathrm{TBK}}{k_4} \right]$$

where the values for k_3 and k_4 can be assumed to be relatively constant at a given age as was the case for the body density measurements.

TBW, the major component of the total FFM, is usually measured by the dilution technique. The subject receives an oral dose of water that is labeled with a non-radioactive isotopic tracer. A sample of body fluid (blood, urine or saliva) is collected from the subject several hours later. The sample must be processed immediately, but can be stored for later analysis using isotope-ratio mass spectroscopy (MS) or Fourier-transformed infrared spectroscopy (FT-IRS). Since the amount of the tracer given to the subject is known, and its concentration in the fluid sample is measured, the total volume of the dilution space can be easily calculated. Also, a correction is needed to adjust for the overexpansion of the tracer beyond the body water compartment. It is assumed that the TBW/FFM ratio is relative constant, such that a value of 0.732 can be used for k_3 in the $\%\mathrm{FM}_{\mathrm{TBW}}$ equation. The hydration of lean tissues, however, may be altered with diseases such as severe malnutrition or edema, so that the estimate for FFM based solely on TBW introduces a significant error in the calculation of %FM.

A clear advantage of the TBW technique is that no bulky instrument is needed for examination of the subject, administration of the tracer, or collection of the fluid sample. Thus, the TBW method is a reasonably good field method.

However, if repeat measurements are need in a relatively short period of time, this can present a problem, since it takes about 30 days for the tracer to fully clear the body.

If frequent repeated measurements on the same person are needed, then the TBK assay may be the better choice. This technique takes advantage of a natural signal that is being emitted all the time from the human body. This signal, which consists of gamma rays, comes from a naturally occurring radioactive isotopic of potassium (^{40}K). One hundred grams of potassium emit about 20,000 gammas per minute with sufficient energy (1.46 MeV) that most will exit the body and are detected using a whole-body counter [9]. To estimate %FM from TBK, it is assumed that the TBK/FFM ratio is relative constant, such that the k_4 values are 59–61 mEq/kg for females, and 62–64 mEq/kg for males [10]. Just as with the TBW measurement, the TBK/FFM ratio can be significantly altered for some diseases and with certain drugs. Another limitation is that most whole-body counters are not portable, and they are not suited for field studies. However, it is well known that the TBK assay is the best choice for monitoring the body cell mass [11].

Bioelectrical Techniques

Bioelectrical techniques have been developed as alternatives to the isotope dilution and potassium counting measurements. The clear advantage of these techniques is that the instruments are small in size, relatively inexpensive, don't require much training of the operator, and the results are immediately available. This technology is based on the general electrical properties of the body, which should be mainly influenced by the FFM. The three most common techniques are: (1) total body electrical conductivity (TOBEC); (2) single-frequency bioelectrical impedance analysis (BIA), and (3) multifrequency bioelectrical impedance spectroscopy (BIS). Each method relies on the electrical conductivity of the body's lean tissues, a property which is influenced by water and electrolyte content of these tissues.

For the TOBEC assay, the body is passed through the open bore of an electrical coil, which produces a very weak electromagnetic field within the bore. When the body is passed through this field, the free charge particles in the body will attempt to align with the external magnetic field causing a small perturbation in the coil's current, which is measured. The procedure takes only a few minutes to perform, and can be repeated as frequently as needed without risk to the subject. Like all bioelectrical assays, the TOBEC technique is a secondary assay, which means that the measured perturbation in the coil (called the TOBEC number) can be calibrated with a more direct assay such at TBW or TBK.

The TOBEC instrument is rather large and requires sufficient floor space so that it has not become a field method. Furthermore, the number of TOBEC instruments, like those for the TBK assay, is limited.

BIA and BIS are also body composition methods based on the body's general electrical properties. For these assays, pairs of electrodes are attached to the body, usually at the hand and foot on the same size of the body. The body's resistance (R) and reactance (Xc) are measured while a very weak alternating electrical current (800 μA) is passed through the body. The BIA assay uses a single frequency (50 kHz), while the BIS technique varies the frequency (5–1,000 kHz). The BIA theory is that the ratio of Ht^2/R is directly proportional to TBW [12]. Some BIA instruments have been designed to measure only the upper body (electrodes on the hands) or lower body (subject stands in the electrodes), while other investigators have chosen to perform segmental BIA measurements (placing multiple electrodes at many sites on the body).

Most of the 30 or more commercially available BIA devices require the input of the subject's gender, age, weight, and height, as well as whether they are active or sedentary. Thus, it is not always clear what algorithm the manufacture has chosen to calculate TBW, FFM, or %FM. Furthermore, it is common to find that many of the prediction equations are using not only the resistance value, but also an additional number of anthropometric parameters. Thus, there are numerous published BIA prediction equations for healthy pediatric populations (table 2). The need for additional terms in these prediction equations mostly likely shows the failure of the basic model used to describe the human body. It would be more reassuring if this model could be modified to better describe the body's electrical properties, such that the additional anthropometric terms could be more fully explained or eliminated.

Dual-Energy X-Ray Absorptiometry

Absorptiometric techniques have been used for 35 years to provide a quantitative measure of the bone's mineral content. Initially only regional bone measurements were possible, since a whole-body scan would take more than an hour to complete. In the mid-1990s this technology made a significant advancement with the development of dual-energy X-ray absorptiometry (DXA). Whereas the earlier instruments used radioactive isotopic sources, DXA uses X-rays, which allowed for a different type of detection system as well, which combined lead to whole-body scan taking less than 15 min. Today's fan-beam DXA systems complete a whole-body scan in about three minutes, at a very low dose (<10 μSv). The DXA assay has virtually become the standard for the assessment of bone mass in postmenopausal women and for most diseases.

Table 2. BIA prediction equations for TBW and FFM in children and adolescents

Age group	Subjects	Equation	Reference [#]
7–25 years	140 M	$FFM = 0.156\ Ht^2/R + 0.646\ Wt + 0.475\ AC - 0.116\ LCS - 0.375\ MAS - 2.932$	Guo et al. [13], 1987
	110 F	$FFM = 0.182\ Ht^2/R + 0.682\ Wt - 0.185\ LCS - 0.244\ TS - 0.202\ SS + 4.338$	
9–14 years	30 M/F	$FFM = 0.81\ Ht^2/R + 6.86$	Cordain et al. [14], 1988
5–18 years	26 M/F	$TBW = 0.60\ Ht^2/R - 0.50$	Davies et al. [15], 1988
10–14 years	94 M/F	$FFM = 0.83\ Ht^2/R + 4.43$	Houtkooper et al. [16], 1989
7–16 years	28 M/F	$TBW = 0.55\ Ht^2/R + 0.79$	Gregory et al. [17], 1991
6–15 years	166 M/F	$FFM = 0.406\ Ht^2/I + 0.36\ Wt + 0.0558\ Ht + 0.56\ sex - 6.5$	Deurenberg et al. [18], 1991
8–18 years	19 M/21 F*	$FFM = 0.84\ Ht^2/R + 1.10$ (African-American) $FFM = 0.524\ Ht^2/R + 0.415\ Wt + 0.321.10$ (European-American)	Lewy et al. [19], 1999
4–18 years	640 M, 597 F	$TBW = 0.475\ Ht^2/R + 0.14\ Wt + 0.725$ $FFM = [0.459\ Ht^2/R + 0.064\ Wt + 0.0558\ Ht + 3.474]/[0.769 - 0.009\ age - 0.016\ sex]$	Horlick et al. [20], 2002
12–18 years**	130**	$TBW = 0.43\ Ht^2/R + 0.20\ Wt + 0.87$ (for males) $TBW = 0.45\ Ht^2/R + 0.12\ Wt + 3.27$ (for females) $FFM = 0.65\ Ht^2/R + 0.26\ Wt + 0.02\ R + 0.87$ (for males) $FFM = 0.70\ Ht^2/R + 0.17\ Wt + 0.02\ R - 11.03$ (for females)	Sun et al. [21], 2003

Ht = Height; R = resistance; I = impedance; Wt = weight; AC = arm circumference; LCS = lateral calf skinfold; MAS = midaxillary skinfold; TS = triceps skinfold; SS = subscapular skinfold.

*African-American population.

**Subset of children in a population of 1,829 subjects, ages 12–94 years.

In order to provide a quantitative measurement of bone, the composition of the overlying soft tissue needs to be known. This is accomplished by analyzing the non-bone pixels in the whole-body scan for their relative fat content. Furthermore, DXA is the only non-imaging technique that also provides information about the regional distribution of body fat.

Body Imaging Techniques

Computed tomography (CT) uses X-rays that are collimated to provide a fan-shaped beam that is passed through the body, while an array of detectors is positioned on the opposite side of the body to detect the transmitted radiation [4]. The X-ray source and detector assembly are rotated as a single unit around the body, and the data are reconstructed to generate a cross-sectional image or 'slice' for each rotation around the body. CT is a quantitative assay that gives the relative density (g/cm^3) of each pixel or voxel in the cross-sectional image. Thus, anatomical regions such as subcutaneous adipose tissue (SAT), muscle, skin, internal organs, visceral fat deposits (VAT), and bone can be identified. The one major disadvantage with routine CT imaging is that the radiation dose required per slice is much higher than needed for a DXA scan. However, the image resolution needed for VAT/SAT analysis can be relaxed, which will reduce the dose significantly [22].

Cross-sectional images of the body can also be obtained using magnetic resonance imaging (MRI) techniques. These images tend to be superior in anatomical quality to those obtained using CT technology. However, the advantage of CT is that the density of each voxel can be determined. One can easily identify the subcutaneous and visceral fat areas on an MRI image, for example. An advantage of MRI is that the lipid content within lean tissues can be obtained [23, 24]. Further investigations in this direction can be expected, especially in families where excess adiposity is associated with specific chronic diseases [25].

Conclusion

Each of the body composition methods presented in this chapter has its own set of advantages and disadvantages [4]. The BIA technique, for example, is relatively easy to perform and has become widely available, but the body composition results for the individual child or adolescent have often been shown not to be much better than simply anthropometric measurements. The DXA procedure has become, for all practical purposes, the reference method for the clinical assessment of bone mineral. This acceptance of DXA will also drive efforts for its approval as a reference for body fatness in children and adolescents. However, there still remain sufficient differences in %FM estimates between the DXA and the 4-C density model that further improvements may be needed before a consensus can be reached [26, 27]. DXA has the added disadvantage that an exposure to X-rays, although small, is required. However, the dose is very small ($<10\,\mu Sv$), and presents no measurable risk to the subject and is well within the variation of the natural background radiation levels.

When the body density model is use, the BODPOD clearly offers an alternative to the more difficult underwater weighing technique [8]. BIA, basically developed as a replacement for the more difficult dilution assay for TBW, appears to have limited accuracy for %FM assessment for the individual child. CT and MRI are excellent choices for measuring subcutaneous and visceral fat distribution, but these technologies are too complex, and of limited availability, to be considered for routine %FM assessment. Their application will probably be more valuable in helping to understand the role body fatness has on adverse health effects associated with obesity.

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Examination and Diagnostic Procedure

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The diagnostic proceedings in childhood and adolescent obesity should comprise clinical and laboratory as well as psychological and psychosocial examination. Clinical examination and laboratory tests are mandatory during the initial presentation of the patient whilst the psychological exploration can be part of an individually adapted treatment regimen. This chapter focuses on the clinical and laboratory diagnosis of childhood and adolescent obesity.

In any case, on initial diagnosis of obesity in a child or an adolescent symptoms of psychiatric disorders, e.g. depression or bulimia nervosa, must be recognized because of therapeutic consequences and the possible contraindication of an obesity intervention in these patients. If symptoms of psychiatric disorders are present, the patient must be referred for further evaluation to a pediatric psychiatrist or psychologist.

Careful medical evaluation of children and adolescents with obesity should aim at excluding any disorders with primary medical association with obesity and at recognizing any manifestation of obesity-related comorbidities. Obesity as a disease in childhood and adolescence consists besides excess body fat of a complex of symptoms, from functional limitations to somatic and psychologic comorbidity that may become evident already in childhood. Somatic sequelae are, e.g., orthopedic complications (Blount disease, slipped capital femoral epiphysis), hypertension, dyslipidemia, type 2 diabetes mellitus, hyperandrogenemia in girls, hyperuricemia, cholecystolithiasis, and the metabolic syndrome.

Common clinical findings in childhood and adolescent obesity, which in most cases do not need further investigation are listed as follows: accelerated height gain and advanced bone age (boys and girls); striae distensae (boys and girls); gynecomastia (boys); pseudohypogenitalism (boys).

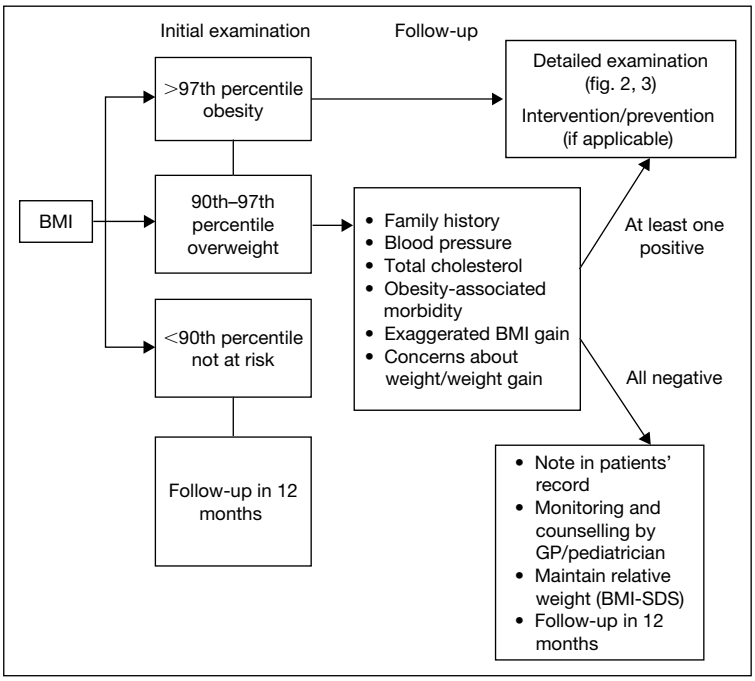

Fig. 1. Examination proceedings (modified from Barlow and Dietz [5]).

Table 1. Examination proceedings depending on the degree of overweight and the presence of risk factors

BMI	Risk factors	Further steps
90th–97th percentile	no	pediatric counselling, follow-up in 12 months
90th–97th percentile	yes	careful examination (fig. 2, 3), if applicable therapeutic or preventive intervention
>97th percentile	yes or no	careful examination (fig. 2, 3), therapeutic intervention

Rational Clinical Diagnostic

Figure 1 outlines a flow sheet for stepwise medical evaluation of children and adolescents presented with suspected obesity (see also table 1). Where applicable, following each step results in further diagnostic proceedings as described in figures 2 and 3.

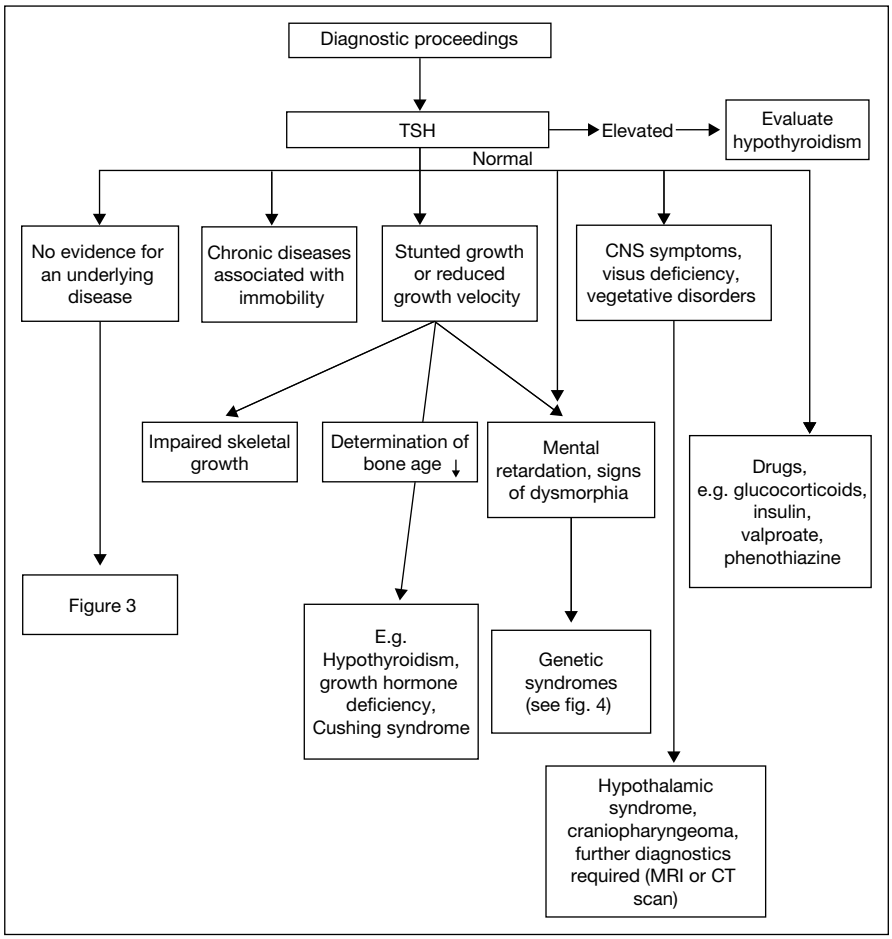

Fig. 2. Exclusion of secondary obesity (modified from Wabitsch and Kunze [1]).

The first level of screening is designed to categorize the excess body weight. Recommended clinical measure is the body mass index (BMI). Depending on national guidelines, obesity in childhood and adolescence may be defined as BMI >97th age and sex specific percentile, children and adolescents with a BMI between the 90th and 97th percentile may be classified 'overweight' [1]. International reference data for BMI values and guidelines can be applied when national references are missing [2].

In overweight patients, additional risk factors should be considered carefully as they contribute to the further diagnostic proceedings. Especially accelerated gains in BMI (upward crossing of percentiles, BMI increments

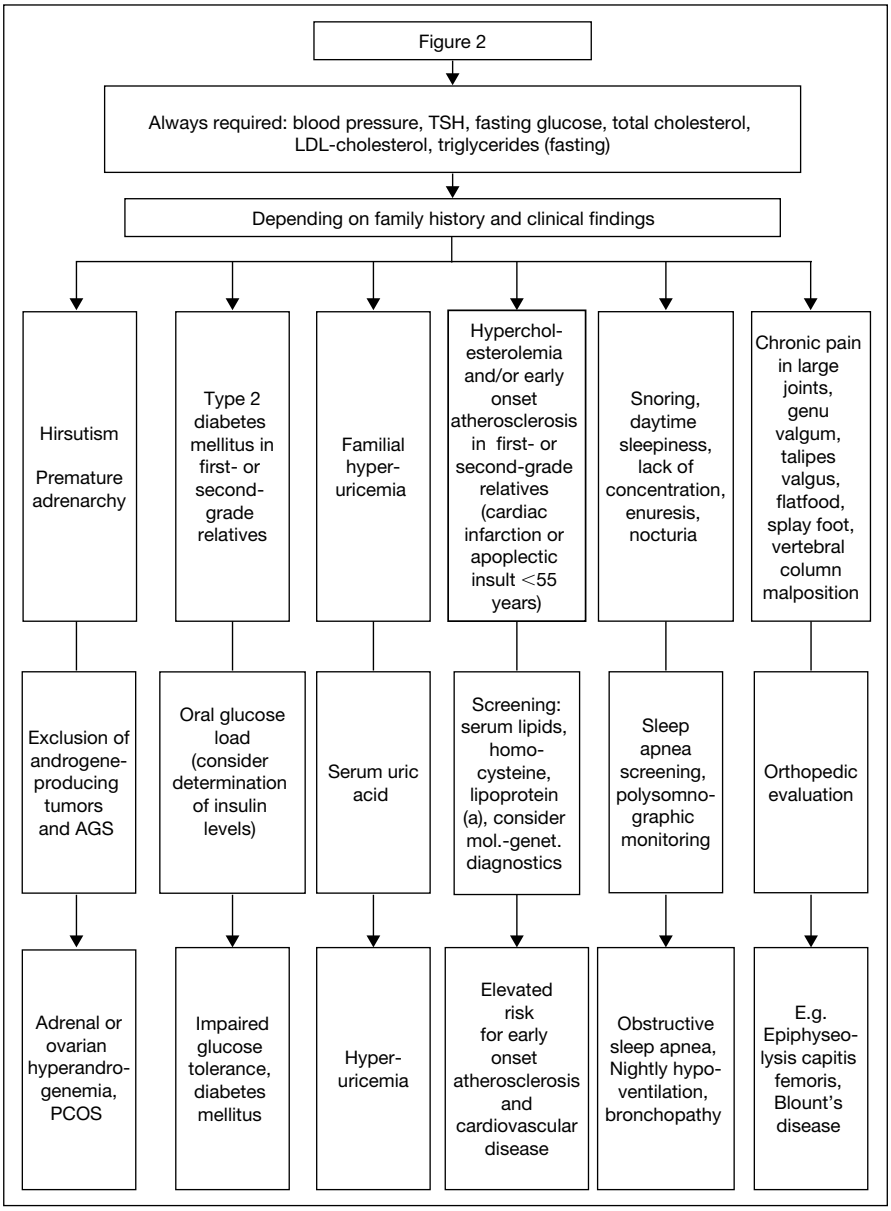

Fig. 3. Health risks and comorbidity.

$>2\,kg/m^2$ p.a.) and a positive family history for obesity (BMI of a parent $>30\,kg/m^2$) or early-onset atherosclerosis (cardiac infarction or apoplectic insult <55 years of age in first- or second-grade relatives) should lead to the same diagnostic procedures as in obese patients. If no additional risk factors are present, patient and family should be counselled and followed up in 12 months.

Further medical evaluation in obese children and adolescents or overweight subjects with one or more additional risk factors has the following three main objectives: (1) determination of the magnitude of excess body weight; (2) exclusion of an underlying, primary disease, and (3) analysis of the individual risk factor profile and comorbidity (e.g. endocrine, metabolic, orthopedic, respiratory, dermatologic, psychiatric sequelae).

Practical Realization and Interpretation

Determination of the Level of Obesity

Body weight and body height must be measured with calibrated scales. Afterwards, BMI-percentile and/or BMI-SDS can be determined. Calculation and graphing tools based on German reference data are available in electronic form on the internet (http://www.a-g-a.de) [3]. In adolescents older than 15 years, the pattern of body fat distribution can be differentiated in central adiposity and more peripheral adiposity. Therefore, waist circumference is measured midway between the lower rib margin and the iliac crest. Hip circumference is measured horizontally over the Trochanter major.

In adult women a Waist-to-hip ratio >0.85 and in adult men a WHR >1.0 are indicators for a central distribution of body fat. Currently, there are no reference values for WHR in children and adolescents, although in older adolescents adult references may be used for orientating classification.

Exclusion of a Primary Disease

Classical diseases causing secondary obesity are rare and often associated with short stature and/or inadequate psychomotoric development. Structured diagnostic proceedings are detailed in figure 2.

Exclusion of Hypothyroidism. Children and adolescents presenting with obesity should receive screening for hypothyroidism. Measurement of TSH concentration in serum may rule out hypothyroidism (e.g. thyroiditis, dysplasia of the thyroid gland, iodine deficiency) which is rarely the primary cause for overweight.

Obesity and Macrosomia in the Newborn Infant. Possible causes of obesity and macrosomy in the newborn infant are the diabetic fetopathia and several overgrowth syndromes, like the Beckwith-Wiedemann syndrome.

Monogenetic Obesity. The currently known monogenetic forms of obesity are described in the chapter by Hebebrand [pp. 80–90]. The most frequent monogenetic obesity in humans is caused by a mutation in the melanocortin-4-receptor

gene (MC4R). In obese populations, the prevalence of this mutation ranges at 5%, so a molecular-genetic screening may become effective in all obese subjects as soon as a causal therapy for this mutation becomes available.

Measurement of Serum Leptin. The serum concentration of leptin is determined by the total body fat mass, gender and stage of pubertal development. Inborn leptin deficiency is extremely rare, therefore leptin measurement is not part of the routine diagnostic regimen and limited to scientific studies.

Risk Factor Profile and Comorbidity

Necessary laboratory and clinical diagnostic procedures are selected depending on clinical findings and the patients' medical and family history according to figure 3.

Laboratory Diagnostics. Laboratory screening should regard the following parameters: total cholesterol, LDL-cholesterol, triglycerides (fasting) and TSH. Depending on family history and clinical findings, measurement of additional metabolic or hormonal parameters is indicated (fig. 3).

Systolic and diastolic blood pressure must be measured with an adequately sized cuff.

In the case of an extreme obesity with a BMI >99.5th percentile for age and sex, additional diagnostic steps are recommended (see below).

Special Anamnestic Data

Calculation of BMI and BMI percentiles from patients' records allows identifying the time point of onset of obesity and assessment of the dynamics of weight gain. Quite commonly, the onset of obesity dates back several years before first presentation for this health issue. Routinely, weight and height of siblings, parents and grandparents should be obtained because of the phenomenon of familial obesity. Additionally, explicit questioning for familial accumulation of cardiovascular risk factors, hypertension, dyslipidemia, hyperuricemia and cholecystolithiasis should be part of the clinical interview.

Obesity-promoting environmental factors are a hypercaloric and low-fiber nutrition and a lack of physical activity. Always ask for regular participation in sports and for average duration of daily TV and videogame consumption.

Familial and psychosocial situation of the patient should be evaluated carefully. Critical for the individual prognosis are amongst others divorce, neglect and working mothers.

Overweight and obese children and adolescents experience significant social discrimination and psychologic stress. Questions about social activities, integration in peer groups, performance at school and everyday harassment and intimidation can lead the way into further psychosocial exploration.

Physical Examination

Children and adolescents with overweight and obesity are taller for age before close of pubertal development, and a body height above the 90th percentile is found quite commonly. Biological age and growth velocity both may be accelerated in childhood obesity. As a general rule we are proposing to regard a body height lower than the 50th percentile for age and gender as noticeable low for a child with marked obesity. In these cases, further diagnostics should be carried out.

Striae distensae, located on the upper arms, chest, abdomen, and thighs, are found frequently in obese children. Obese boys are often presented because of gynecomastia and small genitalia. Predominantly, these are cases of pseudogynecomastia and pseudohypogenitalism. The pseudogynecomastia is caused by the enlarged subcutaneous fat tissue. Additionally, the mammary gland itself can be hypertrophic, which may be explained in part by the obesity-associated hyperestrogenemia. The main cause for the quite common pseudohypogenitalism is the massively increased subcutaneous fat depot in which the penis and scrotum are submerged. In relation to the accelerated skeletal growth, secondary sex characteristics may, however, be delayed in obese boys.

Pubertal development in girls with marked obesity starts early and age at menarche is comparably young. A subgroup of these girls may develop hirsutism and later on abnormalities in menstrual cycles. Typically, these patients show an abdominal pattern of body fat distribution (WHR $>$ 0.85) and an adverse cardiovascular risk factor profile.

If abdominal pain occurs in obese children, gall stones have to be considered as an important differential diagnosis, which can be confirmed by ultrasonography.

Tracking of Obesity

Obese children and adolescents are at increased risk of becoming obese adults. The likelihood of persistence of obesity into adulthood is especially high, when the affected child is older than 4 years of age, extremely obese or has at least one overweight parent. In a 7-year-old obese child with an obese parent, the probability of becoming an obese adult is 70% [4].

Syndromal Obesity

For the diagnostics of syndromal forms of obesity in children, we refer to figure 4. Further information on adapted diagnostic proceedings can also be found in the chapter by Hebebrand [pp. 80–90].

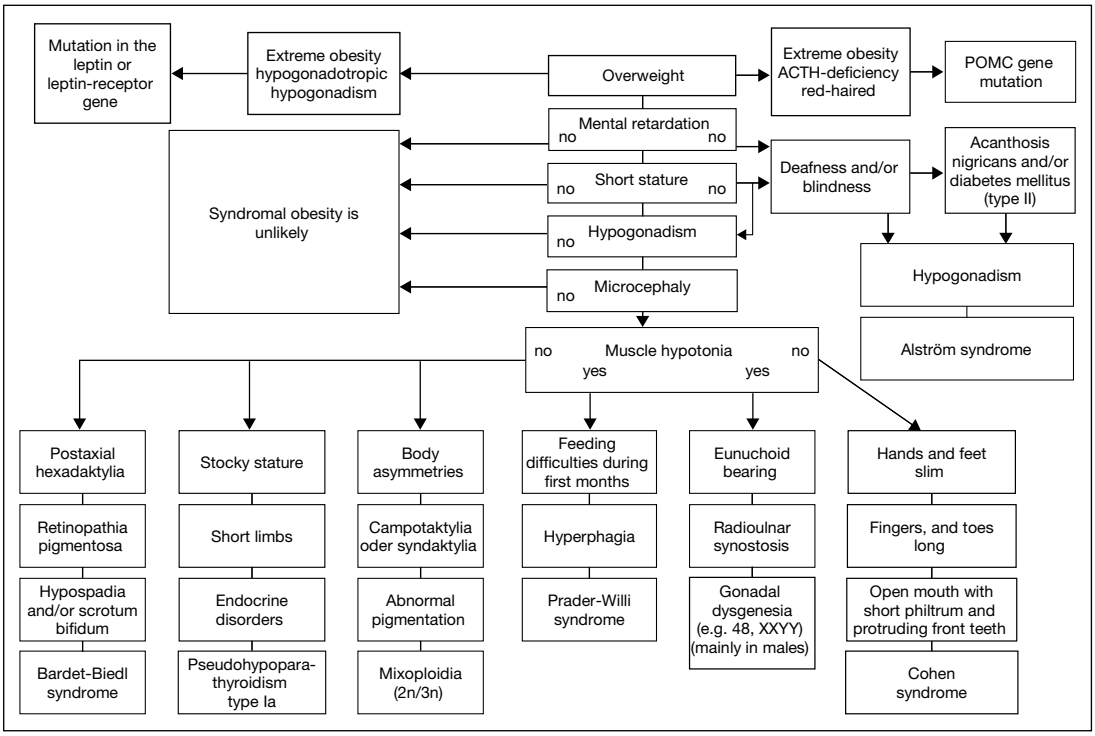

Fig. 4. Syndromal forms of obesity (modified from Wabitsch and Kunze [1]).

Diagnostic Proceedings in Extreme Obesity

Epidemiologic data not only show increasing prevalence rates of childhood and adolescent obesity in many developed and developing countries, but also a parallel trend towards higher mean BMI values in populations of obese children and adolescents. In the following, we suggest additional diagnostic considerations regarding the growing extremely obese subgroup of our patients, which are in need for special attention due to highly prevalent comorbidity. Children and adolescents with marked obesity can show a broad spectrum of obesity-related sequelae that are often underdiagnosed. Special attention during the physical examination of an extremely obese child should be pointed towards hirsutism, intertrigo, acanthosis nigricans and abnormal angulation in the knee joints. The following suggestions are based mainly on the guidelines of the German childhood obesity workgroup (AGA) which are available in electronic form on the internet [1] (http://www.a-g-a.de).

Unfortunately, unlike the WHO criteria for obesity in adulthood, there is currently no uniform definition for extreme obesity in childhood and adolescence available. We are suggesting a cut-off value between the 99.5th and the 99.9th BMI percentile for classifying a child or adolescent as extremely obese.

As outlined above, each extremely obese patient should undergo basic obesity diagnostics consisting of a detailed medical history, physical examination and laboratory testing. Because of the pronounced risk factor profile of these patients, referral to a specialized childhood obesity unit for extended obesity diagnostics has to be considered. In the following paragraphs we describe more extensively the evaluation of children and adolescents with extreme obesity focusing on specific aspects.

Medical Diagnostics in Extreme Obesity

Fundamental for the medical diagnosis of extreme obesity in childhood and adolescence is the detailed anamnesis. In particular, attention should be pointed to the occurrence of familial obesity (family tree with weight and height) and familial accumulation of cardiovascular risk factors. Explicitly ask for family members with diabetes mellitus, hypertension or coronary heart disease, cardiac infarction, apoplectic insult, dyslipidemia or hyperuricemia.

Anamnesis of developmental stages should range from gestation and possible complications, over birth weight and length to psychomotor development, school performance and pubertal development (menarche, menstrual cycle). Evolution of body weight and height should be traced as exactly as medical records allow.

Nutrition anamnesis also starts in early infancy (breast-feeding, feeding difficulties), highlights actual nutrition patterns asks explicitly for eating disorders like hyperphagia, binge eating and others.

All previous treatment interventions, whether self-conducted or within a professional treatment programme, and their outcomes have to be documented (weight cycling).

Attention should be paid also to the individual physical capacity. Dyspnea during physical activity and pain in the large joints are common in obese children and adolescents and should lead to closer orthopedic examination.

Patients presenting with daytime sleepiness, poor concentration and declining performance at school should always receive a sleep apnea screening, as those symptoms are indicators for obstructive sleep apnea or the obesity hypoventilation syndrome.

Physical Examination in Extreme Obesity

The integument of extreme obese children and adolescents gives rich and important information, from metabolic to psychologic alterations, and its clinical assessment is not restricted by the excess fat mass.

Information about the dynamics of recent weight gain can be deduced from characteristic, localization and color of striae distensae. Acanthosis nigricans (sites of predilection: neck, axilla, abdomen) is associated with hyperinsulinism, signs of virilization like hirsutism should remind of hyperandrogenemia and polycystic ovaries in girls. Skin lesions suspect of autoaggressive behavior ('scribing') require extended psychologic exploration. Bulimic behavior may be associated with adamantine lesions.

Palpation, percussion and auscultation are often of only limited significance in extremely obese children and adolescents. Therefore, the indication for ultrasonography of the abdomen can be handled as freehanded. Furthermore, referral to an orthopedic specialist should be handled generously.

Extended Diagnostics in Extreme Obesity

The following diagnostic procedures should be considered depending on anamnesis and clinical findings.

Hyperinsulinism, positive family history for type 2 diabetes mellitus or suspected polycystic ovaries should lead to an oral glucose load with measurement of insulin secretion to detect impaired glucose tolerance, manifest diabetes and/or hyperinsulinism.

If dyslipidemia or positive family history for early onset atherosclerosis are present, serum levels of lipoprotein (a) and homocysteine should be measured to further describe individual cardiovascular risk.

Abdominal sonography detects steatohepatitis, grade of the steatosis hepatitis and gallstones.

Age-matched reference values have to be used when evaluating blood pressure levels, preferably extremely obese children and adolescents should be screened for hypertension using 24-hour blood pressure profiles.

As outlined before, patients with symptoms of sleep apnea like snoring, headaches in the morning, daytime sleepiness and lack of concentration should receive at least a screening for sleep apnea, or even better a polysomnographic examination.

Finally, sports medicine and performance tests including motoric abilities are regularly only available at specialized obesity centers, but can nonetheless deliver important additional information on individual physical capacity and may also function as motivational factors during treatment.

Psychologic Diagnosis in Extreme Obesity

Because of the increased prevalence of psychiatric and psychosocial disorders in extremely obese children and adolescents, an extended psychologic or psychiatric examination paying attention to the following points, seems to be

suggestive in most cases:

- eating disorders (ICD-10: F50)
- intrapsychic or intrafamiliar conflicts
- excessive demand at school/work
- affective disorders (ICD-10: F30–F39)
- anxiety disorders, especially social phobia (ICD: F41–F41.9, F40.1)
- traumatizing experiences, e.g. sexual abuse
- posttraumatic *Belastungsstörung* (ICD-10: F43.1)
- autoaggression
- substance abuse (ICD 10: F1)
- *Störung des Sozialverhaltens* (ICD 10: F91)
- delinquency
- low self esteem
- high-risk sexual behaviour
- enuresis nocturna (ICD 10: F98)

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Epidemiology of Obesity in Childhood and Adolescence

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The prevalence of overweight in adults has increased by about 50% within only 7 years in the USA [1]. A similar trend has been observed in children in the USA and other Western countries [2–6] and overweight has been identified as one of the most important health problems of children [7]. The dynamic of the increasing prevalence is impressive. In Western societies, Australia, Europe, USA, an acceleration of this process has been reported for the 1980s [2, 4]. In the 1990s, there was a shift of the acceleration towards developing countries [8]. These dramatic changes make overweight and obesity a major issue of public health.

The objective of this article is to describe prevalence and secular trends of prevalence rates for childhood obesity on an international level and to assess the changes in the BMI distribution between populations and for different ethnicities, cultural and socio-economic subgroups within populations. Temporal changes regarding the distribution of some known or suspected risk factors for obesity will be described. The potential contribution of epidemiology to elucidate the etiology of the adiposity epidemic will be discussed.

Prevalence and Secular Trends of Prevalence Rates for Childhood Obesity

Time Trends in Childhood Obesity in Different Countries

A two- to nearly fourfold increase in the prevalence of childhood obesity has been reported from different countries all around the world [9, 10]. Table 1 summarizes studies performed in 14 selected countries. These studies were selected because they offer – with certain limitations – the opportunity to compare different global regions. Although nearly all studies reported an

Table 1. Global prevalence of overweight and obesity

Country and year	Criteria of definition	Age group years		Prevalence of overweight %	Increase of overweight, % (time interval)	Average increase of overweight per year, %	Prevalence of obesity %	Increase of obesity, % (time interval)	Reference
Australia 1995	IOTF	4–6	(boys)	10.4		3.5	3.0		[92]
			(girls)	15.3			4.2		
		7–11	(boys)	11.6	20 (1985–1995)		3.7	147 (1985–1995)	
			(girls)	17.2	56 (1985–1995)		6.3	232 (1985–1995)	
Brazil 1997	IOTF	6–9		17.4	260 (1974–1997)	11			[19]
		10–18		12.6	240 (1974–1997)				
Chile 1996	IOTF	0–6					7.2	56 (1985–1995)	[93]
China 1997	IOTF	6–9		11.3	7.6 (1991–1997)	3			[19]
		10–18		6.2	38 (1991–1997)				
Dominican Republic 1996	WHO	0–5		4.9	75 (1986–1996)	7			[8]
Egypt	WHO	0–5		8.6	291 (1978–1996)	15			[8]
England	IOTF	4–11	(boys)	9.0	41 (1984–1994)	4	1.7		[2]
			(girls)	13.5	48 (1984–1994)		2.6		
Germany 1997	IOTF	5–6	(boys)	11.0	45 (1982–1997)	3	2.8		[3]
			(girls)	13.6	43 (1982–1997)		2.8		
Ghana 1996	WHO	0–3		1.9	171 (1987–1994)	21			[8]
Haiti 1995	WHO	0–5		2.8	250 (1978–1995)	28			[8]

Japan 1996	≥120% of standard weight	6	(boys)	4.5	200 (1970–1996)	11			[94]
			(girls)	4.5	170 (1970–1996)				
		12	(boys)	10.5	206 (1970–1996)				
			(girls)	8	170 (1970–1996)				
Morocco 1992	WHO	0–5		6.8	152 (1987–1992)	25			[8]
Russia 1998	IOTF	6–9		10.2	−61 (1992–1998)	−9			[19]
		10–18		8.5	−26 (1992–1998)				
Seychelles 1999	IOTF	4.5–17.4		12.6			3.8		[21]
USA 1988–1994	IOTF	6–9		22.0	86 (1971–1994)	4			[19]
		10–18		27.3	63 (1971–1994)				
USA 1999–2000	CDC	2–5		20.6			10.4		[18]
		6–11		30.3			15.3	283 (1971–2000)	
		12–19		30.4			15.5	154 (1971–2000)	

WHO definition: Weight for height above 2 SD of international reference [20].
IOTF: BMI corresponding to values of 25 and 30 kg/m^2 at 18 years [11].
CDC: BMI above 85th or 95th percentile of the 2000 CDC growth charts [17].

increase in the prevalence of childhood obesity, the individual prevalence rates and the degree of increase differed considerably between the different countries. There was a range of prevalence rates of overweight from 1.9% (Ghana) to 30.4% (USA) and from 1.7 to 15.5% for obesity, respectively. The annual increase of prevalence rates differed from a maximum of 28% in Haiti to a decrease by −9% in Russia.

This variability may indicate true differences in prevalence rates or increments of the respective rates. Data quality may be variable between the countries, but most studies covered at least 80% of population [8]. Therefore, selection bias is an unlikely explanation. Different classification criteria used in the respective countries, however, must be considered. Nine of 14 studies used the definition of the Childhood Obesity Working Group of the International Obesity Task Force (IOTF). The cut-off values for overweight and obesity for different age groups are presumed to represent the widely used cut-off points of 25 and 30 kg/m^2 for adult overweight and obesity [11]. In adults these cut-off values mark a critical threshold beyond which typical overweight-related diseases and health problems appear and are presumed to be of similar relevance in children.

The BMI values of the 90th and 97th percentiles, recommended by the European Childhood Obesity Group (ECOG) as cut-off values in Germany [12] match with those for overweight and obesity in the IOTF definition [13], whereas those for the UK [14] and France [15] differ. The US definition, however, refers to the 85th and 95th percentiles of the CDC growth charts [16, 17]. In table 1 only the publication of Ogden et al. [18] is based on this definition. This explains in part the higher prevalence values compared to the other study in US children [19]. The publication of de Onis and Blössner [8] uses the WHO criteria: overweight is defined as weight for height above 2 SD of an international population [20].

As percentiles are always relative values that underlie alteration with time, it is important, which standard population is used for comparison. In the report of de Onis and Blössner [8] a global prevalence of 2.3% is expected, since 2.3% of values of a normal distribution lie beyond two standard deviations. As the standard population in that study was not the actual world population, but a historical population, a global prevalence of 3.3% was extrapolated to depict the world population of today.

In table 1, the respective cut-off criteria are indicated for each study described. In order to make the different countries comparable despite of the diverse time intervals of observation, the *increase* of overweight was also given as percentage per year.

Another possible explanation for spurious differences in the increase rates are the different starting points. While in industrialized countries already high prevalence rates of overweight are found, developing countries started with lower values, but had remarkably high rates of increase in the past years. In a

very recent study de Onis and Blössner [8] used the WHO Global Data Base on Child Growth and Malnutrition (Geneva) and found notably high prevalence rates of overweight in preschool children in North Africa (especially Algeria, Morocco and Egypt) with 8.1%, and Latin America (4.4%) [8] compared to the global prevalence of 3.3%. The lowest figures of obesity are reported for south-central Asia (2.1%), south-eastern Asia (2.4%) and western Africa (2.6%). These are also the regions with the highest rates of underweight. Despite the growing obesity issue the most important nutrition-related problem of developing countries remains malnutrition and underweight, as emphasized by the authors. In that study, data for trends in overweight were available for 38 countries. Of these, 16 countries showed a rising prevalence of childhood overweight (e.g. Bolivia, Ghana, Nigeria, Morocco, Egypt).

An example of *rapidly* developing countries is the Seychelles in the Indian Ocean (table 1). Some 12.6% of the children are overweight and 3.8% are obese. These figures are as high as in industrialized countries like England or Germany [21], which indicates that rapidly industrializing countries undergo similar cultural changes as Western countries did in the past years.

Are There Different Risk Groups for Childhood Obesity in Different Countries?

The distribution of risk groups varies between developing and developed countries. While in industrialized countries children from families with a poor socio-economic status are more often overweight, the opposite holds true for children in developing countries, where children of the upper middle class are more likely to be overweight. An example of the influence of the socio-economic status on obesity in developed countries is a study about prepubertal schoolchildren in northern Italy [22]: After adjustment for parents' age and area of birth the relative risk of obesity was 1.6 for mother's lowest educational level compared to the highest. For children whose father was unemployed the relative risk of obesity was 2.6.

In developed countries, urban children tend to be less obese than rural children. A study performed in the USA revealed that BMI and skinfold thickness was greater for children living in rural than in urban settings ($p < 0.004$) [23].

In contrast, in developing countries the urban upper class children are more likely to be obese than their peers living in rural areas [24, 25]. In Brazil, the increase of obesity prevalence in urban areas was more than twice as high as in rural areas [19]. In Thailand and in China, the prevalence of obesity was about three times higher in urban areas than in rural areas [26, 27]. In developing societies a strong direct relationship exists between socio-economic status and obesity in childhood [28]. This relation is particularly high in Latin American countries like Bolivia, Brazil, Colombia, Peru or El Salvador [24].

Interestingly, in Brazil the pattern of the prevalence of obesity is shifting to that in developed countries [29]. A substantial reduction (28%) in the prevalence of obesity among upper income urban women in Brazil was reported between 1989 and 1997. It was hypothesized that this may be already a result of an intense mass media work focused on combating a sedentary life style and promoting better food habits [30].

Childhood Obesity and Minorities in Different Populations

The prevalence of overweight and obesity in ethnic minorities has only been investigated in a few studies. Table 2 gives an overview on 4 studies on minorities in France, Germany and the USA.

Among children aged from birth to 4 years living the Paris area, the prevalence of obesity was higher in children of Maghrebian origin compared to French reference children in the 1970s and in the 1990s [6]. In the urban areas of England, several ethnic groups were compared in terms of weight for height [31, 32]: there was a clear trend of an increase in overweight in Indian children, whereas no such trend was detectable in white children and in Afro-Caribbean children.

In Germany, the frequency of obesity in 5- and 6-year-old non-German boys was 2.4 times higher than in their German peers. The respective ratio for girls was 1.9 times. Non-German children were also more likely to be overweight [3].

In the US National Longitudinal Survey of Youth (NLSY) an impressive increase of overweight in African-American and Hispanic adolescents has been observed. These data were adjusted for family income, child age, maternal age, sex, region of residence and urbanization status [7]. A cross-sectional study in San Antonio, Tex., revealed that the prevalence of obesity (BMI $>$ 95th percentile) was greater in Mexican-American (15–28%) and African-American (11–29%) boys and girls than in their white (7–17%) counterparts. The prevalence of overweight (BMI $>$ 85th percentile) was highest in Mexican-American boys (40–50%), Mexican-American girls (34–52%), and African-American girls (33–51%) [33].

Is the Increase in Childhood Obesity Due to a Shift of the Entire BMI Distribution or an Increase of the Upper Tale?

An increase of the prevalence of overweight and obesity, as reported above, can be either due to a shift of the whole BMI distribution or only part of it. If the entire distribution shifts, the 50th percentile (median) will shift as well. If only the upper percentiles of the distribution alter, i.e. fat children get fatter, the median is not affected.

Data from three German school entrance examinations 5 years apart [34] revealed only alterations of the skewness of the BMI distribution (fig. 1).

Table 2. Prevalence of overweight and obesity in minorities

Country and year	Definition criteria of overweight/obesity	Minority	Reference population	Age group years	Overweight*	Obesity*	Reference
France 1970, 1990	>97%	Maghrebian origin	French	4		1.33 (boys 1970) 2.67 (boys 1990) 4.0 (girls 1970) 6.0 (girls 1990)	[6]
Germany 1997	>90%/>97%	Non-German (Turkish, Albanian, …)	German	5–6	1.9 (boys) 1.5 (girls)	2.4 (boys) 1.9 (girls)	[3]
USA 1998	>85%/>95%	African-Americans (AA) Mexican-Americans (MA)	non-Hispanic whites	4–12	1.75 (AA) 1.77 (MA)		[7]
USA 1996	>85%/>95%	African-Americans (AA) Mexican-Americans (MA)	non-Hispanic whites	6–11	0.84 (AA boys) 1.31 (AA girls) 1.35 (MM boys) 1.41 (MA girls)	1.18 (AA boys) 2.06 (AA girls) 1.76 (MM boys) 1.81 (MA girls)	[33]

*Prevalence of overweight/obesity in minorities compared to the reference population.

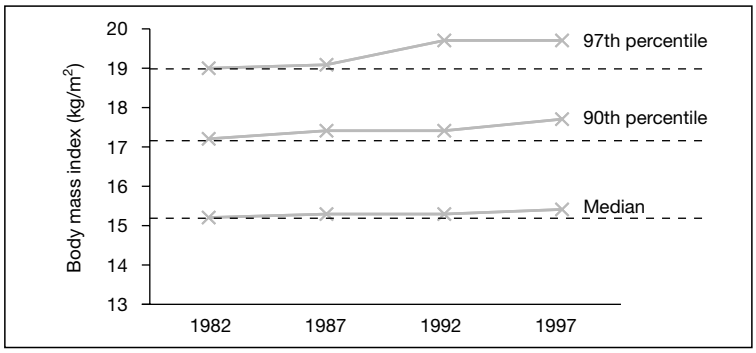

Fig. 1. Distribution of body mass index is shown in relation to time. Data were collected during four consecutive school entry examinations. The diagram for boys is randomly shown; the BMI distribution in girls gives the same characteristics.

The median of the BMI in 5- to 6-year-old boys and girls remained stable, whereas the 90th and 97th percentiles increased in both sexes. Of note, children of non-German origin, most of them progeny of Turkish immigrants, showed a different pattern: the median for the BMI increased as well.

In the US nationwide study NHANES III, the heaviest children were markedly heavier than in previous studies, whereas the rest of the BMI distribution showed little change [35]. The phenomenon of a high increase of the upper percentiles and a moderate increase of the median has also been observed in the Bogalusa Heart Study in Louisiana, USA, [4] in Spain [36] and in Denmark [37].

Essentials

- High *prevalence* rates of childhood obesity observed in developed countries are now increasingly found in developing countries, as well.
- The obesity risk groups in developed countries are the poor, rural children with low socio-economic status, whereas urban upper class children with Western life style belong to the risk groups in developing countries.
- In Western societies children of minorities and migrants are more likely to be obese.

Short- and Long-Term Impacts of Childhood Obesity

Does Obesity in Children Predict Obesity in Adults?

It has been shown that childhood obesity is predictive for obesity in adulthood. Data from the Minneapolis Children's Blood Pressure Study demonstrated that childhood weight and BMI at about 8 years of age were significantly

correlated with young adult weight, BMI, fasting insulin, lipids, and systolic blood pressure [38]. Multivariate analysis of data from the Canadian Trois-Rivieres semilongitudinal study of growth and development revealed that the BMI at an age of 12 years was the sole significant predictor of adult BMI [39]. The prediction of obesity was more precise in adolescence than in early childhood [40].

