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Review

Causative Mechanisms of Childhood and Adolescent Obesity Leading to Adult Cardiometabolic Disease: A Literature Review

Mihai Octavian Negrea [1], Bogdan Neamtu [1,2,3,*], Ioana Dobrotă [1], Ciprian Radu Sofariu [2], Roxana Mihaela Crisan [1], Bacila Ionut Ciprian [1], Carmen Daniela Domnariu [1] and Minodora Teodoru [1]

1 Faculty of Medicine, Lucian Blaga University, 550024 Sibiu, Romania; dr.mihai.negrea@gmail.com (M.O.N.); ioanaadobrota@gmail.com (I.D.); crisanrox@gmail.com (R.M.C.); ciprian.bacila@ulbsibiu.ro (B.I.C.); carmen.domnariu@ulbsibiu.ro (C.D.D.); minodora.teodoru@ulbsibiu.ro (M.T.)
2 Research and Telemedicine Center for Neurological Diseases in Children, Pediatric Clinical Hospital Sibiu, 550166 Sibiu, Romania; ciprianradusofariu@gmail.com
3 Department of Electrical Engineering and Computer Science, Faculty of Engineering, Lucian Blaga University, 550012 Sibiu, Romania
* Correspondence: bogdan.neamtu@ulbsibiu.ro

Featured Application: A brief summary of the current knowledge on the mechanisms of childhood obesity and its repercussions on adult health.

Abstract: The past few decades have shown a worrisome increase in the prevalence of obesity and its related illnesses. This increasing burden has a noteworthy impact on overall worldwide mortality and morbidity, with significant economic implications as well. The same trend is apparent regarding pediatric obesity. This is a particularly concerning aspect when considering the well-established link between cardiovascular disease and obesity, and the fact that childhood obesity frequently leads to adult obesity. Moreover, most obese adults have a history of excess weight starting in childhood. In addition, given the cumulative character of both time and severity of exposure to obesity as a risk factor for associated diseases, the repercussions of obesity prevalence and related morbidity could be exponential in time. The purpose of this review is to outline key aspects regarding the current knowledge on childhood and adolescent obesity as a cardiometabolic risk factor, as well as the most common etiological pathways involved in the development of weight excess and associated cardiovascular and metabolic diseases.

Keywords: childhood obesity; pathophysiology; risk factors

Citation: Negrea, M.O.; Neamtu, B.; Dobrotă, I.; Sofariu, C.R.; Crisan, R.M.; Ciprian, B.I.; Domnariu, C.D.; Teodoru, M. Causative Mechanisms of Childhood and Adolescent Obesity Leading to Adult Cardiometabolic Disease: A Literature Review. *Appl. Sci.* **2021**, *11*, 11565. https://doi.org/10.3390/app112311565

Academic Editor: Veronica Mocanu

Received: 1 October 2021
Accepted: 1 December 2021
Published: 6 December 2021

1. Introduction

The past few decades have shown a worrisome increase in the prevalence of obesity and its' related illnesses [1]. This increasing burden has a noteworthy impact on overall worldwide mortality and morbidity, with significant economic implications as well [2,3]. The same trend is apparent regarding pediatric obesity [4]. This is a particularly concerning aspect when considering the well-established link between cardiovascular disease and obesity [5,6] and the fact that childhood obesity frequently leads to adult obesity [7]. Moreover, most obese adults have a history of excess weight starting in childhood [8]. In addition, given the cumulative character of both time and severity of exposure to obesity as a risk factor for associated diseases, the repercussions of obesity prevalence and related morbidity could be exponential in time [9].

When considering these aspects, it becomes apparent that early intervention for preventing obesity and its related diseases may be the optimal approach. Accurate knowledge of the underlying mechanisms that lead from health to obesity and from obesity to associated disease can prove crucial when determining a strategy for action.

The purpose of this review is to outline key aspects regarding the current knowledge on childhood and adolescent obesity as a cardiometabolic risk factor, as well as the most

common etiological pathways involved in the development of weight excess and associated cardiovascular and metabolic diseases.

Our approach starts by stating the currently accepted definitions for childhood and adolescent obesity and the existing limitations in this regard (Section 2, Defining obesity). A section on the prevalence of childhood obesity follows, in order to highlight the severity of this growing global burden (Section 3, Epidemiology).

Section 4 (The anatomy of obesity) covers the particularities of fat disposition in the body, starting from a macroscopic view and focusing progressively towards the sectional aspects, to peri-organic fat depots, and finally to the microscopic and metabolic characteristics of the constitutive cells of adipose tissues. The mechanisms that lead from weight excess to pathology are discussed within each level of this approach, firstly regarding the general distribution of surface fat describing the mechanisms behind sexual dimorphism in the android versus gynoid fat disposition, as well as their link to obesity-related disease by correlating to a major culprit of cardiometabolic risk, which is central obesity. The physiopathological pathways explaining the connection between central obesity and cardiometabolic risk are discussed in the perspective of the possible role of increased lipolytic activity of visceral adipose tissue altering hepatic and general metabolism. Further on, the particular role of excess fat localized in the proximity of specific organs is presented. Excess perihepatic fat and the flawed intracellular deposition of triglycerides in hepatocytes linked to non-alcoholic fatty liver disease are presented. Epicardial, perivascular, and perirenal excess adipose tissue disposition and their detrimental effect on hemodynamics and metabolism are discussed subsequently. Section 4.4, *Central obesity and metabolically healthy obesity*, summarizes the importance of central obesity related to cardiometabolic risk and raises the issue of apparently metabolically healthy obesity. The final subsection increases the order of magnification in studying the mechanisms behind obesity-related disease and aims to describe the link between particular histological aspects and cardiometabolic diseases. The main topic regards the differences between hypercellular and hypertrophic adipose tissue in respect to their development in childhood versus adulthood, as well as the different cardiometabolic prognosis implied by each entity.

The information in Section 4 emphasizes the need for more refined methods to assess obesity by considering adipose tissue disposition.

Section 5 (Obesity assessment) summarizes current efforts regarding the development of techniques and parameters which better describe weight excess in correlation to the risk of obesity-related diseases. Imaging diagnosis is important to study the obesity distribution characteristics which seem to be relevant to the mechanisms linking obesity to cardiovascular function impairment and cardiometabolic diseases.

Section 6 (Determinant factors of obesity) starts with a short presentation of the physiological aspects of appetite regulation. The following subsections describe the factors that interfere with this schematic representation and can be incriminated in the shift between physiological and pathological. The rationale of this section follows the interplay between genetic causality and environmental factors while focusing on pediatric populations from conception to puberty and adolescence.

Section 7 (Childhood obesity as an adult risk factor) provides a short review of the observational evidence showing childhood obesity leading to adult disease. Section 8 (Mechanisms of obesity-related cardiometabolic disease) aims to describe the mechanisms behind these associations. These two sections mostly refer to cardiovascular and metabolic diseases and the mechanisms incriminated in their development in obese patients, i.e., arterial hypertension, ventricular hypertrophy, heart failure, atherosclerotic vascular diseases (ischemic heart disease, cerebrovascular disease, and peripheral artery disease), type 2 diabetes, and dyslipidemia.

Section 9 (Obesity biomarkers and risk assessment) aims to provide a short review of the known and novel markers associated with obesity and its related diseases, with a focus on pediatric populations, as derived mostly from observational studies.

Section 10 concludes this review, highlighting its main goal, to provide relevant data regarding the physiopathology of obesity-associated disease originating in childhood.

2. Defining Obesity

Conceptually, the World Health Organization defines obesity as "abnormal or excessive fat accumulation that presents a risk to health" [10]. Quantification of excess body fat makes use of the Body Mass Index (BMI) in adults. The BMI is defined by the following formula: $\text{BMI} = \frac{\text{BW}}{\text{H}^2}$, where BW represents body weight (kilograms) and H represents height (meters) [1].

Quantifying obesity in children can prove to be problematic, due to several reasons. Childhood and adolescence, the latter being defined by WHO as "the phase of life between childhood and adulthood, from ages 10 to 19" [11], are marked by a series of significant physiological somatic changes in relatively short periods of time; while in adults, establishing normal values using statistical analysis of anthropometric parameters can yield satisfactory guidelines, pediatric populations tend to be characterized by a greater inhomogeneity in relation to several confounding factors such as age, sex, pubertal stage, and even ethnicity [12,13]. Alternative techniques that can be implemented to quantify weight excess in children are outlined in Section 5, each with its own advantages and caveats.

The currently accepted method to determine a child's weight status makes use of weight charts endorsed by the CDC and WHO that take into account the influence of age and gender. For children under the age of 2, the use of BMI is not recommended. In this age bracket, assessing body weight is accomplished using gender-specific weight-for-height charts. A value greater than two standard deviations above the median for this parameter defines overweight, while a value higher than three standard deviations above the median defines obesity. Gender-specific weight-for-height charts can also be used up to the age of 5. From ages 2 and up, gender-specific BMI for age charts are advocated for determining weight status. The CDC recommends the 85th and 95th percentiles as cutoff points for overweight and obesity, respectively. For children above the age of 5, the World Health Organization defines overweight by a BMI-for-age greater than one standard deviation above the WHO Growth Reference median, and obesity by a BMI-for-age greater than two standard deviations above the WHO Growth Reference median [14,15].

Several authors have proposed a further stratification of obesity with cutoff points at the 95th percentile of BMI-for age (grade 1 obesity), 120% of the 95th percentile (grade 2 obesity), and 140% of the 95th percentile (grade 3 obesity), in order to better define the degree of obesity-associated risk in pediatric populations [16,17].

3. Epidemiology

The prevalence of childhood obesity is on the rise globally, particularly in urban areas [1]. In 2019, an estimated 38.2 million children under the age of 5 were overweight or obese. The prevalence of overweight and obesity among children and adolescents between 5 and 19 years of age has seen an alarming increase, from 4% in 1975 to approximately 18% in 2016. Both genders were similarly affected by this increase [1,18]. A brief overview of the prevalence of obesity in relation to geographic location is presented in Table 1.

Table 1. Childhood obesity prevalence in relation to geographical location.

Location	Year	Type of Weight Excess	Age Group (Years)	Prevalence	References
United States of America	2012	Overweight or obesity	2–5	22.8%	[19]
			6–11	34.2%	
			12–19	34.5%	
		Obesity	2–5	8.4%	
			6–11	17.7%	
			12–19	20.5%	
Latin America	2008–2013	Overweight	0–5	7.1%	[20]
		Overweight or obesity	6–11	18.9–36.9%	
			12–19	16.6–35.8%	
Asia	1999–2017	Overweight	6–11	11.2%	[21]
			12–19	14,6%	
		Obesity	6–11	5.8%	
			12–19	8.6%	
Africa	2017	Overweight and obesity	0–5	8–16%	[22]
Australia	2014–2015	Overweight	2–4	11%	[23]
			5–17	20%	
		Obesity	2–4	9%	
			5–17	7%	
Europe	2011–2016	Overweight and obesity	2–13	21.3%	[24]
		Obesity		5.7%	

4. The Anatomy of Obesity

The distribution of body fat plays an important role in determining the deleterious effect of adiposity on the organism. In this regard, certain anatomical particularities are of significance, as presented in the following subsections.

4.1. Surface Disposition of Somatic Adipose Tissue

One of the first aspects that becomes apparent when observing an individual with excess adipose tissue is the superficial distribution of body fat, with a particular predisposition to certain anatomical areas. The simplest form of categorizing superficial fat distribution is to discern between android and gynecoid obesity patterns. Developmentally, the difference between the two becomes apparent under the influence of sex hormones, typically during adolescence. Android obesity is characteristic for males and implies the distribution of fat around the central areas of the body, particularly the abdomen, whilst in gynoid adipose distribution, usually seen in overweight women, the hips and thighs are the most prominently interested areas [25]. Sexual dimorphism of body fat distribution can be explained in part by the particular sensitivity of adipose depots to the influence of sex hormones. The femoral–gluteal region, for example, is more prone to the inhibitory influence of testosterone on lipoprotein activity [26] as well as the estradiol-dependent increase in the expression of lipolytic a2-adrenergic receptors [27]. In addition, sex hormones also act upon adipocyte maturation. Testosterone suppresses adipocyte formation [28] while estrogen promotes the proliferation of preadipocytes while progestins initiate their differentiation [29].