Whitaker et al. reported the following odds ratios for obesity in adulthood associated with childhood obesity [41]: 4.1 at 3–5 years, 10.3 at 6–9 years, and 20.3 at 15–17 years.

At first glance, these results look impressive. If we take a closer look at the authors' data and calculate sensitivity, specificity and positive predictive value (PPV) for obesity at the age of 6–9 years to predict obesity in adulthood – 43, 93 and 55%, respectively – these results are no longer that impressive: a sensitivity of less than 50% means that for less than 50% of obese adults obesity could be predicted by obesity at the age of 6–9 years.

Must et al. investigated, whether overweight in adolescents of age 13–18 was a good predictor for health problems in later ages and mortality. They found an association with an increased risk of mortality for all causes and disease-specific mortality among men, but not among women. The relative risks among men were 1.8 for mortality from all causes and 2.3 for mortality from coronary heart disease. The risk of morbidity from coronary heart disease and atherosclerosis was increased among men and women who had been overweight in adolescence. The risk of colorectal cancer was increased among men and the risk of arthritis was increased among women who had been overweight in adolescence. Interestingly, overweight in adolescence was a more powerful predictor of all the above mentioned risks than overweight in adulthood [42].

A case-control study performed in Maryland compared mortality of people in their middle ages with body mass in childhood (5–18 years). Odds ratios of mortality increased linearly with prepubertal relative weight ($p < 0.05$) [43].

Obesity-Related Problems in Children

Obesity-related morbidities have also been observed in children, though to a lesser extent than in adults. The insulin resistance syndrome has already been described for children of 5 years of age [44, 45]. In a study in Ohio [46] type 2 diabetes accounted for 33% of all cases of diabetes among African Americans and whites aged 10–19 years with a predominance of girls; most of them were obese, had a family history of type 2 diabetes, and belonged to minority populations.

Further comorbidities of adiposity in children are dyslipidemia, hypertension, chronic inflammatory status, hemostatic disorders, proteinuria, glomerulosclerosis, orthopedic problems like slipped capital femoral epiphysis,

and tibia vara (Blount's disease), and pulmonary problems [47–53]. A strong association of overweight and obesity with asthma was found in 5- and 6-year-old girls [54]. This finding is supported by other studies in adults and adolescents [55–58]. The excess in the prevalence of asthma in obese children is not related to an increase in atopic sensitization but rather a consequence of reduced airways calibers due to thickening of the chest wall because of fat deposition.

Obese children and adolescents are more likely to have problems to find a place in the society which matches with their abilities. Gortmaker et al. [59] performed a follow-up study on 370 obese persons aged 16–24. Seven years later, women who had been overweight had completed fewer years of school, were less likely to be married, had lower household incomes, and had higher rates of household poverty than the women who had not been overweight. Men who had been overweight were less likely to be married. These results were controlled for confounders like socio-economic origin and ability. An effect of overweight on self-esteem was not found. Similar results were obtained in a cross sectional study on draftees in Denmark. At each level of education and intelligence test score the obese subjects showed a significantly lower attainment of social class than the controls. Inclusion of parental social class did not eliminate the difference in attainment of social class [60]. Therefore, a low socio-economic status in obese persons is more likely to be the consequence than the cause of obesity.

Essentials

- Obesity in childhood is a moderate predictor for obesity in adulthood.
- Obesity may already account for morbidities in childhood and adolescence.
- Obesity may interfere with the attainment of a socio-economic status which matches the individual's abilities.

Risk Factor Epidemiology in Obesity Research – A Useful Approach to Understand the Causes of the Adiposity Epidemic?

Since the increase in body mass appears to affect only a part of the society, preventive measures should be targeted at the persons at risk. How can these be identified? Identification of risk factors is domain for epidemiologic research. For overweight and obesity many genetic and behavioral risk factors have been discussed. Obesity of the parents is a major risk factor for childhood obesity [61]. This can be transmitted either by genetic or by tradigenetic inheritance. The latter means adopting habits from parents by imitation.

Genetic versus Environmental Risk Factors

Twin, adoption, and family studies suggested a heritability of fat mass of about 40–70%. Stunkard et al. [62] studied the values for BMI of identical twins reared apart and found intrapair correlation coefficients of 0.70 for men and 0.66 for women. These values were only slightly lower than those for twins reared together. This finding reflects the importance of genetic influences (heritability) on the body-mass index.

About 30 Mendelian disorders associated with obesity have been reported like the syndromes of Prader-Willi-Labhart, Bardet-Biedl, Alstrom or Simpson-Golabi-Behmel. Single gene defects leading to obesity have been discovered like congenital leptin deficiency or leptin receptor deficiency. Further gene defects in the melanocortin system have been described (proopiomelanocortin, proconvertase 1, MC4R) [63]. These genes involved in weight gain do not directly cause obesity but they disrupt the normal controls of ingestive behavior (hyperphagia) leading to increased susceptibility to fat gain when exposed to a specific environment. Genetically defined conditions, however, do only explain obesity in few cases, mainly those with excessive obesity. The twin studies suggest, however, that there may be more genes involved in the etiology of overweight and obesity.

Since the genetic pool is unlikely to have changed within one generation, environmental factors are more likely to account for the adiposity epidemic. The so called 'toxic environment' is characterized by a sedentary life style (television, computers, etc.), limited physical activity (absence of safe playgrounds or parks in the cities), and an increase of high energy, poor quality processed foods and soft drinks, for which the consumption is aggressively promoted by the fast food industry. At the same time serving sizes rise and large meals are disproportionately cheap. Children consume less fruits, non-starchy vegetables, fiber, and micronutrients, because they are less readily available, certainly more expensive, and often less palatable [10].

Environment: Nutrition and Physical Activity

A cohort study in the USA revealed a higher increase in BMI for preadolescents who reported higher caloric intakes and less physical activity. Although the estimated effects were small, their cumulative effects over years could produce substantial gain in body weight [64]. A French cross-sectional study on 10-year-old children [65] revealed that active ingested significantly more energy than less active children, which was accounted for by increased consumption of carbohydrates. The amounts of fat and protein consumed were similar in both groups. In spite of a higher energy intake in the active group, active and less active children had similar BMIs. However, their body composition differed significantly: less active children had a lower proportion of fat-free mass and a higher proportion of fat mass.

The assumption that overweight is caused by an imbalance of energy uptake and expenditure is obvious. Therefore it is reasonable to suspect that the epidemic of overweight is related to a change in caloric intake and physical activity.

Changes in Diet over Time

Total Caloric and Fat Intakes in Different Populations

Data from the United States Department of Agriculture on dietary intake of individuals of 11–18 years of age revealed a considerable shift in the adolescent diet from 1965 to 1996: Total energy intake decreased as did the proportion of energy from total fat (39–32%) and saturated fat (15–12%). Concurrent increases occurred in the consumption of higher fat potatoes and mixed dishes (e.g. pizza). Lower fat milk products replaced higher fat milk products and the total milk consumption decreased. This decrease was accompanied by an increase in consumption of non-citrus juices and soft drinks [66]. Data from the third National Health and Nutrition Examination Survey (1988–1994) and earlier national surveys in the USA also failed to show an increase of the mean energy intake from the 1970s to 1988–1994 except for an increase among adolescent females. Over the same time period, the mean percentage of energy from total and saturated fat decreased, but remained above recommendations, with overall means of 33.5% of energy from fat and 12.2% of energy from saturated fat [67].

The German DONALD study (Dortmund Nutritional and Anthropometric Longitudinally Designed study) revealed no significant changes in intakes of energy and of protein, polyunsaturated fatty acids and added sugars in 2- to 18-year-old subjects between 1985 and 2000. Fat intake decreased significantly in all age groups, as well as intake of saturated fatty acids and monounsaturated fatty acids. This decline was compensated by a significant increase in carbohydrate intake. The changes in macronutrient intake were mainly due to a decreased consumption of fat, oil, meat, fish and eggs, whereas consumption of bread, cereals, potatoes, pasta and rice increased slightly. Despite these improvements in the diet, the fat intake and fatty acid composition were still higher than recommended [68].

In contrast, a nationwide nutritional survey conducted 1984 in Spain demonstrated that the average nationwide fat intake was 42% of energy. In the 1990s, some surveys were conducted at a regional or local level. Children aged 6–10 years had a total fat intake ranged from 38 to 48% of energy. In children aged 11–14 years the total fat intake ranged from 41 to 51% of energy. This reflects an increasing total fat consumption in children in Spain, especially of saturated and monounsaturated fat.

Brazil as a rapidly developing country is of particular interest in this context: A family budget survey carried out in 1996 in Brazil provides data on

the secular trends of dietary patterns of the Brazilian population living in metropolitan areas since 1962. The survey revealed an increase in the diet's lipid content in less-developed regions and of saturated fat in the country as a whole. A reduction of foods with a high total lipid content was found only in more developed regions. These changes may indicate a growing awareness of this population toward a healthier diet. But still a further increase in the excessive sugar consumption was observed, associated with a decrease or even no consumption of beans, vegetables, fruits and complex carbohydrates [69].

Intake of Carbohydrates and Other Changes in Eating Habits

According to data from the third National Health and Nutrition Examination Survey (1988–1994) in the USA, beverages contributed 20–24% of energy across all ages of childhood and adolescence and soft drinks provided 8% of energy in adolescents. Beverage energy contributions and especially soft drink energy contribution were higher among overweight than non overweight adolescents [67]. Data from the 1994 Continuing Survey of Food Intakes by Individuals showed that energy intake was positively associated with consumption of non-diet soft drinks. The mean energy intake was 10% higher for school-aged children who consumed soft drinks compared to those who did not [70]. Similarly, an increase of the contribution of added sugar in soft drinks to the energy intake was reported in Brazil [69].

The consumption of sugar-sweetened drinks may increase the risk for obesity in children. A prospective study on 12-year-old children in Massachusetts demonstrated that baseline consumption of sugar-sweetened drinks was associated with an increase in BMI, which could not be explained by anthropometric, demographic, dietary, and other lifestyle variables [71].

Changing eating habits are another issue: children take fewer meals at home. This is accompanied by less healthy dietary intake patterns, including less fruits and vegetables, more fried food and soft drinks, more saturated fat and a higher glycemic load [72].

Despite a general decrease of energy intake and a shift from consumption of fat to carbohydrates, there is an increase of ingestion of energy dense food [73] and added sweeteners, especially by consumption of soft drinks, which account for one third of intake of added sweeteners in the USA [74]. This shift in nutrition behavior towards high glycemic index meals could partially be responsible for the development of obesity in the respective risk groups in the USA [75].

The high intake of sugar from soft drinks may not have reached Europe yet. The German DONALD study did not reveal any significant changes in intakes of carbohydrates from beverages, though the total beverage consumption increased, but mainly due to an increased consumption of tap water,

mineral water and fruit juice whereas there was no increase in the consumption of sugar sweetened soft drinks [68].

Sedentary Lifestyle

Another import issue of behavior pertinent to obesity is a sedentary life style. Recreational inactivity like watching TV and computer games were associated with an increase of BMI in children of 9–14 years of age. In girls, less physical activity was linked to an increase of BMI [64]. A study in German preschool children revealed that the risk of overweight increased by 70%, when electronic media were consumed 2 h and more per day. The prevalence of daily consumption of electronic media (TV or electronic games) was 75% in this age class [76].

It is not easy to disentangle, whether the reduction of physical activity in obese children is cause or consequence of their adiposity. The egg might be the chicken: less activity leads to less energy expenditure, which aggravates the imbalance between energy intake and spending, finally causing obesity. On the other hand, obese children may avoid physical activity, since it causes discomfort. In an interventional randomized study in Californian primary school children, reduction of television, videotape consumption and videogames led to significant relative decreases in body mass index ($p = 0.002$) and triceps skinfold thickness ($p = 0.002$). Compared to controls, children in the intervention group spent significantly less time watching television and had fewer meals in front of the television [77]. These convincing data show that little physical activity is likely to cause obesity [77, 78].

Further Suspected Risk Factors

There are some recent data suggesting an increased adiposity risk for maternal smoking during pregnancy, whereas breastfeeding appears to be protective. Whether these protective or risk factors can explain the epidemic, remains to be established.

Smoking during Pregnancy

Smoking during pregnancy may increase the risk of obesity through programming, resulting in lifelong metabolic dysregulation, possibly due to fetal malnutrition or toxicity. Following data from the British National Child Development Study (NCDS), the adjusted odds ratios (and 95% confidence intervals) for obesity associated with maternal smoking during pregnancy were 1.34 (1.07 to 1.69), 1.35 (0.95 to 1.92), and 1.38 (1.06 to 1.79), with a statistically significant trend ($p = 0.003$) for medium, variable, and heavy smokers, respectively. Of note, non-diabetic cohort members who smoked at age 16 did not have an increased risk of obesity [79]. Similar results were obtained in a different analysis of the same data set [80].

Data from German school entry health examinations [81] show the same association of maternal smoking before or throughout pregnancy with obesity of the child. The highest prevalence of overweight and obesity was observed in children of mothers who had smoked throughout pregnancy. In children whose mothers claimed to have abandoned smoking in pregnancy, however, the prevalence of overweight and obesity was only slightly lower. This contrasts with the prevalence in children of mothers who had taken up smoking after pregnancy only, which was similar to that in children of non-smoking mothers [82]. Long-term effects of nicotine exposure on neurobehavioral impulse control has been shown in animal models and human studies [83–85]. Since smoking in women of childbearing age has increased during the last decades, smoking during pregnancy might contribute to the causes accounting for the present epidemic of adiposity in children.

Formula Feeding

Several studies indicated that breast-feeding has a positive effect on regulation of food intake in childhood. This seems to work on a behavioral level as well as by metabolic effects. In a study performed in two German cities, breast-fed children were substantially less likely to be overweight at 9–10 years (OR 0.66, 95% CI 0.52–0.87) after adjustment for age, sex, region, nationality, socio-economic status, number of siblings, parental smoking [86]. Further data have been generated in a Scottish and another German study that strengthen the hypothesis [87, 88].

Also, in children in the Czech Republic the overall prevalence of overweight/obesity was lower in breast-fed children: ever breast-fed (9.3/3.2%) compared with never breast-fed (12.4/4.4%). The effect of breast-feeding on overweight/obesity did not diminish with age in children 6–14 years old and could not be explained by parental education, parental obesity, maternal smoking, high birth weight, watching television, number of siblings, and physical activity. Adjusted odds ratios for breast-feeding were for overweight 0.80 (95% CI, 0.71–0.90) and for obesity 0.80 (95% CI, 0.66–0.96) [89].

Essentials

- Twin studies underline the importance of genetic factors for the etiology of obesity.
- The so far identified genetic entities of excessive obesity account for only a minority of cases of obese children. Behavioral changes are more likely to be responsible for the epidemic dimension of the obesity issue.
- Changes in the average nutritional intake with a decrease in the fat and energy intake and an increase of soft drink consumption do not provide a plausible explanation for the obesity epidemic.

- The increase in consumption of electronic media and the decrease in physical activity in children, the key elements of a sedentary life style, might contribute to the causes of the obesity epidemic.
- The increased prevalence of smoking of women in childbearing age might contribute to the causes of the epidemic of childhood adiposity.

Limitations of Epidemiology Research to Provide an Understanding of the Etiology of the Adiposity Epidemic in Children

Temporal changes in the prevalence of different diseases and potentially causal risk factors are usually moderate. Epidemiology provides the tools to measure the prevalence of childhood obesity and of potentially causal risk factors. Some of the limitations of these data are inherent to the type of study used.

Types of Epidemiological Studies

This section describes different study types applied in epidemiology research (table 3). A first approach to population specific issues is surveys. These are designed to assess the prevalence of diseases or their occurrence. The latter is usually called incidence rate. If such prevalence or incidence data are plotted over time and compared to the changes in other observations (exposures) over the same time period, this is conventionally called a correlation or ecological study. Such ecologic studies offer the opportunity to look for associations of exposure and disease on a collective level, e.g. differences in the prevalence rates of obesity and ownership of TV sets between countries or over time. No information can be obtained on an individual level. A simultaneous increase of the prevalence of overweight and the number of TV sets does not necessarily mean that overweight individuals have a TV set. As populations are only considered as a whole, adjustment for confounders (see below) is not possible.

The major part of analytical epidemiological studies in obesity research is cross-sectional studies. These studies include all subjects of a population at a certain time point (or small time interval) and they have etiologic objectives [90], e.g. to assess the association of socio-economic status and obesity. Classical cross-sectional studies on adiposity are the study of Sonne-Holm and Sorensen [60] on draftees in Denmark and their socio-economic status or the investigation of Park on obesity in minorities [33]. As they measure exposure and disease at the same time point, it is not always evident that exposure precedes the outcome. The chicken-egg question may not be an issue for genuine

Table 3. Synopsis of epidemiological study types

Type of study	Characteristics	Useful to
Ecologic or correlational study	• populations as observational units • no information on associations on an individual level • measurement of distribution of exposure and disease	• generate hypotheses
Cross-sectional study	• simultaneous ascertainment of disease status at a given time point and present or former exposure • documentation of present prevalence	• test hypotheses
Longitudinal or cohort study	• prospective evaluation of the effect of exposure on disease • can estimate risks • strength for common outcomes	• test hypotheses
Case-control study	• starts with cases, then respective controls are identified • retrospective analysis of exposure • investigation of rare diseases • several exposures can be examined	• test hypotheses
Interventional trial	• exposition assigned at random • follow-up of study participants	• gold standard for causal inference

traits of the persons studied such as genotypes whereas, for example, eating habits may have been changed in order to treat or prevent obesity.

Cohort studies ascertain the exposure first and then determine the outcome – usually over long time periods. Cohort studies, also called longitudinal studies, are costly and time consuming as they have to follow-up individuals over decennial periods, and there is always an important loss of study participants due to mobility or lack of interest. Bias may result as a consequence of losses to follow-up related to either the exposure or outcome of interest. Such cohort studies might help to assess the influence of childhood obesity on the development of coronary heart disease in adulthood.

Case-control studies are similar to cross-sectional studies in ascertaining exposure and outcome at the same time point. The difference is that they start with the cases and try to identify adequate controls to reflect the exposure the cases would have had if they had not become cases.

Neither cross-sectional nor case control nor longitudinal studies, however, can establish causality, since all of these studies are prone to bias. Well designed and performed interventional studies are the only studies that can prove causality.

The already mentioned study on restriction of television viewing and its impact on childhood obesity is a good example of how causality may be established by an interventional study [77]. Such experimental studies may be designed as field trials, community intervention trials or clinical trials.

Problems in the Assessment of Risk Factors for Obesity in Children

Johnson-Down et al. [91] described that the reported food intakes of overweight children did not meet calculated energy needs. There are different possible explanations for this unexpected finding: One explanation could be that the study participants were on a therapeutic diet. This would be an error due to confusion of chicken and egg. Another explanation could be that study participants did not report their actual eating habits correctly, but told the interviewers what they were supposed to do: eat less. This would be an example of intentional and selective misclassification of the diet resulting in underreporting.

With few exceptions it is impossible to investigate all members of a population, but information on the entire population is desired. So a representative selection of individuals has to be made under the option of generalizability. Thus, during the recruitment of study participants selection biases can occur. This may be due to refusal to participate, or selection of particular study populations like health professionals, or by self-selection, i.e. patients or parents who are more aware of certain health problems for whatever reasons refer themselves to voluntary studies. In a questionnaire study on breastfeeding and childhood obesity breastfeeding mothers of non-obese children might preferentially participate, e.g. to prove the virtue of breastfeeding. This would result in selection bias.

When the effect of a certain exposure is distorted by an unapparent exogenous factor, this is called confounding. Confounding can lead to over- or underestimation of an effect or even alter the direction of an effect [90]. Confounding was a major issue in the assessment of the impact of maternal smoking in pregnancy on childhood obesity. Maternal smoking in pregnancy is associated with a number of known and potentially unknown risk factors for childhood obesity. If information on known risk factors is collected, adjustment is possible in the analysis [82]. For unknown confounders such an adjustment is not possible, however, accounting for spurious results caused by residual confounding.

Well-designed epidemiological studies, however, may provide clues for the understanding of the causes of obesity in individuals and populations. At the present, the etiology of the adiposity epidemic is not yet understood. Thus, potential causes and the course of the epidemic should be kept under surveillance. This opens the field to intensive epidemiologic research.

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Obesity Research and the Physiology of Energy Homeostasis

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Obesity

The rapid increase in the prevalence of obesity, type 2 diabetes, and associated complications is now becoming a major global health problem. In 2001 almost 65% of the adult population in the United States was overweight (defined as having a body mass index (BMI) greater than 25 kg/m^2), compared to 56% seen in 1994 (National Health and Nutrition examination Survey: NHANES). Even the prevalence of obesity in children and adolescents rose from 11 to 15% during this time. If weight gain continues at the present rate, the obesity rate in 2008 will be 39% in the US. Since worldwide, more than one billion adults are overweight and over 300 million are obese, the World Health Organization (WHO) has declared overweight as one of the top five risk conditions in developed nations. Severe obesity defined as having a BMI of >40 kg/m^2 is associated with a 90% risk of diabetes (in the USA, 1 in 5 adults shows a pathologically decreased insulin sensitivity) making obesity the predominant cause of type 2 diabetes. Obesity is strongly linked to chronic diseases such as cardiovascular disease or some types of cancer, and is associated with increased prevalence of psychological disorders, such as depression [1–8].

To successfully fight obesity, we must analyze why dieting is not effective. The brain interprets energy restriction as a threat to survival, especially once a chronically overweight state has been established. To maintain body composition and defend achieved energy stores, neuroendocrine networks reduce energy utilization in response to decreased caloric intake. Subjects feel cold, lethargic

and depressed, and are facing a strong orexigenic drive to that it is ultimately impossible difficult to resist. To cure obesity, researchers must find a way to chronically adjust the control of body composition and metabolic homeostasis based on a 'blue-print' of regulatory pathways regulating energy balance that includes their individual functional relevance as well as their connectivity and interaction patterns. Some of these are active in the periphery exclusively, meaning that they have no apparent effect onto the central regulation of energy homeostasis. These include the role of several transcription factors in peripheral tissues including white fat, liver and skeletal muscle. Conversely, the observation that the brain plays a critical role in the control of energy homeostasis may be explained by the fact that balancing energy metabolism represents a physiological process with an evolutionary essential character. Central nervous circuits sense and integrate peripheral metabolic, endocrine and neuronal signals reflecting current energy status, to then orchestrate a modulating influence on both behavioral patterns and peripheral metabolic processes according to acute and chronic requirements [9, 10].

Diabetes mellitus

Diabetes mellitus is a disease closely linked to obesity. While type 1 diabetes is caused by a deficiency of insulin producing beta-cells due to autoimmunity and independent of obesity, the more prevalent type 2 diabetes is directly related to overweight in humans and rodents. Type 2 diabetes affects at least 6% of the population of westernized countries, while possibly up to half of the affected individuals are currently undiagnosed. Diabetes is the seventh leading cause of death according to the US CDC's National Center for Health Statistics, and is the leading cause of kidney failure, blindness, and amputation in adults. As for obesity the prevalence of type 2 diabetes increases with age: While there is increasing prevalence of juvenile type 2 diabetes, more than 18% of individuals 65 years or older are suffering from diabetes. While obesity is not essential for the development of obesity, and obesity does not automatically leads to diabetes, there is no doubt about the fact the an increase in bodyweight dramatically increases the incidence of diabetes: dependent on the increase of bodyweight an up to 40-fold increased risk for type 2 diabetes is observed. Since type 2 diabetes is caused by a combination of insufficiency of the pancreatic beta-cell to secrete appropriate amounts of insulin and a decreased efficiency of insulin to promote glucose uptake and metabolism in peripheral tissues like skeletal muscle and white fat, to figure out the causative role of obesity on these pathogenetic sequelae is one of the main focuses of current diabetes research [11, 12].

Signals from the Periphery to the Brain

Afferent inputs to the brain with relevance for energy homeostasis include external (visual, olfactory, auditory, tactile) as well as internal stimuli generated by food after its ingestion (pregastric, gastric, postgastric) and postabsorptive stimuli such as those generated by mucosal nutrient transport mechanisms and the associated release of local hormones (e.g. CCK) acting through the circulation or on visceral sensory nerves. Other postabsorptive signals are nutrients, metabolites and hormones acting on sensors in the portal hepatic space (e.g. glucose) or directly on hepatic sensors (e.g. glucagon), as well as metabolites, hormones and other factors originating from various tissues, circulating in the blood or lymph and activating corresponding sensors directly in the brain (glucose, amino acids and leptin). Another way of differentiating afferent signals refers to their abilities to induce a positive or negative energy balance. The gastrointestinal hormone ghrelin for example induces a positive energy balance, while numerous other peripheral hormones such as cholecystokinin (CCK) are known to promote a negative energy balance. Thirdly, insulin should be considered a main coordinator of the crosstalk between periphery and central sensors. Its function as a double-edged sword serves to store nutrient-derived energy as fat and glycogen on the one hand. On the other hand excess insulin, as specifically observed in early type 2 (pre-)diabetes causes hunger both directly as well as via induction of hypoglycemia, which subsequently causes the appropriate neuroendocrine response, i.e. food uptake for elevation of blood glucose.

Endocrine signals reflecting metabolic state arise from several peripheral organs such as the thyroid, the adrenals, the reproductive tissue, the fat tissue and gastrointestinal organs. Being secreted according to the current status of metabolism and energy homeostasis, these hormones convey information to multiple specific areas in the brain. Among the more relevant of these signals, is the gastrointestinal hormone CCK, which was first discovered in 1973. Peripherally released CCK acts centrally to trigger satiety and to initiate a negative energy balance via pathways predominantly localized in the brainstem. CCK is thought to have a physiological role in regulating meal termination and has long been mistaken as the crucial missing factor in the ob/ob mouse. The ob/ob mouse phenotype results from a spontaneous mutation, which was speculated long before its identification to be caused by the lack of a peripheral signal informing the brain about existing energy stores. Although the molecular technology was lacking to isolate the responsible gene or its product, brilliant parabiosis experiments performed by Coleman and coworkers, connecting the circulation of ob/ob mice with that of their genetically normal littermates, yielded the proof of this concept. Positional cloning of the *ob* gene finally led

to the discovery of the proteohormone leptin, which is predominantly produced by adipose cells according to the size of fat stores. Administration of leptin induces a negative energy balance that is mediated by specific neuronal structures in the hypothalamus and the brainstem. Leptin's role in signaling the brain about chronic changes in energy status is completed by insulin conveying additional information about long-term changes of peripheral metabolism to the brain. Centrally administered insulin causes a negative energy balance, while neuron-specific deletion of its receptor is causing obesity. Along with these signals, which are most likely contributing to chronic energy balance regulation, hormones reflecting caloric intake and acute nutritional requirements complete the information flow to the brain. One of these factors, $PYY_{(3–36)}$, a gastrointestinal hormone which is secreted in response to ingestion of food and is thought to act via hypothalamic Y2 receptors, has recently been reported to acutely induce a negative energy balance response to ingestion of a meal. The only known peripherally secreted orexigenic hormone, the gastro-enteric peptide ghrelin, counterbalances energy homeostasis in opposition and completion to the multiple anorectic signals described above. Ghrelin, which induces a positive energy balance predominantly at the same neuronal structures where leptin and $PYY_{(3-36)}$ exert their action, triggers an increased in fat mass in rodents and at the least stimulates hunger in humans. Since ghrelin is secreted in response to caloric restriction and its expression and secretion are rapidly suppressed by food intake, a physiological role in meal initiation as the endogenous 'hunger hormone' has been proposed. A large number of other gastrointestinal hormones and adipokines have been identified as afferent signals being involved in energy balance regulation, but either their exact mechanism of action is not yet understood or their physiological role remains unclear. Intestinal glucagon-like peptide 1 (GLP-1) decreases appetite and food intake in rodents, deletion of receptors for glucose dependant insulinotropic polypeptide (GIP) protects against obesity, while the fat-cell derived interleukin 6 is a cytokine that centrally induces a negative energy balance. The classical endocrine axis, especially the hypothalamic-pituitary-adrenal (HPA), the hypothalamic-pituitary-thyroid (HPT) and the growth hormone/IGF-1 axis, although being largely neglected as afferent signals of acute and chronic energy balance to the brain, certainly also play an important role in the complex networks governing appetite and body weight. Central administration of corticosteroids for example induces appetite and increases fat mass. While the negative energy balance induced by thyroid hormones is mainly attributed to their multiple peripheral effects, T4 as well as T3 receptors are also localized in the brain, where they serve as crucial feedback targets and allow for direct modulation of circuits regulating energy balance. Comparable feedback principles exists for hormones of the somatotropic axis such as growth hormone and IGF-1, which

represent well established determinants of body composition. Apart from these and other hormones, essential metabolic substrates add to the integrated signal emerging from the periphery: glucose and free fatty acids directly inform centrally located sensors about the current state of carbohydrate and lipid metabolism.

But not only endocrine factors and circulating metabolites provide afferent information for central circuits controlling energy balance. Satiety information generated during the course of a meal is largely conveyed to the brainstem by means of afferent fibers of the vagus nerve and by afferents passing from the spinal cord from the upper gastrointestinal tract. This information converges in the nucleus tractus solitarius (NTS) an area in the caudal brainstem that integrates sensory information from the gastrointestinal tract and abdominal viscera, as well as taste information from the oral cavity [13–20].

Signals from the Brain to the Periphery

In parallel to time-resolved integration of the multiple afferent signals conveying at central circuits regulating energy balance, these neuroendocrine networks have to simultaneously orchestrate an appropriate efferent response. While it is clear that these efferent signals, such as hormonal, behavioral, parasympathetic and sympathetic output from the brain to the periphery, are inducing changes in energy expenditure, it is still unclear how appetite induction is triggered by hypothalamic circuits involving the arcuate nucleus and other hypothalamic centers of feeding control.

The autonomic and enteric nervous systems, and the hypothalamic-pituitary-endocrine axes significantly modulate gastrointestinal handling and metabolic processing of food as well as the partitioning and oxidation of metabolites, and thus codetermine the efferent side of the regulatory loop. Behavioral changes expressed through the skeletal motor system (e.g. decreased spontaneous locomotor activity, fidgeting) are one way to maintain or restore energy homeostasis. In addition, temporary deficits can be rapidly restored by increased absorption from the gastrointestinal tract, mobilization from stores, or changes in utilization rates. An important efferent determinant of energy balance is the vagal parasympathetic outflow. Neurons involved in parasympathetic outflow of central and peripheral circuits regulating energy balance are connected with a large number of nuclei and neurons in forebrain, midbrain, caudal medulla, hypothalamus, and dorsal vagal complex, and receive viscero-sensory input via the solitary nucleus as well as endocrine input via the are postrema. Vagal-parasympathetic outflow directly modulates several physiological parameters such as pancreatic secretion, hepatic glycogenesis, salivation, gastric emptying,

intestinal absorption and gastrointestinal hormone secretion, to just name a few mechanisms involved in energy balance regulation. Sympathetic outflow regulating energy balance receives neuronal input from the hypothalamus, frontal cortex, amygdala, midbrain, caudal medulla and directly influences energy homeostasis via targeting brown as well as white adipose tissue, adrenal medulla, skeletal muscle, hepatocyte, pancreatic alpha- as well as beta-cells or skin vasomotor tone.

The classical endocrine axes consisting of hypothalamic releasing hormones, pituitary hormones and peripheral endocrine signals are heavily involved in maintaining the balance of metabolism and energy homeostasis. Hypothalamic releasing hormone (TRH, CRH, GHRH, LHRH, Ghrelin) expression is influenced by activity levels of hypothalamic circuitry known to be crucially involved in central energy balance regulation (e.g. NPY/AGRP-neurons, POMC/CART neurons). Central activation of the hypothalamic-pituitary-adrenal (HPA) axis induces a positive energy balance, while stimulation of the hypothalamic-pituitary-thyroid (HPT) axis produces energy deficits via an increased metabolic rate. The growth hormone (GH) – insulin-like-growth factor I (IGF-1) axis (also called somatotropic axis) promotes lipolysis and muscle growth. Stimulation of the hypothalamic-pituitary-sex hormone axis (gonadotropic axis) causes a negative energy balance via increased fat oxidation and decreased food intake in women (estrogens) and promotes an increased ratio of muscle tissue vs. fat tissue in men (androgens). All these efferent systems described above are usually modulated in concert to achieve the appropriate adaptational metabolic changes as based on information received by a panel of afferent signals and processed by specific neuronal circuitry in the brain. The central networks that are regulating energy homeostasis by balancing endocrine and neuronal efferences with afferent signals indicating energy requirements, also have to adjust to unusual environmental challenges and disease states which might require drastic changes in orexigenic drive or metabolic efficiency. While the respective adjustments of the neuroendocrine networks governing energy balance will mostly reflect an appropriate attempt to counterbalance pathophysiological situation, in many cases these reactive changes will not suffice to re-establish energy homeostasis (i.e. cancer cachexia, diet-induced obesity). To understand how the *human* central nervous system functions to control and adjust appetite, energy expenditure and body composition in health and disease, researchers are facing multiple difficulties. Firstly, in vivo imaging techniques such as positron emission tomography (PET scan) or functional magnetic resonance (FMRI) imaging of the human brain can not yet provide information that is detailed enough to detect, e.g. relevant changes of blood flow in specific hypothalamic nuclei. Secondly, rodent brains are not identical with human brains, although pathology studies

reveal to a surprisingly large extent similar neuronal modalities when comparing mouse, rat and human brains. NPY neurons for example exhibit a different distribution pattern in mice as compared to humans. However, for most neuronal structures involved, primate studies confirm findings from rodents and monogenetic causes of obesity first described in mice or rats (such as ob/ob mutations causing leptin deficiency and therefore morbid obesity) have been confirmed in humans [14–22].

Rodent Models

The analysis of targets and pathways leading to or preventing from obesity is a complicated task, since almost all known naturally occurring models of obesity in rodents may affect several pathways and tissues, hence are not particularly useful to dissect peripheral targets from brain-driven phenomena. Therefore, researchers have been creating genetically modified rodent models to circumvent these problems. Genetic modifications have the unambiguous advantage that they can be restricted to defined cell types by the use of tissue specific promoters. For example, the promoter of the UCP1 gene has been used to direct expression restricted to brown fat cells, the aP2-promoter for white adipocytes, the albumin promoter for liver-specific expression, the muscle creatine kinase promoter for expression restricted to skeletal muscle and heart, etc. Employing this approach researcher were enabled to introduce novel genes into tissue where they normally to not occur, or the expression levels of genes were elevated (so-called overexpression) within any tissue of interest to obesity research. Shortly afterwards, techniques were invented to disrupt the expression of a given gene in mice. This so-called knock-out technique is a versatile tool to inactivate candidate genes which might contribute to obesity in both mice and men. While the first-generation knock-outs were equally affecting any cell within the rodent body, subsequently developed techniques gave rise to the option to disrupt gene expression in defined tissues (as for overexpression, see above). To obtain such a tissue specificity parts of the gene of interest were genomically flanked with so-called loxP sites, essentially recognition sequences for a highly specific restriction enzyme called cre recombinase. While mice carrying the loxP sites only are indistinguishable from their genetically unaltered littermates, and show unaffected expression levels of the flanked gene, they lose the expression of the targeted gene when intercrossed with mice transgenically overexpressing cre recombinase in a tissue specific manner. Using this approach, cre recombinase can be expressed under the control of the promoter listed above (and many others) and directs a tissue specific knock-out of any loxP flanked gene. Lastly, recent techniques additionally

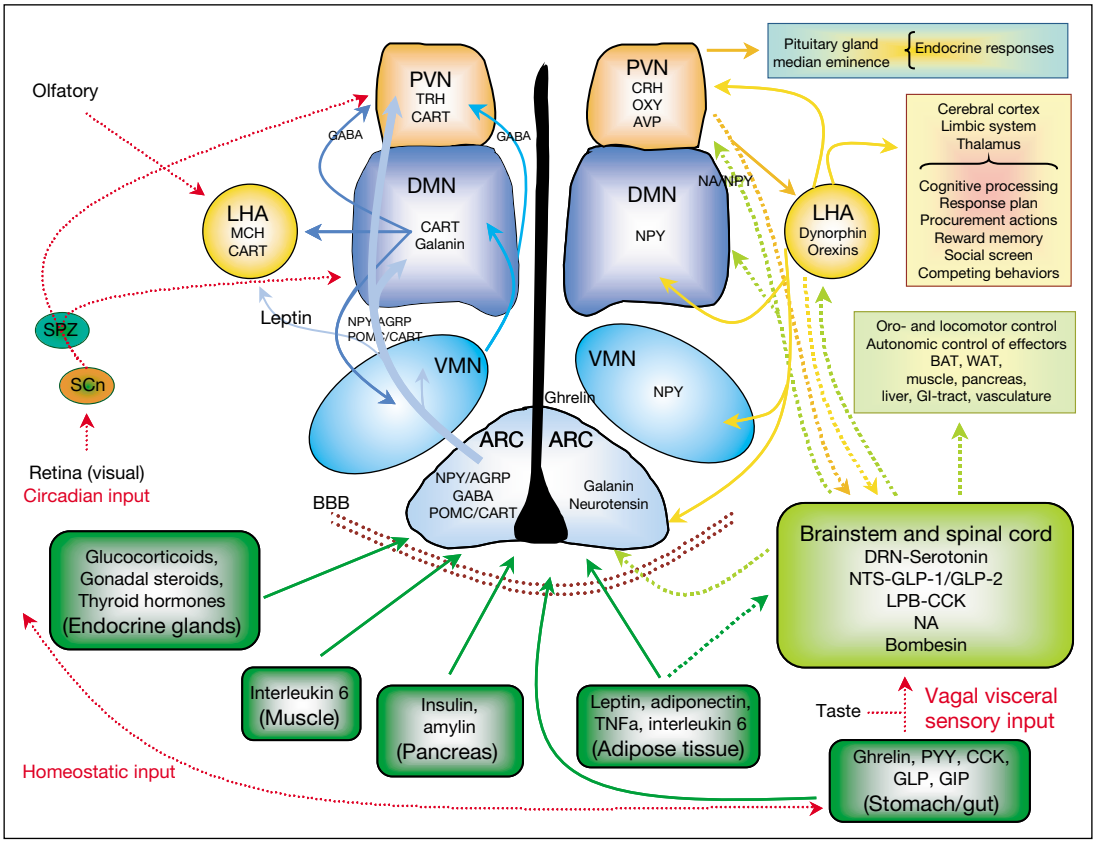

Fig. 1. Signals, ligands, peripheral organs and brain areas involved in the regulation of energy balance are shown in this simplified schematic overview. Peripheral factors and hormones from the adrenal glands, gonadal tissue, thyroid glands, muscle tissue, pancreas, adipose tissue, stomach, gut and other peripheral organs are constantly signaling to the central circuits about acute and chronic energy balance and metabolic homeostasis. Areas in the brain which have been identified as very likely to be involved in the central processing of this afferent information as well as in the continuous adjustment of an appropriate efferent response are the nucleus of the solitary tract (NTS), the lateral parabrachial nucleus (LPB) and other areas in the brainstem region as well as the arcuate nucleus (ARC), the ventro-medial hypothalamus (VMH), the dorso-medial hypothalamus (DMH), the paraventricular nucleus (PVN) and the lateral hypothalamus (LH). Communication between these neuronal circuits relies on the generation and release of neurotransmitters and neuropeptides some which are currently regarded as likely to be involved in energy balance control. While expression of the potently orexigenic agouti-related protein (AGRP) is strictly limited to the ARC, the similarly strong appetite-promoting neuropeptide Y (NPY) is expressed in numerous of the brain areas involved in the regulation of body weight. The exact anatomical and functional blueprint of the projections between these agents and other neuropeptides and

allow the disruption of genes at a defined time point: While the non-conditional as well as the tissue specific knock-out is activated as soon as the promoter becomes switched on during embryonic development, certain hypothesis require the inactivation of genes in a later stage of development. To obtain this goal, the transgenically overexpressed cre recombinase was fused to mutants of ligand-binding domains (LBD) of steroid receptors. While this fusion protein is readily expressed in any cell activating the preceding promoter, in stays in the cytosol, i.e. does not exert its action as a restriction enzyme since chromosomal DNA is located within the nucleus and cannot be reached by the recombinase. To obtain a knock-out event in such animals these are injected with a artificial steroid hormone derivative which specifically enables cytosolic cre recombinase to move into the nucleus where it finally causes chromosomal recombination, i.e. a knock-out event. Employing this technique disruption of genes can be obtained in both, spatially and temporally restricted, fashion. Taken together, these techniques have been of tremendous impact for the dissection of pathways leading to or preventing from obesity [23–25].

The analysis of central neuroendocrine pathways controlling energy homeostasis, mainly based on neuroanatomy and molecular genetic approaches, aims to elucidate how communication networks involving humoral factors, neuropeptides and neuronal circuitry including synapses and neurotransmitters, regulate acute and chronic supply, metabolism and storage of energy (fig. 1, 2). Functional relevance of the putatively involved pathways and factors, however, can only be proven, if equally sophisticated methods are used to detect and analyze in vivo changes in caloric intake, energy expenditure or body composition. To achieve that goal, animal models (specifically rodent models) relevant for the (patho-)physiology of (disease)states defined by (impaired)energy balance, have to be employed.

The best animal model for a disease is one that closely represents most or all of its pathophysiological characteristics. Animal models available for obesity research differ widely in food intake, metabolism, presence of diabetes or insulin resistance, and the extent of obesity presented. Energy balance is the match of energy intake to energy expenditure. Energy intake (EI) can be

neurotransmitters regulating energy homeostasis such as cocaine amphetamine-regulated transcript (CART), melanin-concentrating hormone (MCH), thyroid hormone-releasing hormone (TRH), corticotropin-releasing hormone (CRH), oxytocin (OXY) or vasopressin (AVP) still remains at large. Even less known is the role of the visual, olfactory or circadian input to just name a few which might in part be mediated through specific neuronal circuits in brain areas such as the suprachiasmatic nucleus (SCn) or the supraventicular zone (SPZ).

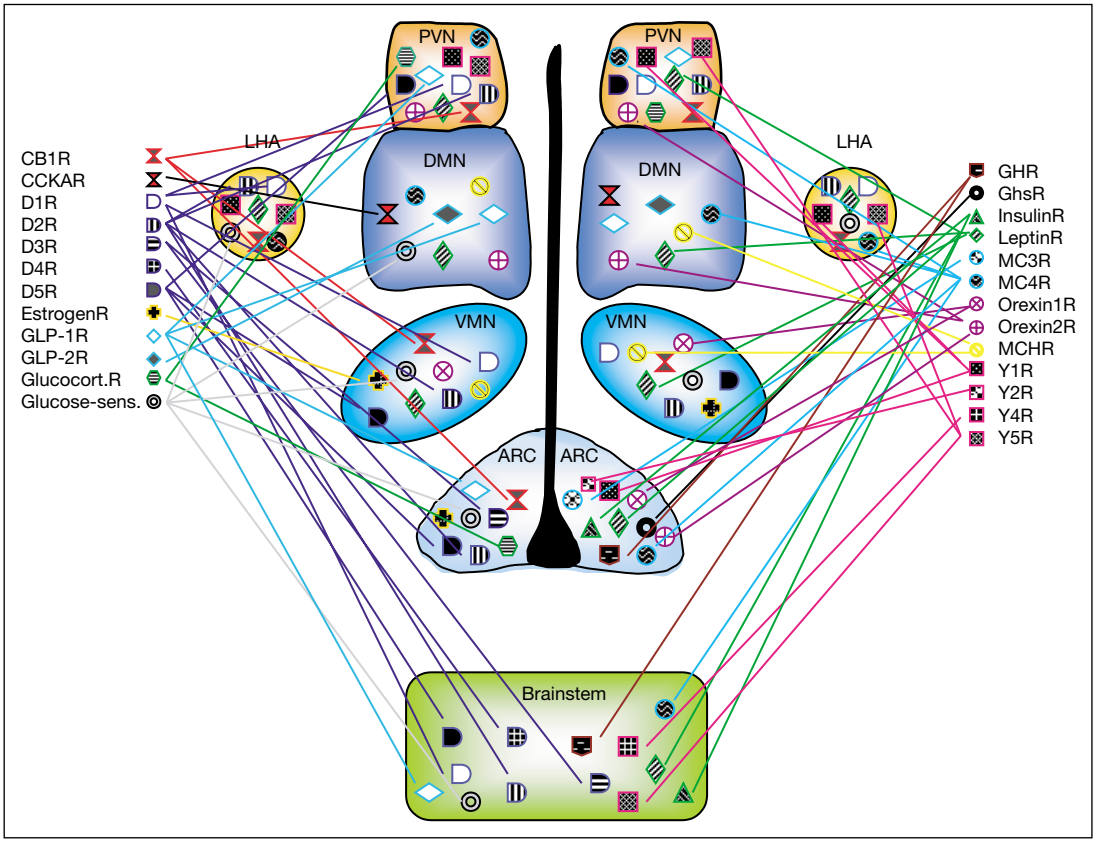

Fig. 2. Central receptors and sensors involved in the regulation of energy balance are shown in this simplified schematic overview. Peripheral factors are constantly signaling to the central circuits about acute and chronic energy balance and metabolic homeostasis. Areas in the brain which have been identified as very likely to be involved in the central processing of this afferent information as well as in the continuous adjustment of an appropriate efferent response are several areas of the brainstem region as well as the arcuate nucleus (ARC), the ventro-medial hypothalamus (VMH), the dorso-medial hypothalamus (DMH), the paraventricular nucleus (PVN) and the lateral hypothalamus (LH) in the hypothalamic region. Populations of neurons in these areas, which by now have been identified as likely to be involved in the central control of energy homeostasis, are carrying cannabinoid type-1 receptors (CB1R), cholecystokinin A receptors (CCKAR), dopamine receptor subtypes 1 through 5 (D1R, D2R, D3R, D4R, D5R), estrogen receptors (EstrogenR), glucagon-like peptide 1 and 2 receptors (GLP-1R, GLP-2R), glucocorticoid receptors, glucose-sensing neurons (Glucose-sens), growth hormone receptors (GHR), ghrelin receptors (GHSR), insulin and leptin receptors (insulinR, leptinR), melanocortin receptor subtypes 3 and 4 (MC3R, MC4R), orexin receptor subtypes 1 and 2 (Orexin1R, Orexin2R), melanin-concentrating hormone receptors (MCHR) and neuropeptide Y receptor subtypes 1 through 4 (Y1R, Y2R, Y3R, Y4R,

measured by calculating the weight of food consumed over a period of time and converting mass to kilocalories (kcal). More sophisticated methods have been used to measure meal size, meal frequency and feeding state. However, for most studies of obesity and energy homeostasis, calculation of daily caloric intake is sufficient. Measurement of energy expenditure (EE) requires a calorimeter. Some instruments directly measure the heat dissipated from an experimental animal or human while more modern equipment indirectly measures heat liberated by assaying carbon dioxide expired and oxygen consumed within a sealed chamber. Energy is consumed and used for work, or it is stored in the form of glycogen (liver and muscle), fat (adipose) or protein (muscle). Energy balance is achieved when energy intake is equal to energy expenditure. A positive energy balance occurs when calories ingested, digested and resorbed are greater than calories expended. A negative energy balance can be produced by decreasing energy intake, increasing energy expenditure, or both. There are many aspects of energy intake that must be considered for the careful study of energy homeostasis. Not all food eaten is digested, and not all digested foods are absorbed. Such variables as the composition of food, feeding pattern, rate of gastric emptying and intestinal transit time may all alter energy intake. Careful study of these variables requires not only measurement of food intake, but also measurement of fecal composition. Study of energy expenditure permits assignment of calories to basal life-sustaining functions such as the energy required for respiration, cardiac function, and all the specialized functions of each organ. In addition, energy is also spent for muscular activity as well as support of the digestive process itself.

Energy is required for generation (growth) and maintenance (repair) of body mass. Thus, the age of animals studied is a very important variable for consideration when studying energy balance. For example, pubertal rats rapidly gain lean mass and show completely different metabolic features than aged rats that may be losing lean mass and accruing fat mass. Environmental conditions must also be considered when studying energy homeostasis. A small, sustained increase in the environmental temperature can induce a positive energy balance in rodents because they expend less energy to maintain body temperature. Although creating an artificial situation, it is necessary to study animals that are single-housed to accurately measure food intake. While

Y5R). It is not only very likely that many of these receptors and their ligands turn out not to play an essential role in energy balance regulation, but it can also be anticipated that these by now identified pathways are only the 'tip of the iceberg' of a much more complex system involving numerous other endocrine as well as neuronal circuits.

this prevents competition for feeding, it also decreases the environmental temperature within a cage and increases the area for locomotor activity or exercise. All manipulations to the animal and its environment must be considered with each experimental design, because just weighing an animal or its remaining food will alter both energy intake and energy expenditure. Like humans, animals have taste preferences and tend to overeat when presented with certain diets or may eat less when presented less palatable diets that are of low caloric density. Moreover, manipulations of food presentation and its timing can drastically alter caloric intake. Rodents tend to overeat when food is presented on the cage floor. Changing the feeding system from cage top to hanging feeders or other containers may cause very significant reductions in food intake. Rodents are nocturnal animals and eat during the dark photoperiod. Longer dark periods may favor hyperphagia, while presentation of food only during the light period may reduce feeding. Finally, infections may not necessarily present with obvious signs but can still severely influence feeding patterns, energy expenditure and ultimately change body weight. The obesity epidemic documented in modern societies and in populations that have moved from impoverished communities to those with abundant food and modern conveniences is used as evidence that obesity results from an interaction of inherited genes with the environment. In particular: (a) decreased energy expenditure (lack of physical exercise), and (b) increased caloric intake (abundant high caloric foods), or both, are blamed for the etiology of obesity in modern societies. Thus, many investigators use wild-type rodents maintained on a high fat diet as a model to study obesity. For example, Long-Evans rats are susceptible to gaining fat when placed on a high fat diet. When they are housed in groups, a dominant social hierarchy is established for feeding and the group conserves heat by assembling together. The rats can be housed singly to prevent competition for food and the ambient temperature of the animal facilities (usually around 728°F) can be increased (for example to 76 ± 808°F) to prevent them from expending energy in purpose to maintain body temperature (‘thermoneutral zone’ = ambient temperature where a specific strain burns the least amount of calories to generate or reduce heat for the maintenance of body temperature). The rats can be weaned onto a palatable diet that is comprised of 40% fat, 40% carbohydrate and 20% protein (based on calories). Alternatively, a ‘cafeteria diet’ can be used. Here researchers try to match eating habits that lead to human obesity by offering the studied rodents large variety of cafeteria food including chocolate, cookies, bread, biscuits, ham, cakes, peanuts, cheese, etc. However, with this diet, nutrient intake is difficult to quantify or analyze. 100 days is the recommended age to start an obesity study, because at this age rats cease to gain lean mass, but readily accrue fat mass. Long-Evans rats are an out-bred strain and body weight is characterized

by a normal distribution. About 4% become morbidly obese (>50% fat mass), 4% remain lean (<10% fat mass) and the remainder is represented by a continuum between the 2 extreme phenotypes. The same principle can be applied to other rat strains (i.e. male Wistar) or mice.