Although visually objectifiable due to the distribution of somatic fat, android obesity is typically associated with a higher accumulation of visceral adipose tissue and has been shown to be responsible for a greater increase in cardiovascular increase when compared to gynoid obesity [30]. The relevance of discerning between these two types of deposits is outlined in the following section.

4.2. Depth of Adipose Tissue

Adipose tissue presents different cardiovascular risk profiles in accordance with the anatomical depth of the surplus. This has led to the distinction between somatic and visceral fat. The latter is responsible for a more significant correlation with an unfavorable metabolic profile and increased cardiovascular risk [31]. One proposed mechanism postulates that an increased lipolytic activity of visceral adipose tissue in comparison to its somatic counterpart leads to an increase in circulating free fatty acids. The anatomical proximity of the portal vein would in consequence lead to an increased hepatic intake of free fatty acids, independently of their systemic concentration. This could lead to decreased local insulin sensitivity, which would determine an increase in insulin production, which in turn would cause a decrease in systemic insulin sensitivity. Furthermore, there appears to be a significant relationship between visceral body fat and increased inflammatory status, a condition which is found frequently in conjunction with increased cardiovascular risk. Visceral adipose tissue also appears to play a part in increasing leptin resistance. The role of leptin in the neuro-hormonal regulation of appetite is outlined in Section 6.1.2. Further mechanisms involved in the noxious effects of visceral adipose tissue are the increase in sympathetic tonus, oxidative stress, and vascular calcification, all of which influence the development of cardiovascular disease. Visceral adiposity appears to have detrimental effects on cardiovascular risk even in the absence of classically defined overweight and obesity, as shown by the fact that patients with normal weight with an increased visceral adipose mass have a higher risk of cardiovascular disease and type 2 diabetes when compared to those with a predominantly somatic disposition of adipose tissue [32–37]. The noxious effects of surplus adipose tissue manifest both in a systemic manner as well as locally [38]. Therefore, in addition to the general assertion regarding the increased risk revolving around the predominance of visceral fat in obese individuals, it has become apparent that a certain predilection of fatty disposition involving specific areas or viscera can increase the risk for particular diseases. One example regards the mechanical effect of predominantly intra-abdominal adipose excess. Pressure generated by abundant intraabdominal fatty tissue can create a predisposition towards developing a series of gastro-intestinal diseases such as gastro-esophageal reflux or hiatal and abdominal hernia. The same conditions can promote chronic venous insufficiency due to venous system compression [39].

In addition to the pure mechanical local effects of adipose surplus, local functional effects can also be incriminated in the mechanisms leading to a series of pathologies, as presented in the following section.

4.3. Local Effects of Adipose Surplus

The adverse functional effects of excess adipose tissue are related to the secretion of proinflammatory and prothrombotic adipokines [40,41], local hypoxia [42], fibrosis [43], and mitochondrial function alteration [44]. Several localizations present a series of particularities worth noting, in lieu of their prominent noxious local effects that also have a systemic resonance.

The effects of perihepatic adipose surplus have already been previously described. Excess adiposity is, however, also associated with the intracellular accumulation of fatty deposits, in the form of triglycerides within hepatic cells, with injurious effects upon their function. The resulting pathological entity is defined as non-alcoholic fatty liver disease, which is frequently associated with metabolic syndrome and weight excess [45,46].

Increased intracellular triglyceride deposits can also be found within striated muscular cells, which may play a role in increasing insulin resistance and may predispose to developing dyslipidemia [47].

A further example of relevant local effects of adipose surplus is with regard to epicardial adipose tissue. In physiological conditions, the epicardial adipose tissue has an important role in the energetic balance of the heart. Through the uptake of excess free fatty acids, it offers a metabolic support for the myocardium during ischemia. In addition, this tissue is responsible for the thermal insulation of the heart, isolating it, and

maintaining the ideal temperature for the optimal functioning of the enzymatic apparatus within the cardiomyocytes. Furthermore, the connective tissue surrounding the epicardium has an important structural role and is maintained by the synthesis of adiponectin and adrenomedullin. Excess adipose tissue surrounding the heart, however, leads to the decrease in adiponectin, an increase in inflammatory markers, myocardial fibrosis and hypertrophy, and cardiomyocyte apoptosis. These mechanisms could help explain the association between increased epicardial adiposity and ischemic heart disease, heart failure, hypertension, left ventricular hypertrophy, dyslipidemia, and insulin resistance [48–53]. Local macrophage accumulation and angiogenesis within epicardial adipose tissue also seem to play an important part in the inflammatory-mediated mechanisms that link increased epicardial fat to worse outcomes in patients with coronary artery disease [54].

Perivascular adipose tissue is defined by a series of particular characteristics involved in the mechanisms behind the obesity-associated cardiovascular risk. The histological distinction between brown and white adipose tissue is of relevance concerning this matter. While brown fatty tissue has a significant thermogenic role, particularly important in newborns, white adipose tissue serves mostly as a deposit for energetic surplus in the form of lipids, releasing them into the circulation and thus making them available to tissues in need, when such a need arises. White adipose tissue is mostly responsible for the mechanisms involved in metabolic obesity-related disease. In certain conditions, white adipose tissue has shown the capacity of transforming into brown adipose tissue (mostly due to exposure to very low temperatures).

Differently localized vessels in the organism present different proportions between white and brown adipose tissue. This variability may be in conjecture with the different predominant functions of perivascular tissue according to localization. Large central vessels, for example, such as the aorta and its main ramifications, are mostly surrounded by brown adipose tissue, thus playing a key part in maintaining central temperature within normal ranges. Peripherally increased perivascular adipose tissue, on the other hand, has been associated with increased insulin resistance [55].