Several strains of rodents have been identified and propagated because of spontaneous mutations that resulted in an obese phenotype. The animals are not only useful when studying biology underlying a specific mutation, but can be used to study obesity itself and are particularly helpful to dissect individual pathways triggered by pharmacological studies of energy balance [26].

Neuroendocrine Factors Regulating Energy Balance: Ghrelin as an Example

Ghrelin, a 28-amino residue peptide hormone, which is predominantly derived from the stomach and circulating in the bloodstream was discovered in 1999 [27]. One year later, it has been reported that ghrelin promotes a positive energy balance and increases fat mass in rodents [28]. These findings were counterintuitive since ghrelin has been first described as a growth hormone secretagogue and therefore believed to have lipolytic – if any – effects on fat mass. Modern methods for in vivo body composition analysis using double-X-ray absorptiometry (DEXA-scan) as well as nuclear magnetic resonance (NMR), which were both specifically developed and adapted for rodent body composition analysis, helped to unmask these impressive effects. But how, by which mechanisms, could such a positive energy balance be generated following ghrelin administration in rats and mice? Increased orexigenic drive causing an increased ingestion of calories was an obvious explanation. However, while central ghrelin administration markedly increased food intake, peripheral administration of ghrelin did not seem to have orexigenic effects when measured every 24 h. The discrete increase in food intake following peripheral (i.p., s.c.) ghrelin administration can only be detected if food intake, i.e. after 1, 2 and 4 h, is carefully monitored, and appears more pronounced in male rodents, on a standard chow and dependant from the rat strain used. A real-time food intake monitoring system allows for several measurements every minute over up to one week and therefore can unmask transient and discrete effects. The so generated data also help to understand meal patterns, including number, duration and caloric extent of each ‘meal’ in rodents. The discrete changes in food intake following peripheral ghrelin administration, however, do not seem sufficient to explain the easily reproducible and solid increase in body fat mass occurring after i.p. or s.c. ghrelin administration. Ghrelin also increases the respiratory quotient (reflecting decreased fat utilization and increased

carbohydrate utilization) and transiently (ca. 120 min after ghrelin injection) decreases energy expenditure as measured with an indirect calorimeter. This decreased energy expenditure following ghrelin administration can however not be verified if exclusively changes over 12 or 24 h are analyzed. Still, the complete extent of ghrelin induced obesity can not be explained, which (in part) may be due to the fact the sensitivity with which indirect rodent calorimetry can detect energy expenditure is still unsatisfactory. Additional methods such as measurement of changes in body core temperature or spontaneous locomotor activity can be employed to obtain a more complete collection of data on ghrelin's effects on energy balance in rodents. Interestingly, ghrelin seems to decrease body core temperature by more than 1°C, an effect possibly reflecting a ghrelin induced impairment of thermogenesis. This effect becomes more pronounced in rodents exposed to 4°C (climate chambers). At these challenging conditions body core temperature decreases by 2–3°C following ghrelin administration, while saline injected controls are able to maintain their body core temperature (as measured by intraperitoneally implanted transponders). Either a two-dimensional infrared light beam system or the same implantable transponders used for temperature measurement can be used to detect changes in spontaneous locomotor acitivity following ghrelin administration – yet another parameter, which influences the net outcome of energy balance and eventually the amount of fat mass accumulated over time. Ghrelin decreases locomotor activity but these effects can only be observed following intracerebroventricular (i.c.v.) ghrelin administration, while peripheral ghrelin injections do not seem to significantly change spontaneous locomotor activity. Last but not least, not all calories ingested are absorbed and used. Therefore, a simultaneous analysis of the metabolic efficiency of the rodent model under the investigated conditions and influences is mandatory. For these purposes metabolic cages are used to separately collect feces and urine while measuring food intake and body weight. Later, caloric content of feces and urine are measured in a bomb calorimeter to detect changes in metabolic efficiency or intestinal absorption following the administration of a drug or the deletion or overexpression of a gene in rodent models. For these purposes of accurately measuring energy balance in rodent models, it is also advantageous to precisely compose rodent chow with a distinct percentage of fat, protein and carbohydrates and to then provide equally shaped pellets, which can be used to compare different diets. While (at least in rodents) stomach-derived ghrelin might not represent the 'hunger-'hormone, the above described observations indicate that ghrelin triggers a positive energy balance via a combination of effects on physiological mechanisms, eventually increasing fat mass [27–35].

Conclusions

Hormonal and neuronal messages from the periphery communicate the environmentally induced necessity for regulatory changes in order to maintain energy balance to distinct areas of the brain, where not only sensations such as hunger and satiety are created, but also outgoing impulses for food seeking behavior, changes in locomotor activity or appropriate modulations of peripheral metabolic drive are triggered. Localization and precise action of these brain centers, as well as the precise mapping of their interactive signal transduction pathways, remain largely unknown despite great scientific progress in this area during the last decade. A fine tuned balance of action potentials, synaptic neurotransmitters, feedback loops and neuropeptide expression levels between regulatory centers in the brainstem, hypothalamic nuclei, basal ganglia, accumbens nucleus and even the cortex underlies the constant adjustment processes described above. The redundant multiplicity of molecular factors and physiological mechanisms governing energy balance, which were generated due to the evolutionary necessity to ensure sufficient caloric intake, is regarded as one reason for the ongoing scientific failure to generate an effective pharmacotherapy against obesity. However, these obstacles may be overcome through the application of post-genomic research, and the understanding that we now lack will emerge progressively. To identify and successfully modulate the essential pathways within the complex neuroendocrine control of energy homeostasis (fig. 1, 2), integrated efforts of research groups with complementary expertise will become necessary. Combining neuroscience with neuroendocrine, systems physiology, biochemistry, genetics, and cell biology approaches with clinical studies approaches may generate sufficient knowledge to generate a pharmacological approach for the effective and safe regulation of appetite, energy expenditure and body composition.

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Genetic Aspects

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Over the past 10 years substantial progress has been made in the molecular elucidation of monogenic forms of obesity both in rodents and in humans [1–4]. This development has had crucial implications for our understanding of childhood obesity, because most of these genetically determined forms typically become manifest in infancy or early childhood. In clinical terms, the most important monogenic form of obesity is due to mutations in the melanocortin-4 receptor gene (*MC4R*), which can be detected in 2–4% of all extremely obese children [5, 6]. It is nevertheless safe to state that only a very minor fraction of those genes involved in body weight regulation have become known. Large-scaled efforts are currently being undertaken to detect additional genes involved in weight regulation and particularly in obesity. The sequencing of the human genome having been mostly completed, the upcoming years will undoubtedly witness the identification of several genes either located within chromosomal linkage regions and/or identified via association studies. In contrast to the genes, underlying monogenic forms of obesity, these future findings will have implications for larger subgroups of the obese population. At the same time, the effect sizes of such gene variants will prove to be substantially smaller than in the monogenic forms of obesity. The complexity of gene-gene and gene-environment interactions needs to be tackled. The respective molecular genetic findings are bound to not only have an impact on the scientific community, but also on clinical practice and even society as a whole. Due to the public interest in this phenotype the respective research results will find rapid entrance into modern day society necessitating a communication process between researchers, clinicians and the public to delineate potential implications. In the medium term we forsee that obesity will be viewed as a more genetically determined condition than is currently the case. Because research is also being conducted in children and has diagnostic implications for this age group, ethical issues need

to be considered. In the light of these current and future developments we will review the current status and attempt to point out the implications of both past and future genetic research for our understanding of childhood and adolescent obesity.

Implications of Heritability Estimates

Twin studies [4, 7] have produced the most consistent and highest heritability estimates in the range of 0.6–0.9 for body mass index (BMI; kg/m^2). These high estimates apply to twins reared both together and apart. It should, however, be noted that only single and comparatively small studies exist for twins reared apart in contrast to the vast amount of studies pertaining to twins reared together, some of which included thousands of twin pairs. Heritability estimates of this magnitude indicate that the genetic component for body weight is almost as high as that for body height.

Except for the newborn period for which a lower heritability of 0.4 has been calculated [8] age does not affect heritability estimates to a substantial degree. Evidently, the influence of the intrauterine environment on birth weight is strong. It is well known that particularly in monozygotic twins other anthropometric measurements, e.g. body height, correlate less well in infancy than in childhood. The feto-fetal transfusion syndrome contributes to this phenomenon, as it substantially reduces the effect of genetic factors at birth and during infancy. Subsequently, however, genetic factors are able to exert their influence, thus accounting for the fact that both height and BMI become more similar. In school-age children high heritabilities already apply. It has been suggested that the heritability of BMI is maximal ($\approx$0.9) during late childhood and adolescence [9]. The genes relevant for weight regulation in childhood presumably only partially overlap with those operative in adulthood [10], thus partially explaining why intraindividual correlations of BMI during childhood and adulthood are considerably lower than between adolescence and adulthood [11].

In comparison to the twin studies adoption and family studies have mostly derived at considerably lower heritability estimates [3, 4, 7]. However, a single large family study [7] has also come up with a heritability estimate of 0.67, which is in the same range as those derived from twin studies. In their family study Maes et al. [7] discussed potential reasons why the high heritability estimates in twin studies may be better than those obtained in other types of family studies including a better control for age effects.

For an adequate interpretation of the high heritability estimates obtained in twin studies it is noteworthy to point out that both direct and indirect genetic effects are subsumed under the genetic component [4]. To illustrate this aspect

let us assume that both infant twins of a monozygotic pair are frequently irritable due to a biologically driven increased hunger (direct genetic effect; such as a mutation in the leptin gene leading to leptin deficiency). This hunger rapidly induces frequent feedings by the caretaker irrespective of his or her background. Thus, even if the twins are separated at birth, the caretakers can be expected to respond similarly as soon as they have learned that bottle feeding soothes the child. This indirect genetic effect actually represents the response of the environment to the genetically based excessive hunger. It is readily evident that in this case the indirect genetic effect is crucial for the development of early onset obesity in both twins. If one of the caretakers of the reared apart twins systematically curtails the infant's energy intake (implying a willingness to deal with the resulting irritability), early onset obesity would ensue in only the other twin.

The illustrated indirect genetic effect might be particularly important in infants and young children who totally rely on their caretakers for food supply. As the twins grow older their relentless hunger would undoubtedly entail that they can increasingly by themselves seek and obtain food. In addition, whereas the initial weight gain might be perceived as an indication of good health, the caretakers themselves could become aware of the obesity and potentially attempt to reduce the twins' energy intake. It is evident, that different patterns of complex child-parent interactions can ensue; indeed, every therapist familiar with the treatment of childhood and adolescent obesity is aware of the different strategies that both obese children and parents pursue depending on the age of the child. Some children might experience that their overeating is socially not acceptable and resort to eating secretly. In this situation the indirect genetic effect is accounted for by modern day society with its ready availability of a large variety of highly palatable foods (and only few requirements for physical activity); the fact that foods, snacks and candies are inexpensive, implies that most children can afford to buy them even without parental permission or knowledge.

Shared and Non-Shared Environment

Another interesting and important aspect of formal genetic studies has been the observation that non-shared environment explains considerably more variance of the quantitative phenotype BMI than shared environment. In the large twin study of Stunkard et al. [12], which encompassed adult twin pairs reared together or apart, shared environment did not explain variance; instead non-shared environment totally explained the environmental component estimated at 30%. This finding is not compatible with our intuitive approach to

obese children and their families: we are inclined to readily attribute both the child's obesity and that of other family members to familial eating and dieting patterns and the familial level of physical activity. However, based on the relative unimportance of shared environment the fact that several members within such a family are obese cannot be attributed to the shared environment; instead genetic factors would account for the familial loading. Taken one step further, it is not important what the mother buys to eat or what she serves. Instead, variance can only be accounted for by assessing what and how much each family member actually eats [13]. As a consequence of the unimportance of the shared environment we would need to focus on what makes BMIs of twins or sibs dissimilar. A list of candidate non-shared environmental experiences believed to promote obesity in children has been outlined [14]. Therapeutic strategies aiming at influencing the shared environment are not incorporating the information stemming from these formal genetic studies. We need to devise ways and means to therapeutically target the non-shared environment.

A word of caution is required. Recent studies indicate that the shared environment might play a more substantial role after all [15]. In addition, it has been argued that past research may have underestimated common environmental effects on BMI because the designs lacked the power or ability to detect them [15]. Using a very large nationwide dataset of Swedish military conscripts, male familial correlations in body mass index (BMI) showed highly significant correlations for BMI for all biological family relations ($r = 0.28$ for father-son pairs; 0.36 for full-brothers, 0.21 for maternal half-brothers, and 0.11 for paternal half-brothers). Both the significantly higher correlation for maternal than for paternal half-brothers (maternal half-brothers are more likely to grow up within the same family than paternal half-brothers) and the significant correlation ($r = 0.06$) found for non-biological quasi father-son relations [16] can be interpreted as evidence for the effect of the shared environment. Clearly, further research is required to pinpoint the potentially age-dependent contributions of both the shared and non-shared environment to the variance of BMI.

Gene X Gene and Gene X Environment Interactions

Formal genetic studies indicate that both additive and non-additive gene effects are important [8]. In their twin study Stunkard et al. [12] estimated that in males 57 and 17% of the variance in BMI are due to non-additive and additive gene effects, respectively. In females the respective percentages were estimated at 37 and 31%. The discrepancy between the higher and lower heritability estimates calculated in the twin and family studies, respectively, is presumably also partially due to the strong effect of non-additive factors, which

can be assessed more reliably in twin studies. The importance of the genetic background including both additive and non-additive effects has repeatedly been documented in inbred mice [17, 18].

Whereas it is widely accepted that several different genes contribute to obesity, the respective implications appear less clear. Evidently, these genes would in some way influence energy intake and/or expenditure. The complexity of the genetic basis of obesity applies both from a metabolic and behavioral perspective. Behavioral genetic research has convincingly demonstrated that approximately 50% of the variance of diverse complex quantitative behaviors is genetically determined [19]. Accordingly, eating a high fat diet or exercising too little cannot only be viewed as having an environmental basis. Instead, gene variants predisposing an individual to choose such a diet or predisposing to physical inactivity need to be considered. Indeed, both the macronutrient intake [20] and activity levels [21] have been shown to be genetically co-determined. Whereas many different studies have addressed the potential consequences of TV watching for childhood obesity [22], there is an absolute scarcity of studies addressing the extent to which TV watching is heritable [23]. It appears that this phenotype, like many other behavioral phenotypes, has an – albeit small – heritable component.

In the light of genotype X environment interactions the recent obesity epidemic is of considerable interest. Because the gene pool of a population cannot change within a generation, environmental changes are presumed to be of eminent importance [24]. Nevertheless, it should again be pointed out that these changes can only have a major impact because according to the thrifty genotype hypothesis our genotypes render us especially obesity prone [25]. Irrespective of the assumed environmental basis of secular trends for both height and weight there is no indication that heritability estimates in family studies are actually declining in the light of the obesity epidemic.

Despite the constancy of the gene pool a genetic contribution to epidemic obesity cannot be totally dismissed. Based on the high rate of parental obesity observed among parents of extremely obese children we have hypothesized that the recent increase of social stigmatization of obese individuals might actually have led to an increase of assortative mating [26]. This mechanism could contribute to epidemic obesity particularly by affecting the upper tail of the BMI distribution. In this context it is worthwhile pointing out that the most dramatic secular BMI increments in children and adolescents have been detected in the overweight and obese range [27, 28].

Recently, epigenetic phenomena have been invoked to contribute to the obesity epidemic. Indeed, it is conceivable that modern day living might affect methylation patterns of specific genes which in turn increase the risk of obesity. On a speculative basis, transmission of such patterns via the germ line cannot

be ruled out. Cloned mice share many characteristics consistent with obesity, which are however not transmitted to the offspring [29].

Molecular Genetic Findings

Monogenic Obesity. The cloning of the agouti [30] and leptin gene [31] in rodent obesity models marked the initiation of the molecular genetics of obesity. Since then autosomal recessive mutations in the genes for leptin [32–34], leptin receptor [35], prohormone convertase 1 (PC1; 36) and pro-opiomelanocortin (POMC) [37] have been shown to lead to early-onset obesity in humans. Not surprisingly, inbreeding was documented in the affected family members with leptin and leptin receptor gene mutations [32, 33, 35]. Compound heterozygosity has been detected for PC1 and POMC mutations [36, 37]. All of the mutations apparently lead to additional phenotypical manifestations including adrenal insufficiency (POMC), red hair (POMC), reduced or impaired fertility (PC1, leptin and leptin receptor) and impaired immunity (leptin gene). Whereas they do not affect intelligence, the pleiotropic effects warrant the consideration that these recessive disorders be classified as syndromal forms of obesity. All of the mutations lead to early-onset extreme obesity mostly or totally induced by an increased energy intake; a reduced energy expenditure as a contributing pathogenetic factor has not been documented. Finally, all mutations are evidently exceedingly rare; mutation screenings in the coding and promotor regions of the respective genes have not revealed other mutations which can functionally readily be linked to obesity [4]. However, linkage and/or association have been reported to markers surrounding or within the leptin gene locus on 7q31 and the leptin receptor locus on 1p32 [4]. In addition, linkage of serum leptin levels and fat mass has been described upon use of markers that localize to the POMC region on chromosome 2q and variation of leptin levels has been associated with POMC polymorphisms [4].

The first autosomal-dominant form of human obesity due to a missense mutation in the gene coding for the peroxisome-proliferator-activated receptor gamma2 (PPARγ2) was discovered in 4 of 121 obese unrelated adult Germans, but not in any of the 237 normal weight controls [38]. Analysis of the mutation by retroviral transfection and overexpression in murine fibroblasts revealed functional deficiencies. The same mutation has not been detected in any further obese individuals including obese German children, adolescents and adults.

The most recent advance has been the identification of functionally relevant mutations in the melanocortin-4 receptor gene [5, 6, 39–43] which result in a co-dominantly inherited form of obesity. In Germany, 2.5% out of over 800 more or less extremely obese children and adolescents have recently been

shown to harbor such mutations [6], which encompass frameshift, nonsense and missense mutations. Worldwide over 30 different mutations have been identified [6], only single of these have been shown to occur more than once; rare compound heterozygous or homozygous cases are even more obese than heterozygous carriers [5, 6]. Pharmacological assays have revealed that these mutations either lead to a total or partial loss of function [5, 6, 43].

Based on family based BMI comparisons between mutation carriers and wildtype carriers we estimate that adult male mutation carriers are 15 to 20 kg heavier than their male wild-type relatives [Dempfle et al., unpubl. data]; estimates for children are not available. The effect size of these mutations is lower than that of the leptin or leptin receptor gene mutations. In accordance with this observation, single non-obese *MC4R* mutation carriers have been identified [42, 43]. Potentially, such non-obese carriers might have additionally inherited an allele(s) protecting them from developing obesity. The weight curves of heterozygous MC4R knockout mice also clearly extend into the range formed by wild-type animals [44]. Similar to results obtained in *Mc4r* knockout mice [44] female carriers in our families are more obese than male carriers [Dempfle et al., unpubl. data].

Phenotypical effects of *MC4R* mutation carriers other than obesity have been shown to encompass an elevated growth rate and a higher bone density [5]. An interesting question is whether or not *MC4R* mutations are associated with aberrant eating behavior and in particular binge eating episodes [45]. Recently, 100% (n = 20) of obese carriers of *MC4R* variants were shown to have binge eating disorder [46]. However, this study mostly included individuals with the Val-103-Ile polymorphism, which in all other studies has not been found to be associated with obesity; carrier frequencies in the range of 2–4% have repeatedly been demonstrated in both cases and lean controls. Furthermore, we did not detect any *MC4R* mutation among extremely obese adults with binge eating disorder [47]. Finally, in our own families we found no evidence for elevated rates of binge eating behavior in both carriers of mutations and the Val-103-Ile polymorphism [Hebebrand et al., unpubl. data]. In conclusion, we do not agree with Branson et al. [46] that binge eating disorder is strongly associated with *MC4R* mutations or polymorphisms.

Based on observations in *Mc4r*$^{-/-}$ mice an elevated food intake seems to underlie the development of obesity [44]. These mice are particularly susceptible to dietary fat [48]. It seems unlikely that a reduced energy expenditure also contributes to obesity. Children with *MC4R* mutations have been shown to eat more at a test meal than controls [5].

A large number of association studies have been performed in ‘normal’ obesity [2]. Whereas many associations have been reported, it is largely unclear, which of these represent true-positive findings. Presumably, the power of many

of these studies is too low to detect minor genes; false-positive findings can result from not correcting for multiple testing [49].

Over 20 genome linkage scans pertaining to obesity and related phenotypes have been performed; specific chromosomal peak regions have repeatedly been identified in different scans [2, 49]. For example, linkage to chromosome 10p originally detected in French families with two or more adult obese offspring [50] was confirmed in a German study [51]. In the first genome linkage scan for childhood and adolescent obesity we found suggestive linkage to some of the regions which had previously been identified in adult scans [52]. It appears a matter of time before the genes within these linkage regions are identified.

The identification of genetic variation underlying obesity should lead clinicians and the general public to more readily consider genetic factors in the multifactorial etiology of obesity. We hope that this will entail less stigmatization of obese children and their families. The fact that 2–3% of extremely obese children harbor *MC4R* mutations currently raises the question as to the inclusion of a systematic mutation screen via sequencing in the diagnostic work-up of obese children. This and future developments require a consensus as to who should be screened, for what purpose and who should finance these potentially expensive diagnostic molecular procedures. In addition, we need to study if and how knowledge of a genetic cause of obesity influences the course of obesity particularly in children.

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Role of Environmental Factors in Childhood Obesity

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While genetic factors play a role in the development of obesity, the dramatic increase of its prevalence in the past 20 years strongly suggests that environmental factors are primarily responsible. The history of humanity during the past 20 years has seen a radical and extremely rapid evolution of the environment. This swift change precludes any possibility of genetic adaptation and should be countered by a rapid and lasting change in behavior. The wealth and variety of food supply available 24 h a day and throughout the year, the change in food dietary properties, the lack of cultural references and the abundance and diversity of information, all create a 'toxic' environment responsible for obesity and eating habit disorders. Obesity is part of a consumer and profit system to the detriment of individuals' health. The current economic cost associated with the frequency of the illness and its morbid complications leads to believe that the money spent is less than the economic profit made. A sudden change in political opinion has occurred and should facilitate and stimulate intervention on behavior and the environment.

The variety of environmental factors involved, their intricacy and mechanisms are extremely complex. We will discuss the most important factors for children in our view namely the influence of television and advertising, eating habits, dietary preferences and psychosocial factors. These factors are involved in one or several of the physiopathological mechanisms of obesity, i.e. diet, inactivity and physical activity, psychosocial factors.

Effect of Television

Television plays an important role in children's socialization [1]. Most households have at least one television [2]. Television and its possible role in

the development of pediatric and adolescent obesity has been an important research focus in trying to characterize the underlying causes of the obesity epidemic. Many, but not all [3–4], studies document cross-sectional and prospective relations between greater TV watching and higher childhood obesity, even after controlling for confounding factors such as socioeconomic status. A longitudinal study (from 1990 to 1996) shows that childrens' overall TV watching increased with no evidence of differential change over time by gender or ethnicity. This increase occurred for weekdays and weekend days and there was no significant difference between seasons. The number of meals per week children ate while watching TV increased over time, along with the number of TVs in the home. The percentage of children with TVs in their bedroom and the percentages of homes with a VCR records have increased [5]. Mean TV/video viewing time increases with the child's age. Interestingly the prevalence of obesity has increased by 1.06–2.5% per hour of TV a day [1–2]. TV hours are significantly related to BMI; however, BMIs are only significantly different between children watching less than 2 h of TV/day and those watching more than 2 h of TV/day and this only in older children. Another study reports that 40% of children had a TV in their bedroom and showed that these adolescents were more likely to be overweight and spent more time (4.6 h/day) watching TV [2].

The number of hours of TV watching in children is also correlated with the number of meals taken while watching TV and the number of hours of TV watching in parents. Interestingly, there was a discrepancy between the reports filled in by children and those filled in by parents with a tendency of parents to under report. Higher maternal education was also associated with less TV viewing early in childhood but not significantly in older children. The role of ethnicity and social income was also reported in conflicting data. Some studies reported a correlation between adiposity and TV viewing in children in low and middle income school districts, while others showed a significant difference between black and Hispanic and white children with a higher TV video viewing in the formers.

Therefore, the number of hours watching TV is probably an important factor in childhood obesity. How does it work?

Does TV Viewing Influence Children's Physical Activity?

Gortmaker et al. [6, 7] agree that activity and inactivity represent distinct domains that could independently affect the prevalence of obesity.

Is pediatric overweight primarily linked to reduced time spent in vigorous physical exercise (activity play and sports) or to increased time spent in sedentary activity? In most of the studies reported, a stronger association has been found between BMI and time spent watching TV [8–10] than between BMI and physical exercise. Moreover, intervention studies focused only on reduction of

TV viewing in children were more effective for weight loss than those focused on increased physical exercise [11–12]. Interestingly, the causal role of TV watching in childhood obesity is also confirmed by the fact that small movements (fidgeting) are suppressed when children watch TV thereby reducing energy expenditure by itself, and this effect may be emphasized for long periods of TV watching [13]. Consequently TV watching acts as a sedentary behavior associated with a very low energy expenditure.

Food Advertising on Television

Television is the largest single media source of messages about food with over 75% of food manufacturers' advertising budgets. The food products advertised most intensively on TV tend to be overconsumed whereas fruit and vegetable which are never advertised are underconsumed [14]. Although televised food advertising targets all age groups, food products are the most heavily promoted category targeting young children [15, 16–18]. Food advertisements account for well over 50% of all advertisements targeting children on national network and food is the most frequently advertised product category on children's TV. It has been estimated that children view an average of one food commercial every 5 min [19–22]. Besides these food advertisements, advertisements for fast food chains have strongly increased in the USA and in Europe during the last 10 years reaching almost a third of all food advertisements in the USA.

The fact that young children are the most targeted population for TV food advertisements reflects marketing analysts' belief that food habits developed in childhood influence lifelong consumption patterns [15, 23–24] and that parents accommodate children's food requests.

The nutritional quality of the foods being advertised on children's TV remained consistently focused on high-sugar content foods (69%), high fat (35–40%) and high sodium content foods (17–20%) [22].

Besides the poor nutritional quality of TV food advertisements, it is important to know that they may mislead children about nutritional attributes of food products. Moreover, TV program contents are also an important source of food messages showing behaviors where food is not used to satisfy hunger but to reward or punish oneself or another person or to relieve tension in social encounters. In these movies, despite obviously poor food habits actors were always thin and beautiful [25–26].

Effects of TV Food Advertising on Children's Food Behaviors

Interest in the topic has recently been revived [27] showing that children exposed to advertising will choose advertised food products at significantly higher rates than non-exposed children [27, 28]. Moreover, two studies showed

that exposure to food advertising increased the total energy intake and their choice of candy over fresh fruit for snack. Another impact of TV food advertisements is how children influence their mother's purchases while shopping. Children exposed to TV food commercials made more attempts to influence their mother's product and brand purchase, and this effect is stronger if the mother watched food advertisements with the child. Along the same lines, mothers watching more TV are more compliant to food requests. The more the children watched TV the more they tried to influence their mothers and 61% of all purchase requests were for food items [24]. Some studies suggest that children's requests for different categories of non food products vary according to child age while requests for cereals and snack foods remain constant across all age groups [22, 24], and that parental compliance was higher for food items. Interestingly, family use of TV also influences children's consumption patterns, children from families with TV on during 1 or 2 meals per day consumed significantly less energy from carbohydrate and tended to consume more energy from fat than others [29].

Association between TV and Children's Dietary Intake

After adjusting for age, BMI, race, family income and physical exercise total energy intake has been found to be positively associated with number of TV viewings per day among girls [9], though for boys it was not significantly different. Another study showed that TV viewing is related to overall energy intake and dietary fat intake [30]. The amount of TV viewed by children is significantly related to their consumption of sweet and salty snacks both at home and at school. An intervention study targeting the reduction of TV viewing [31] showed the complexity of this issue. Four dietary behaviors were used for outcome measures: number of meals eaten in front of the TV, frequency of snacking while watching TV, daily serving of high foods and daily serving of highly advertised foods. The intervention led to a decrease in the number of meals eaten while watching TV and a tendency to reduce daily high-fat food servings.

Other Related Factors to TV Watching and Obesity

In some studies [32] family income has been reported to be associated with TV viewing, with children from low and middle income more affected by TV watching. These results have not been reported in all studies. In a study of low income preschool children, TV viewing was significantly related to the prevalence of child overweight. In other studies involving children and adolescents, black children spent more time watching TV/video than white children. Moreover TV viewing seems to be related to parental education.

An Italian study of children aged 2 through to 8 years reported that less educated mothers have a more positive attitude towards TV than higher educated

mothers, who were more likely to prohibit certain shows and monitor their child's TV use [33]. Race/ethnicity, income, educational attainment, employment are confounding factors in the interpretation of the involvement of factors associated with TV watching. Lower cognitive function and, particularly in this issue, uncritical exposure to messages on TV and choice of TV programs represent other factors which could influence the role of TV watching. Nevertheless, two recent clinical trials in relatively high educated populations demonstrate that reductions in TV/video viewing were associated with reduction in adiposity [34, 35].

Nowadays most studies suggest that TV is partly responsible for the increasing prevalence of obesity in children and adolescents through different pathways: increasing sedentary activity, total energy intake, promoting poor eating habits and consumption of poor nutritional products through food advertisements. Family habits are important factors regulating the effects of TV viewing in children through media-habit, lifestyle habits, culture, income and educational levels. Given that the combination of lifestyle factors are associated to heavy TV use, pediatricians should advise parents about the potentially harmful effect of excessive TV use on their children's nutritional health.

Eating Behaviors

Early Experience with Foods

The knowledge of which behavioral factors influence energy intakes, food preference and food intake control could suggest some strategies for preventive interventions.

One of the first choices that parents make that shapes a child's experience with food and flavors is the choice to breast-feed or formula-feed. There are some data supporting the idea than this early experience with flavors on milk has an effect on milk intake and in later food acceptance [36, 37]. On a short-term basis, it has been demonstrated that flavors in breast milk influence infant's consumption and time attached to the maternal nipple [38, 39].

Interestingly infant adiposity has been related to nutritive sucking style [40], which could be due to specific sensitivity to some flavors. In rats it seems that rat pups learn to prefer their mother's diet due to the flavors of the milk. Formula-fed babies have experience with only a single flavor versus breast-fed babies. In humans, very limited evidence suggests that the varied flavor experience of breast-fed infants can facilitate acceptance of solid foods during the weaning period [41], with breast fed infants showing greater initial acceptance of new foods. This finding is consistent with those showing that early experience with a variety of flavors leads to more ready acceptance of new foods later [42].

Subsequently, infant dietary experience is shaped by infant-feeding decisions and dietary patterns of the mother and it provides the basis for food acceptance and patterns of intake in infancy. Except for sweet and salty foods infants and children are predisposed to be neophobic and reject new foods which can be overcome after 5–10 exposures. These findings emphasize the importance of early experience with food and food acceptance, showing that children come to like and eat what is familiar.

Child Feeding Practices

In this aspect, family pattern is essential and studies have shown that parental eating habits strongly influence nutrients intake of young children. The food environment the parents provide shapes children's preference and food acceptance patterns which in turn are linked to children's adiposity [43–45].

Parents shape their children's eating environment in a variety of ways besides the choice of infant feeding method, the foods they make available and accessible and the extent of media exposure at home, they also interact with children in the eating context. Parents' practices may be especially controlling and may have particularly negative effects on children: for instance [46], parents' feedback to children about eating vegetables. Moreover, contrary to parental beliefs restricting children's access to foods does not produce dislike for the restricted foods [47] whereas limiting over-availability of a preferred food could enhance children's desire to obtain this food.

In addition, maternal feeding practices can influence infant and child intake and particularly his ability to regulate energy intake and the amount of food consumed [48]. This could explain the higher growth rate of formula-fed infants whom mothers can encourage to finish the bottle. Increasing maternal impact on child food intake tends to decrease the child's responsiveness to internal signals of hunger and satiety as a basis for adjusting energy intake. This has also been proven for the responsiveness to food energy density and the way children adjust their intake. Besides this innate behavior children's intake is strongly modified by feeding practices. Parental prompts to eat were positively associated with time spent eating and degree of overweight in children [49]. Parents impose behavioral control (1) when they have problems regarding their own behavior; (2) when they perceive a risk for the child, and (3) when the child lacks self-regulation. In obesity, this parental control impedes children's ability to develop self-regulatory behavior thereby promoting the problem they attempt to avoid [50]. A high degree of parental control is associated with low self-control in children. For girls energy regulation was related to their adiposity with thinner girls doing better than heavier girls. In addition, in girls and not in boys,

parental control is linked to the girl's adiposity. Parental control is linked to the parents' dieting and weight history the most striking story being a thin high jogger mother with an obese daughter. These findings are limited to middle class populations as data remains poor in others.

Moreover, early dieting in girls as young as 9 years of age (44% of high school were dieting) may constitute a risk for the development of obesity and overeating in adolescence and adults [51–54]. Adolescents' restraint scores were positively associated with depression, body dissatisfaction, social anxiety and weight status [55].

A recent study [48] using a self-report child feeding questionnaire in 120 patients (obese and non-obese) reports that total fat mass measured by dual absorptiometry (DEXA) is correlated with weight concern and restriction whereas pressure to eat, responsibility for feeding and monitoring were unrelated to total fat mass. Although the cross-sectional nature of this study does not allow conclusions to be drawn concerning cause and effect these data clearly show that child-feeding practices are key variables that explain more of the variance in body fat than dietary fat intake does [48].

Child Eating Style

Child eating style is also a factor eliciting parental concern. The obese eat at a faster rate than non-obese children [56], this is true for preschoolers as well as school children [57, 58]. Moreover obese children do not decrease the rate of eating towards the end of the meal. Such patterns could be explained by an impaired satiety signal or a lack of response to this signal. This pattern appeared early as infants with more rapid sucking at 2 and 4 weeks have greater BMI at 1 and 2 years of age. Data are lacking on the subsequent evolution of these children.

Food Choices

Among the nutritional factors involved in the increase of prevalence of childhood obesity, the role of high-fat or high-energy food seems to be the strongest. There is no evidence of an innate preference for these foods in children. Although limited, the findings from research with young children [59, 60] are consistent with conditioned preferences for energy foods as it has been extensively reported in animals [61]. Regarding obesity, there has been no research into whether children's ability to learn preferences for high-fat food differs between children in obese and normal weight families. Among adults there are differences between obese and non-obese individuals in their preferences for fat

and for mixtures of sugar and fat [62, 63]. The social context in which children's eating patterns develop become important as a model for establishing food preferences. For children eating is a social occasion and other eaters besides parents, other adults, peers and siblings as well as children's observations of other eating behaviors influence the development of their own preferences and eating behaviors. Findings have suggested that daycare could provide opportunities for expanding the availability and accessibility of foods and for fostering preferences for food modeling effects. Daycare could give the opportunity to test and like some disliked vegetable. Interestingly the same phenomenon occurred to model the preference of chili-flavored foods in young children among Mexican families [64].

Fast Food Restaurant Use among Adolescents

Eating away from home now accounts for almost half of the total food spending in families. Fast food restaurant use (FFRU) has increased strongly and rapidly particularly in adolescents. Data available in the USA showed that the average adolescent visits a fast food restaurant (FFR) twice a week (it is once a week in France: unpublished data) and this represents one third of the away-from-home meals at this age. Nutrient profiles of these away-from-home foods are higher in fat and energy compared with foods eaten at home. A recent study [65] involving 4,746 students reports that 75% of them ate at a FFR at least once during the week preceding the study. This study described the nutrient intake, personal food choices, behavioral and environmental variables associated with FFRU among adolescents. A greater proportion of females (27%) than males (22%) reported never having visited a FFRU during the past week. Older adolescents visit FFRs more frequently. Social economic status (SES) is associated with FFRU among females but not in males, the lower SES visit FFRs more frequently.

FFRU was associated with significantly lower fruit and vegetable grains intake and less milk servings and with significantly higher intake of soft drinks, cheeseburgers, pizza and French fries suggesting that dietary intakes of adolescents who frequently consumed fast food are of poorer nutritional quality. Interestingly, in this study no association was observed between FFRU and obesity. In boys, BMI was even lower in males who frequently visit FFRs. This finding could be due to a lack of prospective data as a 3-year study period showed in young women that an excessive weight gain was associated with frequent consumption of fast food. Another explanation could also be that these boys practiced more team sports than the poor FFR users. Environmental variables are also important in this issue showing that female adolescents in single parent families and adolescents working more 10 h/day reported more FFRU. TV viewing is also

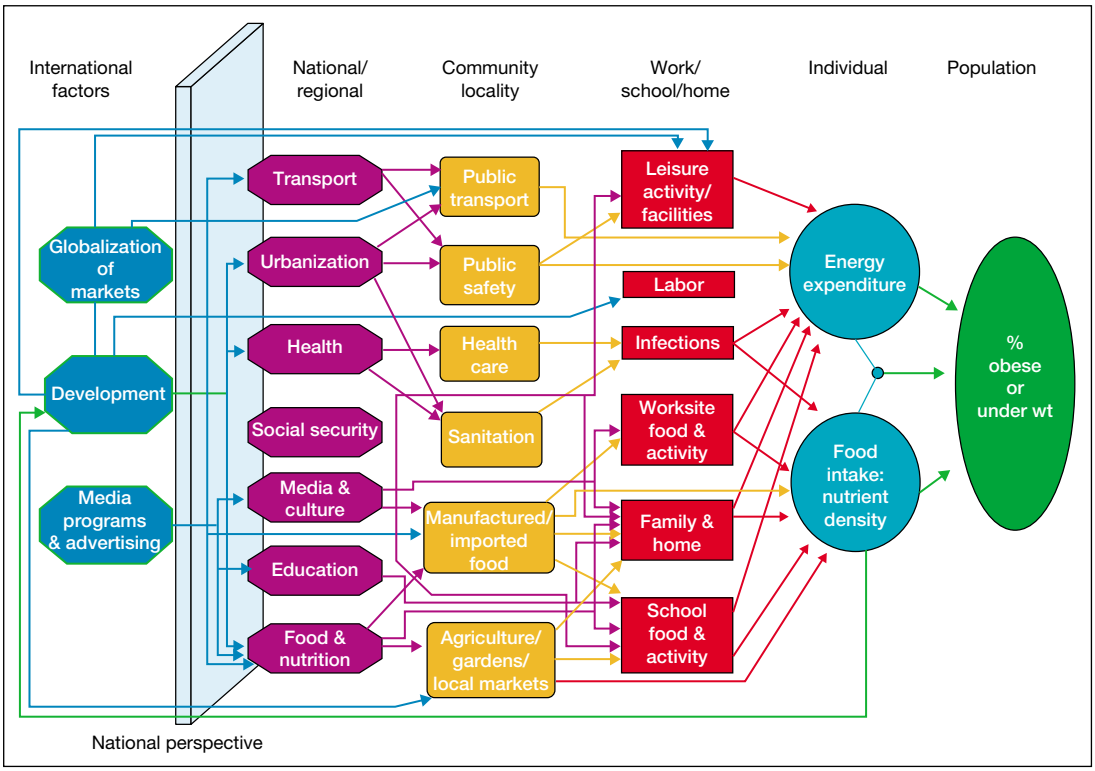

Fig. 1. 'The Causal Web' proposed by the International Obesity Task Force to describe environmental factors involved in the development of obesity. Modified from Ritenbaugh et al. [66].

associated with FFRU in males and females. Moreover, FFRU is associated with less concern about healthy eating, more perceived barriers to healthy eating and lower perceptions of maternal concern for their child's healthy eating. Interestingly dietary behavior and weight concern were not associated with FFRU.

As poor eating habits are associated with FFRU, these adolescents could be at risk of developing obesity. FFR are highly used for different reasons. They should be encouraged to provide healthy food lower in fat and energy, fruit and vegetables and restricting portion size.

Conclusion

In conclusion, research attempting to increase the knowledge of how environmental factors interact with genetic background need to be extensively

encouraged and developed. Pediatricians really want to optimize prevention and care of obesity in children and adolescents. More studies should focus on preschool children (before 6 years) in order to develop concepts for prevention as well as on adolescents in order to optimize the management which is difficult at this age. We decided to add this cartoon drawn by IOTF (International Obesity Task Force) showing the complex network of environmental factors involved in obesity, from the Causal web available at http://wwwiotf.ung/groups/phapalcausalweb.htm (fig. 1).

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Nutrition

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Obesity is a multifactorial disease and diet is only one of many tools used in its management. For each obese child and adolescent different factors contribute to the development of his or her obesity. The main aim of dietary treatment is to add to energy balance and thus to achieve healthy body weight at normal growth and development. Maintenance of healthy weight is brought about by balanced energy intake and energy expenditure. In this chapter we:

- discuss the eating habits of obese and nonobese children,
- give nutritional guidelines for children and adolescents,
- propose methods to realize these guidelines in daily practice.

Eating Habits of Obese and Nonobese Children

Dietary records have been used to examine the relationship between nutrition and adiposity. Measurements of dietary intake are difficult and different assessment methods may lead to different results in individual subjects [1]. In several studies energy intake and expenditure data seemed incompatible [2–16]. Underreporting introduced a considerable and unacceptable error in the estimate of energy intake. Dietary underreporting has been described in obese subjects [2–6, 8, 16]. In conclusion underreporting increase with excess body weight. In addition, psychological aspects of eating behavior were associated with underreporting and may have had an influence. A high cognitive restraint and a high level of disinhibition were both associated with severe underreporting [17]. These biases probably affected the results of many studies. The limitation of dietary surveys, particularly underreporting by obese subjects, have been widely discussed [2–8, 17]. Even if there are some errors in reported intakes, consistent tendencies do emerge from diverse studies.

Most people believe that obese and overweight children have a higher energy and fat intake than normal-weight children. However, no clear-cut associations were found in nutrient and/or food intake and body weight of German children aged 5–7 years. Health and body weight-related quality of food intake (as reflected by the mean dietary pattern index) did not differ between overweight and normal weight children [18, 19]. In addition the distribution of the dietary pattern index is very narrow, i.e. the 10th percentile of score is 24 points and the 90th percentile of score is 37 points of a total of 52 points. These results show that food choices are very similar and independent of the body size of children [20]. Thus, a clear association between overweight and dietary pattern is unlikely to exist. These data are in accordance with measurements on British children aged 1.5–4.5 years where no association was found between diet and body size [21].

The association between dietary fat and overweight has been questioned. Epidemiological data do not consistently show an association between fat intake and overweight in children and adolescents [22, 23]. In a group of 6-year-old French children there was also no relationship between sucrose intake and BMI [24]. By contrast, in a cross-sectional study in US school-age children Harnack et al. [25] found 10% greater energy intake in children who consumed sugar-sweetened soft drinks than in those who did not. Additionally, the results of a prospective observational study indicate a 60% increased risk of development of overweight in middle-school children for every daily serving, after controlling for the effects of confounding factors [26]. Sugar-sweetened soft drinks might promote energy intake and excessive weight gain because of their high glycemic index [27].

In the Muscatine Risk Factors Survey it was found that obese children consumed significantly more energy per day than their nonobese peers but this association became negative when energy was expressed as kJ/kg body weight [28]. Valoski and Epstein [29] also found no significant differences in the caloric and fat content of the diets eaten by obese and nonobese children aged 8–12 years. However, in this study obese children consumed more protein. In another study on Spanish normal-weight and obese children and adolescents there were no between-group differences with respect to energy intake. But obese adolescents derived a greater proportion of their energy from protein and fat and less from carbohydrate [30]. In a study of French children aged 7–12 years, a high percentage of protein in diet was positively associated with BMI as well as subscapular skinfold thickness [31]. There were no associations between energy or fat content of diet and body size or fat mass. Even more confusing, Spyckerelle et al. [32] found a negative association between BMI and energy intake but positive association between BMI and percentage of energy derived from protein in French adolescents.

Contrary to these data an analysis of nutrient intake in 9- to 10-year-old children showed that body fatness was positively associated with fat and protein

but had a negative correlation with CHO intake after controlling for gender and energy intake [33]. In addition, obese children of obese parents enjoy fatty foods and eat them in large quantities [34, 35]. High fat intake predicted adiposity in children in two other studies [28, 36].

Besides quantitative food intake the food choice as well as meal patterns are other important risks for childhood overweight. Several studies reported differences in circadian distribution of food intake between obese and nonobese adults and children. Breakfast of obese subjects added less of daily energy intake than breakfast of nonobese subjects [37, 38]. By contrast, obese children had dinner with higher energy content when compared to normal-weight controls [37, 38]. Other studies showed an inverse relationship between number of daily meals and body adiposity. For example, three meals per day resulted in higher risk to become obese than five or seven meals per day irrespective of energy intake [39, 40]. Five or seven meals a day doesn't mean snacking. Extraprandial eating is practiced by both obese and nonobese subjects [41]. In a field study, it is difficult to assess how snacking and nibbling contribute to energy intake, because underreporting or selective reporting is a frequent observation significantly affecting between-meal eating [42].

Other eating habits show that excessive energy intakes during binges create a positive balance of energy. In obesity, no corrective behaviors such as purging or self-induced vomiting take place in contrast to bulimia nervosa. Some obese subjects report binges with rapid ingestion of large amounts of food accompanied with feelings of loss of control [43]. In addition, obese subjects have a tendency to eat faster than their lean controls [44].

In summary, all children and adolescents, i.e. overweight as well as normal-weight, prefer so-called 'unhealthy' food choices (e.g. fast food). However, there is no clear association between food or nutrient intake and overweight. Although the relation between dietary fat and overweight has been questioned, a high fat intake is a considerable aspect in the development of overweight and obesity, because fat is the most energy dense macronutrient. In addition, there is some evidence that a low CHO and thus a high fat intake promoted adiposity in children. The impacts of other items or rather risks of overweight, e.g. portion size, meal frequency, psychological aspects, are not well referenced in children and adolescents.

Nutritional Guidelines for Children and Adolescents

All the above mentioned results led to the following nutrition guidelines:

- select healthy foods (i.e. foods with high CHO content and low fat and protein contents as well as foods with low glycemic index),

- frequent number of meals a day,
- normal-sized portions and
- flexible control.

These guidelines should replace strictly controlled diets.

The development of a healthy lifestyle has to include changes in both what is eaten and how it is eaten. In younger children most of the recommendations will be targeted at parents. As children age, more teamwork is needed between parents and children. For adolescents, the advice is targeted directly to the adolescent [45].

Foods Choices

Principles of foods choice [46]:

- plenty of low-energy beverages as well as vegetables,
- moderate animal foods (low-fat variants),
- use high fat and sugary foods (i.e. foods with high glycemic index) sparingly.

Because of the importance of nutrition in the prevention and treatment of overweight and obesity as well as growth and development, recommendations for healthy food intake have been set and are outlined in the Food Guide Pyramid [47]. The pyramid provides recommended intakes for five food groups as shown in figure 1. These guidelines of food choice apply for normal-weight as well as overweight children and adolescents. The aim is to achieve energy and nutrient intakes appropriate for age, height and lifestyle. The goal for obesity treatment in children should be to established long-term weight control. The achievement of the median BMI for age and sex is usually an unrealistic goal for treatment. In contrast to adults, children have the advantage that they are still growing in height. As a result, maintenance of weight or modest weight loss, while children continue to grow in height, reduces their degree of overweight [45].

The protein, fat and carbohydrate intake should be 15, 30–35 and 50–55% of daily energy intake. Only 10% of energy intake should come from biscuits, chocolate bars, crisps and other energy dense snacks as well as high-energy lemonades.

The recommendations for food groups are made in terms of servings per day. The objectives for food intake are to increase complex carbohydrate- and fiber-containing foods in the diets to five or more daily servings for vegetables (including legumes) and fruits, and six or more daily servings for grain products. In addition, the content of fat in the diet has to be reduced. Beverages should be low in energy and glycemic index.

In summary, children and adolescents should emphasize foods from grain, fruit and vegetable groups, along with moderate amounts of low-fat foods from the milk and meat group. Choose a variety of grains daily, especially whole grains and choose a variety of fruits and vegetables daily. Choose foods and beverages with a low glycemic index.

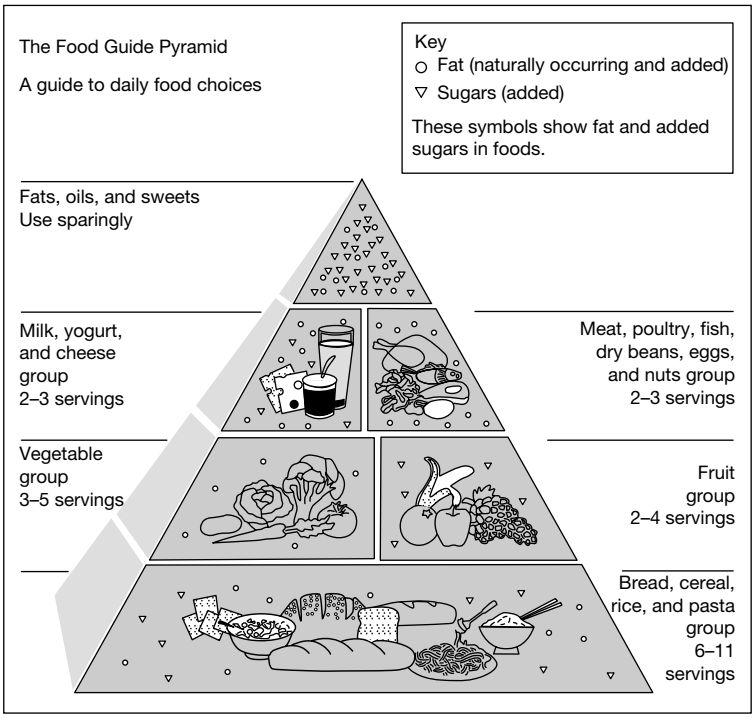

Fig. 1. Food Guide Pyramid (US Department of Agriculture, 1992).

Mealtime Frequency

The recommendations include frequently intakes of the healthy foods. Three to five mealtimes a day were recommended, i.e. breakfast, lunch and dinner and an additional two snack times to avoid hunger only, one in the morning and one in the afternoon. Frequent snacking between mealtimes should be avoided.

Methods to Realize Guidelines in Daily Practice

A panel of pediatric obesity treatment specialists suggest a number of components of successful lifestyle changes in eating patterns which may help realize the guidelines of Foods Pyramid as well fat reduction and in following energy intake reduction [26, 45, 47–59]:

Environmental factors:

- Plan eating to avoid hunger not as a time-filling event.
- Eat only at mealtimes and recognized snack periods.

- Eat, if possible, as a family so there is social intercourse and time is spent during the meal waiting for others to be served. This may contribute to satisfaction from a meal and psychological satiety.
- Eat a meal in a normal-sizes portion. It may be helpful for parents and children to visualize a 'healthy plate' of which half is filled with salad and vegetables, one fourth with starch and one fourth with a protein source (meat, fish, etc.).
- Discourage eating in front of the television or snacking when playing/working with the video or computer.

Foods choice:

- Select whole foods or raw unprocessed foods whenever possible and prepare meals at home.
- Raw ingredients, rather than ready-prepared bought foods, make it easier to see what is being consumed. Many prepared foods are cheaper than their raw ingredients due to supplementation of starches and fat.
- It is more time consuming to eat whole foods, for example apples compared with apple juice. This helps satiety. Wholemeal bread is of similar energy content to white bread, but may have greater satiety effect.
- Drink water or blend water with juice rather than only fruit juice or carbonated drinks. Recognize that whole fruit juice contains a lot of energy in one glass. Drinks with sweeteners even though lower in energy than those with sugar may encourage a sweet tooth and should be avoided.
- Use semi-skimmed milk and low-fat yoghurts and cheese.
- Use margarines and spreads sparingly.
- Avoid sugared or chocolate-coated cereals.
- Avoid biscuits, chocolate bars, crisps and other energy-dense snacks at break times. Preferably eat fruits or vegetables as snacks.

Preparation:

- Grill, boil or steam foods rather than fry them.
- Avoid adding butter or other fats and oil to cooking.
- Avoid thickening gravies.

Behavioral factors:

- Understand and practice a flexible control of eating behavior instead of a high rigid and cognitive control.
- Find strategies to cope with stress and/or with boredom.

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Physical Activity in Obese Children

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It is accepted that obesity is a hazard to health. Follow-up studies of obese adolescents demonstrated that cardiovascular morbidity was significantly increased compared with lean adolescents [1–4]. The effect of adolescent obesity on adult morbidity and mortality seems to be independent of the effects of adolescent obesity on adult weight status [2]. There are different periods during which the risk of obesity is increased: early infancy, adiposity rebound in the period of pre-pubertal growth and adolescent growth phase [5]. Risk factors and life-style factors associated to development of obesity in childhood are well identified [6, 7]: family history of obesity, diet, physical activity, mother education, TV watching. Both dietary and activity patterns result to be responsible for the increasing prevalence of obesity in childhood [8] and, at least, relationship between obesity and these factors reflect the principle of energy balance.

Weight maintenance results from equivalent levels of energy intake and energy expenditure: both these factors are likely targets for obesity prevention and therapy programs, although physical activity provides the main source of plasticity in energy expenditure, even among children [9].

Management of the increasing epidemic of obesity in young people must include prevention strategies concerning nutrition education and physical activity programs. It is also important to underline that obese children often suffer discrimination, and it is imperative that treatment does not contribute to this problem.

Effects of Physical Training in Obese Children

Physical activity is likely to protect from development of obesity, and some Authors have suggested a role in increasing resting metabolic rate (RMR), that constitutes 60–75% of daily energy expenditure. It has been demonstrated [10],

that physical exercise appears to influence resting energy expenditure in man; at contrast, other Authors [11], showed no difference in RMR, overnight metabolic rate (OMR), and sleeping metabolic rate (SMR), at the beginning and after a training program. Furthermore, other authors demonstrated: (1) a relationship between energy expenditure for activity (EEAct), level of activity and adiposity in a group of 9-year-old boys with different body composition: time spent on sedentary activities was proportional to fat mass percentage [12]; (2) in free-living conditions obese children have a higher total energy expenditure (TEE) than non-obese children, and the energy expenditure for physical activity is significantly higher in obese children [13]; (3) energy expenditure assessed by indirect calorimetry during walking and running at the same speed of exercise is significantly greater in obese than in control children, in both boys and girls, with a larger respiratory response to exercise in obese subjects [14], and (4) maximal aerobic capacity while running and cycling measured by oxygen consumption (VO_2) and carbon dioxide production in obese and non obese prepubertal children, was significantly higher in obese children for the treadmill test, with this difference disappearing when VO_2max was expressed per kg fat free mass [15]. In a recent study the adjusted VO_2 peak values for mass and stature was similar in obese and normal-weight girls, suggesting that the obese were not impaired in the pumping capacity of the heart, and in extraction of O_2 at the cellular level [16].

The aforementioned data suggest that physical activity is more expensive for obese than for non obese children, and that the magnitude of workload prescribed in a physical activity program for obesity therapy, should be designed to increase caloric output, rather than improve cardiorespiratory fitness.

Many Authors have studied the influence of physical training on RMR, suggesting an increase of RMR during physical training [17], or indicating an unaltered RMR [18].

In the study of Broeder et al. [19] RMR, expressed in absolute terms, or relative to fat-free weight (FFW) remain unchanged after an extended period of training: in this study physical training was accompanied by a small decline in dietary intake. In a recent meta-analysis, [20] it has been evaluated how exercise training influences the composition of diet-induced weight loss: the percentage of weight lost as fat-free mass for diet-plus-exercise (DPE), subjects was approximately half of that for dietary-restriction-only (DO) subject of the same sex. This meta-analysis provides evidence that exercise training reduces the amount of body weight loss as fat-free mass during diet-induced weight loss. To better understand the efficacy of training in the management of childhood obesity, Blaak et al. [21] studied the effect of training on total energy expenditure and spontaneous activity outside the training hours in obese boys, demonstrating that an added physical activity leads to an appreciable increase in the overall energy expenditure of obese children even though there are no

Table 1. Effects of exercise on fitness in the main studies on the treatment of obesity

Authors	Fitness measure	Treatment months	Results
Becque et al. [65]	VO_2max	5	+
Blomquist et al. [66]	PWC_{170}	4	+
Epstein et al. [62]	PWC_{150}	6	++
Epstein et al. [63]	PWC_{150}	6	++
Ewart et al. [64]	Step Test	4.5	+
Gutin et al. [26]	submaximal exercise	4	+
Gutin et al. [22]	HR response	4	+
Owens et al. [25]	submaximal exercise	4	+
Ferguson et al. [33]	submaximal HR	4	+
Barbeau et al. [23]	submaximal HR	4	+

measurable changes in spontaneous physical activity: training stimulated the energy expenditure during the non-exercise part of the day.

Controlled physical training, without dietary intervention, was studied by Gutin et al. [22] in a group of black obese 7- to 11-year-old girls: the physical training group showed a significant improvement in aerobic fitness and a significant decline of 1.4% body fat, demonstrating that physical training, without dietary intervention, could improve fitness and body composition of obese girls. The interindividual variation in the response of body composition on physical training was studied by Barbeau et al. [23], who were able to demonstrate, in a group of 71 obese children aged 7–11 years, decreased body fat, increased fat-free soft tissue, bone mineral content, and bone mineral density mainly in boys with lower energy intake and more vigorous activity, ethnicity not being correlates to the changes in body composition. In another study [24], bone density increased during the period of physical training while no difference was found for dietary intake of energy, suggesting that regular exercise also without dietary intervention can enhance the body composition in children with obesity (table 1).

Obese children are likely to have high level of visceral adipose tissue (VAT). Owens et al. [25] studied the impact of controlled physical training, without dietary intervention, on VAT in obese children: during physical training obese children were capable of participating to a high intensity physical training over a 4-month period, accumulated significantly less VAT as compared with non-exercising controls, and experienced other beneficial changes in total and regional body composition (table 2).

Physical training demonstrates his efficacy also on modifying cardiovascular parameters in obese children. Furthermore, physical training can shift

Table 2. Effects of physical training (PA) on body composition in obese children

Author	Effects of PA on body fat	Effects of PA on fat-free mass	Effects of PA on fat visceral	Effects of PA on bone mineral content	Duration of physical training
Gutin [27]	decline of 1.4%				10 weeks
Gutin [26]	decrease				10 weeks
Owens [25]	decrease		decrease		4 months
Barbeau [23]	decrease	increase		increase	4 months
Gutin [24]	decline of 1.6%			increase	4 months

hearth-period variability (HPV)-derived indexes of cardiac autonomic function in the direction of less sympathetic activity and greater parasympathetic activity, supporting the idea that the training program was effective in enhancing cardiovascular fitness [26]: physical training, in these series, alters cardiac autonomic function favorably by reducing ratio of sympathetic to parasympathetic activity. Cardiac parasympathetic activity (PSA) measured by HPV was also studied [27] in relation to total body and visceral adiposity in obese children demonstrating that regular exercise that improved fitness and body composition had a favorable effect on PSA in obese children.

Effect of Physical Training on Metabolism and Cardiovascular Risk Factors

Exercise leads to an increase in energy expenditure which is, in the long term, counteracted by increased energy intake [28]. Substrate utilization has been studied in obese subjects in relationship with physical training (fig.1). Exercise training program has been shown to prevent the reduction of basal fat oxidation that is associated with diet-induced weight loss [29]. The impact of high-intensity exercise on energy expenditure, lipid oxidation and body fatness was also studied by Yoshioka et al. [30]: in his series it is shown that high intensity exercise produced a greater postexercise, postprandial oxygen consumption as well as fat oxidation than the resting session, suggesting that high-intensity exercise favors a lower body fat deposition which might be related to an increase in post-exercise energy metabolism, that is mediated by beta-adrenergic stimulation.

Insulin resistance, associated to obesity [31] seems also be reduced by physical training: in a study on obese adult and young rats, it has been showed

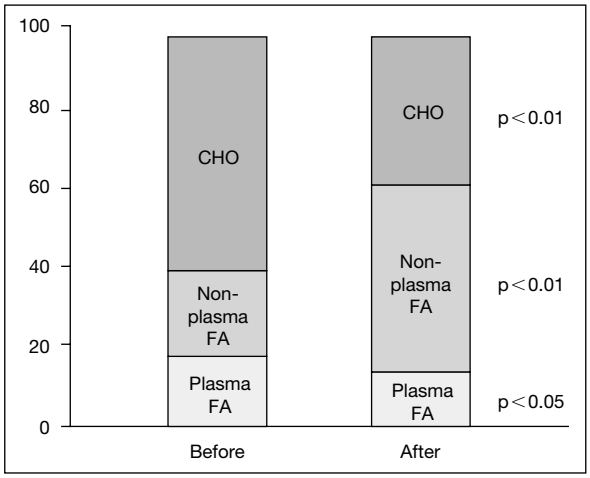

Fig. 1. Effect of endurance training on plasma free fatty acid turnover and oxidation during exercise (with permission from Martin et al. [67]).

that exercise and food restriction can provide protection against development of insulin resistance in fat cells by slowing development of fat cell hypertrophy [32]. In this study physical training is shown to be more effective than caloric restriction, since exercise-trained rats have much smaller and more insulin responsive fat cells than sedentary controls of the same body weight. Ferguson et al. [33] have studied the effects of physical training and its cessation on insulin resistance in obese children: some components (plasma TG, insulin, % fat) of the insulin resistance syndrome are improved as a result of 4 months of physical training in obese children, however, these benefits are lost when obese children become less active. Fasting insulin concentration in relationship to cardiovascular reactivity to exercise in obese children was studied by Gutin et al. [34] demonstrating a significant relationship between fasting insulin concentration and cardiovascular reactivity to exercise, supporting the hypothesis that the relationship between hyperinsulinemia and hypertension is mediated by sympathetic nervous tone and that this process begins in childhood. Physical training seems to have an effect also on plasma leptin concentration in obese children [35]: it has been demonstrated that leptin decreased during a 4-month period of physical training, and increased in the 4 months after cessation of PT; decreasing leptin values were greater in children with higher pretraining leptin concentrations, in those whose total mass increased least and in those whose insulin concentrations decreased most.

Leptin levels seem also to be correlated with RMR: a negative correlation between RMR and leptin levels, independent of body composition has been

demonstrated [36]. In this study, differences were also shown in substrate oxidation rates among DNA sequence variations in the leptin gene (LEPR polymorfism): Lys656Lys showed a trend to oxidize more carbohydrates and less fat than Asn656 carrier.

All these data from the literature stress the beneficial role of physical exercise in obese children, not only for weight loss but also for a significant improvement of the main metabolic parameters (very often altered in these subjects) in fact, if we take into account that long term prognosis of obesity could be severe due to the microvascular complications associated to the disease, the reversibility of metabolic abnormalities is a crucial aspect for the quality of life of these children. If the obese child and his family are well informed and educated about this crucial aspect probably his compliance will be good with a consequent significant improvement of his health.

Genetic Factors, Development of Obesity and Response to Physical Training

The contribution of genetic factors to the development of obesity is estimated to range between 25 and 40% [37]. In most cases obesity susceptibility is a polygenic trait [38]. The number of genes, markers, and chromosomal regions that have been associated or linked with human obesity phenotypes is now above 250 [39].

There is increasing evidence that the major affectors of body fat content, energy intake and energy expenditure are also influenced by genetic factors, as well as responsiveness to dietary intervention [40].

Also predisposition to physical fitness has been evaluated in several studies. The genes and markers with evidence of association or linkage with a performance or fitness phenotype in sedentary or active people, in response to acute exercise or for training induced changes, are positioned on the genetic map of all autosomes and the X chromosome: the 2001 map includes 71 loci on the autosomes and two on the X chromosome [41]. When the genotype is not available, inferences of the genetic influences was made from the phenotype, which is mostly based on the statistical analysis of the distribution in physical activity measures in related individuals and family. These studies express the risk for a relative of a very active or non-active person to be very active, or not, compared to the overall population [42]. If there is a significant association of an allele with a more active or less active phenotype, almost all carriers of this allele will have a high daily physical activity level, and only few of the carriers will show a low daily physical activity level. Maes et al. [43] studied inheritance of physical fitness in 10-year-old twins and their parents: the significance and contribution of

genetic and environmental factors to variation in physical fitness were tested with model fitting. Performance-related fitness characteristics were moderately to highly heritable. Genomic scan on genes affecting body composition before and after training was studied in 364 sib-pairs from 99 Caucasian families [44]. A significant linkage for changes in fat-free mass and the IGF1 genes and suggestive evidence was found for changes in fat-mass and fat-percentage at 1q31 and 18q21–q23, in fat-percentage with the uncoupling protein 2 and 3 genes, and in BMI at 8q23–q24, 10p15 and 14q11, for fat-mass at 14q11, and finally for plasma leptin levels with the low-density lipoprotein receptor gene. This interesting study provides the first genomic scan on genes involved in exercise-training-induced changes in body composition. One of the most important genes involved in the regulation of metabolic response to exercise is the uncoupling protein gene: the uncoupling protein 3 (UCP 3) is a mitochondrial membrane transporter mainly expressed in skeletal muscle that is shown to be associated with obesity, and is also associated in body composition changes after regular exercise [45].

Finally, we could assume that there are many factors (genetic, social, environmental) affecting the predisposition of children (and adults) to practice sports and physical activity, and also affecting the metabolic and cardiovascular effects of PT on MR, RMR, percent fat-free fat mass.

It is obviously assumed that the effect of physical training on obesity in children is dependent by almost all these factors.

The explanation of these different results on the effects of sport activity on childhood obesity it is probably due also to genetic characteristics of the children studied.

Long-Term Studies on Physical Activity in Children Obesity

Unfortunately, there is only a limited number of randomized controlled studies on the efficacy and/or influence of exercise in the treatment and/or prevention of childhood obesity. Physical activity, obesity and cardiovascular risk factors in children were studied in the Belgian Luxembourg Child Study II [46].

A randomly selected population of 1,028 children was studied from a rural area with a high prevalence of obesity and cardiovascular risk factors, demonstrating that physical activity, mainly in boys, contributes significantly to reduction of body fat mass. In another study [47] sports activity (three times per week), nutritional changes and behavior changes was the basis of an outpatient program run for 9- to 12-years-old adipose children since 1987. The control examinations show weight loss and improvement in blood lipid parameters. Children who maintain the correct nutritional habits and remain active in sports, show long-lasting constant weight. This study show the importance of modifying behavior

in physical activity and eating habits: it can be very important, probably more important that a transient caloric restriction. These considerations are also supported by other studies on the effects of decreasing sedentary behavior and increasing activity, also by promoting family-based interventions [48–50]. A two years study on Japanese children reported reduced body weight and body fat after daily, structured aerobic exercise [51]. A 15-week combined aerobic and strength training program resulted in a 3.7% decrease in body fat [52]. A 5–20% decrease in body weight and body fat has been demonstrated, respectively, after combined caloric restriction and physical activity [53].

There is a lot of experimental evidence that physical activity could have positive effects on children obesity by enhancing aerobic capacity, reducing percent of body fat, improving body composition, reducing risk factors associated with obesity and insulin resistance.

Thus, there is evidence to consider physical activity as one of the most important factors for therapy and prevention of obesity in children; to achieve this objective is very important to promote physical activity through behavioral change. To achieve this result, the public/health intervention seems to be most useful and cost-effective for obesity, because the high prevalence of obesity and the school-based interventions seems to be the more appropriate approach. Vandongen et al. [54] enrolled 30 schools randomly assigned to intervention or control condition. Exercise activities were structured and teachers were offered resource package to help with fitness instruction. Increases in endurance fitness were observed in the fitness condition in boys and girls: both exhibited greater reductions in triceps skinfold measures compared to controls. No effects were observed for BMI. In another study concerning a multi-risk factor intervention for cardiovascular risk factor among high school students, physical activity knowledge gains were greater for children in the intervention condition, and differences were also found in resting heart rate, BMI, triceps skinfold thickness and subscapular skinfold thickness [55].

The primary school physical education seems to be important also for the effects on physical activity and obesity prevention during adult life: it has been demonstrated [56] that daily physical education at the primary school level had a significant long-term positive effect on the exercise habits and prevention of obesity during adult life.

Type of Exercise in Obese Children

In children, exercise (defined as behavior that is planned and undertaken with the purpose of improving or maintaining physical fitness) is only a part of daily physical activity.

A 1996 report from the Surgeon General on 'Physical Activity and Health' recommends that 'All people over the age of 2 years should accumulate at least 30 min of endurance-type physical activity of a least moderate intensity, on most preferably all days of the week' [57].

The choice of the type of exercise must be done carefully because it is crucial for the real resolution of the obesity. Of course the different age, sex, gender and degree and duration of obesity explain why it is impossible to suggest a precise type of exercise: it is essential that the type of exercise is chosen for the peculiar situation of that obese child and that it is slowly progressive.

However, it is well demonstrated by many authors [58, 59] that the decrease of obesity is best obtained by a dynamic, aerobic exercise with the use of different muscle groups in different parts of the body.

It is important to begin with exercises in the standing position, followed by cycle ergometer for 10–15 min at a time, dancing and stretching; moreover, walking is another very useful type of physical activity.

Another relevant aspect to remember is that physical activity must include not only morning but also afternoon and (if possible) evening exercises. It is also important that the obese child participates in team games, gymnastics and sports in order to find amusement in his activity; for this purpose, dancing is another good motivator of physical activity especially in adolescents with a consequent improvement of compliance. The exercises should develop the skill, speed, endurance and strength; therefore, if the child improves his general physical fitness, he will enhance his mood and he can become happy to do exercise.

Among the different types of exercises, swimming is the most recommended because this sport involves almost all muscle groups of the human body and gives a significant improve to the physiological body growth. On the contrary, other sports like cycling can be useful but is clearly not complete as swimming for the development of chest muscles and other sports like skating can cause harm to the obese child because genu valgu, which is a common problem for these children, may worsen by skating.

Of course, special exercises for the corrections of orthopedic complications of obesity (e.g. scoliosis) must be suggested.

As a general rule, it is important to underline that all exercise must be performed correctly because incorrect techniques not only reduce their beneficial effects but can also cause serious healthy problems.

Finally, obese children must be encouraged to recognize that there are positive results from their efforts even if not demonstrated in loss of weight; in fact, good results will encourage spontaneous physical activity also during leisure time; in this respect the role of the family and of the friends is essential because they can give obese children their emotional and psychological support that it is essential to increase the possibility of success of exercise training. It has been

demonstrated that the parent activity level is a strong predictor of child activity [60, 61]. In conclusion, exercise and physical activity are important means for prevention and treatment of childhood obesity. The final goal of the exercise for the obese child is the development of a real, continuous, active lifestyle which can assure lifelong health benefits.

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Some Psychological Viewpoints on Obesity

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The study of obesity from a psychological point of view extends over different areas of psychology such as developmental, motivational and social psychology, the psychology of personality, of perception and of psychopathology. The questions asked and the answers that are produced give many interesting perspectives but at the same time produce a somewhat jumbled impression. Partly, it is so because there is no unifying psychological theory of obesity (psychoanalytical theory of obesity is not considered here). Partly it is due to the fact that the descriptions and characteristics given refer both to possible factors that produce obesity and at the same time refer to effects that obesity has on individuals. Often the cause and effect is unclear (e.g. the relationship between obesity and depression) and probably many of the processes take place simultaneously reinforcing each other (e.g. becoming more obese and more depressed).

I think, as many colleagues working in adjacent fields, that the epidemic of obesity has multifactorial causes. Certainly, the societal changes of the last decades are of major importance. What is presented here are viewpoints on different psychological factors contributing to obesity and helping to explain why some individuals become more easily obese, apart from the fact of genetic influence.

I think it is interesting to observe first that culture sets certain premises for how parents and children can eat and behave. Our habits are shaped by society. At the same time modernity has been characterized by increased individuality. This has affected people's relationship to eating and food. In former times, when individual life was controlled to a greater degree by religion and morals, customs as well as economic resources controlled food intake. There existed social controls over when and what individuals could eat [1]. To overeat was once immoral and individuals risked to be publicly denounced by the Church. Scarcity of food, famines, religion and morals jointly prevented most people

from constant overeating and from becoming morbidly obese. Now the situation is different at least in the western world and in westernized societies and cultures. The moral and religious restrictions are weak and it is an individual responsibility to decide when, what and how much to eat. The individual alone must regulate his easily stimulated appetite in the face of unbounded food resources and intense promotion of appealing but unhealthy foodstuffs.

In the following I present three areas of psychological interest. First, I describe some factors influencing the regulation of hunger and of appetite. Second, I describe some characteristics of obese children and third some psychological problems that are associated with obesity. I try also to answer some questions often asked about obese children. How does obesity affect individuals psychologically? Are obese children more depressed and troubled than normal weight children? What happens to overweight children's self esteem? Have severely obese adolescents and young adults been to a greater degree abused physically and sexually than the population in general? What are the links between eating disorders such as bulimia and binge eating and obesity? Do weight-losing programs lead in some cases to the development of an eating disorder, which in turn, only aggravates overweight?

The views presented here reflect findings about young people in our Western world. There are important cultural differences especially when it comes to attitudes towards obesity. In many non-Western cultures to be obese is not, or is less, stigmatizing. On the other hand, the trend seems to be that in the present global culture children and adolescents adopt many western attitudes and ideals. It has been observed for example that body shape and weight ideals are changing towards slimmer figures and less weight among Afro-Americans where traditionally heavier bodies were appreciated. At the same time the incidence of dieting in the group is increasing.

Psychological Factors Regulating Hunger, Appetite and Food Preferences

One aspect of the intricate puzzle of obesity appears to have something to do with the actual regulation of hunger and appetite. The regulation of hunger and appetite is made by complex biological mechanisms. The regulation begins in infancy and is in part influenced by early experiences of nurture and care. Infants learn from early days how much to eat, what to prefer to eat and how fast. Limited evidence [2] suggests that breast-fed and formula-fed children learn slightly different things when it comes to the control of hunger and satiety and preferences for tastes. Children who are breast-fed exert greater control over how much to eat. It is their own feelings of hunger and satiety that control

how much to eat and when to stop. It is probable that breast-fed children develop to a greater extent internal controls for eating. When children are bottle-fed it happens easily that mothers exert control over how much the child eats and encourage the baby in different ways to drink more than the baby would do otherwise. In those cases it is not the child's internal cues that guide him how much to eat but external cues from the environment. Another important observation suggests that breast-fed children show greater acceptance of new foods than bottle-fed (formula fed) children. Breast-fed children learn early to accept different kinds of tastes because different kinds of tastes are transmitted in the mother's milk. Formula-fed children have experience with only a single taste and might therefore be more negative to trying new tastes and accepting a more varied diet. Acceptance of variation might be important in the light of the fact that children by nature prefer foods high in fat and sugar and need to learn liking less caloric and healthier foods.

Breast-feeding has many positive qualities that render it the preferred feeding choice in infancy. The results from studies on bottle-fed versus breast-fed children and obesity are diverse. It seems nevertheless that breast-feeding is more common among normal-weight mothers than among overweight and obese mothers. And it seems that the eating environments in families with obese parents differ in important ways from families in which neither parent is obese. On the one hand, it seems that in many cases the consumption of calorie rich and fat food is high. On the other hand, it seems that many obese parents begin early to control the eating behavior of their children. The controlling probably makes it more difficult for these children to develop their own control mechanisms of food intake. Parents shape their children's eating environments in many ways. First, they do it through the choice of an infant feeding method, i.e. bottle vs. breast-feeding. Second, it is shaped by the foods that are made available at home. Parents function also as models for their children in many ways. They mediate food and taste preferences, attitudes to new foods and table manners. Parents probably convey other subtle information affecting children's eating habits such as eating speed. Parents promote habits affecting weight by encouraging or discouraging television watching in the home. Television in its turn provides eating models through advertisements and promotes sedentary lifestyle.

Many concerned and well-meaning adults try to influence the food preferences of children and adolescents by pervasive messages about health consequences of unhealthy eating. They try also to control the eating of unhealthy foods by forbidding them and by encouraging the consumption of healthy foods. Research findings suggest that these popular practices often have a negative effect. Restricting children's access to foods enhances the liking of the forbidden foods and increases their consumption. Persuading children to eat new foods is equally counterproductive and often produces resistance and even

aversion towards the new food. Children come to like and eat what is familiar. It is natural for infants and children to reject new foods with the exception of sweet and salty foods. Therefore, it is important for children to have early experiences of new tastes and to be gradually and repeatedly exposed for new foods. Modeling, where children see parents and other children eat new and healthful foods, is probably the easiest way to shape healthier eating habits.

Perceptual Factors Influencing Appetite

Our food preferences are based to a great extent on taste, appearance, texture and even the feel and sound of the food and to a lesser extent on the nutritional value. Many obese people seem to differ in systematic ways from many non-obese when it comes to factors that influence appetite. Through a series of experiments, Schachter [3] could demonstrate that many obese people are to a greater extent guided by external cues when it comes to eating. For many obese people it is the sight and smell of food and the time of the day that function as cues for eating. In contrast, normal weight people seem to depend more on inner cues such as stomach contractions, glucose levels and so on. In everyday situations it means that obese people will frequently consume more food because they will encounter many situations that will be tempting. In our culture a lot of foods and sweets are displayed in public places to attract our attention and to hit our senses. Not all obese people are 'externals' but still it seems that externality is one mediating factor contributing to obesity in some individuals.

It seems further that obese individuals are more sensitive and receptive to sensory qualities of food. In several experiments it has been shown that obese people eat significantly more than non-obese when the food tasted good, but eat about the same amount when it tasted unenticing [4]. Adult persons participated in these experiments but anecdotal evidence suggests that there are many gourmets among children too. It is probable that obese children too are influenced more by the positive sensory qualities of food than non-obese.

Children can learn to like almost anything if they start getting it early. The aborigines of Australia find worms delicious. In Sweden some people like rotten fish. Humans learn preferences through associating the food eaten with consequences. For example, nausea leads to strong aversion towards a food that has been consumed. We learn quickly to avoid foods that make us sick. However, learning to select foods that are nutritious and healthy takes more time. Pleasant experiences like feeling well afterwards, pleasant environment and friendly company give positive associations with the food and also increase the liking.

Emotional Factors in Overeating

From clinical experience, we know that some obese children eat even when they are not hungry but because they feel emotionally upset, stressed or frustrated. Possibly the mothers of these children comforted their babies with food when the children cried or showed discomfort. Later in life such people may see food as a consolation. Eating and digestion produce feelings of physical satisfaction, which balance negative feelings of sadness, sorrow or anger.

Parental lack of attention or neglect is a factor predicting obesity. Many mothers from low-income environments can be preoccupied with surviving their daily life stresses and have less capacity to feel and care about the different needs of their children. In such a situation many use food to cope with the stresses and use food as a tool in parenting. The mothers can have difficulties in setting limits with their children around food. Many have inadequate knowledge about normal child development, eating behaviors and healthy food habits. The lack of knowledge makes it difficult to find solutions and alternatives to problems in parenting [5].

Research on adults suggests there is a relationship between emotional distress and overeating. Depression for example usually results in weight loss but some depressed individuals gain weight. It seems that tendency to eat more when depressed is mediated if the person is high in self-restraint [6]. People who often diet tend to be restrained eaters. Restrained eaters are people who continually worry about how much and what they eat. Restrained eaters often feel hungry, are readily tempted by the sight and smell of food and consciously attempt to control their eating. But when emotionally upset they easily lose control and overeat or eat foods high in calories. Different negative emotions (anxiety, sadness, dissatisfaction and so on) cause these individuals to breach their intentions to diet. Afterwards many of them feel guilty and unhappy because they have eaten the 'forbidden foods'. The feelings of guilt and failure easily start a vicious circle of overeating and reinforced negative emotions.

Socio-Economic Status, SES, and Family Problems in Obesity

Obese children have more often parents of low SES than normal weight children [7]. And families of low SES often have more social and psychological problems than the population in general. Psychological problems may play an important role in the development and maintenance of obesity. Parenting style in low SES families is to a higher degree characterized by neglect and permissiveness. And this type of parenting style is common in families where

children have psychological problems. Emotional distress in early childhood can affect the energy balance by shifting behavior into overeating and physical inactivity. Emotional distress could also affect hormone balances, which in turn could have negative effect on fat accumulation.

Difficult psychiatric conditions are sometimes associated with obesity. A recent study showed that borderline personality was associated with higher body weight, probably due to deficits in self-regulation [8]. The nature of this association and implication for obesity is, however, unclear. For example, it has been postulated that many patients described as borderline have in fact been sexually abused in childhood. They have developed symptoms similar to borderline that more aptly should be seen as complex posttraumatic stress symptoms [9]. Patients showing this set of problems require more effort in the treatment of obesity as they more easily abandon treatment and are defeated by their sense of having failed.

Depression in Obese Children

High prevalence of internalizing problems is found in children with different chronic diseases and children with obesity are no exception [10]. Internalizing problems are defined as lack of self-confidence and a lasting feeling of insufficiency, which can manifest itself in withdrawal from social situations and from achievement demands. Internalizing problems are often a sign of sub clinical depression and a risk factor for more aggravating adjustment problems later [11].

However, studies comparing obese and non-obese persons have generally failed to find differences in global aspects of psychological functioning. One probable explanation is that obese individuals in clinical treatment have more problems than obese individuals in the general population [12].

Older studies comparing obese and non-obese adult populations have often failed in demonstrating the predominance of depression in obese. In several more recent studies depressive symptoms among clinically obese patients have been reported. Especially obese women seem to suffer from depression to a much higher degree than non-obese.

Usually it is believed that social stigmatization associated with obesity causes individuals to become depressed. Obese children develop more easily negative thoughts about themselves, experience fewer positive and more negative social interactions and encounter more physical difficulties (which also reduces their physical activity). Obese children learn also to feel helpless and vulnerable if they have tried to control their weight and failed to do so. All these are potential factors causing depression.

The study of depression in children has up to the last decade been rather limited, because of disagreement about the existence of depression in children in general and about possibly different manifestations of depression in children [13]. It was only at the end of the 1980s that a majority agreed to the view that mood disorders in children have basically the same manifestations as in adults, a view adopted for example in DSM-III-R from 1987.

Depressed children show, in accordance with adults, depressed mood, feelings of worthlessness, diminished ability to think and concentrate and loss of energy. A recent survey at National Center for Childhood Obesity in Sweden showed that obese children judged themselves to have these symptoms and that the parents judged their children to have less stamina compared to healthy children.

According to the presentation so far depression would be a result of negative experiences associated with obesity. But there is also some preliminary evidence that depression might be an important risk factor for the development of obesity, at least for some adolescents [14]. In some individuals depression is followed by an increase in weight and subsequent obesity.

To get further insight into the role of depression and other psychiatric conditions more data about early psychological development will be of help. A new international completing diagnostic and statistical manual for children aged 0–3 years is under development. The focus of attention there is psychiatric problems in infancy. This promising field of research might help us to find early precursors to obesity. Depression, anxiety and posttraumatic stress disorder are serious conditions in infant psychiatry and these states may play a contributing role for early acquisition of obesity.

Do Obese Children Have Lower Self-Esteem than Non-Obese?

A factor often associated with depression is self-esteem. In many studies normal levels of self-esteem in obese children have been reported. This is surprising considering the fact that obesity is stigmatizing and that people in our contemporary culture identify who they are with how their own bodies compare with idealized types. In an investigation of self-esteem in youths aged 14–18 years in Sweden [15] the team came to the conclusion that there was no difference in self-esteem between the obese adolescents and non-obese. The only exception was that the obese individuals rated themselves lower in physical characteristics. A prospective large survey of 1,090 obese children in the USA [16] showed that obese children develop decreased self-esteem during the transition from preadolescence to adolescence. The slightly contradictory results suggest nevertheless that obese children are affected in their self-esteem

by obesity but that there are differences in to what extent depending on sex, race and age. Pre-adolescent girls, for example, are affected by overweight in their physical self-esteem but not in their global. It seems furthermore that some children are able to compensate for their lowered self esteem in physical characteristics by feeling confident about their skills and talents.

Results from treatment studies [17] show that weight loss treatment programs appear to improve self-esteem, at least initially. But we know that it is difficult to loose weight permanently and little is known how repeated attempts at loosing weight affect self-esteem. Clinical experience suggests that some adolescents develop eating disorders, depressions, and poor confidence in their capacity to ever gain control over weight as a result of repeated failed attempts to lose weight.

Sexual and Physical Abuse in Obese Children

Of importance for both the development of obesity in some individuals and for treatment is the issue of sexual abuse. In the last decades it has been more fully acknowledged that many children are abused. Research has increasingly demonstrated that mistreatment – e.g. physical punishments, sexual abuse, verbal insults, violent quarrels and alcohol abuse by parents – is a common experience for many children. Abuse in childhood is a risk for adult obesity and many other diseases and health risk behaviors [18]. There is a graded relationship between how many different kinds of mistreatment or neglect a child has experienced and the probability of developing diseases and risk behaviors in adulthood. If a child has experienced many different kinds of mistreatment then the risk increases that the child will demonstrate different health problems. Mistreatment has psychological, behavioral and somatic consequences. Low self-esteem, distrust, depression, body dissatisfaction and even self-hatred are common psychological outcomes of severe abuse. Examples of behaviors include self-destructive behaviors of varying degree such as suicide attempts, drug or alcohol abuse, binge-eating and weight control behaviors such as dieting and purging. Many abused children develop in adulthood somatic symptoms, e.g. headaches, chronic pain, gastrointestinal problems and obesity.

Women are especially vulnerable to sexual abuse. It is estimated that between 15 and 30% of all women have been sexually abused as children. Some data suggest that abuse is a contributing factor that significantly increases the risk of developing eating disorders and obesity. One psychological mechanism behind this is that many people react to the psychological distress by comforting themselves with food. Many abused girls and boys, especially if the abuse was sexual, react to the abuse also by becoming severely dissatisfied with their

bodies. This leads in many cases to attempts to control body weight by behaviors typical of eating disorders – bingeing, purging, etc. Bingeing and bulimic behaviors may in turn lead to obesity. Some sexually abused individuals (mostly women) may develop obesity as a defensive mechanism against undesired sexual advances. By becoming obese they keep potential proponents at a distance.

It is important to take the possibility of abuse into consideration when planning the treatment for overweight. Patients with a history of sexual abuse lose less weight during treatment and more often than other patients discontinue treatment [19]. It is, therefore, important to address the emotional sequels of abuse. To help patients who have suffered abuse requires tact and sensitivity. This group of patients needs time and confidence to disclose extremely painful and degrading experiences.

Identity as Obese

Childhood and adolescence is of primary importance for identity formation. A child's view of himself is partly formed in the process of interaction with his environment. Peers' comments and reactions as well as how the child experiences how he is managing in his environment are two important factors shaping identity. Many obese children experience that they are not managing their physical surroundings as well as children who are slim. Many obese adolescents feel rejected and ignored by peers and adults. Other people look at them and see in them only a fat person. Individuality is not recognized. The fiction writer Margaret Atwood captures this in her novel 'Lady oracle' where she lets an obese adolescent girl say, 'all fat women look the same… fat women are not more noticeable than thin women; they are less noticeable, because people find them distressing and look away'. Many people associate obesity with lack of control. Adolescents who are conditioned to this view experience hopelessness and shame. To consider oneself as lacking control is very disturbing at an age when one struggles to have control of one's life and pretends to be in charge of the affairs.

Some obese adolescents adopt a negative view of themselves as big, cumbersome and unattractive persons. When this negative self-image becomes the core identity of an individual it is difficult to change. A request or appeal to lose weight may be experienced as a threat because for the young person it means giving up his only identity. And it is better to have any identity, even a negative one, than to have none. Even individuals who manage to lose weight can have difficulty changing this negative self-image. Persons who were obese as adolescents and succeeded in losing weight often retain their negative self-image such as being big and clumsy.

Bullying

Bullying is both a contributing factor to obesity and an impediment to gaining control over one's weight. Bullying is a common problem worldwide affecting some 20% of children [20]. It seems that bullying is most intense between the ages of 7 and 12. Many bullies chose obese children as their target for teasing and harassment because their appearance is conspicuous and they are seen as different. Obese children are vulnerable because they are sensitive to comments about their looks. Bullying has many negative consequences for the victim. Bullying leads to feelings of sadness, sleeping disturbances and low self-esteem. This in turn may increase behaviors that aggravate obesity, e.g. consoling oneself by eating, reduced social contacts and reduced physical activity. Children who have been criticized during physical activities develop negative attitudes toward sports and exercise less [21].

Obesity and Eating Disorders

An area of functioning that attracts the attention of all professionals working with obese children is their eating habits. Evidence points to the fact that obese persons overeat. It seems also to be a pattern that many obese individuals systematically underestimate their food consumption. The underestimation is not deliberate. The individuals really seem to have difficulty to remember how much they ate. It has also been observed that obese children eat faster and fail to show the normal pattern of slowing down the rate of eating toward the end of a meal. It is still not clear what role these different patterns have in obesity.

It is estimated that between 20 and 30% of obese adults engage in binge eating and bulimic behaviors [22]. Especially obese girls are at risk for developing an eating disorder. For many bulimic patients the disorder starts in adolescence. And many adult bulimics have a history of childhood obesity. It seems clear that there is a connection between bulimia and obesity but we don't know the exact nature of the association. Some investigators have suggested that repeated attempts at loosing weight might cause binge eating disorder. A contributing factor could be that in some people dieting, even in moderate forms, leads to considerably increased sensitivity of serotonin receptors [23]. The alteration in brain serotonin neurotransmitters could lead to deregulation of eating.

Obese adolescents with bulimia or binge eating have more often than obese adolescents without eating disorder additional emotional and behavioral problems. Many start early with dieting and have many unsuccessful attempts of weight reduction. They report difficulties in perceiving hunger and satiety. Many feel that they lack control over eating. Their self-esteem is low and they

are to a great extent dissatisfied with their bodies. The risk of a major depression later in life is also increased for this group [24].

When planning the treatment of obese children it seems wise to consider the risks of promoting eating disorders. It is important that potential bulimic tendencies are not aggravated by health care professionals' recommendations for dieting and exercise.

Concluding Remark

Psychology has an important role in both research and treatment of obesity. We still need to know more about psychological factors that influence eating behaviors, activity, well-being and healthy weight. It could be stated that obesity is a consequence of maladaptive behavior. There are many psychological factors that influence behavior – from feeding style in infants to parenting styles and emotional factors. These issues affect children in individual ways. Therefore, the circumstances of obese children need to be analyzed individually. In order to gain control over weight the child and the parents need to make permanent changes. The changes affect habits and habits are difficult to alter. It is important to find circumstances that facilitate change as well as obstacles preventing change. These kinds of necessary changes cannot be imposed on parents and children. Information and advice is important but not enough. Parents and adolescents need help in exploring their problem and clarify their values and feelings that may contribute to obesity as well as identifying feasible goals and choices. Parents, and children when they have become mature enough, need to accept responsibility for their lifestyle. It has been suggested [25] that shared responsibility where parents provide different healthy foods but where children decide when and how much to eat is the most accessible way – at least in our democratic and individualistic culture.

However, it is unfair to shift all responsibility to parents and children. The type of lifestyle that is contributing to obesity is a result of the culture we live in. Different institutions, organizations and businesses shape this culture. Many messages that are directed through mass media to children and adults influence them towards over nutrition, sedentary life and dissatisfaction with their bodies. It is a trend nobody wants to take responsibility for.

I wonder also if successful treatment should be gauged by attained BMI? Other aspects of how young persons are affected by obesity ought to be taken into account and attended to. The quality of life of the obese partly depends on how they think and feel about themselves. It is important to help those who have low self-esteem, negative identity, and are depressed and risk developing an eating disorder. It is not always helpful if patients suppose that their main

goal is to attain 'normal' weight. In many cases it is an unrealistic goal, which inevitably leads to an experience of failure. Many end up feeling incompetent and rejected. As a consequence many give up altogether their attempts at weight control and healthier lifestyle.

Too much, too little as well as wrong food can be fatal. In the middle ages people in some places in Europe consumed contaminated food because of hunger. The scarce and adulterated food made them sick and probably kept them in a semi permanent state of hallucination and madness [26]. In our days anorexia is a serious condition leading in many cases to death. Obesity on a large scale has become only recently an important public health problem in those parts of the world where food is abundant and over nutrition possible. From a philosophical point of view, it can be said that lack of moderation leads to problems. Maybe obesity is only one symbol of our excessive culture?

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Musculoskeletal Consequences of Obesity in Youth

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Obesity is a common disease in industrialized countries and we observe an increasing prevalence of early onset in childhood: at present it is the most prevalent nutritional disease of children and adolescents in the United States, where it affects 1 in 5 children [1]. The epidemiological situation in European countries is not very different and from recent surveys it can be estimated that 10–20% of children are obese [2, 3].

A high body mass index (BMI) does not have a negative influence on the locomotor system in general. A recent study for example reports a protective effect of moderate overweight on bone density in the elderly [4]. There is no doubt, however, that an association between obesity and several musculoskeletal disorders exists. While this relationship might theoretically be purely coincidental in many individuals, there is also enough evidence that neurological or systemic dysfunction in orthopedic disorders can cause obesity. Fiore et al. [5], for example, showed that children and adolescents with myelomeningocele often have a BMI above the 95th percentile. On the other hand, obesity can also directly lead to dysmorphism and structural damage of lower extremity joints due to overload. In these cases musculoskeletal consequences that characterize the situation in obese adults are preceded by abnormalities that might begin in early childhood.

Aim of this chapter is to discuss some major sources of musculoskeletal morbidity for which the causal effect of obesity is established.

Flatfoot

Obese children are often presented to orthopedic surgeons with their parent's concern about foot problems. In most cases, the young patients have a flatfoot deformity and complain of no or only moderate pain.

Although there is no universally accepted definition for flatfoot, the deformity is characterized by increased eversion of the subtalar complex during weight-bearing with plantar flexion of talus and calcaneus, a dorsiflexed and abducted navicular and a supinated forefoot. The clinically recognizable low or absent longitudinal arch results from the malalignment of different subtalar joints. While flat feet are often flexible in the beginning (normal foot morphology and arch height without weight bearing), the pathology can become fixed or rigid (marked deformity with and without weight-bearing) after some years due to secondary structural changes.

Flatfoot is not a pathologic condition per se: normally developing infants have flexible flatfeet and gradually develop a normal arch during the first decade of life. Reduction of the physiologic subcutaneous fat pad under the medial row as well as a slowly maturing bony arch by longitudinal and slightly oblique growth of calcaneus and metatarsals normally result in a gradual development of the 'normal' foot. There are some risk factors, however, which can affect this process of maturation and lead to marked pronation deformities: Major contributing factors are ligamentous laxity, rotational deformities, equinus, tarsal coalitions and obesity. Especially an excessive elevation of body weight can be very detrimental to the development of a pediatric foot, as the constant mechanical overload during weight-bearing forces the subtalar complex in increased eversion.

Numerous surveys of pediatric foot deformities have looked at an association with elevated body weight. Riddiford-Harland et al. [6] calculated the BMI of 431 children from Australian primary schools and took static weight-bearing footprints of each participant. They found a significant difference in measured parameters (footprint angle and indices) between obese and non-obese subjects and concluded that excess body mass appears to have detrimental effects on the foot structure of prepubescent children. Bordin et al. [7] evaluated the incidence of flat foot by photo-podoscopic examination in 243 primary school pupils and calculated the Cole index (ideal ratio between the ideal BMI at the 50 degrees percentile of weight and height as function of age, sex and real BMI) of all participants from anthropometric data. The incidence of flat foot in the study group was 16.4% and the frequency of obesity and overweight was found to be 27.3% (Cole index >120). An analysis of variance showed a significant difference between the Cole index in subjects with flat feet and normal feet.

In our recent investigation [3] we determined the clinical prevalence of flat foot in a study group of 411 children (215 girls and 196 boys) with a mean age of 14.5 years (9–17 years) who required in- or outpatient pediatric treatment due to severe obesity (individual BMI more than 2.8 standard deviations over age-specific mean values [8]). The mean BMI in this study group was

32.9 kg/m^2. We found flat feet in 77 children (18.9%), 66 participants (16.1%) had flexible and 11 participants (2.7%) fixed deformities which did not resolve with off-weight-bearing. Due to the lack of a control group it is very difficult to interpret these data, although the prevalence of flat foot was somewhat higher in a subgroup of extremely obese patients (mean BMI 35.2 kg/m^2).

It might be interesting to compare the results of our investigation with data from a German field study in 345 high school pupils (age 10–13 years): with clinical examination the authors determined a prevalence of flat foot of 19.1%, but could not find a correlation between body weight and foot deformity [9].

One recent study confined the analysis not only to static measures, but looked also at the plantar pressure patterns in prepubescent children [10]. The investigators obtained foot plantar pressures using a mini-emed pressure platform in 13 obese (mean BMI 25.5 kg/m^2) and 13 non-obese children (mean BMI 16.9 kg/m^2) matched for gender, age (mean age 8.1 years) and height. The calculation of force and pressure during static and dynamic loaded and unloaded conditions revealed interesting differences in gait pattern: Although rearfoot dynamic forces of obese study participants were significantly higher than those of controls, these forces were experienced over significantly higher mean peak areas of contact. Therefore, rearfoot pressures experienced by the two groups did not differ. However, the mean peak dynamic forefoot pressures generated by the obese study participants were significantly higher than those generated by the non-obese subjects. The authors conclude that foot discomfort-associated structural changes and increased forefoot plantar pressures in the obese foot may hinder obese children from participating in physical activity.

Another investigation looked at foot mechanics during walking in obese and non-obese female adults [11]. The severely obese participants (BMI 41.14 kg/m^2) had significantly greater forefoot abduction and rearfoot motion than normal weight females.

There are also some investigations, where no correlation between foot deformity and body weight could be demonstrated. In a survey of 2,300 children from India, Rao and Joseph [12] found no difference of mean BMI values in participants with and without flat foot deformity. Jerosch and Mamsch [9] also could not find a correlation in their investigation of German high school pupils. Garcia-Rodriguez et al. [13] report an increased prevalence of flat foot only in their 4- and 5-year-old group of overweight Spanish children, whereas in elder participants no such correlation could be established.

It is very difficult to discuss these results as different study designs and a lack of valid data regarding inter- and intra-observer reliability of clinical investigations impairs comparability. Even the studies which found higher prevalence rates of flat foot in obese children when compared to non-obese children

cannot conclude the clinical relevance of their results without any doubt. Due to the lack of valid data regarding the natural history of flat foot, not every deformity must be considered as a pathological one which requires treatment. Only few investigators look at associations of foot trouble and body weight in adulthood and if they do so, it is very difficult to recall the time of exposure to obesity as a potential risk factor [14]. Bruckner and Rosler [15] for example, who performed a cross-sectional evaluation of 103 women and report a dependence of painful foot deformities on body weight, have difficulties in attributing the symptoms to a clearly defined causal pathology.

Although most studies seem to indicate a correlation between high body weight and foot deformities in children as well as in adults, further investigations into possible consequences of obesity, particularly any effects on pain development and discomfort, are necessary therefore.

Tibia vara (Blount's Disease)

Idiopathic tibia vara, also described as osteochondrosis deformans tibiae or 'Blount's disease' is a disorder characterized by abnormal growth of the proximal tibial physis, which results in progressive varus angulation below the knee [16, 17]. The disease can be classified into three age-onset groups: infantile (less than 3 years), juvenile (4–10 years) and adolescent (11 years and older). All three forms of tibia vara have similar clinical, roentgenographic and histopathologic characteristics, but differ in the amount of remaining growth, the magnitude of medial compression forces across the knee and recurrence rates after surgical correction [18]. Similar histopathologic findings with injury to the growth plate as demonstrated by fissuring and clefts in the physis as well as fibrovascular and cartilaginous repair tissue at the physeal-metaphyseal junction indicate a common etiology of all three groups [19]. The observations are also similar to histopathologic findings in slipped capital femoral epiphysis (SCFE), suggesting a common etiology [18].