Excessive perirenal adipose tissue can lead to the increase in intrarenal pressure, with potential involvement in the development of microalbuminuria. Perirenal adipose tissue is implicated in a series of processes related to cardiometabolic risks such as maintaining renal vascular tonus and inflammatory marker secretion [47].

4.4. Central Obesity and Metabolically Healthy Obesity

The aforementioned principles can be used to delineate two major types of adipose tissue disposition which start to develop during childhood or adolescence. Central obesity, with the adipose tissue predominantly concentrated around the viscera, is considered to have an increased unfavorable effect on cardiovascular risk [56,57]. A recent meta-analysis of prospective studies evaluating the link between abdominal obesity and cardiovascular risk has shown a strong association between the parameters describing central obesity (waist circumference, waist:hip ratio, and waist:height ratio) and cardiovascular diseases (including ischemic heart disease, cerebrovascular disease) [58]. The deleterious effect of visceral adipose surplus appears to manifest itself even in otherwise normal-weight individuals (according to BMI values) which show evidence of excess abdominal adiposity (measured by waist circumference for example) [59].

Central obesity has been shown to be a strong risk factor for cardiometabolic disease, not only in adults but in children and adolescents as well [60–66]. Moreover, it seems to exhibit a stronger correlation with cardiovascular risk in children when compared to BMI-defined obesity [67,68]. In addition, the development of central obesity during childhood appears to persist into adolescence and adulthood as well [69–71].

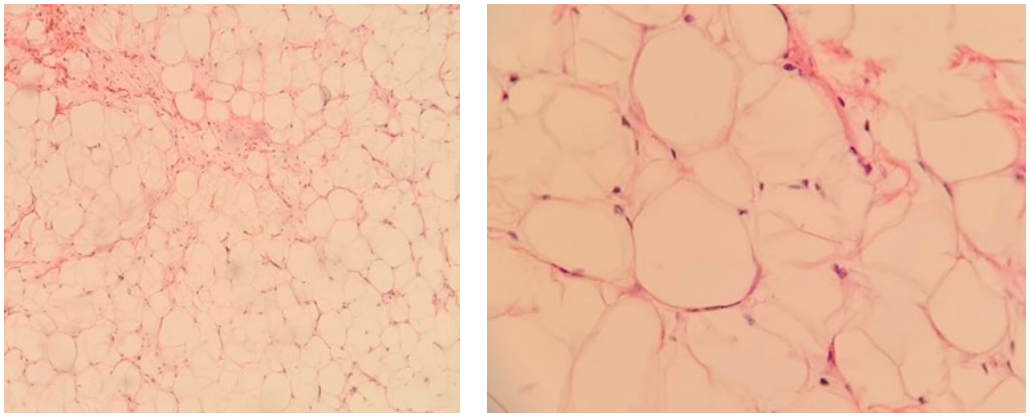
Conversely, due to the apparent predominant impact of visceral fat on cardiovascular risk, the existence of a so-called "metabolically healthy obese" pattern has been postulated, where most of the weight excess is accounted for by somatic adipose tissue, with relatively reduced visceral fat excess [72]. A large observational study involving 3.5 million

individuals, however, has shown an increased risk of incident cardiovascular events in this population compared to individuals with normal weight [73]. With this observation, "safe obesity" might in fact represent a form of precursor state that can be found before the manifestation of the metabolic disbalances traditionally associated with obesity.

4.5. Histological Aspects

The adipocyte is the fundamental cellular unit of adipose tissue. Beyond the role of a mere energetic depository, adipocytes act as a part of a system similar to a standalone endocrine organ by secreting a large variety of peptides and metabolites involved in weight regulation. In addition to the metabolic functions exerted by means of the enzyme pathways involved in beta-oxidation and free fatty acid metabolism, many of the adipokines secreted by these cells have a proinflammatory and procoagulant influence. Other peptides are implicated in insulin resistance and hunger regulation, with a significant effect on body weight and cardiovascular obesity-associated risk. Many of the substances secreted by adipocytes have a still unknown role and are a key interest for medical research [74].

Adipose tissue is highly cellular in nature. The adipocytes that conglomerate in order to form this tissue can respond to external stimuli that determine the increase in adipose mass, either by increasing their individual dimensions or by increasing the physical number of cells. The increase in adipocyte size defines adipocyte hypertrophy. This type of response is typically found in android obesity, with a high proportion of visceral fat. Hypercellular obesity, on the other hand, has a more variable character, frequently identified in individuals that become overweight since childhood. It is however almost always present in severely obese patients, regardless of age. Hypertrophic obesity generally develops during adulthood and has a strong connection with cardiovascular risk. This type of obesity usually responds well to body weight interventions, which are generally inefficient in hypercellular adiposity. This particular resistance to treatment is one of the main aspects that drives the imperative need for assertive preventive action during childhood [75]. Figures 1 and 2 were taken with permission from the pathology laboratory of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu, and display the different histological appearances of hypertrophic and hypercellular adipose tissue.



(**a**) (**b**)

Figure 1. Adipose tissue stained with hematoxylin and eosin (H&E); (**a**) original magnification ×10, adipose hyperplasia tissue with thickened fibrous septae and increased vascular network. (**b**) original magnification ×40, adipose tissue demonstrating enlarged (hypertrophic) adipocytes. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

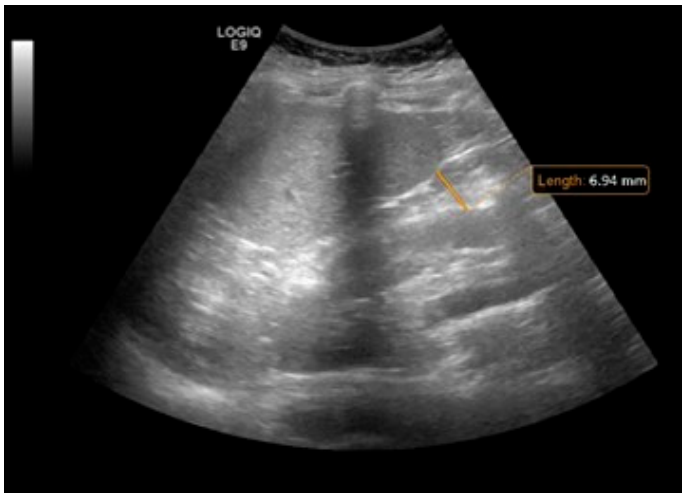


Figure 2. Ultrasound image showing the thickness of the inter-spleno-renal adipose tissue corresponding to the inferior renal pole = 6.94 mm. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