The clinical characteristics of most study groups with tibia vara are very similar and often focus on marked obesity besides normal height, black race and slowly progressive genu varum [Thompson et al., 1984]. In a very well documented series of 8 patients with juvenile-onset as well as 9 patients with adolescent-onset disease, Thompson and Carter [18] found marked obesity in all children. While the mean height of the children was in the 75th percentile (range 50th to 95th percentile) the weight exceeded the 95th percentile in every case by a mean of 20 kg (range 10–61 kg).

Dietz et al. [20] reported a series of 18 patients with infantile- and juvenile-onset disease. Twelve children (67%) had weights for height greater than 120%

ideal body weight (mean 156% ideal body weight). An interesting finding in this study group is a highly significant correlation between the body weight and the femoro-tibial shaft angle. From this result, the authors conclude that the degree of obesity might be a primary determinant of the tibial deformity. Due to a greater risk of recurrence the obese patients had also more osteotomies than the non-obese children in this population.

In a recently presented group of 19 patients with late-onset tibia vara, the average weight was 258 lb and all adolescents weighed >95th percentile [21].

Wenger et al. [19] found that most children with adolescent tibia vara maintain a mild degree of infantile physiologic genu varum. In these cases predisposing factors, such as obesity, extreme activity, or rapid growth, injure the posteromedial physis continuously. The result of repetitive trauma in a limb already in mild varus is growth suppression and further varus. Another interesting hypothesis for the etiology of adolescent tibia vara was presented by Davids et al. [22]: In a biomechanical investigation the hypothesis was examined that dynamic gait deviations to compensate for increased thigh girth due to obesity ('fat-thigh gait') could result in increased loading of the medial compartment of the knee during the gait cycle. With three-dimensional motion analysis certain gait deviations like dynamic stance-limb knee varus, increased stance-limb knee rotation, and swing-limb circumduction could be identified. These loading conditions, in conjunction with excessive body weight, can obviously generate compressive forces of sufficient magnitude to alter physeal growth.

Although in most investigations the relationship between the onset of obesity and the onset of Blount's disease could not be determined due to a retrospective study design, there is enough evidence to conclude a causal effect of elevated body weight in the pathogenesis of the disease. The natural history is somewhat unclear, but a majority of patients seems to develop knee osteoarthritis [21]. Therefore, it is justified to suggest that the development of obesity in a child with physiologic bowing should be viewed with concern and efforts should be directed at weight reduction.

Slipped Capital Femoral Epiphysis (SCFE)

Slipped capital femoral epiphysis (SCFE) is a failure of the upper femoral epiphysis allowing displacement of the femoral head on the neck and is also called 'epiphyseolysis'. Weiner [23] has described the different etiologic theories very well and presents a concept of pathogenesis, which includes recent histomorphological as well as clinical data: A delicate imbalance of puberty hormones weakens the physis by negatively impacting on the collagenous

framework of physis and perichondral ring as demonstrated by severe morphologic changes at all metabolically active levels of the growth plate. Constant shear forces acting on this weakened physis exceed its ability to resist displacement. Main mechanical risk factors for a progressive displacement are an increasingly oblique physis lying in a relative degree of retroversion and a large body mass.

The commonly encountered large body mass seems to play a significant role in the disease process. Many investigators discussed that risk factor and even described study populations with SCFE where most involved children and adolescents are overweight or obese [20, 23–26].

Whether obesity is simply a matter of excess body mass or a biochemical disorder, with as yet unknown hormonal alterations is not known [23]. Wilcox et al. [24] presented a group of SCFE patients with body weights above the 80th percentile, thyroid levels below the 25th percentile, and markedly decreased testosterone levels. Due to the anabolic effect of testosterone versus estrogen the mechanical strength of the growth plate in females seems to be stronger than in males, which could explain a male preponderance of SCFE. If relative hypothyroidism exists, the growth plate strength probably also is weakened.

At present it is unclear if mechanical overload alone, alterations in the hormonal balance alone or both risk factors together are needed to cause the specific pathology of the growth plate. Obesity, however, seems to play a major role in the probably multifactorial disease process.

Apart from the different classification types of SCFE, which all lead to hip or thigh pain with weight-bearing (stable slip) or even inability to walk (unstable slip), there is probably another entity, which shows a subclinical course: Murray [27, 28] has described a ‘tilt deformity’ of the femoral head as a consequence of excessive physical activity during the growth period, which does not cause remarkable pain and is therefore often not recognized. Like the painful slip in classical SCFE, however, this more or less mild deformation of the epiphysis can cause hip OA in the long term. Segesser [29] for example analyzed a patient cohort with hip OA and found an association between tilt deformities and a history of professional sports activity.

The different entities of a clinically painful slip (stable or unstable), which requires surgical treatment, and a mild subclinical deformation of the growing hip (always stable and obviously painless) are probably a major reason for differing reports in the literature regarding the incidence of SCFE. Kelsey et al. [30] estimated an incidence of approximately three per 100,000 per year in the southwestern US general population, while Jerre et al. [31] found an incidence of 0.08% in a Scandinavian survey. The definition of SCFE (with or without inclusion of subclinical findings like a mild tilt deformity) and the design of the study (e.g. hospital- or population-based, type and extent of radiographic

investigation) will influence the results of prevalence and incidence studies to a certain degree. From hospital-based cohorts with advanced hip osteoarthritis (OA) we know, however, that the incidence of symptomatic and asymptomatic slips together must be higher: In a meta-analysis of published studies which evaluate morphological changes of the hip as risk factor for OA ('secondary osteoarthritis') 5–50% of arthritic hips are attributed to former SCFE [32]. In the 'Ulm Osteoarthritis Study' [33], for example, we could radiographically detect a tilt deformity as underlying hip pathology in 7.1% of all 420 participants with advanced hip OA (220 females and 200 males with a mean age of 63.3 years).

The prevalence of hip OA in Caucasian populations in the age group of 60–70 years is around 10–20% [34]. If in 7% or even more of all hip OA patients a tilt deformity would be a main risk factor, the incidence of SCFE must be substantially higher as proposed.

When we consider obesity as a main risk factor for epiphyseal slips, it would be important to estimate the prevalence or incidence of radiographic changes in a patient cohort with elevated body weight. In a recent investigation of the Pediatric and Orthopedic Departments at the University of Ulm 411 children and adolescents (215 girls and 196 boys, mean age 14.5 years) necessitating treatment for marked obesity (BMI >2.8 standard deviations) were screened for hip pathology [3]. All participants underwent a clinical examination of both hips and in case of an abnormal range of motion (e.g. diminished internal rotation) hip radiographs were obtained consecutively. In 54 patients a radiographic examination (a.p. pelvis and axial view) was performed and the 'femoral-head-ratio' according to Murray [27] as a measure of epiphyseal tilt determined: The centre points between the most lateral part of the greater trochanter and of the narrowest portion of the femoral neck are joined and the line extended proximally to traverse the femoral head. The greatest width on each side of this line to the edge of the femoral head is then measured. Division of the figure for the lateral portion into the figure for the medial portion produces a coefficient designated as the femoral-head-ratio. Values greater than 1.35 indicate the presence of a tilt deformity. In the radiographically investigated subgroup of 54 obese patients, we identified 11 individuals with an elevated femoral-head ratio (5 boys and 6 girls). The mean body weight in these patients was 99.8 kg, the mean BMI was 36.8 kg/m^2. Only one third of these patients reported minor and occasional complaints in hip and/or knee joints. No study participant had undergone surgical treatment of SCFE prior to entry and no patient showed clinical or radiographic signs of SCFE at examination.

Due to ethical considerations we did not perform radiographic investigations in the total cohort of 411 obese children. The study design implicates other methodological problems as well (sensitivity, specificity, and reliability of

measurement techniques not assessed) and we are faced with a considerable selection bias, as only patients involved in treatment programs due to severe obesity were included. The results indicate, however, a higher prevalence of SCFE-like tilt deformities in the patient cohort of severely obese children as would be expected in the normal population. As the deformities are relatively mild and the natural history with regard to development of hip OA is somewhat unclear in these cases, we would not perform surgical interventions.

If the elevated body weight as a general risk factor for the development and progression of OA will not be reduced over time in the patients, however, a negative influence on their future hip situation cannot be excluded and they should be carefully watched.

Knee and Hip Osteoarthritis

We have no detailed information from large and well-documented cohorts about the natural history of obesity-induced foot, knee and hip deformities discussed above. There is enough evidence, however, that at least major disturbances of joint anatomy in advanced tibia vara as well as SCFE can lead to early and severe cartilage degradation with clinical and radiographic signs of OA. In these cases cartilage surfaces cannot tolerate daily mechanical loading over time, as the transmission of forces is altered due to joint incongruency.

Another interesting question is, however, if even anatomically normal joints – without evidence of axial deformation or epiphyseal tilt – tolerate high mechanical loads over time in obese patients or if they also develop osteoarthritic changes. A positive association between obesity and OA of the knee has been observed in several large studies [35–39] and weight loss has been shown to reduce the incidence of knee OA in women [40]. Recent studies also report an association between high BMI and OA of the hip, but results are less compelling [39, 41–44]. In all these series no special emphasis was given to specific deformities of hip or knee joints.

In the Ulm Osteoarthritis Study [45], we tried to assess independent associations of obesity (30 or more kg/m^2) and overweight (25 or more but less than 30 kg/m^2) with radiographically defined OA patterns in men and women with advanced knee and hip OA. As we looked for specific anatomic changes of the investigated joints (tilt deformity, axial malalignment of the legs) as well, an analysis with and without these confounding risk factors for OA was possible. We observed a positive association between obesity, overweight and BMI and a pattern of bilateral radiographic knee osteoarthritis and the association was even more pronounced after controlling for potential confounders.

No association, however, between relative weight and bilateral OA was observed in participants with hip OA.

There is still an ongoing discussion about the contribution of local biomechanical factors and systemic or metabolic factors to explain the higher risk of OA in obese populations. In our study, a metabolic link between obesity and OA is not very likely, as we found an association in knee disease but not hip disease.

The time sequence between obesity and OA pattern can not be addressed in a cross-sectional study. Theoretically, OA could lead to higher body weight through a sedentary life style. Neither the results of our study with different associations in knee and hip disease (in contrast to similar functional impairment in both study groups) nor data from other case-control or even cohort studies support this theory. Mechanical rather than systemic effects of obesity appear to be a reason for the causal relationship with OA.

Conclusions

In conclusion, we can find associations between obesity in children and specific deformities of feet, knee and hip joints. Although the natural course of these deformations is not very well documented, it can be assumed that at least tibia vara and slipped capital femoral epiphysis lead to clinically relevant knee and hip OA. Even without manifest deformation of a single joint through high body weight the continuous mechanical overload seems to result in cartilage degradation as well. Strong associations between obesity and knee OA (and also weaker associations between obesity and hip OA) support this theory. Meanwhile there is enough evidence that obesity and OA are linked together in a causal relationship.

Considering the adverse effects of elevated body weight on the musculoskeletal system, we must increase our efforts to lower the incidence and prevalence rates of overweight and obesity in children, adolescents and adults.

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Lipids and Lipoproteins in Childhood Obesity

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Prevalence of obesity in children and adolescents has increased during the last decades in almost all countries worldwide. From cross-sectional and longitudinal studies of many countries and different ethnic groups there is ample evidence that obesity in children and adolescents is associated with altered lipids and lipoproteins and with other well-known risk factors for cardiac disease in adulthood, e.g. insulin and blood pressure.

Among cardiovascular risk factors which are associated with increased morbidity and mortality lipids and lipoproteins are of special importance and in many studies childhood obesity has been shown to be associated with increased levels of total cholesterol, LDL-cholesterol and triglycerides and decreased levels of HDL-cholesterol [1–4]. However, the degree of obesity is consistently more strongly associated with HDL-cholesterol and abnormal lipid profile in male adolescents than in female adolescents [5, 6].

Recent data clearly show the importance of body fat distribution and in particular of visceral fat even in the adolescent age group [3, 7–9].

The importance of increased lipids and lipoproteins is underlined by the fact that tracking of unfavorable lipid levels from childhood and adolescence to adulthood was reported in several longitudinal studies [10–13], and moreover by the fact that obesity in early life is associated with early stages of atherosclerosis [14].

Weight reduction, which often results in normalization of increased lipids and lipoproteins [15, 16], is therefore an important factor in the treatment of obese children and adolescents in order to postpone negative health effects in adulthood.

Prevalence of Elevated Lipids and Lipoproteins in Childhood Obesity

In many studies, childhood obesity has been shown to be associated with altered levels of lipids and lipoproteins, and obesity increases the likelihood of elevated concentrations of total cholesterol, LDL-cholesterol and triglycerides and low levels of HDL-cholesterol.

In The Cardiovascular Risk in Young Finns Study, in children and adolescents aged 3–18 years not only serum insulin was correlated positively with BMI but also serum triglycerides and HDL-cholesterol were inversely correlated with obesity [1, 2].

In seven cross-sectional studies conducted by the Bogalusa Heart Study between 1973 and 1994 obesity (Quetelet index: >95th percentile) in 5- to 17-year-old children was associated with elevated LDL-cholesterol and triglycerides and decreased HDL-cholesterol. Although the sensitivity (23–62%) and positive predictive value (9–24%) of overweight was generally low for each risk factor, many of the ORs were substantial. Overweight schoolchildren with a Quetelet index <85th percentile were 2.4 times as likely to have an elevated level of total cholesterol as normal-weight children, and the odds ratios for other associations were 3.0 for LDL- cholesterol, 3.4 for HDL-cholesterol and 7.1 for triglycerides [17]. Table 1 shows the results of the study in whites and the differences in gender, which were not significant. Most associations tended to be stronger among whites than among blacks but there were no significant differences for lipids and lipoproteins.

In general, various measures of overweight and obesity have been found to be related weakly to levels of total cholesterol and LDL-cholesterol ($r \sim 0.05$–0.15), [5, 18–21] but more strongly to levels of HDL-cholesterol and triglycerides [5, 18, 19, 21, 22]. Although the results generally agree well within the investigations, comparisons across studies can be influenced by differences in the age and race distribution of the sample, the specific weight-height index or skinfold thickness, and the statistical techniques used.

Obesity/Adiposity and Lipids and Lipoproteins

Obesity is characterized by an excess of body fat. Whereas subcutaneous fat is visible on physical examination because it is spread over the whole body, visceral or abdominal fat is not apparent and obviously visible. Visceral fat, however, is the most metabolically active fat in the body and is able to undergo lipolysis quickly. Abdominal fat is surrounded by viscera and metabolic products, e.g. triglycerides or free fatty acids are drained immediately into the portal

Table 1. Estimated ORs between overweight (Quetelet Index >95 P) and adverse risk factor levels among 5- to 17-year-olds [17]

Risk factor	n	Screening characteristics for overweight, %[1]		ORs (95% CI)[2]		
		sensitivity	positive predictive value	overall	white boys	white girls
TC >200 mg/dl	747	24	18	2.4 (2.0–3.0)	3.6	2.2
TG >130 mg/dl	502	47	24	7.1 (5.8–8.6)	7.0	6.5
LDLC >130 mg/dl	653	28	18	3.0 (2.4–3.6)	4.4	2.4
HDLC <35 mg/dl	702	25	17	3.4 (2.8–4.2)	3.8	3.2
High levels of						
Insulin	273	62	21	12.6 (10–16)	15.8	27.7
SBP	371	34	13	4.5 (3.6–5.8)	7.1	4.5
DBP	395	23	9	2.4 (1.8–3.0)	3.1	3.4

n = Number of children with risk factor. Of the 9,167 5- to 17-year-olds, 1,147 had a Quetelet index between the 85th P and 94th P, and have been excluded from all analyses. Of these 8,020 schoolchildren, insulin levels were available for 5,487 persons who were examined in the final four (of seven) examinations in Bogalusa.

[1]Sensitivity is the proportion of children with risk factor who are also overweight. Positive predictive value is the proportion of overweight children who have adverse risk factor level. Specificities for all risk factors ranged from 88 to 90%.

[2]ORs are based on the cross-tabulation of overweight and specified risk factors. An OR of 2.4 for TC indicates that among overweight children, the ratio of children with high TC levels to children with other TC levels is 2.4 times higher than the corresponding ratio among non-overweight children. All ORs are have been adjusted for age and the seven examinations (six indicator variables) in logistic regression models; the overall ORs were also adjusted for race and sex.

system and into the liver. Metabolic derangements in adults, e.g. dyslipidemia, hyperinsulinemia and cardiac risk factors have been associated with the amount of visceral fat.

Body mass index (BMI) is the preferred method of defining overweight and obesity in childhood and adolescence. The BMI reflects the amount of body fat and often is used for a proxy for measurement of body fatness in adults but also in children and adolescents. Many studies investigating the association of overweight and obesity with lipids and lipoproteins use the BMI as indirect index of obesity and body fat. However, these results may not be comparable to studies using direct measurements of (intra-abdominal) adipose tissue.

During the last years the role of body fat distribution, visceral body fat and intra-abdominal fat and the relationship with specific risk factors in obese children and adolescents has gained more and more interest.

Cohort studies in adults have shown that a preponderance of body fat in the abdomen, upper body or trunk is predictive for cardiovascular heart disease and diabetes and is associated with adverse levels of total cholesterol, LDL-cholesterol as well as elevated triglycerides and low levels of HDL-cholesterol [23, 24]. Recent data indicate that body fat distribution, in particular abdominal body fat distribution in adolescent girls is associated with an adverse risk factor profile [3, 4, 25, 26]. However, the importance of fat distribution among children and adolescents is less certain than in adults: negative and contradictory findings are published and so far there is no conclusive evidence on the importance of body fat distribution in childhood [27, 28]. The main reasons for this are the difficulties in studying fat patterning in early life: there is only a small portion of intra-abdominal fat present before adulthood [29], there are considerable physiological changes in skinfold thickness during childhood and adolescence [30], and anthropometric indices appropriate for use in adults are not suitable in children [31]. Moreover, most anthropometric measures for body fat and fat distribution are highly intercorrelated and it is not surprising that associations with lipids are fairly similar.

Two recent studies examined the relation of body fat distribution and cardiovascular risk factors: an analysis of the Bogalusa Heart study that comprised 2,996 children and adolescents aged 5- to 17-years-old [17] and investigated subscapular and triceps skinfolds, and waist/hip circumferences with various risk factors (lipids, lipoproteins and insulin). In this study forward stepwise regression was used to identify measures of body fat distribution that best predicted the presence of risk factors. After adjusting for several co-founding factors, e.g. age, sex, race, body weight and height, waist circumference was significant for triglycerides, and HDL-cholesterol, subscapular skinfold for LDL-cholesterol and triglycerides (table 2). Hip circumference was only significant when waist circumference was present and triceps skinfold provided no additional information. Central or abdominal distribution of body fat was related to adverse concentrations of LDL-cholesterol, HDL-cholesterol, and insulin. These associations were observed whether fat patterning was characterized by using waist circumference alone (after adjustment for weight and height) or waist-to-hip ratio. Compared with a child at the 10th percentile of waist circumference, a child at the 90th percentile was estimated to have, on average, higher concentrations of LDL-cholesterol (0.17 mmol/l), and lower concentrations of HDL-cholesterol (-0.07 mmol/l). These differences, which were independent of weight and height, were significant at the 0.001 level.

Table 2. Relation of waist, hip and skinfold thickness measures to level of lipids and insulin [17]

		LDL-cholesterol mmol/l	Triglycerides mmol/l	HDL-cholesterol mmol/l	Insulin pmol/l
Individual measures	Waist	+0.12[a]	+0.09	0.07	+7
	Hip	–	−0.04	+0.04	−5
	Subscapular skinfold	+0.13[b]	+0.08	–	–
	Triceps skinfold	–	–	–	–
	F-statistic	(28)	(27)	(22)	(21)
Ratios	Waist/hip	+0.12	+0.08	−0.08	+7
	Subscapular/triceps	–	+0.07	−0.05	–
	F-statistic	(19)	(24)	(31)	(31)
Principal components	Generalized obesity	+0.19	+0.08	–	–
	Central fat patterning[c]	+0.08	+0.08	−0.09	+6
	F-statistic	(28)	(36)	(46)	(31)

[a]Values represent the predicted change in lipid or insulin levels associated with a change for each anthropometric dimension between the 10th and 90th centiles, based on stepwise regression and adjusted for race, sex, age, height and weight. Dashes indicate that the variable was not significant, $p > 0.01$.

[b]F-statistic tests that all added anthropometric characteristics have zero coefficients. An F-statistic of −7 is significant, $p < 0.001$.

[c]The second principal component was a linear contrast of the waist circumference with the hip circumference and triceps skinfold thickness.

In a recent cross-sectional study, Maffeis et al. [26] studied the relationship between anthropometric variables and lipid concentrations in a sample of 818 prepubertal children aged 3–11 years. To assess the clinical relevance of waist circumference in prepubertal children height, weight, triceps and subscapular skinfolds, and waist circumference were measured and plasma levels for total cholesterol, HDL-cholesterol, LDL-cholesterol, apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB) were determined. A multivariate linear model analysis showed that ApoA1/ApoB, HDL-cholesterol, total cholesterol/HDL-cholesterol, and systolic as well as diastolic blood pressure were significantly associated with waist circumference and triceps and subscapular skinfolds, independent of age, gender, and body mass index.

Therefore, there seems to be growing evidence that the assessment of body-fat distribution could identify subjects with the highest risk of adverse lipid profile and hypertension. Waist circumference as well as subscapular and triceps skinfolds may be helpful parameters in identifying prepubertal children with an adverse blood lipid profile and hypertension. Waist circumference, which is easy to measure and more easily reproducible than skinfolds, therefore may be considered in clinical practice.

Tracking of Lipids and Lipoproteins

Several longitudinal studies reported tracking of adverse lipid levels from childhood to adulthood: in the Muscatine Study 2,446 subjects were initially examined at ages 8–18 years and were re-examined as young adults at ages 20–25 or 26–30 years. Measurements of cholesterol, height, weight, and triceps skinfold thickness were obtained during childhood. Lipids, lipoprotein fractions, as well as lifestyle, medication, alcohol, and tobacco use were determined during the adult examination. Elevated levels of cholesterol during childhood were associated with elevation of lipids and lipoproteins in adult life. On average, of children found to have cholesterol levels greater than or equal to the 90th percentile for their age and gender, on a single measurement 43% remained above the 90th percentile, 62% remained above the 75th percentile, and 81% remained above the 50th percentile. The authors conclude that obesity acquired in adolescence and the young adult years has deleterious effects upon adult cholesterol levels and lipoprotein fractions.

Similar long-term effects of childhood obesity regarding lipids and lipoproteins are reported from the Bogalusa Heart Study [11]: this longitudinal cohort was constructed from two cross-sectional surveys in a community-based population over an 8-year period: 1,606 children and young adults aged 5–23 years participated in the first survey. Subjects with levels of insulin consistently in the highest quartile showed significantly ($p < 0.001$) higher levels of body mass index ($+9\,kg/m^2$), triglycerides ($+58\,mg/dl$), LDL-cholesterol ($+11\,mg/dl$), and VLDL-cholesterol ($+8\,mg/dl$), and significantly ($p < 0.001$) lower levels of HDL-cholesterol ($-4\,mg/dl$). 739 young adults aged 20–31 years were followed up. As adults, individuals with consistently elevated insulin had 36-fold increased ($p < 0.05$) prevalence of obesity and a 3-fold increased rate of dyslipidemia. Moreover, there was a clustering of various components of syndrome X, which intensified as BMI increased in a subset of children studied longitudinally in the population [12].

Long-Term Consequences of Altered Lipids

There are numerous reports on the short- and mid-term consequences of obesity in children and adolescents, but of special interest are not only acute metabolic changes in lipid profiles but also the long-term effect on cardiovascular morbidity and mortality. During the past few years a small number of studies investigated the long-term effects of childhood obesity. Moreover, few studies demonstrated that altered lipids and lipoproteins even in adolescence and early adulthood have directly consequences on carotid intimal-medial thickness and other subclinical cardiovascular disease.

Several prospective and retrospective studies with varying sample size and follow-up intervals, as well as a few studies with baseline information on obesity during childhood or adolescence and adult health outcomes several years later exist [32–37]. The main findings of all studies are similar: overweight in adolescence, particularly in men, is associated with an increased morbidity and mortality from CVD, atherosclerosis and colorectal cancer. All-cause mortality is highest for those with the highest percentage of body fat as adolescent men, but not for the group of adolescent women. There is good evidence to suggest that this increased morbidity and mortality from CVD and atherosclerosis at least in part can be explained by the metabolic changes of lipids and lipoproteins.

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY) study collected arteries, blood, and other tissue from approximately 3,000 persons aged 15–34 years dying of external causes and autopsied in forensic laboratories [14]. In all persons measurements of gross atherosclerotic lesions in the right coronary artery, American Heart Association (AHA) lesion grade in the left anterior descending coronary artery (LAD) as well as serum lipid concentrations, intimal thickness of renal arteries (for hypertension), and adiposity by body mass index (BMI) together with thickness of the panniculus adiposus were available. In young men the BMI was associated with both fatty streaks and raised lesions in the RCA and with AHA grade and stenosis in the LAD. The effect of obesity – defined as a BMI $>30\,kg/m^2$ – on right coronary artery raised lesions was greater in young men with a thick panniculus adiposus. As found in several other studies before, obesity was associated with non-HDL-cholesterol and (inversely) HDL-cholesterol concentrations (fig. 1). However, in young women BMI was not associated with coronary atherosclerosis although there was trend among those with a thick panniculus adiposus. The results of the study demonstrate that obesity is associated with accelerated coronary atherosclerosis in adolescent and young adult men. The conclusions of the PDAY study are consistent with results of long-term follow-up studies, which show that obesity in youth not only predicts obesity in adulthood, but also predicts CHD morbidity and mortality. Moreover, the results of the study indicate that obesity in adolescents and young adults accelerates the progression of atherosclerosis decades before clinical manifestations appear. One of the promoting factors for accelerated atherosclerosis probably is changes in lipid metabolism caused by excessive body fat.

Similar conclusions were drawn from The Muscatine Study [38]. Carotid intimal-medial thickness was measured in young and middle-aged adults in 346 men and 379 women aged 33–42 years who were representative of a cohort followed since childhood and who live in Muscatine, Iowa. Aim of the study was to determine the relationship of intimal-medial thickness with risk factors measured in childhood, at the time of studying, and as a 'load' from childhood to adulthood. Carotid ultrasound studies were performed and the mean of the

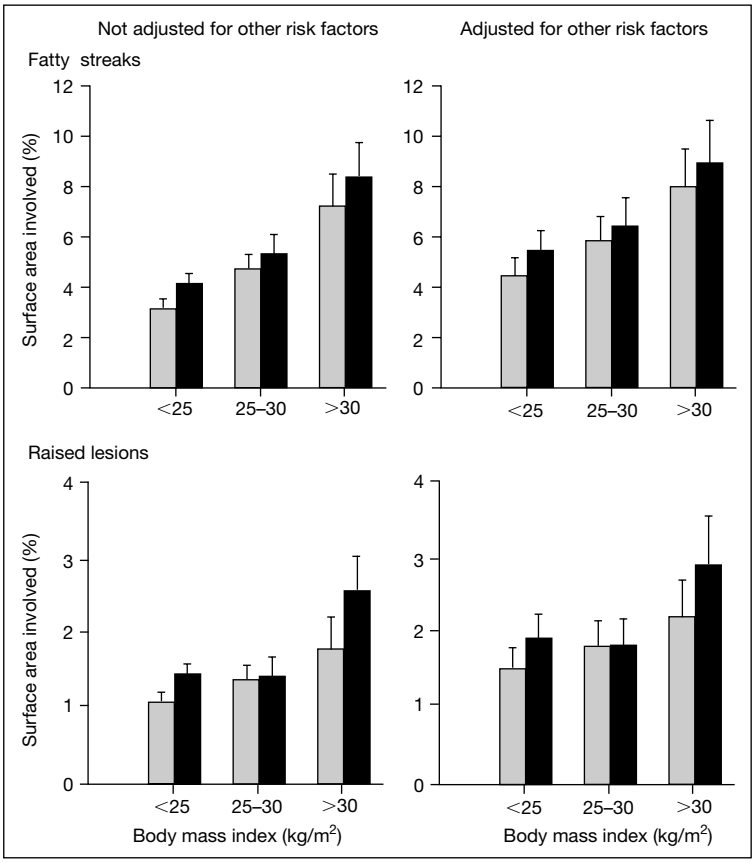

Fig. 1. Extent of RCA lesions (mean ± SE) in men with all risk factor measurements by BMI and panniculus thickness, adjusted for race and 5-year age group, without and with adjustment for other risk factors. Light gray bars indicate panniculus thickness median for sex and BMI; black bars, panniculus thickness >median for sex and BMI [39].

measurements of maximal carotid IMT at several locations was determined for each subject. On the basis of multivariable analysis, the significant current predictors of IMT were age and LDL-cholesterol in both sexes. Total cholesterol was a significant childhood predictor in both sexes, while childhood body mass index was significant only in women. For men, LDL-cholesterol, HDL-cholesterol, and diastolic blood pressure were predictive of carotid IMT in a risk factor load model, whereas in women, LDL-cholesterol, body mass index, and triglycerides were predictive. Higher carotid intimal-medial thickness in young and middle-aged adults was associated with childhood and current cardiovascular risk factors.

From several similar studies there is growing evidence that obesity and dyslipidemia in children and adolescents is associated with a considerable risk for increased morbidity and mortality from atherosclerosis in adulthood [39–42].

Consequences of Weight Reduction on Lipids and Lipoproteins

The consequences of weight reduction in children and adolescents in order to reduce and stabilize body weight and to reverse adverse metabolic abnormalities have been reported in several recent studies [15, 16, 43, 44]. The studies consistently show that weight reduction decreases or even normalizes risk factor levels: significant improvements were observed for total cholesterol, LDL-cholesterol, HDL-cholesterol and triglyceride levels. Falls in serum cholesterol and triglyceride levels correlate with percentage weight loss. The type of reduction diet seems not to have great importance on the effect of lipids and lipoproteins: a reduction in serum cholesterol, LDL-cholesterol and triglyceride levels without reducing serum HDL-cholesterol is obtained with a balanced low calorie diet as well as with very low calorie diets [3, 45, 46]. Several studies found sex-differences in the improvements of lipid profiles: girls tend to be more susceptible to a decrease in LDL level, which might result in an increased cardiovascular protective effect [41].

Some studies indicate that the positive effects of weight reduction are more pronounced in those children and adolescents with an abdominal body fat distribution: during a 6-week program significant reductions for total cholesterol and LDL-cholesterol in obese adolescents were observed. However, girls with abdominal obesity (WHR >0.88) had greater reductions in serum cholesterol, LDL-cholesterol, and uric acid than did girls with gluteal-femoral obesity (WHR <0.81). In a multivariate-regression analysis, Wabitsch et al. [3] found these differences partly explained by the greater weight loss of the girls with abdominal obesity. They suggest that during weight reduction girls with abdominal obesity exhibit more beneficial changes in the atherogenic risk factor profile than do girls with gluteal-femoral obesity, partly because of a greater weight loss.

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Childhood Obesity and Coronary Heart Disease

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Although there are several short-term complications of severe obesity among children [1–3], obese children also have an increased risk for coronary heart disease (CHD) in adulthood. The current chapter reviews the relation of childhood obesity to various CHD risk factors, atherosclerosis, and clinical disease in adulthood. Many of the presented data are from the Bogalusa Heart Study (Louisiana, USA), a long-term study of the early natural history of CHD [4]. This panel design of this study, which conducted seven examinations of children (ages 5–17 years) and four examinations of young adults (ages 18–37 years) between 1973 and 1995 [5], allows for both cross-sectional and longitudinal analyses.

Obesity and CHD Risk Factors in Childhood

Despite the inherent limitations of weight-height indices in quantifying adipose tissue, the body mass index (BMI, kg/m^2) has been used as a surrogate measure of obesity among adults for many decades, and is now widely used among children. However, because BMI levels in early life vary substantially ($r \sim 0.5$) with age and height [1], it is necessary to represent BMI levels relative to a child's age and sex peers.

BMI levels among children can be classified by estimating levels at age 18 years from current BMI, and then applying the adult cutpoints of 25 kg/m^2 (overweight) and 30 kg/m^2 (obese) to these extrapolated values [6]. Sex-specific BMI-for-age centiles and Z-scores have also been developed from US data [7], and these values will be used throughout this chapter. It has been recommended that children with a BMI $\geq$95th centile of these US data, which roughly corresponds to an expected BMI between 25 and 30 kg/m^2 at age 18 years [6], be

considered overweight. It should be realized, however, that because the relation of BMI to various diseases differs by ethnicity [8], a single classification scheme may not be appropriate for all children.

BMI levels among children show a non-linear relation to adverse levels of lipids, insulin, and blood pressure (fig. 1, upper panel), with the prevalence of adverse levels increasing markedly at very high BMI levels [9]. In these analyses of 5- to 17-year-olds (n = 23,758) from the Bogalusa Heart Study, risk-factor cutpoints were chosen so that prevalence of adverse levels of each characteristic was 5%. BMI was most strongly associated with levels of insulin ($r \sim 0.5$), and although the prevalence of adverse levels varied from $<1\%$ among the thinnest children to only 3% at the 85th centile of BMI, almost 40% of the children with a BMI $>$99th centile had a high insulin level. Among these severely overweight children, the prevalence of other risk factors ranged from 15% (low HDL cholesterol) to 33% (high triglycerides).

Slightly stronger associations were observed with waist girth than for BMI. For example, whereas levels of HDL cholesterol showed a correlation of $r = -0.29$ with BMI, the correlation with waist girth was $r = -0.33$. Furthermore, HDL cholesterol levels were more strongly correlated with the subscapular skinfold thickness ($r = -0.28$) than with the triceps skinfold thickness ($r = -0.21$). Although the importance of visceral fat in these associations is uncertain [10], it is likely that these contrasting associations reflect some aspect of body fat distribution.

The relation of childhood obesity to the clustering of multiple risk factors has also been examined [11], and data from the Bogalusa Heart Study are summarized in the bottom panel of figure 1. Overall, about 20% of the examined children had adverse levels of at least one of the five risk factors considered, but this percentage varied from 10% among the thinnest children to 70% among the heaviest children. Similar to the findings for the individual risk factors, the associations were markedly non-linear. The increase was most striking for those with $\geq$3 risk factors, with the proportion increasing from 0% (thinnest children), to $\sim$1% (85th BMI centile), and to $\sim$10% (99th BMI centile). As the presence of multiple risk factors is strongly associated with the early stages of atherosclerosis [12], the recent secular increases in the prevalence of overweight ($\geq$95th centile) and severe overweight ($\geq$99th centile) among children [13, 14] are of particular concern.

Concurrent with these increases in childhood obesity, the prevalence of type 2 diabetes has also increased substantially among adolescents [15, 16]. Obesity is very common among these newly diagnosed cases, and it has been found that most of the increase in type 2 diabetes among Pima Indian children can be accounted for by changes in childhood obesity and intrauterine exposure to diabetes since 1970 [15].

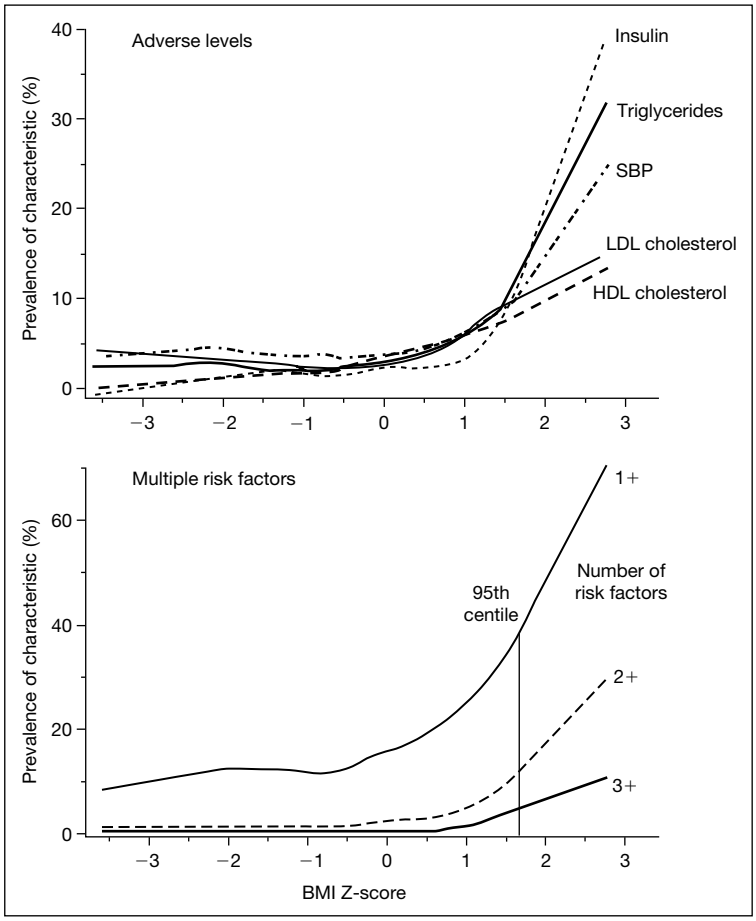

Fig. 1. The top panel shows the relation of BMI (Z-Scores) to the proportion of 5- to 17-year-olds in the Bogalusa Heart Study having adverse levels of insulin, triglycerides, LDL cholesterol, HDL cholesterol, and systolic blood pressure. Adverse levels were defined as those >95th centile (race, sex, and age specific); adverse levels of HDL cholesterol were <5th centile. BMI Z-scores were calculated from national US data, and Z-scores of 1.04, 1.64 and 2.33 correspond to the 85th, 95th and 99th centiles of BMI, respectively. The bottom panel shows the relation of BMI Z-scores to the prevalence of children having one or more, two or more, or three or more of the five risk factors considered.

In addition to these associations, childhood obesity is associated other CHD risk factors, such as left ventricular hypertrophy, elevated levels of C-reactive protein, homocysteine and lipoprotein(a), and various pro-coagulant factors [17, 18]. Furthermore, whereas childhood BMI is inversely associated with levels

of HDL cholesterol and large HDL, it is positively associated with levels of small HDL [19]. These contrasting associations with HDL subclasses may also increase the progression of atherosclerosis [20].

Longitudinal Associations with Adult Complications

Risk Factors

It has been estimated that ~40% of overweight children will be obese in adulthood (positive predictive value), while 15 to 20% of obese adults had been overweight as children (sensitivity) [21, 22]. Although these estimates are greatly influenced by the cutpoints used to define overweight and obesity [23], correlational analyses also indicate a moderate degree of tracking for BMI. For example, over a (mean) 17-year follow-up of 2- to 17-year-olds, the correlation between childhood and adult levels of BMI was 0.61 [24].

Although adults who had been overweight children have adverse risk factor levels [25], the persistence of obesity throughout life suggests that these associations may reflect the importance of adult, rather than childhood, weight status. This possibility was examined a cohort study of 2609 children (ages 2–17 years) who were followed for an average of 17 years (table 1) [24]. As compared with adults who had been relatively thin (BMI <50th centile) children, those who had been overweight in childhood had a 12.4 kg/m^2 higher BMI, a 7 mg/dl lower HDL cholesterol level, and adverse levels of other risk factors (first two columns).

However, within categories of adults who were normal-weight (adult BMI <25 kg/m^2) or obese (≥30 kg/m^2), risk factor levels varied only slightly according to childhood weight status (final four columns). For example, there was a 1 mg/dl difference (<25 kg/m^2) or no difference (≥30 kg/m^2) in HDL cholesterol levels according to childhood weight status within categories of adult BMI. Furthermore, normal-weight adults who had been overweight children had a *lower* (−23 mg/dl, $p < 0.05$) mean triglyceride level than did other normal-weight adults, likely resulting from a relative decrease in BMI levels [26] in this group of overweight children who became normal-weight adults. Overall, these findings indicate that the relation of childhood obesity to adult risk factors is indirect, resulting from the persistence of childhood obesity into adulthood.

Atherosclerosis

The initial stages of atherosclerosis are associated with maternal hypercholesterolemia among neonates [27]. Based on pathology studies of children and young adults, childhood obesity also appears to be important in the

Table 1. Mean risk factor levels in adulthood by categories of adult BMI and childhood BMI centile; the Bogalusa Heart Study

	Childhood BMI centile		Adult BMI, kg/m^2			
			<25 kg/m^2		≥30 kg/m^2	
			Childhood BMI centile		Childhood BMI centile	
	<50	≥95	<50	≥95	<50	≥95
n	1,317	186	950	12	96	144
Childhood BMI centile	24	97	22	96	28	98
Adult levels						
Age, years	27	0	27	−2	29	−2
BMI, kg/m^2	22.5	+12.4*	21.1	+2.5*	33.2*	+4.9*
Triglycerides, mg/dl[a]	82	+16*	76	−23*	130	−6
LDL cholesterol, mg/dl	112	+9*	107	0	130	−4
HDL cholesterol, mg/dl	52	−7*	54	+1	42	0
Insulin, mU/l[a]	8	+6*	7	0	17	0
SBP, mm Hg	112	+5*	111	−6	117	2
DBP, mm Hg	72	+4*	71	−3	77	+1

[a]Geometric means are shown for levels of triglycerides and insulin.

*$p < 0.05$ for difference in adult levels between persons whose childhood BMI was <50 centile or ≥95 centile.

development of these early lesions. For example, among subjects who died (ages 2–39 years) from external causes, previously measured BMI was associated ($r = 0.24$–0.41) with the extent of fatty streaks and fibrous plaques [12]. Furthermore, although some correlations were not statistically significant, raised lesions in the coronary artery also appear to be associated with subcutaneous fat (as assessed by the thickness of the panniculus adiposus) and BMI measured at death among 15- to 34-year-olds [28].

The relation of childhood obesity to atherosclerosis has also been studied using B-mode ultrasonography, a non-invasive technique that can quantify the intima-media thickness (IMT) of the carotid artery [29]. Despite various limitations [30] carotid IMT is thought to be a marker of generalized atherosclerosis, and IMT among adults is associated with obesity and other CHD risk

factors [31], arteriographically documented coronary artery disease [32], and subsequent CHD [33]. Furthermore, weight loss decreases the rate of IMT progression [34].

Although there have been fewer studies of children, hypercholesterolemia is associated with carotid IMT by age 6 years [35]. Several cross-sectional studies have also found that obesity in childhood and adolescence is associated with carotid IMT [36–38], and in most studies the predictive ability of BMI is similar to that for lipid and lipoprotein levels. Although childhood obesity was not associated with carotid IMT in some studies [39, 40], it was found to be associated with other characteristics of the carotid artery, such as wall stiffness or endothelial dysfunction.

The most interesting use of B-mode ultrasonography, however, is in longitudinal studies can examine the relation of childhood obesity to carotid IMT in adulthood. For example, levels of BMI and triceps skinfold thickness among 8- to 18-year-olds were predictive of the adult carotid IMT (ages 33 to 42 years) in the Muscatine Heart Study [41]. Although the longitudinal associations with carotid IMT were statistically significant only among women ($r = 0.18$ for childhood BMI), these relationships over an approximately 25-year follow-up period are noteworthy. These findings also extend an earlier report from the same group [42] showing that childhood weight is related to coronary artery calcification (assessed by electron beam computed tomography) in adulthood. In this earlier study, the observed associations between childhood weight and the presence of adult calcification were slightly stronger among men (odds ratio = 2.9) than among women (odds ratio = 2.1).

It would be very interesting to determine if the longitudinal relations of childhood obesity to carotid IMT and coronary artery calcification in adulthood were mediated by the persistence of childhood obesity into adulthood, or if the effects of childhood obesity were independent of adult weight status.

Coronary Heart Disease

There are reports of pathologic changes in the conduction system of obese children [43], and several cohort studies [44–48] have examined the relation of childhood obesity to CHD in adulthood. Whereas some children have been followed prospectively [47, 48], other investigators have identified cohorts in adulthood who had baseline (historical) data previously collected by schools [44, 45] or in preparation for military service [46]. In addition, the relation of BMI at age 18 years, based on the recalled weight of middle-aged adults, to subsequent CHD has been examined [49, 50].

These long-term studies, many of which span over 50 years, are very difficult to conduct, and some investigators have been able to re-examine (or trace) only about one half of eligible subjects [45]. Furthermore, there are many

differences in the design and analysis of these studies, including (1) the classification of overweight (typically the upper fourth or fifth of the BMI distribution); (2) sample sizes than range from 508 [47] to >78,000 [46], and (3) mean, baseline ages that ranged from ~8 years [48] to 19 years [44]. In addition, few studies have data on BMI levels in both childhood and adulthood [45, 47, 49, 50], and in all cases, one of the two estimates is based on self-reported weight, increasing the possibility of misclassification.

Despite these differences, the results of these studies suggest that overweight children are at increased risk for CHD in adulthood, with relative risks (RRs) generally ranging from 1.7 to 2.6. These consistent findings, which can be contrasted with those of studies of adult obesity, may be due to the long follow-up periods, as well as to the lack of confounding by preclinical disease and cigarette smoking. In addition, the strength of the relation of obesity to CHD decreases with age among adults [51], and it is possible that this interaction with age extends to adolescents and children. However, it is unclear if the relation of childhood obesity to adult complications varies by the length of follow-up, or if there is a J-shaped relation, with the optimal BMI level being slightly below the median [46, 48]. Although it has been suggested that childhood obesity is more strongly related to adult CHD among boys than girls [47], associations with adult carotid IMT are stronger among girls [41].

As is the case adult risk factor levels [24], it is also possible that the increased risk among overweight children for CHD may be due to adult (rather than childhood) weight status. The results of the Harvard Growth Study [47] provide the strongest evidence supporting an independent effect of childhood obesity, in which adjustment for adult BMI only slightly reduced the relation of childhood overweight (BMI >75th centile) to CHD morbidity (RRs of 2.8 vs. 2.5) over a 55-year follow-up period among men. These investigators, however, found that childhood overweight was not related to CHD morbidity or total mortality among women.

In contrast, other results have emphasized the greater importance of adult weight status. For example, overweight (>20% above average weight) children in Washington County had relatively high rates of vascular disease in adulthood [45], but the highest rates were seen among thin children who became overweight in adulthood. Somewhat similar results were reported by the Nurses Health Study [49], in which the relation of (self-reported) BMI at age 18 years to subsequent CHD was entirely attributable to the persistence of obesity throughout life; controlling for adult BMI reduced the RR among those with a BMI >23.3 kg/m^2 at age 18 years from 2.0 to 1.0. It is possible that weight gain after the cessation of growth, which would largely reflect accumulated fat mass, may be more pathological than weight gain during growth and development [1].

Conclusions

Overweight children are at increased risk for adverse levels of CHD risk factors, atherosclerosis, and CHD in adulthood. Although it is possible that the adult complications are due to the persistence of obesity throughout life, these consequences will become increasingly evident due to the recent secular increases in childhood obesity. In addition, the risks associated with the high BMI levels currently seen among children may be substantially greater than those associated with the less severe levels of childhood overweight seen before 1970.

Because of the long follow-up periods needed to study the relation of childhood obesity to CHD, non-invasive techniques such as B-mode ultrasonography and electron beam tomography, will likely provide the most useful information on the relation of childhood obesity to atherosclerosis. The difficulties in preventing and reversing obesity, along with the frequent nonadherence of adolescents to lifestyle changes and medical treatment, will complicate treatment and prevention efforts.

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Type 2 Diabetes mellitus in Children and Adolescents: The European Perspective

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An increasing incidence of type 2 diabetes mellitus had been observed since the mid nineties, although the occurrence of type 2 diabetes mellitus used to be very rare in children and adolescents until recently. A striking increase in both the prevalence and the degree of obesity in children and adolescents in many populations around the world is causing this phenomenon. For example, investigators in Cincinnati, USA, reported an increase of type 2 diabetes in a review of 1,027 children diagnosed with diabetes from 1982 to 1994. In Germany, only 70 patients below an age of 15 years have been identified in the systematic, nationwide 'dpv' diabetes survey, while it has been suggested that more than 5,000 youths would meet the diagnostic criteria of type 2 diabetes. The prevalence of type 2 diabetes mellitus is also very high in Australasia, depending on ethnicity and the degree of obesity [1–7]. The relation between type 2 diabetes and obesity is referred to as one of the most challenging health issues at present. The presently available data on type 2 diabetes in children and adolescents are summarized in order to show preventive and therapeutic strategies against type 2 diabetes in this age group.

Definition and Epidemiology

At present, obesity is the most common chronic disease in the developed countries and even in developing countries around the world [8–14]. The prevalence of impaired glucose tolerance among children and adolescents with marked obesity has been reported to be as high as 25%, and type 2 diabetes mellitus could be detected in 4% of those children [8].

Table 1. Epidemiology of type 2 diabetes (estimates) in children and adolescents

Published cases	USA, Australasia, India, Spain, Britain, Eastern Europe, Germany, Italy, Australia, etc.
Prevalence	20–50/1,000 (Pima Indians) to 1/1,000 (white Caucasian)
Incidence	1–7/100,000/year (Cincinnati; estimates for France and Germany)

Population-based incidence and prevalence data on type 2 diabetes at a young age are not available to date for many countries in the world. On the other hand, cases of type 2 diabetes at young age have already been reported in the literature in recent years from many ethnic groups including white Caucasians, Hispanics and blacks from around the world (see references).

The number of obese children and adolescents is increasing worldwide, and it has been estimated that about 22 million children younger than 5 years of age are affected [15]. In addition, the prevalence of overweight at a young age is increasing [16]. In the United States overweight prevalence among children aged 4–12 years had increased by 1998 to 21.8% in Hispanics, 21.5% among African-Americans and 12.3 among non-Hispanic whites [16]. In addition, screening for abnormal glucose tolerance in adolescents with polycystic ovary syndrome also yields a high number of affected individuals with impaired carbohydrate metabolism. Of 27 subjects with polycystic ovary syndrome 8 had impaired glucose tolerance and 1 had previously undiagnosed diabetes when the group was screened with a 75-gram glucose challenge and glucose was measured after 2 h. The metabolic abnormalities were seen among lean and obese subjects [17, 18].