A further aspect to be considered upon examining the cellular foundation of adiposity is regarding the maturation of adipocytes, as they differentiate from preadipocytes. Characterizing the stimuli responsible for the initiation of this process and identifying the factors that lead to preadipocyte recruitment, differentiation, hypertrophy, and/or apoptosis could play a key role in defining the mechanisms behind weight excess. Research in this field could provide potential targets for weight reduction by means of controlling the process of adipocyte proliferation, thus avoiding the development of hypertrophic, metabolically dysfunctional adipocytes responsible for increasing cardiovascular risk, insulin resistance, and the risk of recurrence after weight loss [76].

5. Obesity Assessment

Utilizing the BMI in general practice has the advantage of accessibility and ease of use, in addition to providing a good overall image regarding obesity-associated risk of morbidity. The relationship between BMI values and cardiovascular risk has been validated in numerous studies in the form of a U-shaped curve, implying the existence of an optimal interval for this parameter, bordered on one side by the morbidity correlated with undernutrition and that pertaining weight excess on the other [77,78]. The BMI, however, offers only a gross approximation of one's body weight in relation to height, with no regard for body composition, ignoring the different densities of specific tissues, such as muscle mass and bone tissue, which are under great influence of the specific developmental phases during childhood and adolescence. This applies both in regard to percentual contribution to body weight, and the variable intrinsic structure and density of non-fat tissue throughout specific growth phases (i.e., bone mineralization in accordance with growth stage for example). In addition, growth stage charts only take into consideration the relationship between BMI and gender and age, with no regard concerning the wide range of acceptable values for height in children of a certain age, in and of itself an important marker for the growth stage of a child and, implicitly, the corresponding physiologically variable body composition [79]. A further aspect in which body composition plays a major role is in regard to race. An African child will, for example, for the same BMI value, have a higher percentage of muscle mass than a Caucasian one, whereas an Asian child will have a higher value of body fat percentage [80]. In addition, the BMI offers no insight regarding the distribution of body fat within the body, and the implications presented in Section 4.

To this avail, significant effort has been made in researching methods that better assess obesity in children, with the desire of identifying parameters that better correlate to obesity-associated risk, as presented in the following sub-sections, adapted from [81].

5.1. Inferential Methods

These methods rely, similar to the BMI, on inferring the weight status based on measurements requiring relatively simple instruments.

5.1.1. Anthropometric Parameters

Although the BMI is the most widely utilized anthropometric parameter in general practice, several others can be taken into consideration for estimating obesity-associated risk. Abdominal circumference, for example, has shown a strong correlation with hypertension and intraabdominal adiposity and is used to define metabolic syndrome [82]. The waist-to-height [83] and waist-to-hip ratios [84] also correlate with cardiovascular risk, providing insight on the disposition of both somatic adipose tissue as well as the proportion between somatic and perivisceral fat. Central obesity in children, defined in the current literature as WHtR ≥ 0.5, was correlated with poorer dietary habits when compared to their peers without central obesity [60]. Further refined parameters, such as the ABSI (A Body Shape Index) as defined by the formula $\mathrm{ABSI} = \frac{\mathrm{WC}}{\mathrm{BMI}^{\frac{2}{3}} \times \mathrm{H}^{\frac{1}{2}}}$, where WC is waist circumference (centimeters), BMI is body mass index, and H is the height (meters), and the Hip Index, defined by the formula $\mathrm{HI} = \mathrm{HC} \cdot \left(\frac{\mathrm{h}}{166}\right)^{0.310} \cdot \left(\frac{\mathrm{BW}}{73}\right)^{-0.482}$, where h is HC is hip circumference and h is height in cm, have shown great potential in determining adipose distribution and in inferring obesity-associated risk [85,86].

Neck circumference correlates with the risk of developing certain respiratory diseases, some of which (obstructive sleep apnea, for example) are frequently associated with cardiovascular disease [87–89].

5.1.2. Skinfold Thickness Measurement

The measurement of skinfold thickness in certain key areas of the body (bicipital, tricipital, subscapular, suprailiac, and thigh area) can be implemented in adults to assess adipose tissue disposition. The inhomogeneity of pediatric populations, however, poses significant difficulty in the applicability of standardized equations for determining adipose tissue distribution based on these measurements. The method is also particularly cumbersome, and involves a steep learning curve. The relatively minimal material requirements of the technique are, however, an important advantage, as is the potential of providing relevant results if appropriate protocols are developed for pediatric patients [90–99].

5.2. Methods of Determining Body Composition

The utility of these methods relies on their ability to determine body fat percentage, without, however, offering information regarding the particular distribution of adipose tissue. The most common techniques are outlined in Table 2.

5.3. Imaging

Using imaging techniques for the assessment of weight status allows for the differentiation between visceral and somatic adipose tissue. As such, the methods described for determining body composition and imaging are complementary. Table 3 outlines commonly used means of image acquisition for the evaluation of obesity. All of these techniques can be used to obtain images for the gross quantification of visceral to somatic adipose tissue proportion, as well as measurements of the local fat depots described in Section 4.3.

Sectional imaging (CT or MRI), using a single section (generally at the level of L4–L5), with the help of dedicated software, the ratio between abdominal wall adipose tissue surface and visceral adipose tissue can be calculated in order to evaluate the proportion between visceral and somatic fat [129–141]. MRI can also identify cardiac remodeling found in obese patients [142].

The following images (Figures 3–11) taken from obese children provide examples of the aforementioned imaging techniques.

Table 2. Methods of determining body composition.