Type 2 diabetes mellitus in children was first reported in white UK teenagers [19–21], Japanese youths [22], Indian adolescents [23] and young adults and teenagers in Central Europe [4] (table 1). Most of these individuals had marked obesity (body mass index more than +3 SDS or >99th percentile) [19–21].

In all ethnic groups in the Unites States, the incidence of type 2 diabetes has increased substantially over the past several years [17, 19]. In fact, in the United States, in some populations, type 2 diabetes is now the predominant form of diabetes in children and adolescents [2, 5, 6, 15]. Varying biological responses to overweight in different racial/ethic groups differently contribute to the development of type 2 diabetes during adolescence (fig. 1). Type 2 diabetes is usually associated with significant obesity and is only very rarely diagnosed in lean subjects. In the USA, children as young as 8 years are now being diagnosed with the disease [19, 24–29].

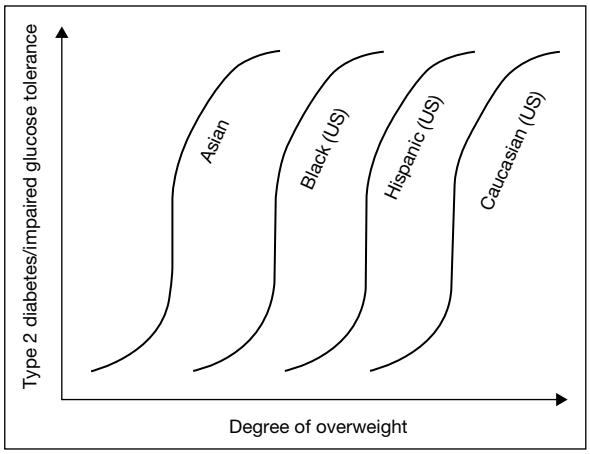

Fig. 1. Relation between the degree of obesity/overweight and the occurrence of impaired glucose tolerance and type 2 diabetes in children and adolescents. Dependence on ethnicity.

Table 2. Candidate genes putatively implicated in the regulation of glucose homeostasis and hence in the pathogenesis of type 2 diabetes

Insulin signaling cascade
Insulin receptor
Insulin receptor substrates (IRS-1, til-4)
Enzymes (PI3kinase, tyrosine kinases, phosphatases, serine kinases, etc.)
Transcription factors
Tissue-specific (insulin-sensitive) factors
Glucose transporters (GLUT 4, etc.)
Glycogen synthase
Enzymes (PEPCK, etc.)
Potassium channel
Sulfonylurea receptors
Factors released from fat tissue (see table 5)

Pathogenesis

Both genetic and environmental/exogenous factors play in concert in the pathogenesis of type 2 diabetes [2, 3, 5, 19, 21, 30–32]. Family histories, ethnicity and the concordance in monozygotic twins all point to inheritance of the disease. Possible candidate genes putatively implicated in the regulation of glucose homeostasis in man and hence in the pathogenesis of type 2 diabetes are listed in table 2.

Table 3. Life-style factors that possibly contribute to the global epidemic of type 2 diabetes

Obesity
Physical inactivity
Inappropriate diet
Stress
Westernization, urbanization

Table 4. Factors contributing to derangement of glucose homeostasis in the development of and progression towards type 2 diabetes mellitus

(1) Insulin sensitivity
Disturbed insulin sensitivity
Insulin resistance
(2) Beta-cell dysfunction
Insulin secretion (hypo-, hyperinsulinemia)
Insulin deficiency
(3) Others
Insulin clearance
(Counter)regulatory responses (resistin?, glucagon, leptin?)

However, the striking increase of the number of individuals being affected over a short period of time point to exogenous factors as very strong pathogenetic candidates. Changes in life style which might be contributable to the global epidemic of type 2 diabetes are listed in table 3.

Pancreatic beta- and alpha-cell dysfunctions have by now been described in children with type 2 diabetes (table 4), and insulin insensitivity seems to be an early marker for the onset of type 2 diabetes [25].

Adipocytes which expand in obesity synthesize and secrete several factors and signaling proteins (table 5). These factors are known to alter insulin secretion, insulin sensitivity and even cause insulin resistance under experimental and clinical conditions. Thus, the adipose tissue seems to play a role of major significance in the pathogenesis of type 2 diabetes.

Genetics Factors

Candidate genes that may be involved in the pathogenesis of type 2 diabetes are listed in table 2. However, those factors are not yet as well defined as the role of HLA genes in the pathogenesis of type 1 diabetes. At present, several rare mutations explain less than 5% of all cases of type 2 diabetes.

Ethnic factors seem to play an important role as basal and post-challenge insulin are significantly higher in African-American, Mexican-American and Pima Indian children compared to Caucasian children. These ethnic differences

Table 5. Factors secreted from adipose tissue (expanding in obesity)

Metabolites	Signaling proteins
Fatty acids	leptin
Glycerol	adipsin
acetate,	acylation-stimulating proteins (ASP)
etc.	plasminogen-activator inhibitor-1(PAI-1)
	interleukin-6, -8
	tumor necrosis factor-α (TNF-α)
	adiponectin
	renin-angiotensinogen
	resistin
	prostaglandin

are independent of adiposity, while adiposity is associated with greater insulin levels in all ethnic groups examined. African-American children are more likely to develop type 2 diabetes at the same degree of adiposity, while Mexican-American children may be more likely to develop syndrome X due to greater obesity-related hyperinsulinemia and dyslipidemia [27].

Environmental Factors

The global epidemic of obesity and type 2 diabetes mellitus is contributable to alterations in life style during the past decades (table 3). Without any doubt, obesity is the major risk factor for the worldwide increase of type 2 diabetes in children and adolescents. Juvenile obesity may be defined as body mass index >97th percentile corrected for age and sex [9, 11–15, 29–33]. Changes in specific eating patterns as well as alterations of the level of physical activity at a young age may explain the increase in adiposity among children. Increases have for example occurred in respect to the number of meals eaten at restaurants, food availability, portion sizes, snacking and meal-skipping as well as in regards to hours spent in front of the TV set [34, 35].

Clinical Features

Diagnosis of Diabetes mellitus

Diabetes mellitus is defined regarding the criteria outlined by the World Health Organisation and the American Diabetes Association [3]. Patients frequently present with typical symptoms, such as elevated blood glucose level, polyuria, polydipsia and unexplained weight loss. Also other, less-specific

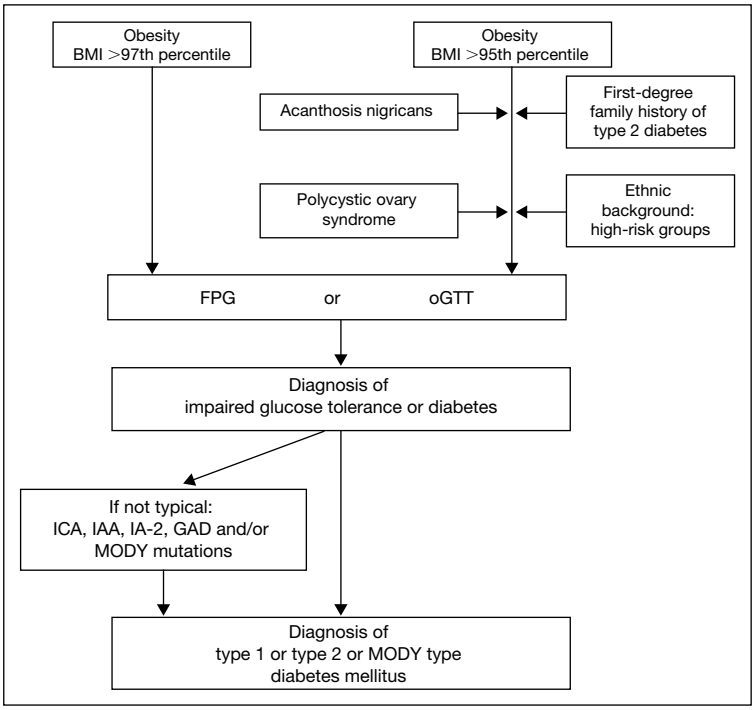

Fig. 2. Proposed algorithm to diagnose impaired glucose tolerance and type 2 diabetes in obese children and adolescence.

symptoms such as acanthosis nigricans and hyperandrogenism may represent clinical indicators for the presence of type 2 diabetes in an individual [24]. A simple algorithm will help to establish the diagnosis (fig. 2).

Screening

The population with a special risk to develop type 2 diabetes mellitus should be screened already at a young age of life: obese children with a family history of type 2 diabetes and particularly African-Americans, native Americans and Hispanic children. Other than in adults, in children and adolescents with newly diagnosed diabetes, type 2 diabetes counts for 5–45% of cases [32].

In some cases it might be advisable to determine autoantibodies, for example to IA-2 and GAD65, to define or rule out autoimmunity or even to carry out molecular analysis for differentiation of MODY types in order to clearly classify diabetes in a patient [3, 31, 36, 37]. However, autoantibodies to IA-2 and GAD65 might be found in patients with type 2 diabetes as well. Thus, they are not specific for type 1 diabetes mellitus [31].

Data on glucose metabolism in children and adolescents (i.e. glucose production, gluconeogenesis, and insulin sensitivity) have been published recently by Sunehag et al. [38], which will be valuable helping to interpret metabolic studies in obese children and children at risk to develop type 2 diabetes.

Co-Morbidity

Among the most common sequelae of primary childhood obesity are hypertension, dyslipidemia and psychosocial problems [10, 11, 12, 14], predisposing for additional co-morbidity such as cardiovascular disease in early adulthood [39]. For this reason, obese children and, even more important, children and adolescents with diabetes mellitus should be carefully examined with regard to blood pressure monitoring and check of lipid status [25, 27, 33, 39, 40]. It is mandatory to involve orthopedic surgeons and child psychiatrists into the treatment regimen of those patients. In adulthood, it has been shown that alcohol and illicit drug use are associated with an earlier onset of type 2 diabetes [30]. As a consequence of the epidemic of overweight and obesity, a new epidemic of childhood hypertension has also been recognized in children. Ambulatory blood pressure monitoring is a helpful tool to investigate children and adolescents at an early stage of the disorder [39, 40].

Treatment

For the treatment of diabetes mellitus, several therapeutic strategies have to be included and taken into consideration: psychological and family therapy interventions, lifestyle/behavior modification and nutrition education. Regular exercise is especially emphasized [11, 39, 41–43]. Multidisciplinary outpatient treatments are considered to be the most effective [44]. Health insurance providers and policy-makers should strongly support obesity prevention programs as the most cost-effective therapy of type 2 diabetes. Both exercise and physical activity have a significant effect on body weight reduction as well as on insulin sensitivity and a reduction of serum interleukin-6 concentrations [45]. Any comprehensive treatment protocol for type 2 diabetes should therefore include exercise programs and physical training. Most importantly, lifestyle intervention programs have turned out to be more effective and more efficient than pharmacotherapy for the prevention of progression from impaired glucose tolerance to overt type 2 diabetes in obese adults [3, 45].

However, for long-term treatment of very obese adolescents as well as individuals with type 2 diabetes, pharmacotherapy may be necessary [28]. The clinical picture in children with type 2 diabetes and the fact that most affected patients come from families with type 2 diabetes mellitus have led physicians

to conclude that affected children will respond to the same treatments used in adults and that clinical courses will be similar to those described in adults. However, data is very limited about experience in children with most of the drugs that are being frequently used for glycemic management in adults with type 2 diabetes.

At present, metformin is being studied as therapy for both type 2 diabetes and obesity in children and adolescents. Metformin has been shown to decrease hyperinsulinemia and insulin resistance in adults, but also to reduce plasma leptin, cholesterol and free fatty acids [46, 47]. Since metformin also seems to reduce appetite in obese children with type 2 diabetes, it may be beneficial and prove to be the drug of choice in the long term. However, side effects include gastrointestinal problems and should not be neglected [45–47].

In the acute state of type 2 diabetes, children are treated with insulin. Some of these children will have to be transitioned to oral antidiabetic agents. Very recently, multicenter trials of metformin used in children with type 2 diabetes mellitus have been completed in the United States. Metformin was found to significantly improve glycemic control in 82 subjects with type 2 diabetes aged 10–16 years. Doses of up to 1,000 mg twice daily were reported to be safe and efficacious [47]. At present, metformin is a safe and effective treatment option for type 2 diabetes mellitus in pediatric patients [2, 5, 47].

With regard to therapy of co-morbidities which frequently accompany type 2 diabetes mellitus in children, such as hyperlipidemia and hypertension, there are no evidence-based guidelines as to what therapy should be used.

Prevention

The financial and societal consequences of the emerging epidemic of obesity and type 2 diabetes are substantial and demand a prompt public health response. Emphasis must be placed upon preventive strategies [26]. As prevention has to start very early in life and perhaps even before extrauterine life [11], a population and community approach for prevention of obesity and hence type 2 diabetes in childhood and adolescence seems to be the most promising and reasonable treatment strategy available at the moment. A multidisciplinary team approach is asked for to develop and secure preventive strategies. Good nutrition and modest exercise for pregnant women as well as monitoring of intrauterine growth of the child are mandatory. After birth, rapid weight gain should be avoided and principles of good nutrition and physical activities should be taught at all ages [42]. Breast-feeding should strongly be recommended. Children's food choice can be influenced by early intervention and guidance. The cost-effectiveness of group and mixed family-based treatments for childhood

obesity has been tested and proven. It is therefore to be concluded that family-based, behavioral treatment of obesity is the best strategy to prevent type 2 diabetes [45, 48].

Perspectives

Obesity is the most common chronic disorder in the Western World [10, 11]. Childhood obesity is associated with substantial co-morbidity and late sequelae [11, 14]. While diagnostic strategies are clear and straight forward, treatment remains difficult. In our opinion, much more attention should be given to prevention and the development of preventive strategies early in life. Physicians should make the public aware of both the childhood obesity epidemic and its serious consequences and among them most importantly of type 2 diabetes. In conclusion, it is becoming increasingly clear, that very obese children above the age of 10 years should be screened for the presence of impaired glucose tolerance or overt type 2 diabetes. Prevention and treatment of type 2 diabetes should finally become one of the prime targets of public health intervention programs [3, 17, 19–22, 24].

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Type 2 Diabetes mellitus in Children and Adolescents: The New Epidemic

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Recently there has been an explosion of type 2 diabetes mellitus (T2DM) among children and adolescents with particular impact in minority groups [1–10]. The incidence of T2DM is steadily escalating throughout the world in people from a wide range of ethnic groups and all social and economic levels [11–14]. According to the WHO 'an apparent epidemic of diabetes has occurred which is strongly related to lifestyle and economic change'. This warning was already sounded in 1991 [15]. Matters have definitely gotten worse since then. Recent projections suggest now that by the year 2010 there will be more than 230 million diabetic individuals in the world [16].

The first description of T2DM in youth was probably described already by Elsa Paulsen [17] in 1968. She studied 66 obese children with an oral GTT and found 5 to have an impaired GTT and 7 with diabetes mellitus by GTT applying current criteria. Four of the children with DM and 5 with impaired glucose tolerance (IGT) were from families with diabetes in parents and/or grandparents. Until recently, pediatricians were taught T2DM did not exist in children and atypical diabetes in children was classified as MODY, a monogenic, insulinopenic class of diabetes [18, 19]. Subsequently, an increased occurrence of T2DM was reported in children among the Pima Indians [1]. This was followed by alarming reports of an increased occurrence of T2DM in Mexican-American children from California, Texas, African-American children from Ohio, Arkansas, New York, Caribbean-Hispanic children from New York and from First Nation children from Canada [1–10].

This nearly epidemic rise of T2DM in youth is, however, not limited to the Americas; it has now been reported from many countries around the globe from both developed and less-developed nations [13, 20–23].

The occurrence of T2DM has been attributed to the rising rate of childhood obesity and an increasingly sedentary lifestyle in genetically predisposed individuals. Several studies report a steady increase in obesity in the past 30 years among American children [24–26].

There are currently no nationwide epidemiological data focusing on T2DM. The prevalence has been established at between 2 and 50 per 1,000 in various populations; rates have been increased as much as 10-fold over the past 2 decades [3, 14]. In 3 studies conducted in the past decade among adolescents aged less than 19 years, T2DM accounted for 33–50% of all diabetes in that age group. These figures may actually underestimate the actual magnitude of the problem because T2DM is more likely to be misclassified, misdiagnosed as T1DM or simply go unreported [14]. Up to 50% of persons with T2DM are currently undiagnosed, yet are at risk for all the long term sequelae of T2DM (hypertension, hyperlipidemia, microalbuminuria). More than 40% of the children of those with T2DM have an increased lifetime risk for also developing T2DM [27]. Within the United States African-Americans have a 2-fold increase in risk, Hispanics a 2.5-fold increase and native Americans (First Nation Americans) a 5-fold increase compared to Whites. The risk is slightly higher for females and those living in poverty, probably secondary to the added risk of higher rates of obesity [27, 28].

Epidemiology

The clinical spectrum of T2DM in children forms a wide spectrum from incidental diagnosis to severe clinical symptomatology. In its mildest form the diagnosis is made incidentally in obese children during routine evaluation with detection of glycosuria and hyperglycemia. Some patients present with severe insulin deficiency, weight loss and even ketoacidosis [29, 30]. Often these patients are initially diagnosed as having T1DM with negative autoimmune studies. Initial insulin requirements decline usually when glucose toxicity is controlled. There is no specific laboratory test for T2DM, though absence of immune markers is often helpful. Jones et al. [30] documented that obese children of all ethnicities can be antibody positive. In an efficacy study of metformin in multi-ethnic adolescents referred with a diagnosis of T2DM, of 481 patients screened, 10% were antibody positive.

Recently, a component of immune destruction of beta cells has been documented in a subset of T2DM patients – latent autoimmune diabetes of adults (LADA). There is every reason to assume that LADA can also occur in adolescents [19].

Unstimulated C-peptide values are often diagnostic and are distinctly higher at diagnosis in T2DM as compared to T1DM at diagnosis [18, 19, 30].

Table 1. T2DM in US studies: demographic characteristics

	Pinhas-Hamiel [3] 1996	Scott [4] 1997	Hale [6] 1998	Onyemere [7] 1998	Grinstein [8] 2003
Number	54	50	101	155	89
African-American, %	68	74	12	74	43
Hispanic, %	N/A	2	83	26	37
White, %	32	24	5	N/A	0
Asian Indian, %	0	0	0	0	3
Age at diagnosis, years	13.8	13.9	13.9	13.4	14
F/M ratio	1.7	1.6	3	1.8	1.6
BMI, kg/m^2	38	35	N/A	32	34.4
AN, ()	60	86	92	N/A	89
FH of T2DM, %	85	N/A	100	50	96

Even the clinical signs for T2DM lose some of their discriminating power: as children's BMI increases across the board even T1DM children may present now more frequently as obese children [30, 31, 32].

The majority of T2DM children and adolescents in the US present with:

- obesity
- acanthosis nigricans
- are prepubertal in age (range 6–18 years, mean 14 + 2.3 years)
- have a strong family history of T2DM
- and belong to a minority population

(see also table 1).

In the series described and followed in the Bronx, 48% had polyuria and polydipsia at the time of diagnosis, 13% complained of fatigue and 22% of weight loss. The mean BMI at diagnosis was 34.7 + 9.0 kg/m^2. Upto 20% had a BMI within 1 SD of the mean for age. Particularly the non-obese patients were more often symptomatic at time of diagnosis with polyuria, polydipsia and weight loss. These systems may have led to their near normal BMI at diagnosis [8].

It should be stressed that 30% were completely asymptomatic at the time of diagnosis and were found to be hyperglycemic after glucosuria had been detected by routine urinalysis performed by the primary care physician.

The patients with acanthosis nigricans (AN) had higher insulin levels at diagnosis than those without AN. Nine of the 50 females had mild hirsutism and 2 had polycystic ovarian syndrome. Birth weight by history was normal. The biochemical data at time of presentation again underscore the heterogeneity of adolescents with T2DM. Although the majority of the patients were hyperinsulinemic at the time of diagnosis, nearly 17%, had insulin levels under 10 mU/ml. Girls had higher mean insulin levels than did boys. Mean blood

sugar at the time of presentation was 321 + 184 mg/dl. The mean HbgA1c at time of diagnosis was 10.9% = 3.3 (normal less than 6.45). Less than 7% had a normal HgbA1c at time of presentation. Five patients presented in DKA and ketonuria was present in 31 patients.

Risk Factors and Pathophysiology of T2DM

In adolescents with T2DM insulin resistance is clearly one of the earliest abnormalities accompanied by multiple risk factors listed in figure 1.

In the fully established diabetic picture, the common pathophysiology involves decreased glucose uptake, decreased beta cell function and an increased hepatic glucose production [33–36]. Glucotoxicity caused by undetected, prolonged hyperglycemia and lipotoxicity interfere with residual insulin action further, may therefore compound the picture and may also hamper therapeutic success with oral antidiabetic agents. To date metformin is the only oral drug approved for diabetes therapy in pediatrics in the United States [30].

Obesity, especially visceral fat accumulation, appears to be a major risk factor for T2DM [3, 5, 20, 21]. Obesity is now the most common nutritional disease of children in the US, 25% are already obese or are at risk of becoming obese [37, 38]. In Japanese children, the increasing evidence of T2DM appears to parallel the increasing prevalence of obesity from 1975–95 [22]. Consumption of sugared soft drinks nearly doubled in the last 15 years in the US [28, 39, 40]. In addition, an increasingly sedentary lifestyle, number of hours of television and intake of saturated fats all contribute to the rise in T2DM. The epidemic of T2DM in minority children has to be viewed with the knowledge in mind that African-American children have a higher degree of insulin resistance and have at baseline higher insulin levels than Caucasian children [41, 42].

This genetic predisposition based on race is further compounded by the positive family history of T2DM. Among our population up to 65% of patients had a first-degree relative with T2DM [8].

Puberty itself is associated with physiologic insulin resistance. As elegant studies by Arslanian and coworkers have shown, the physiologically increased growth hormone secretion during normal puberty is probably responsible for the transient insulin resistance that evolves during puberty. This would also explain at least in part why the peak age of T2DM is in mid-puberty [43].

T2DM as Part of the Metabolic Syndrome

T2DM is part of a larger complex called metabolic syndrome, insulin resistance (IR) syndrome or syndrome X. This syndrome has many components

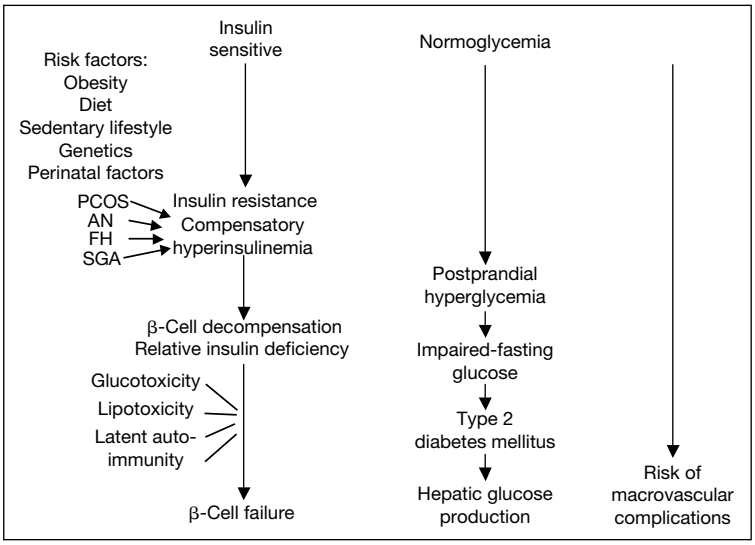

Fig. 1. The natural history of type 2 diabetes mellitus. PCOS = Polycystic ovarian syndrome; AN = acanthosis nigricans; FH = family history; SGA = small for gestational age infant. Modified from Ludwig and Ebbelin [28].

and clearly the most dangerous long-term risk is that of coronary, cerebral and peripheral vascular diseases [44]. The definition of IR or metabolic syndrome by the WHO (1998) or the NCEP Adult Treatment Panel III (2001) is given in table 2 [45, 46]. Recently, the ADA has lowered the upper normal level of fasting glucose to 100 mg/dl (table 3) [47].

Abnormalities associated with IR are:

Glucose intolerance (IGT) or manifest DM

Dyslipidemia

Hemodynamic changes: BP, sympathetic tone, sodium retention

Hemostasis: PAI-1, fibrinogen

Endothelial dysfunction: mononuclear cell adhesion, endothelial dependent vasodilatation

Reproductive: PCOS or ovarian hyperandrogenism

Defined by its most specific physiologic manifestation, i.e. insulin resistance, is actually impedance to the ability of insulin to promote the uptake of glucose into the skeletal muscle and its conversion into glucagon [48]. Insulin resistance is, however, a much more generalized condition, e.g. the ability of insulin to promote increased muscle blood flow through the activation of endothelial nitric oxide synthase is blunted in insulin resistant subjects parallel to the decrease of glucose transport into muscle [48].

Table 2. Definitions of the insulin resistance or metabolic syndrome by the World Health Organization (1998) and the National Cholesterol Education Program Adult Treatment Panel III (2001) criteria

WHO	NCEP ATP III
(IFG or IGT or diabetes)* and/or insulin resistance + 2 or more of: Waist-hip ratio >0.85 (women) or >0.9 (men) and/or body mass index >30 kg/m^2 Triglycerides ≥150 mg/dl and/or HDL cholesterol <35 mg/dl (women) or <40 mg/dl (men) Blood pressure ≥140/90 mm Hg Microalbuminuria: urinary albumin excretion rate ≥20 μg/min or albumin/creatinine ratio ≥30 mg/g	3 or more of: Abdominal obesity: waist circumference >35 inches (women) or 40 inches (men) Triglycerides ≥150 mg/dl HDL cholesterol <50 mg/dl (women) or <40 mg/dl (men) Blood pressure ≥130/85 mm Hg Fasting plasma glucose ≤110 mg/dl

*IFG + impaired fasting glucose: fasting plasma glucose (FPG) 110–125 mg/dl and 2-hour post-oral glucose (2hPG) <140 mg/dl; IGT + impaired glucose tolerance: FPG <110 mg/dl and 2hPG 140–199 mg/dl; Diabetes + treatment for hyperglycemia or FPG ≥126 mg/dl and/or 2hPG ≥200 mg/dl: + insulin resistance + clamp-assessed glucose uptake below the 25th percentile, or homeostasis-model assessed (HOMA: fasting insulin/fasting glucose × 22.5) insulin resistance above the 75th percentile, as measured among subjects with no metabolic abnormalities.

The gold standard for the clinical assessment of this stage was and is the insulin clamp. This elegant but cumbersome insulin clamp test is impractical outside of research settings [49, 50].

Other clinically useful methods are [44, 51]:

1) HOMA IR (homeostasis model assessed; fasting insulin/fasting glucose × 22.5). This test takes advantage of the fact that in no diabetic insulin resistant subjects, normoglycemia is modulated through increased insulin secretion.
2) FSIVGTT (frequently sampled i.v. GTT).
3) OGTT.
4) G/I ratio.
5) 'Quicki' test.

It should be noted that the definition of IR in non-diabetic subjects is arbitary. If is defined as the bottom 10% of HOMA values (M value, higher M = more sensitive) in lean, non-diabetic individuals, then 26% of obese individuals are insulin resistant [52]. IR is considerably higher in morbidly obese

Table 3. ADA criteria 2003: glucose levels (mg%)

	Normal	Impaired	Diabetes
Fasting	<100	>100; <126	>126
2-Hour PP	<140	>140; <200	>200

subjects. A patient may, for example, have an abnormal M value but still have a normal GTT. Only a minority will have an impaired GTT. Impaired glucose tolerance is then accompanied not just by IR but also by deficiencies in insulin secretion. In impaired glucose tolerance there is always also beta-cell insufficiency. Defective insulin signaling in the beta-cell itself can result in beta-cell failure and when coupled with obesity in clinical diabetes [53].

The rate progression of IGT to T2DM ranges from 2–14% per year depending on additional risk factors such as ethnicity, obesity, etc. The rate of progression in children is not known. The majority of individuals who exhibit IGT do not go on to develop clinical diabetes. The primary determinant of progression to these more clinically significant states is rather a further decline in insulin secretion than worsening IR [54]. Any feature or condition associated with IR/hyperinsulinism should alert the physician to screen youths at risk for IGT and/or T2DM. The ADA consensus conference recommends for screening purposes the use of obesity as a major criterion with two additional minor criteria (e.g. family history, high-risk minority population or features of syndrome X). The suggested age for screening is age 10 or earlier if onset of puberty precedes this age. It remains to be determined whether a fasting plasma glucose or a 2-hour oral GTT is a better screening tool. It is already clear that children as young as 6 years of age can present with T2DM and furthermore it is becoming evident that fasting plasma glucose level screening may miss children at risk [20].

Prevention and Treatment

Two central principles regarding the management of T2DM need to be emphasized [28]:

1. Frank DM is a late metabolic decomposition. The increased risk of cardiovascular complications begins early in the disease process (hypertension, hyperalbuminuria). The importance of a healthy diet and a physically active lifestyle should be emphasized for all overweight children.
2. Because T2DM is caused by relative insulin deficiency in the setting of insulin resistance, optimal therapy requires obviously measures to decrease insulin resistance.

Weight Loss

The cornerstone of therapy for T2DM is weight loss. A multidisciplinary approach involving dietary modification, increased physical activity, decreased sedentary time and behavior therapy offer the best chances for successful intervention [55–58].

Diet

In addition to lower calories, a low-carbohydrate, high-fat diet is recommended. Polyunsaturated fat from vegetable and marine sources decreases risk. Habitual consumption of low glycemic index foods may also lower risk of T2DM and improve metabolic control once it has developed. A low glycemic index diet may also facilitate weight loss, though this possibility has not yet been examined in long term clinical trials [28].

Physical Activity

Increased physical activity increases insulin sensitivity and glucose tolerance. Sedentary activities such as television have been shown to increase the risk for obesity [28].

Medical Therapy (Table 4)

The goal of therapy for adolescents with T2DM should be to maintain glucose levels as normal as possible in order to avoid the micro- and macrovascular complications [8]. The ADA recommends maintaining a fasting glucose level of 80–120 mg/dl, bedtime blood sugar, 100–140 mg/dl and a HgbA1c less than 7% [59]. In our population, initial therapy consisted of Metformin 500 mg b.i.d. Insulin was used if the patient presented in DKA, with ketosis or if good glycemic control was not achieved with diet and maximal doses of oral medications (metformin 1,000 mg twice daily after meals). Insulin was used as the only form of initial therapy in those patients in whom a diagnosis of T1DM instead of T2DM was initially suspected. In the follow-up, as glycemic control improved and HgbA1c fell, insulin was tapered and discontinued first, followed by metformin. If blood sugars remain persistently elevated above normal or the HgbA1c level increased further, with diet and exercise, metformin was re-initiated at does up to 2,000 mg/day [18].

Metformin does not only have insulin sensitizing effects, but also has been described to have an anorectic effect and the ability to decrease fatty acid oxidation with a reduction in plasma triglyceride and low-density lipoprotein cholesterol levels [60, 61].

Metformin has also been used in the treatment of impaired glucose tolerance in obese adolescents in a research study [62]. Side effects such as gastrointestinal complaints, nausea and diarrhea occur in the beginning of treatment in up to 40% of patients but are usually mild and self-limited. Patients with T2DM are obese and may have steatohepatitis at the outset. In our experience

Table 4. Drugs for treatment of T2DM

Drug type	Action	Effect on blood glucose	Hypoglycemia risk	Increase in weight	Effect on lipids
Biguanides (Metformin)	lowers hepatic glucose output, increases hepatic insulin sensitivity	++	0	0	+
Sulfonylureas	increase insulin sensitivity and secretion	+++	+	+	0
Meglitinide (repaglinide)	increase in first phase insulin secretion	+++	0	+	0
Gucosidase inhibitors (acarbose)	slows hydrolysis and absorption of sugars	+	0	0	+
Thiazolidinedione (rosiglitazone, pioglitazone)	increase in insulin sensitivity in muscle and fat tissue	+	0	+	+
Insulin	lowers hepatic glucose output	+++	+	++	+

metformin does not cause fatty liver. Very rarely lactic acidosis has been observed. Baseline assessment of CO_2, creatinine levels and liver function tests are recommended. Metformin is contraindicated in pregnancy, hepatic, renal or respiratory disease or when radiographic contrast agents are used. Metformin does not cause hypoglycemia and it may cause welcome weight loss. In our patients on metformin alone there was a mean reduction of BMI of 9 + 2%. Other drugs that increase insulin sensitivity are a glucosidase inhibitors.

Agents that increase insulin levels such as sulfonylureas and meglitinides may lead to further weight gain and also hypoglycemia. They are currently not recommended in T2DM in children and adolescents. Thiazolidinediones are not currently approved for use in children.

Patients requiring insulin often experience further weight gain, the dose required is usually less than 0.4 U/kg/day, much less than in T1DM. By 3 years after diagnosis 83% of our patients were able to maintain a HgbA1c of less than 7% without insulin [18].

A recent survey of members of the Lawson Wilkins Pediatric Endocrine Society (LWPES) in North America revealed that approximately 48% of youth with T2DM were treated with insulin (typically twice a day) and 44% with oral hyopyglycemic agents. Among the latter 71% received metformin which is clearly the first-line drug for T2DM, 46% received sulfonylurea, 9% thiazolidinediones and 4% meglinitide [63]. A therapeutic decision tree for treatment of T2DM is suggested in figure 2. Please note that sulfonylureas may further increase weight and should therefore not be used as first-line drugs.

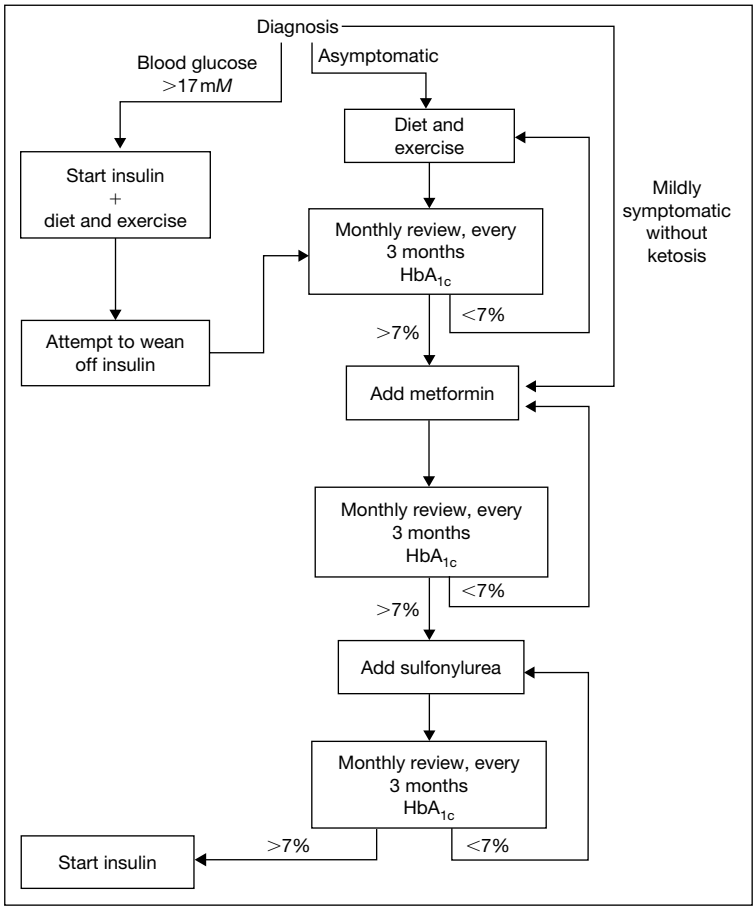

Fig. 2. Treatment decision tree for outpatient management of T2DM [64].

Conclusions

T2DM and obesity in youths are a worldwide phenomenon. We need to recognize not just the tip of the iceberg, manifest T2DM, but we need to focus on the larger issues of IR and metabolic syndrome in children and adolescents. 'Prediabetes' is being increasingly found in obese youth. It is characterized by severe insulin resistance and altered myocellular and abdominal fat partitioning [63, 65]. Babies from SGA (small for gestational age) are at increased risk for insulin resistance, particularly when there is early postnatal catch-up growth [66]. As the clinical epidemiology of childhood diabetes is changing rapidly he major task for pediatricians remains and is prevention [67].

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Multidisciplinary Management of Obesity in Children and Adolescents – Why and How Should It Be Achieved?

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Introduction

Definition and Epidemiology of Obesity

The degree of body fat mass depends upon ethnic background, gender, developmental stage and age. The most useful non-invasive clinical measures to define obesity are the body mass index (BMI, weight in kilograms divided by the square of height in meters), waist circumference, waist-to-hip ratio (WHR, to assess upper body fat deposition), and skinfold thickness [1–3].

Direct measurements of body fat content, e.g. hydrodensitometry, bioimpedance or DEXA, are useful tools only in scientific studies. The BMI is easy to calculate and correlates significantly with direct measures of body fatness. Thus, it has become the standard parameter to define obesity clinically [1–4]. A child with a BMI above the 97th centile in regard to age and gender is considered to be obese. A child with a BMI greater than the 90th but below the 97th centile would be considered to be overweight [1–3, 5].

Projected rates for obesity (BMI $\geq$30 kg/m^2) in adults in the United States are 20% for the year 2000, 30% for the year 2015 and over 40% for the year 2025 [4, 6–8]. Similar to adults, childhood obesity has reached epidemic proportions in all industrialized countries. The current age-adjusted prevalence may be as high as 20–30%. In 1999, in a cross-sectional study in the city of Leipzig, Germany, involving more than 2,500 children and adolescents between 7 and 18 years of age, revealed that 29% of the subjects were overweight (BMI between 90th and 97th centiles), and 16% were obese (BMI above 97th centile). In the same geographical area, a population-based study revealed an incidence of

Table 1. Factors contributing to the development of obesity

Environmental/exogenous factors
• Increase of sedate activities (TV viewing)
• Decrease in physical activity
• Shift in diet towards more fast/prepackaged foods with high fat/calorie content
• Loneliness and social isolation
• Psychosocial/family problems
Genetic/endogenous factors
Possibly polymorphisms and/or mutations in any of the following:
• Adrenergic receptors
• Leptin
• Leptin receptors (Ob-R)
• Melanocortin receptor 4 (MC4-R)
• SOCS-3
• Tumor necrosis factor (TNF)
• Pro-opiomelanocortin (POMC)
• Melanocyte-concentrating hormone (MCH)
• Melanocortin receptor 3 (MC3-R)
• Neuropeptide Y (NPY)
• NPY receptors
• Corticotropin-releasing hormone (CRH)
• Thyrotropin-releasing hormone (TRH)
• Urocortin
• Orexin A and B
• Galanin
• Neurotensin
• Serotonin
• Others

obesity in children and adolescents of around 12% [2, 3]. Interestingly, not only the number of obese children is increasing, but also the tendency towards even more excessive weight [2, 3, unpubl. data].

Etiopathogenesis and Comorbidity of Obesity in Childhood and Adolescence

The high incidence of childhood obesity is due to multiple factors. Both genetic/endogenous and environmental/exogenous factors contribute to the development of a high degree of body fatness early in life (table 1). Twin studies suggest that at least 50% of the tendency toward obesity is inherited [1–5].

There is also increasing body of evidence that responsiveness to dietary intervention is genetically determined [9–12].

Several monogenic causes of obesity have been identified. Genetic alterations of the *ob* gene (leptin) [13–17], the leptin receptor [18] as well as the melanocortin-4 receptor (MC4-R) [19–21] have been shown to be associated with severe obesity.

However, in most patients, a multifactorial etiopathogenesis contributes to the development of obesity. Exogenous factors such as overconsumption of fat-rich diets, the excessive use of modern media and in particular television viewing [22–24] and lack of physical activity (sedentary life style) [25] are the most important risk factors for the development of obesity in childhood and adolescence. Nutrition and diet early in infancy is thought to influence growth rate and body fatness beyond infancy. Taken the available data together, many authors support a model in which susceptibility to obesity is determined largely by genetic factors, but the environment determines individual phenotypic expression [1–5].

A BMI greater than 28 kg/m^2 is associated with an increased risk of morbidity such as stroke, ischemic heart disease, sleep apnea syndrome, orthopedic diseases or type II diabetes mellitus in adulthood. Even more concerning are data indicating that adolescents whose BMI had been greater than the 75th percentile are prone to an increased risk of death from cardiovascular disease as adults [1–5, 26].

The most common sequelae of primary childhood obesity are, among others, hypertension, dyslipidemia and psychosocial problems (table 2), predisposing for yet again additional comorbidity such as cardiovascular disease in early adulthood. Approximately 60–85% of obese preschoolers will stay obese in adulthood. Thus, the comorbidity represents a major health burden in industrialized societies. In addition, childhood obesity seems to increase the risk of subsequent morbidity whether or not obesity persists in adulthood [2, 3, 5, 26].

Recent studies indicate that impaired glucose tolerance is present in up to 25% of obese children, and type 2 diabetes can be identified in up to 4% of obese adolescents [27].

Therapeutic Approaches

Multidisciplinary Treatment Options

Because obesity is a risk factor for numerous medical disorders, psychosocial problems and excess mortality, it is indeed imperative that effective treatment be developed and be widely available and instigated. Therapeutic strategies should be multidisciplinary and should include psychological and family therapy interventions [28], lifestyle/behavior modification [29], exercise

Table 2. Comorbidity of obesity in childhood and adolescence

Psychosocial-psychiatric
• Poor self image
• Social isolation
• Autoaggression
• Suicide
• Promiscuity
• Drug and alcohol addiction
• Bulimia
• Binge eating
• Smoking
• (Enuresis)
Cardiovascular and respiratory
• Accelerated atherosclerosis
• Hypertension
• Hypoventilation
• Sleep apnea
• Snoring
• Pickwickier syndrome
• Reduced lung capacity
Endocrine/metabolic/gynecological
• Hyperinsulinemia/insulin resistance
• Early puberty
• Polycystic ovaries
• Dysmenorrhea
• Dyslipidemia
Orthopedic
• Slipped capital femoral epiphyses
• Coxa vara
• Blount's disease
• Legg-Calve-Perthes disease
• Back pain

programs [25] and nutrition education [30] (fig. 1). In this context, the role of regular exercise has to be emphasized [25, 31–35]. Intermittent exercise (high intensity followed by low intensity sports) results in greater reduction in weight and fat. Such approaches also increase compliance/adherence rates of the youths. Optimal results are being achieved by combining programs to reduce sedentary behaviors based on specialized, structured exercise prescriptions [33, 35–37].

Multidisciplinary outpatient treatments are considered to be the most effective [33, 35]. Thus, networking of primary care physicians, public health/school medicine institutions, specialists of pediatric and adolescent medicine, social workers, child psychologists and dietitions as well as sport educators

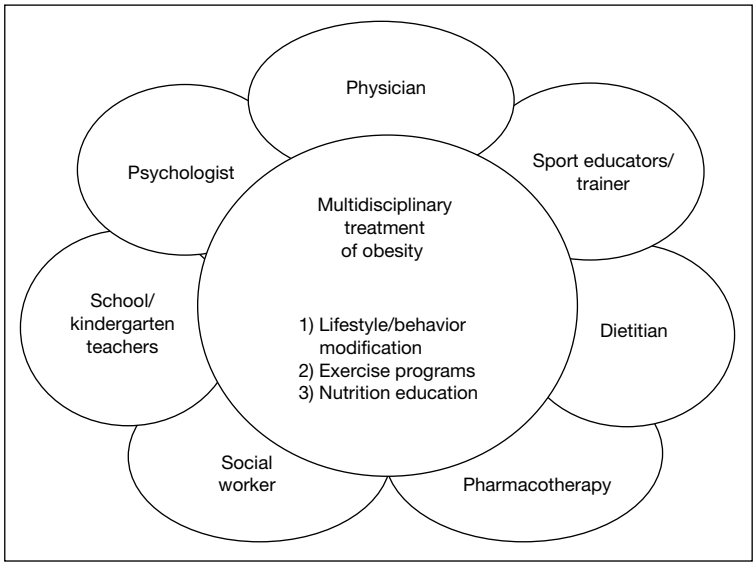

Fig. 1. Multidisciplinary approach to obesity therapy.

should be achieved (fig. 1). Such networking concepts should be strongly supported by health insurance providers and politicians. Using such approaches, some groups have reported high success rates and sufficient long-term weight reduction in small groups of children studied [33–37].

Lifestyle and Behavioral Modification

During the last years and even decades, physically inactive behaviors have been increasingly promoted. Children walk less in order to get to school or to play with friends. The home environment frequently does not allow our youngsters to play in the streets or to do outdoor activities as safely as in the past. Favorite leisure-time activities now include video and computer games as well as television programs rather than physical exercise [38].

However, the significant increase of obesity in not only a result of changes of individual lifestyle and habits, but also of general features in the industrialized countries. Unfortunately, costs and availability of healthy foods vary around countries and according to the time of year. Thus, 'junk food' is more easily available and affordable to a growing number of individuals. It is essential that local and national governments, schools, and supermarkets make healthy diets and active lifestyles accessible and affordable for families all over the country. Healthy living as well as individual health and nutrition education has to be

promoted by the government in order to stop the current epidemic of obesity in the Western World [38, 39].

The fact that changes to a healthy lifestyle, including appropriate eating patterns and exercise, is more easily incorporated into adulthood if learned early in life strongly suggests that treatment of obesity as well as cognitive awareness for a healthy lifestyle should start in childhood [40].

Psychological, Group and Family Therapy Interventions

For the treatment of childhood obesity, different strategies of psychotherapy have been used, the most important of which are family or cognitive behavioral therapy. The main goal of all psychotherapies is to create an awareness for lifestyle changes.

The several types of psychotherapy should be chosen according to the age of the obese individuals. As pre-schoolers normally accept groups formed from outside, group teaching is a promising approach. In contrast, older children prefer to create their own groups; therefore, individual treatment might be preferable. As the family of origin is very important not only in early childhood but also with teenagers and adults, family therapy can be helpful with all ages of obese individuals [40].

As family members are normally closest to obese children and adolescents, their emotional and psychological support is crucial for successful and lasting changes of lifestyle in the context of obesity therapy. Thus, it is advisable that treatment regimes should be adhered to by as many members of the family as possible. Family arrangements to meet the obese child's diet and exercise programs should be accompanied by encouragement, sensitive support and appreciation by family members. The positive effects of even slight weight loss can encourage further pursuit of restrictive diets and further weight loss.

Exercise and Physical Activity

The enzymatic activity shows a characteristic profile in lean and obese subjects. Obesity-prone subjects have decreased activity of fat-oxidizing enzymes in skeletal muscles. Moreover, smaller areas of type 1 and type 2B muscle fibers could be found in post-obese vs. non-obese individuals [41]. The hydroxyacyl coenzyme A activity, a key enzyme in β-oxidation of fatty acids, is significantly negative when correlated to relative adiposity [42]. These results suggest lower fatty acid oxidation rates in obese individuals and might explain the increased fat deposition in these subjects.

It is well established that an individual adapted to a higher level of dynamic, aerobic motor activity during growth may develop greater activity in specific enzymes which metabolize and utilize fatty acids. In addition, aerobic exercise

increases cardiorespiratory capacity. The utilization of fat metabolites during muscle work is facilitated by the increased enzymatic activity of the skeletal muscle. Thus, aerobic exercise is the most suitable form for obese children and adolescents [42].

At the beginning of exercise programs, the interest of the obese child should be focused on increased exercise and physical activity. The reduction of body fat is best achieved by dynamic, aerobic exercise. Thus, it can be ideal to start exercise programs with swimming, since these can help make movements easier for those who are extremely obese. Later in the therapy program, after some weight reduction and adaptation to increased physical activity, it might be easier for the kids to exercise from lying down or sitting positions or to use cycle ergometers [43].

Finally, exercise in the concept of obesity therapy not only aims to reduce body weight but also to correct posture and to reduce comorbidity. As the need of obese individuals as well as the degree of obesity and the social background show a significant variability, it is essential to individualize and adapt each exercise program according to the special features of the particular child.

Nutritional Education

As obesity is a multifactorial disease, diet is only one of several treatment approaches. Dietary intervention should be related to the child's age, the severity of obesity and the presence of comorbidities. Evaluating the child's nutritional status is essential prior to prescribing any diet [44].

Children and adolescents with moderate obesity and no comorbidities can be treated with a balanced low-caloric diet (BLCD). In a BLCD, the energy intake is reduced by about 30%, balanced with 20% energy derived from protein, 30–35% from fat and 45–50% derived from carbohydrates, respectively [44].

In patients with severe obesity (BMI far above the 97th percentile) and who are already affected by secondary complications of overweight and obesity, however, a very-low-calorie diet (VLCD) should be considered rather than BLCD. In VLCD 800 kcal/day or fewer are provided [45]. The calories can be either partially balanced (protein 25%, fat 30%, carbohydrates 45%) or unbalanced (protein 66%, fat 24%, carbohydrates 10%). The latter is also referred to as protein-sparing modified fast (PSMF), as it is supposed to spare lean body mass while producing rapid weight loss. Severe obesity in childhood and adolescence is most widely treated with PSMF [44]. However, since VLCDs and PSMFs can produce rapid and remarkable weight loss, one has to take into consideration that this can later lead to a 'yo-yo' syndrome of loss and regain of body weight. Thus, these groups of diets should be used very carefully in this age group of obese patients and only under strict medical supervision.

In general, a nutrition plan has to be developed and discussed in accordance with the obese individual's specific needs and the child's social background.

Pharmacotherapy and Available Compounds

Since the efficacy and success rates of the available treatment strategies for obesity are very limited, long-term treatment including extended pharmacotherapy may be necessary for some very obese adolescents [46–52].

However, anti-obesity drugs, i.e. appetite suppressants and thermogenic drugs, have not been approved for use in children. Some centrally acting noradrenergic agents and serotoninergic agents are being used to treat obesity in adults. Thermogenic drugs are either epinephrine or caffeine or alternatively atypical beta-adrenergic agonists. Digestive inhibitors such as lipase inhibitors and fat substitutes have been used in children and adolescents in off-label use and in only a few clinical studies.

Taken together, three main modes of action of anti-obesity drugs can be distinguished: substances that act upon: (1) energy intake; (2) energy storage, or (3) energy output. Agents which influence energy intake either act through the brain by modifying eating behavior as well as suppressing appetite or exert their actions by altering gastric emptying, causing malabsorption or relay satiety back to the brain. Drugs that modify energy storage either decrease lipid storage or increase lipid oxidation in the fat tissue. Lastly, energy output can be regulated either in the brain or in skeletal muscle and brown adipose tissues [47–49].

At present, two of the anti-obesity medications, orlistat and sibutramine, are increasingly being used in adults. Orlistat binds to gastrointestinal lipases and causes a partial inhibition of fat resorption from the gut. In contrast, sibutramine causes a centrally mediated increase in satiety and energy expenditure. When combined with a hypocaloric diet, both drugs lead to a moderate additional weight loss of some kilograms within 6 months [47, 49].

Metformin is at present being studied as therapy for both type 2 diabetes and obesity in children and adolescents. However, great care should be exerted when anti-obesity medication is to be prescribed to adolescents or children [3, 47]. Several previously widely used medications have recently been withdrawn from the market because of concerns about side effects in adults. Most if not all of these drugs have not yet been studied in respect to efficacy, safety and long-term effects in children and adolescents [2, 3, 35, 46–52].

If one is to summarize all available data from clinical studies of anti-obesity pharmacotherapy in childhood and adolescence it is clear that all therapies must be considered within the framework of a multidisciplinary approach with the support of an interdisciplinary team, including primary care physicians, public health/school medicine institutions, specialists of pediatric and adolescent

medicine, social workers, child psychologists and dietitions as well as sport educators [1–3].

Surgical Intervention

Laparoscopic adjustable gastric banding is being increasingly considered as the treatment of choice in very obese adults [53, 54]. Early complications of such interventions and significant late complications such as pouch dilatation and stomach slippage have been rare [53]. However, in one series in 7.5% of 146 cases operated on reoperations were necessary [55]. Recommendations of an international workshop on gastric banding for adult obesity are summarized in the following: (1) good patient selection has to be made; (2) standard surgical practice has to be adhered to, and (3), last but not least, no surgery must be performed without the support of an interdisciplinary team which has to include internists, psychologists and dietitians [53]. Whether or not such invasive treatment options will ultimately be considered in adolescents is still open to debate.

Perspectives

Childhood Obesity as a Major Burden for the Economy

Obesity in childhood and adolescence has already become a major factor in health care planning systems and within the health care industry. The financial burden of childhood obesity for industrialized societies can only be estimated. Approximately 70 billion dollars is the annual economic cost due to medical expenses and lost income as a result of complications of adult obesity in the USA. At least another 30 billion dollars is thought to be spent on diet foods, products and programs to lose weight [56–59]. According to a recent report by Fontaine et al. [56], the BMI associated with the greatest longevity is 23–25 kg/m^2 for white and 23–30 kg/m^2 for black adults. For any given degree of overweight, younger people generally had a greater degree of years of life lost than had older subjects. Since obesity apparently shortens life expectancy markedly, especially among young adults, the economic loss for the society already has become enormous.

The fact that obesity is associated with a significant increase in morbidity and mortality and that obese people are often stigmatized both socially and in the workplace contributes to the economic cost of obesity albeit in an unknown and almost incalculable way [36, 59].

Prevention and Costs of Prevention

Prevention of obesity has to start very early in life, perhaps even before extrauterine life [60]. A population and community approach for prevention

seems to be the most promising and reasonable. However, primary prevention has been proven to be difficult or impossible in most societies at this point of time [2, 3, 61]. Again, a multidisciplinary team approach is crucial to develop and secure preventive strategies. Good nutrition and modest exercise for pregnant women as well as monitoring of intrauterine growth of the child are mandatory. After birth, rapid weight gain should be avoided and principles of good nutrition and physical activities should be taught at all ages. Breast-feeding should strongly be recommended [60]. Children's food choice can be influenced by early intervention and guidance. Parents should be encouraged to make healthy foods easily available to the child and serve these foods in positive mealtime situations in order to help their child to develop healthy food habits [61]. As for treatment strategies, multidisciplinary teams should be formed. Such teams should always include a physician, a nutrition specialist and a psychologist but mainly consist of school nurses, teachers and kindergarten teachers. Joint actions by physicians, health authorities and politicians both in the community and also using modern media and mass media are being asked for to implement nationwide prevention programs. Such programs have to take into account cultural and racial preferences and attitudes in respect to food preparation and eating habits. Taxes on fast foods and soft drinks should be considered, while nutritious foods such as fruits and vegetables could be subsidized for the poorer income classes. Nutrition labels should be required on fast-food packaging. Last but not least, food advertisement and marketing directed at children should be banned while funding for public-health campaigns for obesity prevention should be increased [2, 3, 5]. Recent changes in federal tax laws in the United States may influence the roles of health plans in promoting physical activity and thus may assist treatment and prevention of obesity [57].

Conclusions

Obesity is the most common chronic disorder in industrialized societies [9]. In some countries, the prevalence of juvenile obesity already exceeds that of allergic disorders including both asthma and eczema. Its impact on individual lives and on health economics has to be recognized by physicians and the public alike.

Childhood obesity is associated with substantial comorbidity and late sequelae. While diagnostic strategies are clear and straightforward, treatment remains difficult and frustrating for the patient, family and the multidisciplinary team caring for children and adolescents with obesity. In our opinion, much more attention should be given to prevention and the development of preventive strategies at all ages. Prevention should in any case start very early in life. Finally,

public awareness of the ever increasing health burden and economic dimension of the childhood obesity epidemic has to be considered by the public and by politicians.

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Bariatric Surgery

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Surgical treatment of obesity has been performed throughout the last 50 years in adults. The techniques have varied, and today mainly four methods are used; gastric banding with fixed or variable band (GB), gastric bypass (GBP) and vertical banded gastroplasty (VBG). The techniques are schematically presented in figure 1. All these methods can today be performed by laparoscopic surgery [1, 2] and the risk of postsurgical complications is low [3–5]. Regarding two other types of surgery, bileo-pancreatic bypass and duodenal switch, the information is more limited and it is also possible that the side effects are more pronounced [6–10]. Jejuno-ileal as well as other types of intestinal bypass procedures are not currently in use due to severe side effects [11].

Bariatric surgery is the only method by which a long-standing and pronounced weight reduction has been obtained in a large number of obese patients [4, 12–14]. In the Swedish ongoing SOS study, the long-term effects of surgery are compared with low-energetic conventional treatment. The control group is not randomized. This weakness is compensated by a large number of patients enrolled. The incidence of diabetes was dramatically reduced in the bariatric surgery group. Furthermore, there was also pronounced reduction of hypertriglyceridemia and increased levels of HDL-cholesterol [15]. The prevalence of hypertension was initially reduced in the bariatric surgery group, but at follow-up after 8 years there was no significant difference between the groups [14]. However, of major importance is that the quality of life was considerably increased both after 2 and 4 years follow-up [16, 17] and there was a correlation between the degree of weight reduction and health-related quality of life.

The complication rates in the SOS-study are low taken into consideration that most of the patients were not healthy at the time of the operation. The post-surgery mortality was 0.25% [3, 5]. 12% of the first 1,164 patients in the surgery group were re-operated within 4 years of follow-up. The reasons were

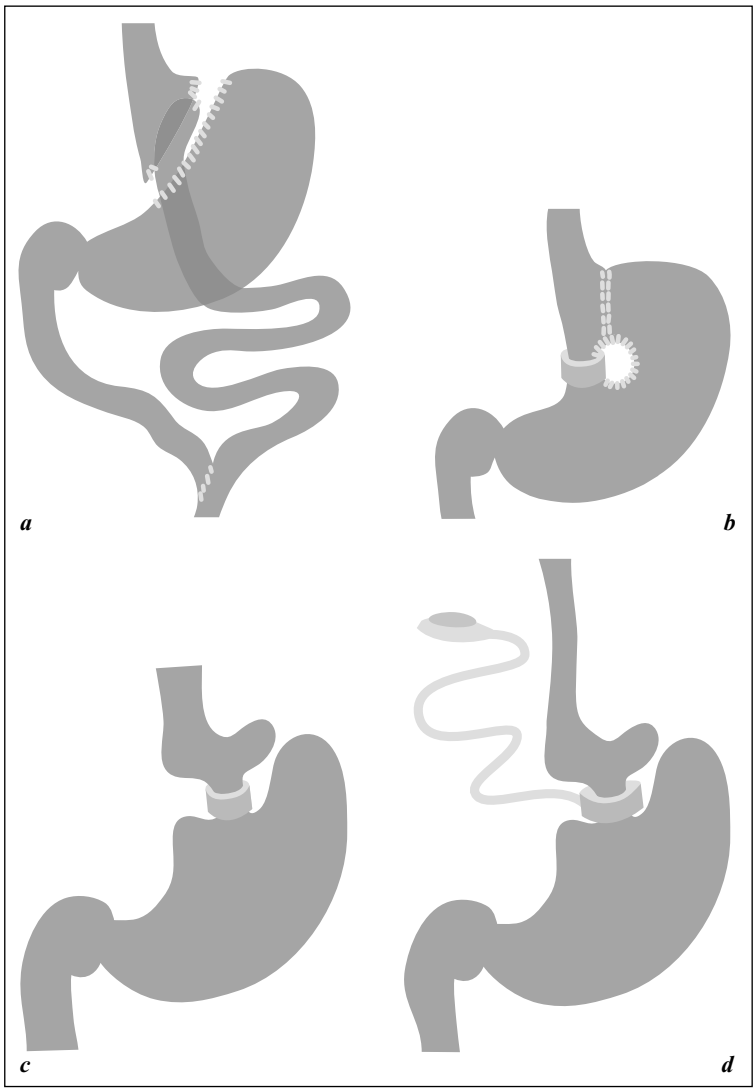

Fig. 1. Commonly used bariatric surgery procedures: (***a***) gastric bypass; (***b***) vertical banded gastroplasty; (***c***) gastric banding with fixed band, and (***d***) gastric banding with variable band (figure by Gunnar Kaj, Stockholm).

poor weight reduction or technical complications. The frequency of re-operations was highest in the GB group [5].

The positive results have led to a booming demand for bariatric surgery in many countries, above all in the United States. Between 2001and 2003 the

number of bariatric procedures in the United States is expected to rise from 50,000 to 120,000 per year [18]. In children and adolescents no controlled or prospective studies are published. However, there are approximately 200 cases presented in five follow-up reports [19–23]. The quality of the reports as well as the follow-up time varied considerably. The age of the subjects varied between 8 and 20 years and all subjects were extremely obese. The negative side effects presented were gallstones (a well-known problem associated with the weight reduction per se) and anemia. In one study two deaths were reported [21]. No one seemed to be directly related to the surgery intervention, but rather to the morbid obesity.

Most of the patients seem to have considerable improvement of quality of life and health at follow-up. In one study 100% were positive to the surgery [22] and in another 85% [19]. All signs of severe obesity co-morbidity disappeared in one [20] and in another study oxygenation was markedly improved in subjects with sleep apnea syndrome [21]. However, it has to be emphasized that these case presentations do not satisfy any reasonable requirements. The results were in many cases based on telephone interviews, or questionnaires sent by post and only on a few occasions clinical examinations. Despite these concerns the results are surprisingly positive and stress the need of prospective studies including careful medical and psychological examinations.

There are many ethical problems involved if bariatric surgery is considered for childhood obesity. For all children surgical restriction of food intake is also a restriction on the personal integrity. Children with mental retardation, e.g. Prader-Willi syndrome or subjects with eating disorders or children with hypothalamic obesity are all patients who cannot handle food intake and they should not be exposed to bariatric surgery. The least invasive surgical method is gastric banding and the band is also relatively easy to remove. On the other hand, gastric banding is the bariatric procedure, which is marred by most problems and seems also to be least effective. Furthermore, gastric banding does not encourage healthy eating habits as high energy density liquids and sweets are well tolerated. Gastric bypass is the method, which seems to be most favorable when both effect on weight loss and negative side effects are considered. However, it is an extensive operation and for children with a long life expectancy it can be questioned whether it is ethically justified. It is to be hoped that within ten years more potent anti-obesity drugs are available and an active conservative treatment is maybe preferable in most cases of childhood obesity. In subgroups of children and adolescents with severe otherwise untreatable obesity life expectancy and quality of life are so severely affected that it may well be ethically justified to try surgical treatment. This should preferentially be done in controlled clinical trials.

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Pharmacological Treatment of Childhood Obesity

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The awareness within the western societies of the health hazards associated with obesity has increased considerably throughout the last 5–10 years. This is also valid for childhood obesity. Previously, obesity before adulthood was considered more a psychosocial burden than a medical concern. However epidemiological studies indicating that obesity that appear early in life more severely affects life expectancy [1] in combination with data indicating a correlation between childhood obesity and various forms of co-morbidity [2–6] have put increased pressure on the medical society to offer children with obesity more effective treatment alternatives. Since behavioral treatment alone has a limited effect [7] pharmacological treatment has to be taken into consideration especially for adolescents with severe obesity.

Possible Targets for Obesity Treatment

Pharmacological treatment with direct focus on weight reduction can roughly be divided into three groups:

1) Central nervous system acting drugs, interfering with neurons involved in appetite/satiety regulation. One such drug is on the market, sibutramine. A subgroup consists of agents that block or mimic hormones from the periphery, which interfere with appetite control. Examples of adipose tissue or gastrointestinal hormones of interest are leptin, which is secreted from adipocytes and ghrelin, an appetite-stimulating hormone secreted from the stomach. Despite a lot of efforts from the pharmaceutical industry, no drugs of this type are yet on the market. Somatostatin analogues may serve as examples as conceivable anti-obesity drugs with such an effect although they presently are approved for other indications.

2) CNS or peripheral acting drugs aiming to increase energy expenditure. They can in turn be divided into drugs, which stimulate energy expenditure in general, or drugs that specifically stimulates the utilization of fat. Sibutramine has some effect on energy expenditure.
3) Drugs that specifically inhibit energy uptake from the intestine. Orlistat is one such substance, which reduces fat uptake.

Methodological Aspects on Clinical Trials on Anti-Obesity Drugs

There are some methodological problems involved in the evaluation of the effects of anti-obesity drugs. In contrast to the situation with most other medical drugs, it is easy for obese patients themselves to evaluate whether the anti-obesity test drug is effective or not by using a simple bathroom scale. If the results are too disappointing patients don't want to remain in the clinical trials, which leads to a high number of drop-outs. One way to reduce this effect is to give both the placebo group and the group, which receive the active drug dietary and behavioral support sufficient to induce at least some weight loss. This is also often combined with a run-in period with a very low calorie diet. Those who are loosing weight are considered responders and they are thereafter included in the clinical trial. This is to some extent paradoxical since those who are most in need of anti-obesity drugs are the patients who do not respond to behavioral treatment. Taken together, this makes it more difficult to obtain significant differences between placebo and test drug, which has to be considered when the effects of obesity drugs are evaluated. On the other hand, weight reduction can sometimes be observed in clinical trials due to the combination of drug and dietary and behavioral support which is not possible to achieve in everyday clinical life.

Drugs Available Today

Orlistat

Orlistat (Xenical®) reduces intestinal fat uptake by inhibiting lipase activity. Orlistat was developed primarily as a cholesterol-lowering drug, but it was shown in early studies that it had properties that could be useful for the treatment of obesity. Orlistat has to be taken before every meal to be effective. If too much fat is ingested diarrhea and soiling will occur. Thus, the weight reduction effect is therefore depending on both the reduction of fat uptake and the awareness of the risks of diarrhea and the deliberate avoidance of food with high fat content. In one study 27% of the patients reported problems with

soiling and 8% have reported incontinence problems during the first year of treatment [8]. The negative side effects were reduced during the second year of treatment, which probably was secondary to increased awareness and reduced fat intake.

Other side effects have been rare. Some patients have complained of pruritus and in very rare cases signs of hepatitis have occurred. Orlistat was approved 1997 in USA and 1999 in EU.

In adults the effect of orlistat has been demonstrated in at least six RCT studies [9–14]. The effect of weight reduction is better than placebo, but still in most studies modest. 22% of the subjects (16–27%) have obtained at least 10% weight reduction and in the placebo groups 11%. It has to be emphasized that both groups in all studies had a pronounced support by dieticians and nurses. One interesting observation is that patients who were on orlistat for 1 year had an on-going weight reduction during a second year after the shift to placebo [14]. Thus, it is possible that orlistat treatment may have some positive long-term effects on behavior, especially regarding fat intake. This could be of interest to explore more carefully in children.

Orlistat has no systemic effects, which makes it an attractive candidate for childhood treatment. Therefore surprisingly, data from children and adolescents are scarce. McDuffie et al. [15] have studied the effect of the combination of orlistat and behavioral treatment in a 12-week open study. 20 adolescents with severe obesity were studied. 17 subjects completed the study. Weight decreased significantly (4.4 kg or 3.8% reduction of initial weight). The adverse effects were limited to gastrointestinal problems and decreasing vitamin D levels in three subjects despite multivitamin implementation.

We have in a similar study investigated orlistat treatment in severely obese 8- to 12-year-old prepubertal children with a focus on tolerance, safety and psychological well-being [16]. The most important finding was that children in this age group were able to comply with the orlistat treatment as indicated by mild and tolerable gastrointestinal side effects and positive results on psychological evaluations. The medium weight loss was 4 kg.

These two pilot studies indicate that obese children and adolescents are able to reduce their fat intake to avoid gastrointestinal side effects. Orlistat may therefore be suitable as a component in behavior modification program for obese children. However, before we have confirming results from placebo-controlled studies orlistat treatment cannot be recommended for childhood and adolescent obesity.

Sibutramine

Sibutramine (Reductil® or Meridia®) was initially developed as an antidepression drug. It is a serotonin-noradrenaline re-uptake inhibitor. It appeared

early in clinical trials that it was useless as an anti-depression drug, but a pronounced side effect was weight loss. Despite that sibutramine has similarities to amphetamine in its working mechanisms, the addiction potential is negligible.

In at least one study sibutramine also seems to have effects on blood lipids, which was more pronounced than could be expected by the weight reduction alone. Especially HDL-cholesterol increased 2–3 times more than was expected from weight reduction. This increase was more pronounced among female subjects [17]. This indicates that sibutramine may have direct positive effect on the lipid profile.

In adults sibutramine has a significant effect on weight loss in studies up to 2 years [17–19]. The mean weight loss has been between 3 and 6 kg greater than in the placebo groups. As with all other types of obesity treatment, there are responders and non-responders. Approximately 25% of the patients in these studies have had a remaining weight loss of 10%. This figure was approximately twice as high as in the placebo groups. As mentioned above all subjects received behavioral therapy.

Major side effects are increased blood pressure, increased heart rate and obstipation. In Italy 2002, sibutramine was withdrawn from the market due to two deaths with possible linkage to sibutramine. However, a few months later sibutramine was again approved since it was shown that the drug did not cause the deaths.

In children, no studies have been published so far. In 13- to17-year-old adolescents the effect of sibutramine treatment for 6 months has been studied in a randomized double-blind placebo-controlled trial, followed by an open-labelled treatment period of 6 months [20]. In addition, all 82 subjects received behavioral therapy. During the first 6 months the placebo + behavioral treated group had a mean weight loss of 3.2 kg whereas the sibutramine group lost 7.8 kg, which corresponds to 8.5% reduction in BMI. These data may indicate that at least some adolescents benefit from sibutramine treatment, but extensive studies are required before sibutramine can be generally recommended for the treatment of adolescent obesity.

Caffeine-Ephedrine

In some countries the combination of caffeine and ephedrine is approved for obesity treatment. There is a limited support for this indication in adults [21]. In adolescents one study has been published. Thirty-two subjects were enrolled for 6 months in a double blind placebo controlled trial [22]. The mean weight loss in the caffeine-ephedrine group was 6.6 vs. 0.5 kg in the placebo group. The mild side effects did not differ significantly between the groups but the severe problems palpitation, insomnia, excessive sweating and diarrhea occurred in

1 of 13 patients in the placebo group and 5 of 16 in the caffeine-ephedrine group. Both the effects on weight loss and the side effects have to be carefully documented in further long-term studies.

Growth Hormone

Growth hormone has considerable effects on body composition. Growth hormone deficiency in children and adults has increased total body fat mass and reduced lean body mass. Growth hormone treatment reduces fat mass, increases lipolysis and has positive effects on lipid profiles [23]. In obese subjects circulating growth hormone levels are very low. This is most probably because relatively high levels of circulating IGF-1, produced in the increased amounts of adipose tissue, induce a negative feedback on hypothalamus and thereby reduces hypopituitary growth hormone secretion. In short-term studies in adults beneficial effects of growth hormone treatment have been observed, but the long-term effects are uncertain [23, 24]. In children growth hormone treatment for 6 months in a small group of prepubertal boys, growth hormone was shown to increase lipolysis, reduce the percentage of body fat and increase the HDL- and LDL-cholesterol ratio. No negative effects were observed on insulin sensitivity [25].

Effects of growth hormone on obesity are of potential interest, but it has to be emphasized that the studies so far have been explorative and experimental and there is no indication for growth hormone treatment of simple obesity. There are on-going trials with small molecules with some but not all of the effects of growth hormone [26].

Somatostatin

Somatostatin is a multipotent inhibitory hormone, which inhibits both endocrine and exocrine secretory functions. Somatostatin suppresses growth hormone as well as insulin and glucagon secretion. Somatostatin is synthesized both in the brain and in the spinal cord, but also in the intestine. Long-acting somatostatin analogues are approved drugs for the treatment of acromegaly. In patients with overweight due to hypothalamic damage, often secondary to tumor surgery, excess insulin secretion has been observed. It has been suggested that hyperinsulinemia together with hypothalamic resistance to leptin and insulin are the causative factors for obesity among these patients [27–29]. The depression of insulin secretion by somatostatin analogues may therefore, in theory, be beneficial.

In a double blind placebo controlled six-month trial, the somatostatin analogue octreotide was tested. 18 subjects with hypothalamic obesity were included. Compared to placebo, the octreotide-treated group showed significantly lower

weight gain [30]. The mechanisms are probably both related to the reduction of insulin secretion and the recently observed finding that somatostatin depresses ghrelin secretion [31]. Although the results are promising for patients with extremely severe obesity, further studies are required before a general recommendation can be done.

Drugs in Clinical Trials: What Is in the Pipeline?

Despite huge efforts from the pharmacological industry not many new drugs can be expected on the market within 3–5 years, which reflects the problems involved in pharmacological obesity treatment. Appetite is fundamental for survival and most probably a potent interference with appetite regulation increase the risk of unacceptable side effects. At moment, two drugs are in late stage or phase 3 clinical trials, axokine and rimonabant. Axokine is a recombinant human variant of the protein ciliary neurotrophic factor or CNTF. CNTF is produced in the CNS and not present in the peripheral circulation. Axokine, which has to be injected, had in a double blind study a satisfactory weight reduction effect. A concern, however, is the appearance of anti-axokine antibodies among 45–87% of patients [32].

Rimonabant is acting via the cannabinoid CB1 receptor. Endogenous cannabinoids and marijuana are acting via a group of receptors among which CB1 induces increase in appetite, an effect that is blocked by rimonabant [33]. No data are yet available from the ongoing phase 3 study.

Ethical Considerations

The need of more effective treatments has not superseded the ethical concerns about pharmacological treatment of childhood obesity. The childhood obesity epidemic is most probably caused by environmental factors and therefore pharmacological treatment is in most cases not the first line of treatment. Even more, many pediatricians dissociate themselves from the thought of giving 'pills' to obese children. The demands of long-term safety regarding drugs for the treatment of obesity in childhood must be very high since it is entirely in the long-range childhood obesity is life threatening. This is particularly of importance when CNS-acting drugs are considered. The effects on the developing brain may not be the same as in adults and carefully conducted long-term studies are required. At moment no anti-obesity drug fulfils these criteria. However, in all medical treatments a careful risk-benefit analysis has to be performed. There are a large number of obese children and adolescents with severe obesity

and alarming signs of complications. For these children it is very important to evaluate whether or not anti-obesity agents are safe and functional. This has to be done in double-blind, placebo-controlled clinical trials and the lack of such studies is noteworthy.

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Transfer into Adulthood

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Obesity has become a medical problem of growing importance in children and adolescents. Over the last 20 years the increase in the epidemic of obesity has been particularly pronounced in the young population [1]. At present, between 10 and 20% of all children and adolescents in the industrialized countries suffer from overweight or are obese depending on age, social class and country. This alarming development has been demonstrated by numerous epidemiological studies from many countries all over the world [2].

There is general agreement now that the current lifestyle which is characterized by an abundance of calorie-dense, easily accessible and cheap food and a sedentary lifestyle with leisure-time activities such as television viewing or computer games provide an extremely adipogenic environment and increase the risk of weight gain. This detrimental lifestyle is most mendacious for members of the lower social classes where the awareness for a healthy weight and lifestyle is lower than in better educated classes.

The problem of childhood obesity has now been unanimously recognized by the public and pediatric endocrinology is taking care of this tremendous challenge. However, our knowledge on the consequences of obesity and effective approaches to tackle this problem at early ages is rather limited. Nevertheless, it is obvious that a combination of measures including primary and secondary prevention strategies are urgently needed to control the obesity epidemic. It is already expected that the trend of decreasing cardiovascular morbidity and mortality in adults observed over the past 40 years may be reversed as the current population of overweight children and adolescents become adults.

Two other trends are also important for the discussion of the obesity problem. First, the increase in BMI is restricted to the already overweight and obese children indicating an increase in severity [3]. Secondly, in contrast to the former natural course of body weight there is an earlier beginning of overweight and

obesity, i.e. a shift from adulthood into younger ages, particularly adolescence. Thus, in line with adulthood obesity, childhood-onset obesity is becoming a condition that is apart from the genetic predisposition more and more influenced by environmental factors which promote weight gain.

What Determines the Risk of Obese Children to Become Obese Adults?

To date, limited information is available about the probability of an obese child to stay obese as young adult. In a retrospective study by Whitaker et al. [4], a large group of children was followed up from birth to young adulthood, defined as 21–29 years of age. Among those who were obese during childhood the chance of obesity in adulthood ranged from 8% for 1- or 2-year-old children without obese parents to 79% for 10- to 14-year-old children with at least one obese parent. After adjustment for parental obesity, the odds ratios for adulthood obesity associated with childhood obesity ranged from 1.3 for obesity at 1 or 2 years of age to 17.5 for obesity at 15–17 years of age. In addition, parental obesity more than doubled the risk of adulthood obesity in both obese and non-obese children. These data indicate that the risk of becoming obese in young adulthood strongly depends on the age of childhood obesity and on parental obesity. In particular, obesity among older children seems to be an important predictor of adulthood obesity [4]. Similar data were provided by the prospective Bogalusa Heart Study. Children and adolescents at ages 2–17 years were reexamined after a mean follow-up of 17 years at ages between 18 and 37 years. Among the overweight children defined as ≥95th BMI percentile, 77% remained obese as adults, defined as BMI ≥30 kg/m^2 [5]. Thus, there is growing evidence that most obese children and adolescents carry their excess body weight into adult life.

Health Hazards of Childhood Obesity

The health hazards of overweight and obesity in children and adolescents has long been underestimated. There is now a rapidly growing literature clearly showing that most comorbidities and risk factors known to be associated with adulthood obesity are already present in conjunction with childhood obesity, at least in milder forms and at lower frequencies. Potential complications of childhood obesity include hypertension, type 2 diabetes mellitus, dyslipidemia, left ventricular hypertrophy, nonalcoholic steatohepatitis, obstructive sleep apnea, orthopedic problems and psychosocial handicaps. For example, obese children are at an approximately 3-fold higher risk for developing hypertension than

non-obese children of the same age and ethnicity [6]. When obese children are able to lose excess body weight there is a proportionate decrease in systolic and diastolic blood pressure [6, 7].

Obesity and the Metabolic Syndrome

Similar to the situation in adults, childhood obesity is followed by the development of a specific risk factor clustering which is termed metabolic syndrome. In the Minneapolis Children's Blood Pressure Study weight gain in excess of normal growth during childhood was found to be a determinant of adult cardiovascular risk. When 679 children were followed up from 7.7 years of age until 23.6 years of age, increases in weight and BMI were significantly related to young adult levels of insulin, lipids and systolic blood pressure. Similar findings were reported from the Bogalusa Heart Study. Likewise, childhood BMI was a predictor of early adulthood clustering of cardiovascular risk factors such as elevated blood lipids, blood pressure and plasma glucose in this study. Thus, childhood obesity was found to be a powerful predictor for the development of the metabolic syndrome and underlines the importance of weight control early in life [8].

Childhood Obesity and Atherosclerosis

Recently, there have been reports indicating that childhood obesity is associated with an adverse cardiovascular risk profile and early signs of atherosclerosis. In one of these studies in severely obese children, both an increased arterial stiffness and endothelial dysfunction were observed in comparison to non-obese children. These functional disturbances were associated with dyslipidemia, insulin resistance and an abdominal pattern of fat distribution [9]. Furthermore, an autopsy study provided compelling evidence that up to 38% of adolescents with cardiovascular risk factors exhibit fatty streaks in the intimal surface of the aorta [10]. Finally, a long-term observational study in obese adolescents suggested that after a follow-up of 55 years an increased risk of morbidity and mortality from cardiovascular diseases as well as death from colorectal cancer was observed, independently of adult weight [11].

Childhood Obesity and Type 2 Diabetes

The central role of obesity in the development of type 2 diabetes mellitus in adults is well established. This metabolic disease is characterized by multiple

micro- and macrovascular complications which result in an extremely elevated risk of premature death. Thus, prevention of diabetes is of utmost importance. Recent studies clearly indicate that childhood obesity promotes the development of overt type 2 diabetes during adolescence and is a predictor of development of type 2 diabetes in adulthood [12]. However, the risk of developing type 2 diabetes is strongly influenced by family history of type 2 diabetes, the pattern of body fat distribution and ethnicity [12]. In a recent study of 520 severely overweight children and adolescents of Caucasian origin, 6.7% exhibited signs of impaired carbohydrate metabolism after an oral glucose load. The subjects with impaired glucose metabolism were characterized by a family history of diabetes mellitus and a greater severity of overweight [7]. In addition, the children at risk had higher blood lipids, higher blood pressure and higher fasting insulin and HOMA, respectively, indicating presence of the metabolic syndrome. It is conceivable to assume that this subgroup is at particular high risk to develop all the adverse consequences of type 2 diabetes early in adult life and to have an elevated risk for atherosclerosis.

Quality of Life and Psychosocial Situation

Another important aspect is that obesity in adolescents and young adults has a substantial adverse impact on the subjective quality of life and the socioeconomic situation. A recent study suggested that the health-related quality of life in severely obese children and adolescents is significantly lower than in lean healthy controls and similar to that in children and adolescents diagnosed as having cancer [13]. Furthermore, it was demonstrated in a review that body self-esteem is lower among obese children and adolescents as well as young obese adults than among their non-obese peers [14]. Another example indicating the high psychosocial burden is that young obese women were found to have a lower household income, lower education and lower rates of college completion and marriage [15]. Thus, these data suggest that obesity is an important determinant rather than a consequence of poor socioeconomic status.

Principal Considerations Concerning the Actual Treatment of Childhood Obesity

In view of this information a long-term strategy for the management of adolescence obesity is warranted. There is a high probability that obesity at this age is a chronic, life-long problem that requires long-term weight management. However, the perspective of obesity as a chronic disease is not reflected by the

current practice of obesity management in adolescents. Usually, weight loss programs for this age group are restricted to limited periods of time, mostly periods of 6–12 months. However, even such short-term weight management programs are frequently not covered by health insurances [16].

To date, most intervention programs for the treatment of childhood and adolescence obesity focus on approaches to change diet and increase physical activity to address the main causes of the impaired energy balance. Most weight loss programs for children and adolescents include parents or have other family-oriented strategies [17]. However, such concepts have been shown to be only of limited short-term success. Moreover, there is very little information available on the long-term results of such programs. In a small study with a long-term follow-up examination, 6- to 12-year-old children were randomized to three different treatment forms including a control group. Children in the child and parent group showed significantly greater decreases in % overweight after 5 and 10 years than children in the control group and the child only group [18]. Unfortunately, apart from this study there is no information on the long-term outcome of treatment programs for obese children and adolescents.

The current situation is that as soon as obese adolescents are no longer treated by pediatricians they are probably lost to medical care unless they are highly motivated and take over the responsibility for the continuation of medical care during young adulthood. However, in most cases the desirable continuation of weight management programs does not occur. This may become particularly disastrous as these subjects are at an age when tremendous changes in the personal living conditions take place. Young people leave their families, start to live alone or together with peers and are facing many other challenges with the consequence that they may reduce attention for their weight problem and may have less support from their previous social environment, e.g. from their parents. In addition, increased stress from any source during this period may even promote further weight gain and aggravate the associated health problems.

There is no doubt that obesity management in this situation requires specific components that are different from those developed for the treatment of childhood obesity and take the new living conditions into consideration. Weight loss programs for these age groups will only be successful if the patients are able to cope with these new challenges. To date, specific programs that are developed for and validated in this age group at transition to adulthood are not available. This descriptive analysis makes clear that there is a dramatic gap in the medical care of young obese subjects suffering from obesity between adolescence and young adulthood that needs to be rapidly filled.

An important obstacle for such programs is that current structures of health care in most countries are not prepared to offer appropriate medical care for this difficult transition period from adolescence to young adulthood. A main

problem is that obesity is formally not recognized as a disease and reimbursement of treatment costs is usually not covered. If there are programs for obese children and adolescents that are covered by health insurance funds they are restricted to short periods. Unfortunately, there is no common strategy to integrate pediatricians and general practitioners or internists who provide care for obese patients during this transition phase. In view of the dimension of the obesity problem during adolescence and young adulthood the development of such integrated strategies should receive high priority.

Is There a Need to Change Treatment Strategy during Transition from Adolescence to Adulthood?

The current recommendation for the treatment of childhood and adolescence obesity consists of a family-based approach that is focussing on a healthy lifestyle in the setting of a family [17]. This approach includes an active lifestyle and a healthy balanced diet. In this concept, physical activity is at least equally important as a healthy diet, as many children and adolescents can be rather easily encouraged to practice physical activity. At the same time, children and adolescents are less aware of and interested in following a balanced diet as the impulse for eating is more spontaneous and less driven by cognitive control of eating compared to adults. As the growth process from adolescence to adulthood is accompanied by more or less dramatic changes in mental status, communication style and lifestyle, group sessions and cognitive control of eating may become more appealing and promising although this assumption is only speculative and has not been examined in controlled trials.

Extended Spectrum of Treatment Options for Obese Adults

In contrast to the situation in obese children and adolescents, there are many additional options for the treatment of obese adults. These options include very-low-calorie diets, weight-lowering drugs and bariatric surgery among others. There is a bulk of scientific literature concerning the benefits and risks of such treatment modalities for obese adults. In general, these methods are more invasive than lifestyle intervention and have a calculable risk of adverse effects. Current evidence-based guidelines for the treatment of overweight and obesity in adults include these options as second choice in case the conventional approaches are not successful [19].

The above-mentioned intensive treatment options have not been investigated systematically so far for the management of childhood and adolescence

obesity, mainly due to their potential risks and unclear benefit-risk ratio. Only recently, smaller studies were published indicating that weight-lowering drugs such as sibutramine [20] and orlistat [21] as well as gastric bypass surgery [22] and laparoscopic gastric banding [23] are possible effective treatment options for severely obese adolescents. However, among the more intensive treatment options only bariatric surgery appears to be powerful enough to produce long-lasting substantial weight loss in severely obese adults, although the experience is rather limited.

It is very likely that these methods that were originally developed for the treatment of obesity in adults will be more frequently used in obese children and adolescents in the near future. One explanation for this trend is that the number of children and adolescents with severe forms of obesity is rapidly increasing and conventional family-based treatment programs may not be effective enough to achieve the desirable weight goals. To accelerate this development it would be appropriate to combine the expertise of pediatricians and internists and, thus, to facilitate this transfer process. However, it is clear that a lot of work is to be done to assess which intensive therapies are applicable in which patients. There is complete agreement among experts that the benefits and risks of intensive weight management therapies for young patients must be weighed very carefully and such treatments should considered only for children and adolescents who have not responded to conventional weight-management programs but have significant complications or are at particular risk, e.g. obese children with a family history of type 2 diabetes or hypertension [24]. Another prerequisite for the application of such treatments is that they should be restricted to specialized centers that have sufficient expertise in this area. Thus, until more extensive efficacy and safety data are available, medications for weight loss and bariatric surgery techniques should be used only on an experimental basis within controlled trials.

What Are the Current Recommendations for the Treatment of Obesity in Adults?

When pediatric patients with obesity become adults, i.e. reach the age of 18 years, the current recommendations for the treatment of obesity in adults can be applied. Evidence-based treatment guidelines for obese adults have been developed during recent years in a variety of countries and are the basis of most weight loss programs offered by hospital-based and primary care medicine. In principle, the first step in the treatment of obesity in adults is a non-pharmacological, multicomponent approach combining a moderately hypocaloric diet (500–1,000 kcal below actual energy expenditure), increase in physical activity and behavior

modification usually provided in guided group sessions at weekly or biweekly intervals. Using this approach a mean weight reduction by 5–10% can be expected [2, 19].

Additional drug treatment should only be considered if this basal program has proven to be ineffective, defined as weight loss less than 5% of initial body weight or if additional weight loss is desirable to improve comorbidities. It is important to note that adjunct drug treatment should not be extended over 1–2 years. Another important aspect is that drugs should only be used if the BMI is equal to or exceeds 30 kg/m^2 or at least 27 kg/m^2 in the presence of obesity-related comorbidities such as type 2 diabetes or hypertension [25]. An alternative to additional drug treatment is a very-low-calorie diet for up to 12 weeks that is followed by a long-term weight management program. The latter concept has recently been found to provide good short- and long-term results [26].

Treatment Perspectives for Obese Adolescents with Type 2 Diabetes and Impaired Glucose Metabolism

Obese adolescents with type 2 diabetes represent a subgroup that deserves special attention, as these patients have an excess risk of micro- and macrovascular complications which are probably preventable by good metabolic control and weight loss. Moreover, there is growing knowledge from clinical trials on how to achieve glucose homeostasis. Recent studies demonstrated that administration of metformin, usually given 500 mg twice daily, to overweight pediatric patients with type 2 diabetes ameliorates metabolic control. In one of these studies, HbA1c levels fell from a mean value of 8.2 to 7.2% indicating a similar effect as in overweight adults with type 2 diabetes [27]. In addition, metformin did not have a negative impact on body weight and blood lipids [12].

Metformin is also a potentially effective drug to prevent the onset of type 2 diabetes in subjects with impaired glucose tolerance. In the Diabetes Prevention Program, administration of metformin 850 mg once or twice daily significantly reduced the conversion to diabetes by 31% in the whole population of adults. However, metformin was particularly beneficial in subjects with a BMI $\geq$35 kg/m^2, in those with high fasting glucose concentrations and in younger adults aged 25–44 years. In these subgroups, metformin alone was almost as effective as intensive lifestyle intervention. Interestingly, treatment with metformin also resulted in a moderate weight loss of 2–3 kg. It is currently unknown as to whether metformin is similarly helpful to prevent the development of type 2 diabetes in adolescents or young adults with obesity and what are the long-term efficacy and safety of the drug. Another unanswered question is as to whether this intervention only delays rather than truly prevents the development of type 2 diabetes.

In conclusion, the transition from adolescence obesity to adulthood and the subsequent transfer of obese patients from pediatric to adult medical care is still a strongly neglected area. Although it is obvious that obese adolescents are very likely to remain obese in young adulthood and that there is an accumulating risk of obesity-related comorbidities no weight management programs exist that are tailored to the specific requirements of this age group. However, it becomes more and more plausible that at least severely obese adolescents may benefit from more intensive treatment options that were traditionally restricted to obese adults. However, due to a rather limited experience and unknown benefit-risk ratios such therapies should be only considered in an experimental setting. There is an urgent need to define and evaluate specific long-term weight loss and management programs for this transition period and to develop better structural prerequisites to meet the specific requirements. Such efforts also require a coordinated and integrated action of pediatricians and internists.

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Health Economics of Overweight and Obesity in Childhood

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Health Economics – What It Is

In health systems all around the world, stakeholders such as health departments and health-purchasing agencies, insurance companies, hospitals or primary care teams are faced with choices about the best way to use their limited resources (time, skills, and purchasing power) to achieve their objectives [1]. Economic evaluation methods are useful tools in clarifying choices and making such choices explicit. The conceptual framework of economic evaluation differs according to (a) the type of decisions which it helps to clarify, and (b) the viewpoint of the decision-maker.

All methods of health economic evaluation have one common principle: they examine one (or more) possible interventions and compare the inputs or resources necessary to carry out such interventions with their consequences or effects. Resources can be used only once, i.e. they are not available for an alternative use. In order to make comparisons between the options, it is necessary to find a common unit of value for each of the inputs, during and as a consequence of the intervention (e.g. costs in a precise currency with defined purchasing power). Often the health consequences (outputs) are also valued in common units (e.g. as change in mortality, adjusted by changes in quality of life or disability).

The various methods of economic evaluation differ in the way they itemize and value inputs and consequences. Such differences reflect different aims and viewpoints of the decision-making problems [1]:

- *Cost-minimization analysis* (*CMA*): When the consequences of the intervention are the same, then only inputs are taken into consideration. The aim is to decide the cheapest way of achieving the same outcome.

- *Cost-effectiveness analysis* (*CEA*): When the consequences of different interventions may vary but can be measured in identical natural units, then inputs are costed. Competing interventions are compared in terms of cost per unit of consequence.
- *Cost-utility analysis* (*CUA*): When interventions which we compare produce different consequences in terms of both quantity and quality of life, we express them in utilities. These are measures which comprise both length of life and subjective levels of well-being (the best known utility measure is the quality-adjusted-life-years or QALYs). In this case, competing interventions are compared in terms of cost per utility (cost-per-QALY).
- *Cost-benefit analysis* (*CBA*): When both the inputs and the consequences of different interventions are expressed in monetary units so that they compare directly and across programmes even outside health care.

Many studies of use of resources in health care do not make explicit comparisons between options for care. In these studies health consequences of a defined diagnosis are linked to the estimated costs by using empirical data and mathematical models for predictions and calculations. Such a cost-of-illness (COI) analysis is not an economic evaluation, but nevertheless can be considered as economic study and can contribute to our understanding.

Different categories of costs contribute to the economic burden of a disease or a risk-factor [2]:

- direct expenses for ambulatory or hospital medical care, drugs and other treatments such as physical therapy, transport, nursing, etc.
- indirect costs, mainly due to the inability to go to work and the global loss of productivity secondary to precocious death (excess mortality)
- intangible costs, i.e. compromised health-associated quality of life, e.g. due to disease-associated pain.

Many cost-of-illness studies include only direct expenses since indirect or intangible costs may be difficult to estimate.

Health insurance companies as well as governmental health authorities have to decide whether to invest in preventive interventions which can avoid the very onset of a disease (e.g. in case of obesity the manifestation of diabetes mellitus or arterial hypertension), or in curative interventions which lengthen survival and/or modify the quality of survival. Regarding overweight and obesity in children and adolescents, health insurance companies may have to decide whether to fund a school-based obesity prevention program or a hospital-based multidisciplinary intervention for obesity treatment. Or they may have already decided that both alternatives are worth trying and they want to define the best way of achieving success. In both cases, conclusions drawn from health economic evaluations would be of interest for decision-makers.

Health Economics of Obesity in Childhood and Adolescence – What We Know

Obesity is not only a risk factor for premature mortality but particularly for chronic conditions which lead to disability and/or loss of productivity. In societies where many people survive into old age the effect of obesity on health care is of major importance. Estimations of direct costs of adult obesity vary, depending on the definition of obesity and assumptions about the impact of obesity on diseases, between 1% and 5% of total national health care expenditure (based on data from several countries in Europe and North America) [3].

Unfortunately, comprehensive health economic evaluations of obesity in childhood and adolescence have not been published [2]. In one of the rare examples of health economic studies, Wang and Dietz [4] recently examined the trend of obesity-associated diseases in hospitalized patients aged 6–17 years in the USA using a multiyear data file of the National Hospital Discharge Survey, 1979–1999. In the years 1979–1984, approximately 0.36% of all hospital discharge protocols listed obesity as primary diagnosis. In the years 1997–1999 this percentage increased to $1.07 \pm 0.08\%$. During the same period the discharges of diabetes nearly doubled (from 1.43 to 2.36%), the diagnosis of gallbladder disease tripled (0.18 to 0.59%), and that of sleep apnea increased fivefold (0.14 to 0.75%). This trend in the burden of disease led to an increase in obesity-associated annual hospital costs from USD 35 million (0.43% of total hospital costs) to USD 127 million (1.7% of total hospital costs; each based on 2001 constant US dollar value).

Health Economics and Epidemiology of Childhood Obesity

In Germany, cross-sectional data from the Kiel Obesity Prevention Study (KOPS) [5] obtained in the years 1995–1998 showed that 3.5% of all 5- to 7-year-old children at school entry had a body mass index (BMI) above the 97th percentile of national age- and sex-specific growth charts [6]. Using data from school entry examinations in Bavaria from the years 1982 and 1997 Kalies et al. [7] demonstrated an increase in the prevalence of obesity from 1.8 to 2.8%. In the region of Brandenburg, 5.8% of boys and 4.9% of girls were obese at school entry in 1999; in the same year a BMI above the 97th percentile was seen in 5.9% of boys and 7.9% of girls at the age of 16 years [8]. Similar prevalence rates were seen in schoolchildren aged 13–15 years who were assessed in Hamburg in 1998 (5.2% of boys and 6.4% of girls were obese) and in Osnabrück (Lower Saxony) in 1999 (5.1% of boys and 7.6% of girls were obese).

Table 1. Predictive value of a body mass index (BMI) above the 95th percentile at 6–9 years of age for obesity in adulthood according to Whitaker et al. [11]: the specificity of childhood obesity for the prediction of obesity in adulthood was 98%, its sensitivity was 23%

Predictor: BMI >95th percentile at 6–9 years of age	Outcome (obesity in adulthood)		
	+	−	sum
+	24	11	35
−	79	524	603
Sum	103	535	638

Based on these epidemiological data, Reinehr and Wabitsch [9] estimated that approximately 1 million children and adolescents in Germany are currently obese. Gunnell et al. [10] showed that obesity-related illnesses manifest themselves mainly in adulthood, thus causing relevant economic burden only lately in life. This may be one of the explanations for the apparent lack of health economic studies on childhood obesity described by Stratmann et al. [2].

Longitudinal data analysis from a US health maintenance organization has shown that childhood obesity not necessarily tracks forward into adulthood [11]. In about one third of children at the age of 6–9 years a BMI above the 95th percentile did not persist into early adulthood (age 21–29 years) while roughly three quarters of all cases of obesity in young adults were not predicted by a BMI above the 95th percentile during childhood (table 1). The likelihood ratio for a positive test result (LR+) of 11.5 indicates that a BMI above the 95th percentile at 6–9 years of age is a good predictor of adult obesity, while the likelihood ratio for a negative test result (LR–) of 0.8 shows that a BMI below the 95th percentile at 6–9 years of age does not reliably rule out obesity in adulthood.

Such calculations show the difficulties that decision-makers in evidence-based health care planning may encounter: Is it acceptable to invest in a general screening programme at school entry which allows the detection of only 25% of children at risk for persistent obesity leaving 75% undetected? Is it acceptable to treat obese school children who have a 30% chance of not being obese as adult even without any intervention? In order to answer these questions appropriately, data from health economic evaluations would be of great value. Yet, such data are not available at present.

The specific epidemiology of overweight and obesity in childhood and adolescence may be the main obstacle for a comprehensive study on its health economics. Even a cost-of-illness study would require life-long follow-up of

Table 2. Settings and funding of interventions for the prevention and treatment of childhood obesity in Germany

	Intervention	Setting	Funding
Primary prevention	information, education and counseling (IEC) on healthy lifestyle for all children and adolescents	community, schools, mass media	public-private partnership, schools, health insurance companies
Secondary prevention	screening and identification of persons at risk, followed by recruitment into an effective disease prevention programme	family, school, on the job, or during leisure activities	public health authorities, schools, health insurance companies
Tertiary prevention	treatment and rehabilitation of overweight and obese children and adolescents	ambulatory health center, rehabilitation clinic, hospital	health insurance companies, public pension funds

a cohort of overweight children (due to the 'natural' variation of the incidence of obesity in this age group). Only life-long repeated assessment of changes in BMI and development of obesity-associated diseases might allow the calculation of direct and indirect costs of childhood overweight (including obesity-associated precocious deaths) [2]. The second barrier for a comprehensive study on health economics of overweight and obesity in childhood and adolescence is the lack of effective interventions for its prevention and treatment [12–15].

Health Economics and Current Clinical Practice

Dietz [16] listed 4 significant barriers which limit treatment of childhood obesity in the United States: the lack of time available for counseling families with an obese child, the lack of effective treatment protocols, the lack of commitment of primary care providers to care for affected patients, and – most importantly – the lack of insurance reimbursement for obesity therapy [17].

Current clinical practice shows that health insurance companies in Germany are financing both ambulatory treatment and hospital care of obese children and adolescents (table 2). Costs for ambulatory diagnosis of obesity and associated diseases, information, education and counseling (IEC) on obesity (pathogenesis, associated risks, treatment and long-term prevention), as well as medical follow-up during treatment are covered by all insurance schemes. Out-of-pocket payments for the families of obese children and adolescents are usually necessary for regular physical activity, e.g. in specialized fitness centers or a gym.

Primary care providers in Germany may be not committed to care for overweight and obese children and adolescents even despite insurance reimbursement. Willingness of pediatricians to provide appropriate ambulatory treatment may be reduced because of (a) a perceived lack of feasible and effective treatment strategies, and (b) reimbursement rates which are considered far too low for coverage of all appropriate services needed by this patient group.