Method	Functioning Principle	Advantages	Disadvantages	Ref
Dual-energy X-Ray absorptiometry	Variable X-Ray absorption of different tissues	Proven accuracy in animal studies	Use of algorithms not tailored to pediatric populations Unsatisfactory reproducibility X-Ray exposure	[100–103]
Bioelectrical impedance analysis	Variable electrical impedance of different tissues, in accordance with different water content	Non-invasive	Error susceptibility due to the approximation of the water content of each tissue Use of algorithms not tailored to pediatric populations Cumbersome protocol Imprecise results for extreme values of the determined parameter	[104–108]
Hydrostatic weighing	Variable density of different tissues, determined by comparison with the density of water	Non-invasive	Error susceptibility due to the approximation of the density of different tissues which can be particularly variable in pediatric patientsProblematic adherence to measuring protocol of pediatric patients	[109–112]
Air displacement plethysmography	Determining body density by measuring different parameters obtained during a series of thermodynamic processes.	Non-invasive Very good adherence to measurement protocol Can be used even in newborns and infants	High cost Error susceptibility due to the approximation of the density of different tissues Error susceptibility due to approximations regarding the thermodynamic processes involved	[113–121]
Stable isotope dilution techniques	Calculating total body water based on the ingestion of stable isotopes with uniform distribution within the body and the variable water content of different tissues	Non-invasive Relatively low cost No adverse effects documented yet	Error susceptibility due to the approximation of the water content of different tissues	[122,123]

Table 3. Imaging modalities for evaluating obesity.

Method	Functioning Principle	Advantages	Disadvantages	Ref
Ultrasound	Reflection of ultrasound waves at the interface between tissues of different densities Measurement of subcutaneous adipose tissue thickness and approximation of visceral adipose burden based on the thickness of preperitoneal fat	Non-invasive Readily accessible	Operator-dependence Lack of standardized measurement protocol Insufficient data on pediatric patients	[124–128]
Computerized Tomography	Varying absorption of X-rays in different tissuesSectional imaging and 3D reconstruction	High accuracy	Contraindicated in pediatric patients for adiposity evaluation due to high X-Ray exposure	[129,130]
Magnetic Resonance Imaging	Sectional imaging technique based on the behavior of protons under the influence of a variable high-intensity electromagnetic field	High accuracy Non-invasive	High cost	[131–141]

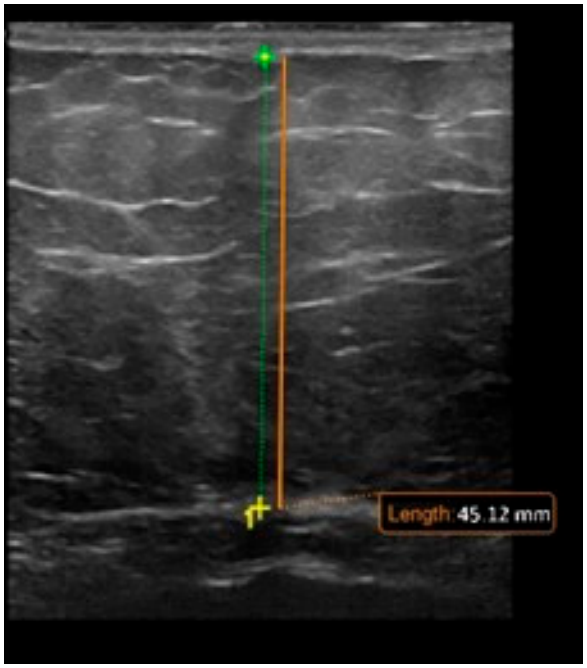


Figure 3. Ultrasound image showing subcutaneous abdominal wall adipose tissue thickness = 45.12 mm, approximately 2 cm below the umbilicus. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

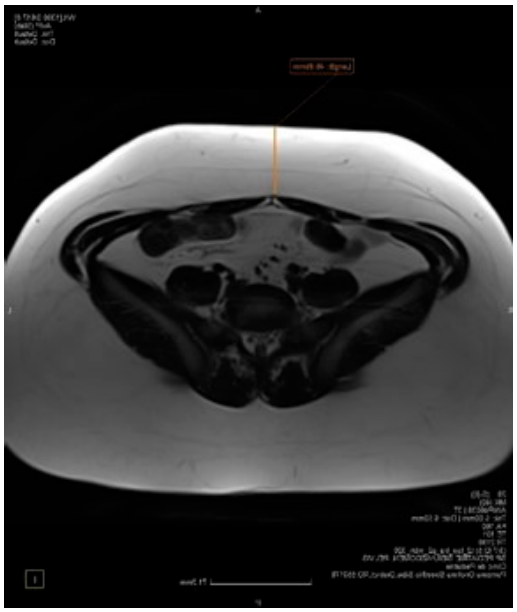


Figure 4. MRI T2 HASTE, T5 transversal section showing the measurement of abdominal wall subcutaneous adipose tissue thickness (46.85 mm). Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

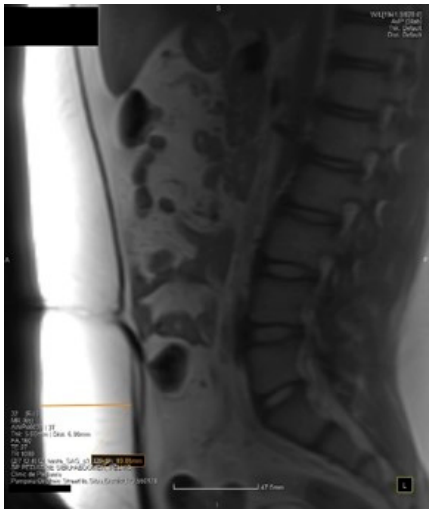


Figure 5. MRI T2 HASTE, sagittal section tangent to T5 showing the measurement of abdominal wall subcutaneous adipose tissue thickness (49.85 mm). Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

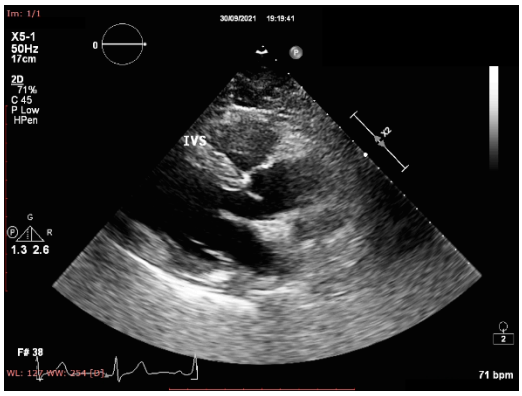


Figure 6. 2D Echocardiography, parasternal long-axis view showing concentric left ventricle hypertrophy Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