Dietz and Gortmaker [18] summarized the existing barriers to appropriate obesity treatment in the US:

- The traditional organization of pediatric health care does not allow the treatment of children and their parents in groups.
- Only few health care providers perceive themselves as being competent enough to use behavioral treatment strategies.
- The extremely short time frame of direct patient interaction in a pediatrician's office is not sufficient for the identification of necessary individual behavior changes and does not allow an effective support of the patient and the family in the practical use of behavioral management strategies.
- A multidisciplinary treatment program of proved effectiveness is not generally available.
- Health funding agencies cover the real cost of obesity treatment only partially.

A recent study in the US [19] has demonstrated that medical evaluation of overweight children and adolescents by pediatric health providers falls short of recommended practices [20], while emotional and behavioral assessments were generally consistent with recommendations [21]. Pediatric practitioners viewed child and adolescent obesity with concern and felt that intervention is important. However, providers complained about a lack of patient motivation, difficulties in parent involvement, and the absence of support services [22]. Areas of self-perceived low proficiency of providers were in the use of behavioral management strategies, guidance in parenting techniques, and addressing family conflicts.

German health care providers traditionally use hospital-based weight reduction programmes in order to provide obesity treatment: In the year 2001, a rehabilitation program of 3–6 weeks' duration was offered to 5,964 overweight and obese children and adolescents in hospital settings associated with the National Pension Fund 'Bundesversicherungsanstalt für Angestellte' (Verband der Rentenversicherungsträger: Stationäre Kinderheilbehandlungen im Berichtsjahr 2001, Table 70.00 M; http://www.vdr.de). Health insurance companies offer similar services in hospital settings and fund (at least partially) a multitude of providers of a regional interdisciplinary ambulatory weight reduction program [23]. Neither long-term clinical efficacy nor cost-effectiveness of such interventions has been reliably demonstrated in the past [9, 24].

However, epidemiological data on probabilities of forward tracking of obesity from childhood into adulthood [25] in combination with the published effect size of a German ambulatory education and treatment program for obese children ('Obeldicks') [26] allow us to discuss the following scenario in terms of health economics:

- A 12-year-old girl with defined obesity (e.g. BMI above the 97th percentile of her age-specific growth chart) may have a probability of 0.5 to be obese (BMI $\geq$30 kg/m^2) at 35 years of age. In other words, without any intervention, 50 of 100 obese 12-year-old girls will become obese women; the 'control event rate' (CER) is 0.5 [27].
- This girl participates in an ambulatory treatment program for obese children and adolescents ('Obeldicks') which has a published success rate of 34%, defined as the percentage of participants with a BMI below the 97th percentile of the age- and sex-specific BMI growth chart at the end of the 12-month treatment period [28].
- Assuming that this treatment effect persists into adulthood in about 60% of all participating girls, the long-term success rate would be approximately 20%. Thus, 20 of 100 girls participating in the 'Obeldicks' program would not be obese as 35-year-old women.
- Assuming that this treatment effect is independent of the inherent risk for persisting obesity (i.e. the effect is seen both in women who would or would not become obese without any intervention) 10 of 100 girls would not be obese as adults in addition to those 50 of 100 whose obesity would not persist even without any intervention. Thus, the 'experimental event rate' (EER) in this scenario is 0.4 [27].

The absolute arithmetic difference between the control event rate (CER) and the experimental event rate (EER) is called 'absolute risk reduction' (ARR) [27]. In our scenario of 12-year-old obese girls participating in the 'Obeldicks' program, the ARR is 10%. The inverse of the absolute risk reduction (1/ARR) is telling us the number of patients that we need to treat in order to prevent one additional bad outcome (number-needed-to-treat, NNT). In case of the 'Obeldicks' program, an estimated NNT of 10 tells us that the participation of ten 12-year old obese girls in the one-year treatment program helps one additional obese girl to avoid obesity at 35 years of age. Thus, after 'Obeldicks', obesity tracks forward in 4 instead of 5 of these girls.

Should an insurance company cover the cost of the 'Obeldicks' program for obesity treatment in childhood with a NNT of 10? In drug treatment, similar NNTs are considered as 'pretty impressive' [27]. If direct costs for participants in the 'Obeldicks' program are known, decision-makers might even convert this NNT into an amount of money to be spent for successful prevention of adult obesity in one female client.

In order to fully estimate the attractiveness of the 'Obeldicks' approach, both long-term results and potential adverse effects of the program (and the resulting costs) have to be considered as well. This could be done using the methodology of classical 'evidence-based medicine' [27]: the number-needed-to-treat (NNT, a derivative of the absolute risk reduction, ARR) and the 'number-needed-to-harm' (NNH, a similar derivative of the 'absolute risk increase' for potential side effects of an intervention) are combined into an 'effort-to-yield ratio' (also called 'poor clinicians' cost-effectiveness ratio').

The calculation described above is, however, mostly hypothetic: (a) we do not know the exact risk of forward tracking of obesity in Germany; (b) we do not know the long-term effectiveness of a multidisciplinary obesity education and treatment program, and (c) we do not know the potential bias of preselection of participants even on short-term results (e.g. treatment could be effective only in those girls who would lower their relative BMI with advancing age even without that intervention!). Thus, from an economic perspective the current willingness of health insurance companies to finance weight-reduction programs for children and adolescents seems not really to be 'evidence-based': these interventions are potentially ineffective in the long term and can therefore not be 'economic' (i.e. cost-effective).

Future Research

The analysis of current practice of health financing in Germany leads to the impression that funding agencies prefer to spend money on interventions with unknown effectiveness rather than not to intervene at all. However, since resources in health systems are available only once, health financing agencies should try to guarantee their rational allocation. In the case of childhood obesity the available money could be spent in effective primary prevention programs (health education and changes in obesigenic environments) instead of multidisciplinary treatment programs. Unfortunately, such prevention programs are currently not available, too [29].

If the data needed for rational decision-making are not available they should be generated using appropriate methods of clinical and health systems research. The willingness of health insurers to finance weight reduction programs for obese children and adolescents should not be abused by providers for getting 'a bigger part of the cake'. Current practice must urgently be flanked by considerable efforts to generate those data on epidemiology, short- and long-term treatment efficacy and side effects which are badly needed for cost-effectiveness calculations and rational decision-making. Appropriate financing of this kind of applied health systems research is, however, one of the major challenges of the German health system at present.

There are specific difficulties in defining, developing, documenting, and reproducing complex health interventions that are made up of various interconnecting parts and thus subject to more variation than a drug [29]. On the other hand, controlled trials of complex interventions are of increasing importance because of the necessity to provide the most cost-effective health care. An expert workshop of the Medical Research Council (MRC) in the UK recently described a phased approach using qualitative and quantitative research methods that should lead to improved study design, execution, and generalizability of trial results [29].

The suggested framework for trials of complex interventions sets up 5 steps towards implementation which are interconnected by an iterative rather than by a linear process of development. Identifying which stage of development has been reached in specifying the intervention and outcome measures should give researchers and funding bodies reasonable confidence that an appropriately designed and relevant study is being proposed. Even if such trials do not necessarily need a randomized design, reporting of trial results should follow the rules of the CONSORT statement [30].

Using the sequential phases of drug development as a model, Campbell et al. [29] characterize the steps of this iterative process as follows:

- Preclinical phase: Theory and observation. Researchers must identify the evidence that the intervention will have the desired effect; to this end the theoretical basis for the intervention must be reviewed and empirical evidence from previous studies must be searched for.
- Phase I: Exploration and modelling. During this phase researchers may use modelling or simulation techniques, qualitative testing and descriptive studies in order to identify relevant components of the intervention, their interrelationships, and the underlying mechanisms by which they will influence outcomes.
- Phase II: Data gathering and explanation. The information retrieved from exploration and modelling is used to develop the optimum intervention and study design, e.g. through comparative testing of delivery and acceptability of different versions of the intervention, definition of the control intervention and piloting outcome measures. An exploratory trial (ideally with randomized design) should allow the assessment of the expected effect size, thus providing a sound basis for calculating sample sizes for the definitive clinical trial (phase III).
- Phase III: Definitive clinical trial. The findings of trials of complex interventions are more generalizable if they are performed in the setting in which they are most likely to be implemented. On this background researchers have to address questions of study design (randomized vs. cluster-randomized vs. controlled or observational cohort studies), study plan (criteria for

inclusion and exclusion, sample size, methods of randomization, if necessary), and conduction (financing, documentation and data collection, avoidance of drop-outs).

- Phase IV: Observation and evaluation of long-term implementation. The purpose of this phase is to examine the implementation of the intervention into practice by long-term surveillance, paying particular attention to the rate of uptake of the service, the stability of the intervention over time, any broadening of subject groups, and the possible existence of adverse effects.

Specific research questions which have to be addressed during the different developmental phases of a complex intervention for prevention and/or treatment of childhood overweight and obesity are listed in table 3. The main outcome study should use cluster-randomization as a study design because such a study may allow the calculation of the effect size at the level of the intervention group [31].

The primary (family) pediatrician is responsible for case management (diagnosis and therapy), using evidence-based clinical guidelines including a consented stepwise approach for obesity treatment in youth. In a cluster randomization design, each family pediatrician is randomized to a group of providers who follow exclusively one of any given alternatives of the decision algorithm when counseling and treating obese patients. Family pediatricians are responsible for repeated evaluation and documentation of clinical outcomes (main indicator: change in life style which results in reduced percentiles on BMI growth charts).

Program providers who want to participate in the evaluation study must demonstrate their ability to fulfill predefined quality indicators of concept, structure, and processes, and to obtain predefined results; programs need to be accredited by health insurance companies who offer individual funding of weight reduction programs for their members. Additional funding should allow conducting additional research studies on social, genetic or psychological factors which predict the natural course of overweight and obesity as well as treatment effects in individual patients. Finally, a health economic evaluation (e.g. a cost-minimization analysis or a cost-effectiveness analysis) should be performed.

Available information in the published literature indicates that complex interventions for obesity treatment in children and adolescents will probably not lead to continuous weight reduction if they are not flanked by a simultaneous increase in healthy eating habits and physical activity, and a reduction of sedentary life styles in the general population. Interventions in families, schools and communities should promote such primary prevention measures in order to reduce general overweight as well as induce social changes, thus facilitating a healthy lifestyle also in obese children and adolescents and their families.

Table 3. The five-step approach towards implementation of evidence-based complex health interventions for prevention and treatment of childhood obesity: open research questions

Step	Description	Questions to be answered
1	Theory and observation (including analysis of published data)	What is the target population of the intervention: primary or secondary prevention or treatment/tertiary prevention? How large is it (epidemiology)? What is the desired outcome and effect size (quantify behavioral change, weight reduction, changes in metabolic or physiological surrogate markers)? What are the main components of the intervention? Which information should be given and why?
2	Exploration and modelling	Which hypothesis should be tested? How to define the standard procedure, how to define the experimental intervention (e.g., duration, intensity, qualification of providers, methods to be used, importance and proportion of single components, prediction of individual success by social and motivational factors)?
3	Data gathering and explanation	What are, if not yet known, the optimum duration and intensity of the intervention, qualification of providers, methods to be used, importance and proportion of single components? Is prediction of individual success by social and motivational factors possible? Which are the constant and variable components of the experimental intervention? How is the acceptability of the intervention (focus group discussions, interviews)?
4	Definitive clinical trial	How is the study design: randomized, cluster-randomized (preferred), controlled trial or observational cohort? Which are criteria for inclusion and exclusion? What is the estimated sample size? Which methods of randomization (if necessary) are used? How is the study financed? How is documentation and data collection organised? How can drop-outs during follow-up be avoided?
5	Observation and evaluation of long-term implementation	Is it possible to replicate the effects of the intervention in an uncontrolled setting? What is the rate of uptake of the service in the target population? Does the concept and performance of the intervention remain stable over time? Is the intervention requested by or offered to other target populations (broadening of subject groups)? Are there identifiable adverse effects of the intervention?

Despite the fact that genes that predispose for obesity were positively selected during human development, it is clearly possible for human beings to remain at normal, 'healthy' body weights even in the obesigenic environment of modern industrial and post-industrial societies. What it requires is a consciousness of the problem, a motivation to remain lean, and appropriate tools, confidence and self-image to sustain the effort through the years [32]. Health authorities in the USA therefore promoted a strategy for the improvement of child and adolescent health through more physical activity and increased physical fitness [33, 34]. Public-private partnerships should fund interventions in communities, families and schools which aim at changes in obesigenic environments as well as obesigenic behaviors. Design, planning and implementation of such interventions should, however, follow a similar step-wise, iterative process as described above for complex treatment programs and should include health economic evaluations [35].

Conclusion

A comprehensive health economic analysis of prevention and treatment of childhood obesity is currently unavailable and will probably not be performed in the near future. Data from clinical epidemiology show that genetic and behavioral predisposition increases the risk of children from 'obesigenic' families for being obese as adults. The question whether it is possible to reduce this risk under the given conditions of living in modern societies by the use of complex interventions for treatment of overweight and obese children and adolescents ('weight-reduction programs') has to be answered by a controlled clinical study, preferentially with cluster-randomization design. In the context of such a study data for health economic evaluations (e.g. cost-effectiveness analysis or cost-minimization analysis) should be generated. Current evidence indicates, however, that interventions for primary prevention may be more (cost-)effective than treatment programs or activities for secondary prevention of childhood and adolescent obesity.

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Prevention of Overweight and Obesity

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The prevalence of obesity and its comorbidities has been steadily increasing over the last 50 years. Obesity, once established, is difficult to treat. Therefore, prevention of obesity is a public health agenda as well as a high priority research goal [1, 2]. Since the long-term consequences of childhood overweight are well documented there is need for early intervention. Some authors assume that early intervention in a pediatric population is superior to intervention strategies directed at adults [1, 3, 4]. Prevention of pediatric obesity may be the only effective treatment of adult obesity. This article tackles preventive strategies, suitable periods of early intervention, recommendations, settings as well as measures of outcome. In addition we will review the results of controlled studies in the area of prevention of childhood overweight. The reader is also referred to two recent review articles [5, 6].

Preventive Strategies

Faced with the obesity epidemic obesity needs to be addressed by a public health approach as well as interventions aimed at individual subjects. In practice different prevention strategies are used [1]. First, intervention strategies are directed at everyone in a community with the aim to stabilize or to reduce mean BMI within a population (i.e. *universal prevention*). Second, *selective prevention* is directed at high risk individuals (e.g. children of obese parents). It is concerned with improving the knowledge and skills of people to increase competence and personal autonomy and, thus, to prevent excessive weight gain. Third, *targeted* or *secondary prevention* is directed at overweight and obese children and adolescents to prevent further weight gain and/or to reduce body weight.

Suitable Periods for Obesity Prevention

Although most people become obese as adults there is a significant association between BMI in childhood or adolescence and in adults [7–11]. The persistence of obesity into adulthood appeared to rise linearly throughout childhood. In addition childhood overweight was shown to be predictive for adult morbidity and mortality. Antecedents of adult disease (hypertension, hyperlipidemia, abnormal glucose tolerance) occur with increased frequencies in obese children and adolescents [12–19]. There is evidence for life-long persistence and health consequences of overweight and obesity in many children. All these data suggest that obesity prevention should start early in life. Specific periods for the development of overweight and obesity have been identified in children. These include the prenatal period, the period between the ages 5 and 7 (so-called adiposity rebound) and adolescence [4]. Preventive strategies should therefore consider critical periods of early onset of obesity (e.g. adiposity rebound, adolescence).

Recommendations to Prevent Weight Gain

Preventive strategies aimed at childhood and adult obesity are mainly based on the knowledge of risk factors and beliefs about the etiology of the disease. Risk factors of childhood obesity included parental overweight, a low socioeconomic status (SES), high birth weight, early timing or rate of maturation, low physical activity/ high inactivity, dietary intake (including early infant feeding practices) as well as psychological factors [18–20]. These risk factors are related but their exact relationships are unknown at the individual as well as at a population level. Although most risk factors for obesity seem to be self evident, their confounding or cumulative effects on the development of obesity as well as their clustering and their effects over time on the causal pathway to the development of obesity remain unclear in children (as in adults). A quite comfortable life style and an almost unlimited individual consumption are associated with the marked increase in the prevalence of overweight and overweight-related diseases [19, 21].

Simple recommendations to reverse the increase in obesity prevalence include eating regular meals, decreasing portion size, avoiding snacking, drinking water instead of calorie containing beverages, reducing dietary fat below 30% of energy intake, cutting down TV-time ($<$1 h/day) and being more active [22]. Since children are growing adequate nutrient intake rather than weight-reducing diets are recommended for overweight children. Since there is some evidence that frequent consumption of sugar-sweetened soft drinks and fast

food, frequent eating in restaurants as well as large portion size are all associated with increased energy intake and risk of weight gain in children [23, 24], healthy meals within the home environment and small or medium portion sizes are prudent recommendations. However, emphasis is now more on physical activity rather than on dietary changes. Activity recommendations for children and adolescents based on existing evidence and expert opinion have been proposed by health authorities [25]. All children and adolescents (5–18 years)

- should participate in physical activity of at least moderate intensity for 1 h daily,
- those who do little activity should participate in physical activity of at least moderate intensity for at least 0.5 h daily.
- At least twice weekly some of the activities should help to enhance and maintain muscular strength and flexibility and bone health.

All adolescents (11–21 years)

- should be physically active daily, or nearly every day, as part of play, games, sports, work, transportation, recreation, physical education or planned exercise, in context of family, school, community activities,
- should engage weekly in three or more sessions of activities that last 20 min or more at a time that require moderate to vigorous levels of exertion.

Should Preventive Strategies Targeted to a Risk Group?

Besides environmental and behavioral determinants of body weight the importance of genes for body weight and obesity has been demonstrated in animals and humans [26]. This idea also implies the existence of a risk group, which may need special attention. Since, however, the prevalence of obesity increased within a genetically stable population the importance of obesity promoting and/or inhibitory characteristics of the macroenvironment is evident [19, 20]. The enormous secular change in obesity is evidence that environmental factors are most important. Indeed large family studies showed that the heritability of different measures of body fat content is limited and varied between 5 and maximally 40% of the age- and gender-adjusted phenotypic variance [26]. Although the concept that some people may have inherited a greater susceptibility to storage excess energy than others is attractive, most prospective studies on the impact of different metabolic phenotypes (e.g. subjects with a reduced metabolic rate and/or high fat oxidation) on weight changes were done in selected populations (e.g. Pima Indians) [27] and could not be reproduced in other populations [28, 29]. These data indicate that in genetically heterogeneous populations (1) metabolic factors are at least weak predictors of

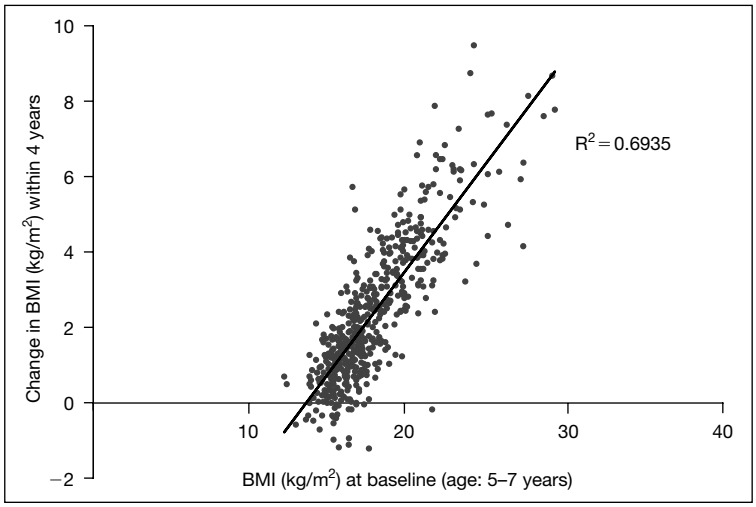

Fig. 1. Results of 4-year follow-up of prepubertal children of the Kiel Obesity Prevention Study (KOPS). Correlation between BMI at baseline (age: 5–7 years) and change in BMI within 4 years (n = 529).

weight gain, and (2) the propensity to become obese is not due to measurable and inherent metabolic abnormalities.

At present we do not have evidence to suggest targeted interventions in specific (e.g. genetically predisposed) subjects. However there is good evidence for close associations between nutritional status of parents and their children [cf. 30]. Overweight parents frequently have overweight children. Detailed knowledge of interaction between (1) children and adolescents of obese parents, and (2) the environment may add to future intervention programs. It was shown recently that a low SES together with parental overweight is a considerable risk factor for childhood overweight [31]. There is also evidence from studies in prepubertal children that basal weight is associated with weight gain (i.e. a high normal weight is a risk of disproportionate weight gain; fig. 1). Thus interventions directed at a high normal weight (i.e. >50P and <90P) and overweight children with obese parents and a low SES should be encouraged.

Outcome Measures of Obesity Prevention Programs

Outcome measures of obesity prevention are objective measures of the nutritional state (e.g. BMI), comorbidities (e.g. plasma lipid levels), health knowledge, behavior (e.g. diet, physical activity, sedentary behavior) and/or

competence. To be sure about the effects long-term follow-up data are necessary. At present there is no scientific consensus about suitable follow-up periods in obesity prevention studies [1, 32]. Taking into account the criteria for evaluating the outcome of approaches to treat obesity published by the Food and Nutrition Board of the Institution of Medicine [32], 'long term' is considered for follow-up periods of at least 1 year. However, more prolonged observation periods are needed for evaluation of prevention programmes (e.g. to measure the effect on incidence).

Suitable outcome measures differ between different strategies of prevention. Outcome measures of *universal prevention* are:

- reduction in the incidence of overweight and of obesity in the general population,
- an overall reduction in average BMI of the population,
- improvements in nutritional intake, eating habits, exercise and other health-related activities,
- improved knowledge, attitudes and norms regarding nutrition, weight, eating habits and exercise,
- decreased rates of comorbidities, and
- public policy and environmental change indices.

Outcome measures of *selective prevention* are:

- prevention of weight gain,
- reduced incidence of overweight or obesity in individuals at risk,
- decreased excessive dieting among dieters, and
- improved lifestyle patterns (e.g. healthy diet, more activity, less inactivity).

Outcome measure of *targeted prevention*:

- reduction in the number of obese-related comorbidities and
- increase in the number of obese subjects who are successful in attaining and maintaining a relatively small weight loss (e.g. about 10% of initial body weight), and
- a decrease in the number of subjects who gain weight (e.g. >2 kg).

Obesity Prevention in Children and Adolescents: Results of Controlled Studies

Interventions to prevent weight gain include school programs, correspondence programs, individual or group counselling including behavior change methods and a public health approach. At present there are numerous uncontrolled activities in the area of prevention of childhood overweight. However, there are also some controlled and randomized studies. These studies differ with respect to strategy, setting (school, family, primary care, public health),

duration, focus, variables of outcome and statistical power. Interventions tackling obese children are considered as treatment but may also be seen as prevention of adult obesity. Some studies did not specifically address obesity but atherosclerotic risk factors including a high body weight. Others have the more general idea of health promotion and, thus, the authors did not specifically tackle risk factors of overweight. The studies also differ with respect to duration of intervention as well as of the observation period. We feel that the follow-up period should be at least 6 months but in the studies cited below it reached a maximum of 10 years. The authors used various outcome variables including BMI, fat mass, parameters of risks and comorbidities as well as indicators of health habits. This also limits the comparison between studies. Nearly all authors come out with mean values obtained in groups of children (intervention versus non-intervention group). At present there is an overall lack of detailed analysis within specific subgroups as well as data on the effect of intervention on the incidence of overweight and obesity.

School-Based Interventions

SPARK (Sports, Play, and Active Recreation for Kids) was a school-wide intervention in fourth grade 9-year-old children from seven suburban elemental schools in southern California [33]. In 1990 a school-based physical activity promotion program was offered by certified physical education specialists or classroom teachers within 4 schools. Data were compared with three control schools where usual physical education was done. The children were followed for 2–3 years and total data sets were obtained from 305 boys and 244 girls. By spring 1992 there were no group differences in BMI as well as skinfold thickness. Thus, the authors concluded that physical activity alone is not sufficient to reduce adiposity in children.

The 'Know Your Body' project (**KYB**) was initiated in 1975 by the American Health Foundation [34]. The aim of the program was to modify the population distribution of risk factors for chronic diseases. It was evaluated in a 5-year field trial in the New York City area. The program was school-based, and teachers-delivered. Parental participation in curriculum activities and attendance at seminars were intended. As result favorable effects on health knowledge, dietary habits, blood cholesterol and rate of initiation or cigarette smoking were reported [34–36]. However, KYB appeared to have no effect on body mass index. This is in line with another school-based intervention following the KYB program [37]. After 2 years these authors found that nutritional intake (less energy, fat and sodium, more fiber, respectively) as well as physical activity improved in children of the intervention schools.

These data were in line with two school-based studies, conducted in Finland (**The North Carolina Youth Project**) and Norway, respectively. In this

study the follow-up period was 2 years [38, 39]. Community-based programs targeted seventh to eighth grade and fifth grade to seventh grade students. Both, the Finish and the Norwegian activities resulted in favorable changes in food consumption as well as in blood cholesterol levels. In contrast, no favorable effect on obesity was observed. The authors speculated that to tackle obesity requires more intensive and individualized interventions.

Manios et al. [40–42] adapted the KYB school health promotion program on the island of Crete (i.e. the **Crete experience**). The objective of that study program was to promote health habits (including dietary practices) in children with the ultimate aim to reduce the cardiovascular risk in adult life. A school-based intervention directed at children together with seminars organized for parents was implemented. At 3 years follow-up measurements obtained in a subgroup of 288 (intervention group) and 183 control children, respectively, revealed positive changes in health knowledge and behavior as well as in plasma lipids in the intervention group. When compared with controls the age-dependent increase in BMI was smaller in children of the intervention group ($+0.7$ vs. $1.8\,kg/m^2$; $p < 0.001$). However, the concomitant measurements of fat mass by anthropometric methods showed only small and mainly non-significant between group differences.

Using a similar program (i.e. an 8-week classroom-based intervention consisting of knowledge and attitude programs) in 1,274 third and fourth grades (boys) in North Carolina, the authors of the Cardiovascular Health in Children Study (**CHIC**) reported an immediate increase in health knowledge and self reported physical activity in response to an 8-week exercise program and an 8-week program on nutrition and smoking [43]. In the intervention group there was a nonsignificant decrease in blood cholesterol and blood lipids. The authors found a non-significant intervention effect on BMI [44].

The Child and Adolescent Trial for Cardiovascular Health (**CATCH**) is a randomized controlled school health intervention involving a baseline cohort of more than 5,000 children from 96 (56 intervention and 40 comparison) randomly assigned schools [43, 45–48]. At the school level total fat content (to 30%), saturated fats (to 10%) and sodium content (to 600–1,000 mg/serving) of food service was reduced and the amount of moderate-to-vigorous physical activity within physical education class time was increased up to 40%. CATCH employs classroom instructions (i.e. 15–24 lessons), school health environments, school food service and school physical education. Tobacco use was a further content area of the trial. At a 3-year follow-up dietary fat content decreased from 32.7 to 30.3% in intervention schools but remained unchanged (32.7 to 32.2%) in control schools. Intervention students also maintained higher daily vigorous activities than control students (between group differences between 8.8 and 13.2 min per day). Despite these favorable changes there were no further between group differences in BMI, blood pressure and plasma lipids.

Planet Health is a further school-based health behavior intervention program [49]. Over a period of 2 years 1,295 ethnically diverse grade 6 and 7 students from public schools (i.e. middle schools) participated in an interdisciplinary intervention aimed at (1) decreasing TV time as well as consumption of high fat foods, and (2) increasing vegetable intake and moderate to vigorous activities. Intervention units were developed with extensive teacher input and focus groups using a variety of methods including debates, case studies and projects. When compared with controls the prevalence of obesity among girls decreased but remained unchanged in boys. There were positive and sex-independent changes in TV-hours and nutrition. The reductions in body weight were related to reductions in time spent watching TV.

In a further randomized controlled school-based trial (**The Robinson primary school intervention**) 192 third- and fourth-grade students received 18 lessons within a 6 months classroom curriculum in order to reduce television, videotape and video game use [50]. Six months after completion of intervention the number of hours per week spent for TV, videotape and video games decreased but nutrition habits (e.g. frequency of snacking in front of TV, daily serving of high fat foods) remained unchanged. Concomitantly BMI, triceps skinfold thickness as well as waist to hip ratio all improved in the intervention group when compared with controls. These positive results provide evidence that targeting only sedentary behaviors had short-term effects of BMI.

A school-based health promotion programme (Active Program Promoting Lifestyle Education, **APPLES**) aimed at reducing risk factors of obesity was tested in 10 schools in Leeds [51, 52]. APPLES aims to link the school with family and community and focuses on the whole school community including parents, teachers, catering staff and school environment. Nutrition education and physical activity program could be successfully implemented into school curriculum. The results showed that school level changes to tackle risk factors of obesity could be produced (i.e. there were positive changes in school meals, playground activities and high levels of participation). However reinvestigations at 12 months showed that the program had little effects on children's behavior except for a modest increase in vegetable consumption. Also no differences in BMI between children of intervention schools versus control schools were seen. The latter finding questioned the value of school-based interventions [53].

Some authors have studied the effect of obesity prevention (or treatment) in ethnic minorities in the USA [54–56]. Data have been published on intervention directed at American-Indian schools taken into account the cultural perspective [58]. The studies aimed at obesity prevention by change in food intake and energy expenditure. A school education curriculum aimed at increasing knowledge and changing health behaviors showed successful results. Although

weight data were not reported in all studies the interventions affected dietary intake and resulted in differences in percentage calories from fat.

Taken together school-based interventions alone improved some aspects of healthy behaviors but were without effect on nutritional status in most studies. However, only 2 or 3 out of 10–12 studies showed some positive effects on BMI or fat mass. One study suggests sex-specific differences in the effect of intervention on nutritional status. Since none (except one) of the school-based intervention studies specifically addressed the confounding effect of sex the effects of intervention on nutritional status may have been camouflaged by the proportion of boys in the study populations.

Family-Based Interventions

Family resemblances in weight status are well documented [30, 57, 58]. Besides possible genetic links parents select environments that may promote overweight among their children. This environment includes parent's own eating behaviors and child-feeding practices. Family environment during early and middle childhood have a major impact on food preferences, pattern of food intake, eating style, activity preferences and sedentary or active lifestyles. The development of family-based prevention programmes for childhood overweight has been considered as a primary public health goal. At present most studies in this area had addressed obese children together with their parents. There are also some studies tackling parents only.

The Special Turku Coronary Risk Factor Intervention Project for babies (**STRIP**) aimed at introducing healthy lifestyle principles in late infancy [59, 60]. This was a randomized prospective project introducing a low saturated fat and low cholesterol diet at the age of 7 months. Parents of 540 intervention children were individually counselled. At a mean age of 24 and 36 months the authors observed positive changes in fat and cholesterol intake. However, the intervention had no effect on height and weight.

The effectiveness of group counselling for children and their parents was investigated within a 3-year follow-up study in the former USSR [61]. 477 intervention children and 528 controls at a mean age of about 12 years were recruited based on the prevalence of cardiovascular risk factors. The children were advised to increase fruit and vegetable intake, to use vegetable oils and to restrict the consumption of fatty meat and fish. When compared with controls there were significant reductions in diastolic blood pressure and BMI in the intervention group.

Long-term effective management of overweight and obese children by a family-based intervention was reported by some authors [62–64]. Flodmark and co-workers could show that family therapy was effective to prevent the progression of severe obesity in 10- to 11-year-old children [62]. Before intervention

mean group BMI was 24.7 (family therapy), 25.5 (dietary counselling alone) and 25.1 kg/m^2 (control group = no intervention). BMI reached 25.8, 27.1 and 27.9 kg/m^2, respectively, after 1 year ($p < 0.046$ for family therapy vs. controls). The increase in BMI was 5% in the group receiving family therapy vs. 12% in the control group ($p < 0.02$). However, the groups differed with respect to the number of children with severe obesity (i.e. BMI >30 kg/m^2; 1/20, 5/19, 14/48 in the three groups, respectively).

Epstein and colleagues completed four randomized controlled studies [64–67]. Three of these studies involved obese children with obese parents. These authors were most successful when children were treated together with their parents. The follow-up period lasted up to 10 years. The effectiveness of these interventions was well documented by weight changes, a reduced prevalence of obesity as well as lifestyle changes. The 10-year decreases in percent overweight were −7.5% vs. +14.3% in the control group. The data of Epstein et al. [68] were supported by a 5-year follow-up study after nutrition and exercise interventions with a cognitive behavioral programme in obese children. Within this program parents served as consultants rather than as active participants. After 5 years, reductions in percent overweight were 23% again suggesting long-term effects.

Family-based interventions showed no effect on body weight in other studies. Within the Dietary Intervention Study in Children (**DISC**) more than 600 8- to 10-year-old children with an LDL-cholesterol level above the 80th age- and sex-adjusted percentile were recruited [69]. The intervention was performed over a period of 6 months to reduce the intake of total fat, saturated fat and cholesterol. At 3-year follow-up intakes of total fat, saturated fat and cholesterol were all lower in the intervention group. This finding was associated with favorable changes in plasma lipids at unchanged BMI.

Taken together all family-based intervention studies resulted in long-term changes in health-related behaviors in obese children and adolescents but had no or only moderate long-term effects on nutritional status.

Bringing Two Strategies Together: School-Based and Family Based Interventions

KOPS (i.e. Kiel Obesity Prevention Study) was started in 1996 and is planned to run until the year 2009 [5, 70]. Up to now within KOPS a population of 4,997 5- to 7-year-old and 3,750 10- to 11-year-old children was recruited. One part of KOPS assesses the long-term effects of 'low level' interventions (i) at school for all children, and (ii) within 'overweight families' for overweight children. Up to now 780 children underwent a 6- to 8-hour curriculum of school intervention within the first classes (i.e. at age 6–7 years) and 138 of these children could be re-investigated at age 10–11 years (i.e. after a 4-year follow-up).

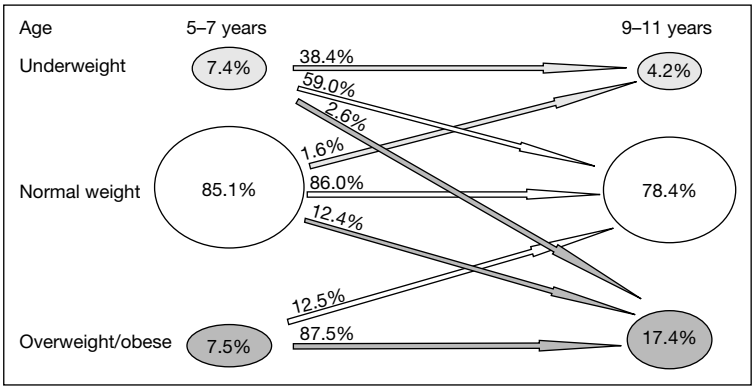

Fig. 2. Results of 4-year follow-up of prepubertal children of the Kiel Obesity Prevention Study (KOPS). Nutritional status at baseline (age: 5–7 years) and at 4-year follow-up (n = 529).

These data were compared with 249 control-children matched for age, sex, BMI, TSF, parental overweight and SES. In Addition 92 families are offered family-based counselling which takes place within the family setting (i.e. 3–5 visits at home). A structured sport program was also offered to overweight children of this cohort. 26 children who underwent family intervention could be re-investigated 1 year later.

Outcome measures of KOPS are nutritional state, health habits and risk factors for disease. Family history of diseases, parental weight and height, SES, parental alcohol consumption and smoking habits were also considered as confounding factors. Our first cross-sectional and 4-year follow-up data show (1) a spontaneous increase in the prevalence of overweight (fig. 2); (2) 88% of children who were overweight at T0 remained overweight at T1 (i.e. the persistence is very high); (3) the 4-year incidence of overweight is about 50%, and (4) intervention has only small long-term effects on the prevalence of overweight but reduces its incidence by about 30% (fig. 3). Comparing the median of BMI or triceps skinfolds in the population of children in intervention and control schools demonstrated a beneficial effect of intervention. This is most pronounced in girls (fig. 4). Within a 1-year observation period family intervention was capable to normalize increases in fat mass and BMI of children. However, a low SES serves as a barrier against intervention measures [Langnaese et al., unpubl. data].

Taken together, the first long-term follow-up data of KOPS support the idea that prevention decreases the incidence without affecting the persistence of overweight. Thus, to tackle the obesity epidemic measures of prevention have to be combined with effective strategies to treat obese children and adolescents.

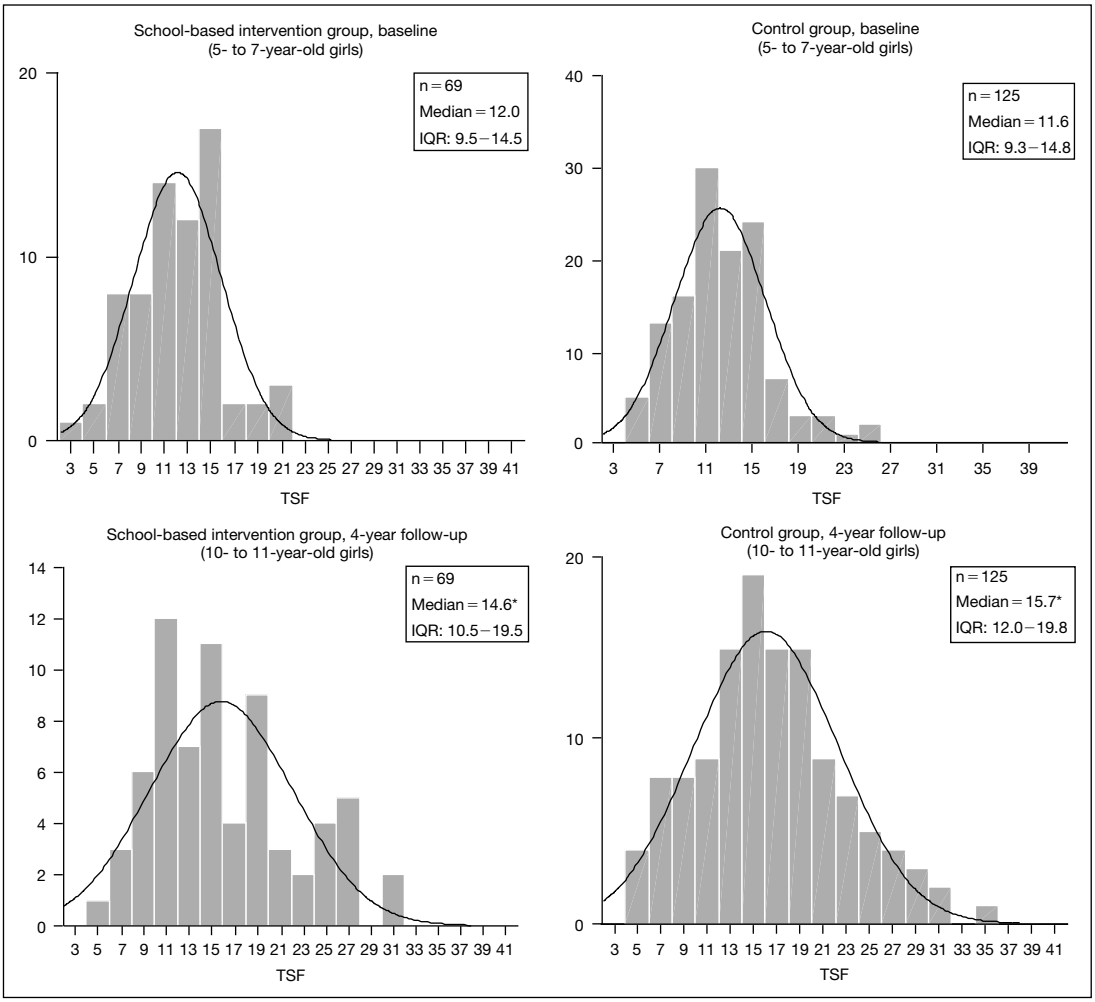

Fig. 3. Results of 4-year follow-up of prepubertal children of the Kiel Obesity Prevention Study (KOPS). Prevalence, persistence and incidence of normal weight and overweight in children of the control group (= without intervention; n = 249) and the intervention group (with school-based intervention within the first year of school; n = 138). Children were matched for basal BMI (i.e. BMI at the age of 5- to 7-years), parental BMI and socioeconomic status (SES). Overweight was defined as >90 P of triceps skinfolds. Reference data were taken from a data base of children in North West Germany from 1980 [see ref. 70 for further details].

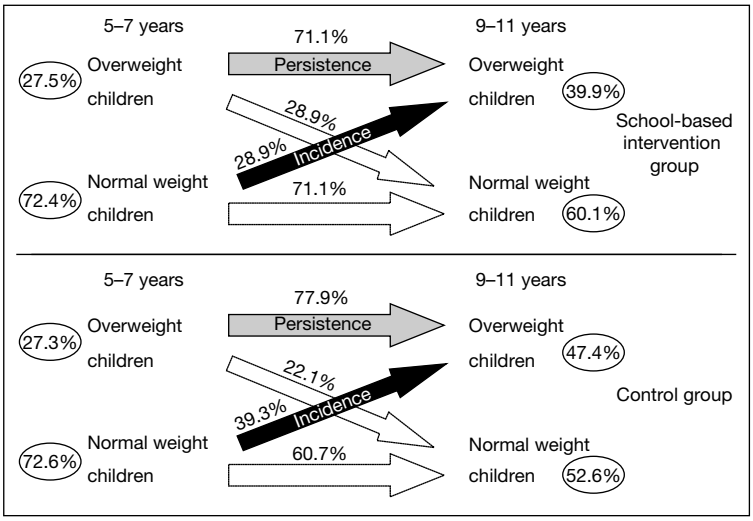

Fig. 4. Results of 4-year follow-up of prepubertal children of the Kiel Obesity Prevention Study (KOPS). Results obtained at baseline and 4 years after school-based intervention in KOPS. Histograms: The distributions and the median of triceps skinfold thickness (TSF) of girls of the intervention and control group at baseline and 4-year follow-up.

There is evidence that when compared with boys girls seem to have a better outcome. Family-based interventions may add to school intervention. However a low SES serves as a barrier against treatment.

Health Promotion in Primary Care

Besides schools and clinics general practices may provide a suitable setting for health promotion for adolescents. Effective prevention of adult disease may be brought about by treatment of childhood overweight and obesity in primary care. However, the effectiveness of these efforts is not well documented. As to our knowledge there are only very few reports of health promotion for teenagers. Since small effects were observed in studies on health promotion in adults a randomized, controlled trial investigated the effect of an intervention promoting healthy life style based on models of self efficacy, behavior change and teenager's attitudes [71]. In this study 1,488 teenagers were randomized. The message was given within a 20-min consultation by a practice nurse. Participants of the control group are sent questionnaires at home. The prevalence of overweight was 27%. 64% of the teenagers did not eat healthily and 39% did not exercise regularly. Teenagers' greatest concern was about diet and exercise. At 3 months follow-up 17.6% (intervention

group) and 11.8% (control group) of the teenagers reported positive changes in diet. The corresponding numbers of positive changes in exercise were 17.1 and 11.6%. Thus health promotion had modest short-term effects on teenagers' lifestyle.

Taken together these are only very first data on the effect of health promotion in primary care. The short-term effects were rather small.

Public Health or 'Ecological' Approaches

Most authors agree that action is primarily required at societal level to counter the environmental influences on physical activity and dietary intake (i.e. universal rather than targeted prevention) [1, 2, 19, 20]. Since 1980 public health policy of some countries (e.g. US, England, Australia) as well as recommendations of the WHO have included prevention of obesity by individuals and populations as an explicit goal. However, implementation plans have focused mainly on individual behavior change, with calls for federal action. Only rarely have implementation plans attempted to address factors in the society and the environment that encourage individuals to overeat and to follow a sedentary lifestyle. Although a concept of an ecological approach to the obesity pandemic was formulated as a new paradigm (i.e. obesogenic environment rather than genetics is the driving force for the increasing prevalence of obesity) [72], at present we do not have collaborative strategies with multiple sectors which impact on the problem. As to our knowledge Swinburn and co-workers were first to apply a framework for identifying and prioritizing environmental interventions for obesity (i.e. the ANGELO framework) [73]. The same group of authors also followed the effect of a community-based intervention program in Samoan communities [74]. Aerobic sessions and nutrition education were offered as interventions. After 1 year there were positive effects on physical activity but no effect on nutrition (knowledge as well as behavior). The mean 1-year weight change was -0.4 kg in the intervention community (vs. a weight gain of $+1.3$ kg in a control community).

Following these ideas strategies and some national activities have been implemented in 'Acting on Australia's weight' [75]. Although fascinating and promising, the effect of these strategies has to be evaluated by follow-up investigations. Mass media education (e.g. BBC's 'Fighting Fat, Fighting Fit (FFFF)' campaign) may add to the success of these strategies [76, 77]. Although the effectiveness of such campaigns in publicizing the issue of obesity and the need for lifestyle changes is well documented participation from groups most in need of lifestyle changes (e.g. the overweight, men, those with lower levels of education) was poor [76]. Using questionnaires 5 months after the campaign most of the female participants reported reductions in weight, fat and snack intake [77]. Concomitantly exercise as well as fruit and vegetable intake were all

increased. These data show that mass media campaigns might make at least a short-term contribution to weight control at the population level.

Taken together there is strong need for a public health approach to tackle overweight and obesity. At present we have only first scientific evidence that addressing the 'obesogenic environment' makes a contribution to weight control at the population level. There are no specific public health approaches to tackle childhood overweight. In addition, the effects of interventions (e.g. mass media education) were not specifically measured in populations of children and adolescents.

Realistic Expectations

There are only few 'successful' studies on prevention of childhood and adolescent obesity. This impression might be in part due to unrealistic expectations. The 4-year follow-up results of KOPS show that school-based intervention resulted in a reduction in incidence of overweight by 26.5% (fig. 4). Concomitantly persistence of overweight was high and only minor effects on persistence were seen in the intervention group (i.e. 71.1 vs. 77.9%, n.s.). The data also showed that within 4 years there is doubling of the prevalence of overweight in the control group. Thus any measure of prevention has to 'fight' against this trend. Since (i) school-based intervention had almost no effect on overweight children, and (ii) 'only' affected normal weight children the beneficial effect on incidence had only a weak effect on the prevalence of overweight. If we assume a long-lasting effect of intervention over the next 4 years (which is unlikely in the absence of further interventions) we come out with a prevalence of overweight of 45 versus 57% in 13- to 15-year-old children in the intervention group and the control group, respectively. Taken into account the limited sensitivity of our outcome variables (e.g. the BMI) it will be difficult to find significant between-group differences. Thus, it is evident that if preventive measures in schools are effective they will show only small effects on the prevalence of overweight within short time (i.e. over a period of 4–8 years after intervention). We should also make up our minds that (at least today) no scientist will be capable to do controlled long-term studies (e.g. exceeding a follow-up period of more than 4 years) in the area of prevention. Most of what we can do in this area is semiquantitative work, which cannot reach the high standard of well-controlled, randomized and placebo-controlled studies (e.g. in pharmacological treatments of obesity). It should be also mentioned that measures of health promotion are unspecific (i.e. they do not specifically tackle overweight). They may or may not affect body weight, but, concomitantly, they also may or may not be of benefit with respect to other aspects of a healthy life style.

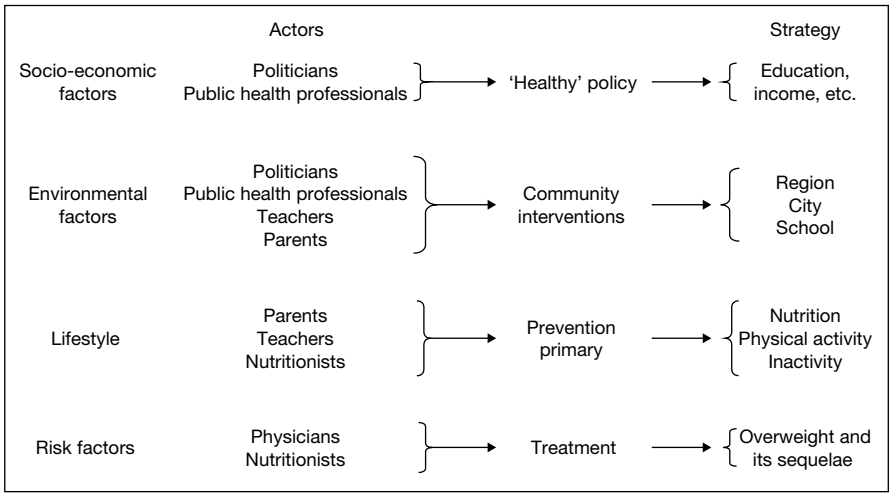

Fig. 5. Strategies and actors of treatment and prevention of overweight and obesity.

There is no doubt that we need best research evidence in the area of obesity prevention. But we should also accept the limits of scientific research. However, problems associated with studies on prevention and also prevention itself do not a priori invalidate the current concepts of prevention.

Conclusion

There are only few controlled studies on prevention of overweight and obesity in children and adolescence. These studies differ with respect to strategy, setting, duration, focus, variables of outcome and statistical power. Thus strictly spoken these studies do not allow general conclusions with respect to the value of preventive measures. Studies aimed at cardiovascular health showed nearly no effect on body weight. All school-based interventions aimed at prevention of overweight and obesity show some improvement of health knowledge and health-related behaviors. There are also some short-term effects on nutritional state in children which seem to be more pronounced in girls. There is first evidence that school-based interventions are capable to reduce the incidence of overweight without effects on its persistence. At present we feel that (i) school curricula on health promotion have to be established and implemented for all children, and (ii) there is evidence that middle and high social class as well as intact families were able to benefit better from treatment than families sharing other characteristics. Targeted prevention in obese children

was most successful when children were treated together with their parents. Although some positive effects were reported simple interventions in a single area (like a school health education program) are unlikely to work on their own. The influences of the parents, peer group pressure, advertising, self-image, etc. have to be taken into account to develop tactics to match the complexity of the causes (fig. 5). Thus, the development of effective preventive interventions likely requires strategies that effect multiple settings simultaneously [4]. At present, there is no concerted action but many strategies in health promotion are followed in isolation. Faced with the epidemic of overweight there is need for national campaigns and action plans on childhood overweight and obesity [75, 78]. It is tempting to speculate that this will also increase the value of isolated approaches (e.g. in schools or primary care settings).

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