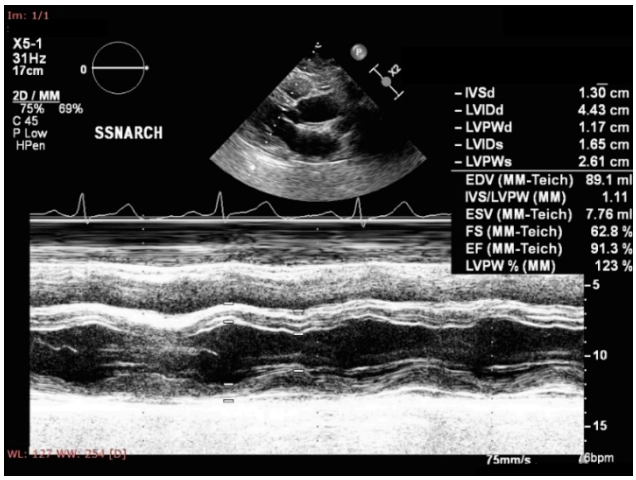


Figure 7. M-Mode Echocardiography of the same patient showing cardiac chamber and wall measurements. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

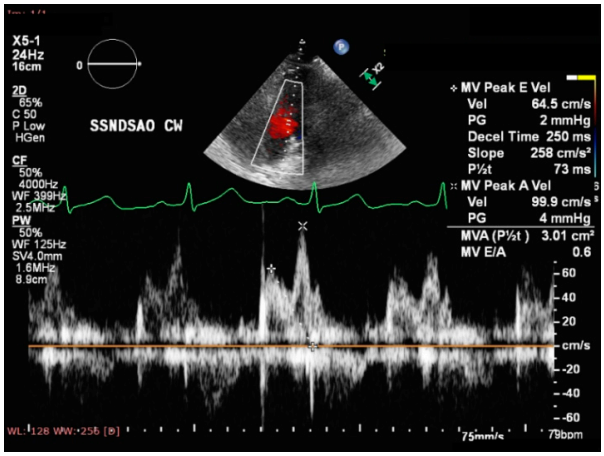


Figure 8. PW Doppler Echocardiography of the same patient showing grade I diastolic dysfunction (impaired relaxation). Prepared by the authors. Courtesy of the Pediatric Clinical Hospital, Lucian Blaga University of Sibiu.

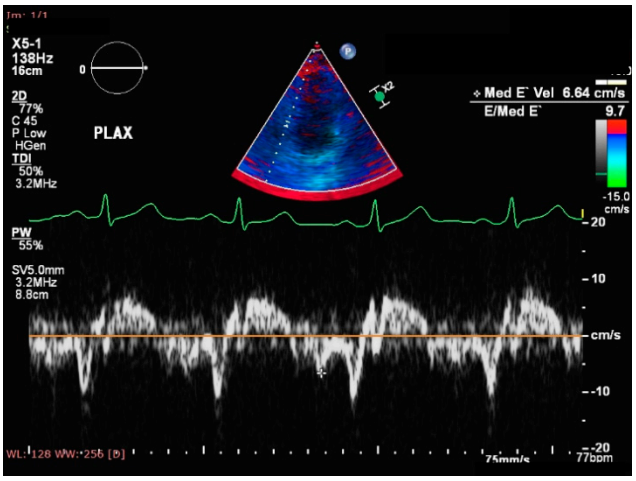


Figure 9. Tissue Doppler Echocardiography, four chamber view, tissue Doppler, estimation of LV filling pressures by measuring E/E′. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

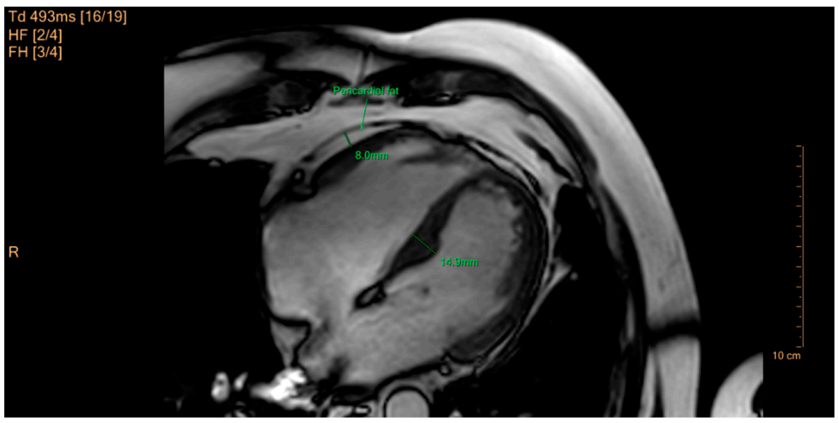


Figure 10. Cardiac MRI, BTFE sequence, cine four chamber view, 8 mm, telediastolic measurement of interventricular septum exhibiting hypertrophy (14.9 mm), epicardial fat thickness of 8 mm lateral of the right ventricle. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

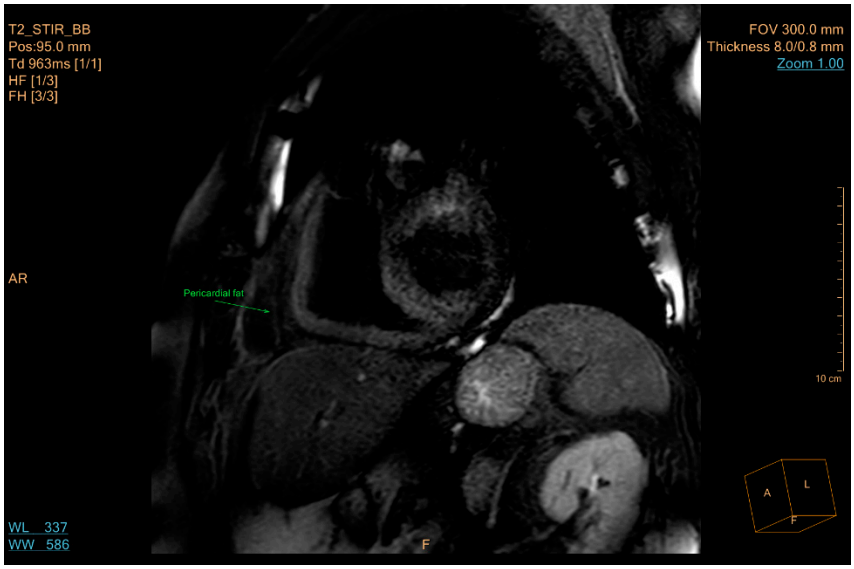


Figure 11. Cardiac MRI Philips Ingenia 3Tardiac T2-STIR sequence, short-axis view, 8 mm, showing hypointensity lateral of right ventricle signifying adipose tissue. Prepared by the authors. Courtesy of the Pediatric Clinical Hospital Sibiu, Lucian Blaga University of Sibiu.

The importance of a holistic approach to obesity assessment methods is two-fold.

Firstly, these methods can provide quantifiable insights concerning the processes involved in the development of high cardiometabolic risk-associated obesity. The "limited expandability" theory suggests that the ill effects of visceral adiposity are mediated by the limited capacity of somatic adipose tissue to deposit lipid excess in the circumstance of sustained positive energy balance [143–145]. The precise capabilities of SAT in this regard may be genetically preconditioned, as shown by studies examining the differences between obese adolescents with different VAT/SAT ratios, where an increased VAT/SAT correlated with the downregulation of lipogenic and adipogenic genes and decreased SIRT1 expression [146]. Nevertheless, it seems plausible that once the storage capacity of SAT is reached, surpluses secondary to lipid metabolism may be diverted towards visceral adipose tissue and non-adipose tissues [147]. The interplay between the specific characteristics of each fat depot (as described in Section 4.3) and the altered diversion of lipid metabolites towards key structures and organs involved in insulin sensitivity may play a key role in explaining the lipotoxicity of VAT [148]. Sustained positive energy balance may affect not only the overall capacity to store lipids of adipose tissue, in the sense of achieving a maximum tolerance, but also the capability of coping with the need to manage ever-increasing energy depots leading to altered adipokine and inflammatory marker secretion and consequent dysregulation of appetite and metabolism [149]. CT and MRI can provide an objectifiable assessment of the resulting aspects, including in pediatric populations, by measurement of specific fat depots (VAT, SAT) and ectopic fat depots such as the hepatic fat fraction, pancreatic fat fraction, and intramyocellular fat [138]. This allows us to create the connection between the descriptive processes involved in lipotoxic fat accumulation and the parameter-based interpretation necessary to real-world evaluation.

Secondly, the different methods of assessing obesity can provide a varied translation into pathology and clinical rationale. Due to the limitations of each technique, providing different truncated views of the association between obesity and cardiometabolic risk can aid in forming a more detailed general picture. More precisely, parameters obtained from different techniques correlate to each other in accordance with the underlying physiopathological pathways leading to disease. This applies to children and adolescents as well as adults. For example, overweight and obesity in children as evaluated by DEXA correlates with higher cardiac measures [150,151]. Increased VAT, as measured by anthropometric methods or sectional imaging, has been linked to unfavorable lipid profiles [138]. The

interconnection between adipose tissue localization and imaging-derived cardiovascular parameters, certain serological biomarkers and functional assessment techniques strengthens the coherence of the various data points obtained from different methods. A pertinent example in this regard is related to levels of adipocyte fatty acid-binding protein (FABP4) in children and its connection to total body fat, abdominal fat, body fat distribution, aerobic fitness, blood pressure, cardiac dimensions, and the increase in body fat in time, as presented by Dencker et al. [151]. FABP4 is an adipokine involved in weight control, metabolism, and atherosclerosis. This study illustrates how the use of several different techniques, including anthropometric parameters (BMI), clinical measurements/indicators (blood pressure, tanner stage), body composition measurement methods (dual-energy X-ray absorptiometry), imaging diagnosis (Echocardiography), functional assessment (indirect calorimetry during stress testing), and circulating biomarkers (FABP4) provide cohesive results.

It can be viewed that the common denominator of the techniques presented in the section on obesity assessment, and the fundament behind their cohesion is linked to the physiopathological mechanisms involved in weight excess and associated cardiometabolic disease, of which they all provide different interpretations.

6. Determinant Factors of Obesity

Alteration of the balance between energy intake and expenditure is the main culprit typically incriminated in the etiology of obesity. When caloric intake exceeds consumption, the excess is stored in the form of lipids in adipose tissue. Chronic exposure to this disbalance leads to an increase in adipose mass [1]. There is evidence, however, that the etiology of excess body weight extends beyond this simplified approach, as is further described. A brief overview of the physiology of appetite regulation is also provided in order to better visualize at which points certain mutations for example hamper these processes.

6.1. Neurohormonal Regulation of Appetite

The sensation of hunger is the product of a complex interaction between the central nervous system, with a key role attributable to a series of hypothalamic nuclei, and a large number of hormones, many of which are secreted by the gastrointestinal tract [152].

6.1.1. Hypothalamic Centers

The hypothalamus acts as the most important relay between the rest of the central nervous system and incoming orexigenic/anorexigenic stimuli. Integrating the information processed within the hypothalamic nuclei leads to the generation of the sensation of hunger or satiety. The most important nuclei are the arcuate nucleus of the hypothalamus (ARC), the paraventricular nucleus of the hypothalamus (PVH), the ventromedial nucleus of the hypothalamus (VMH), and the lateral hypothalamic areas (LHA). A schematic representation of these areas, the types of neurons found within, and the effect of regulatory peptides involved in modulating appetite, as well as the main neural connections between these centers and other relevant neural structures, is outlined in Figure 12, and described in [153] as well.

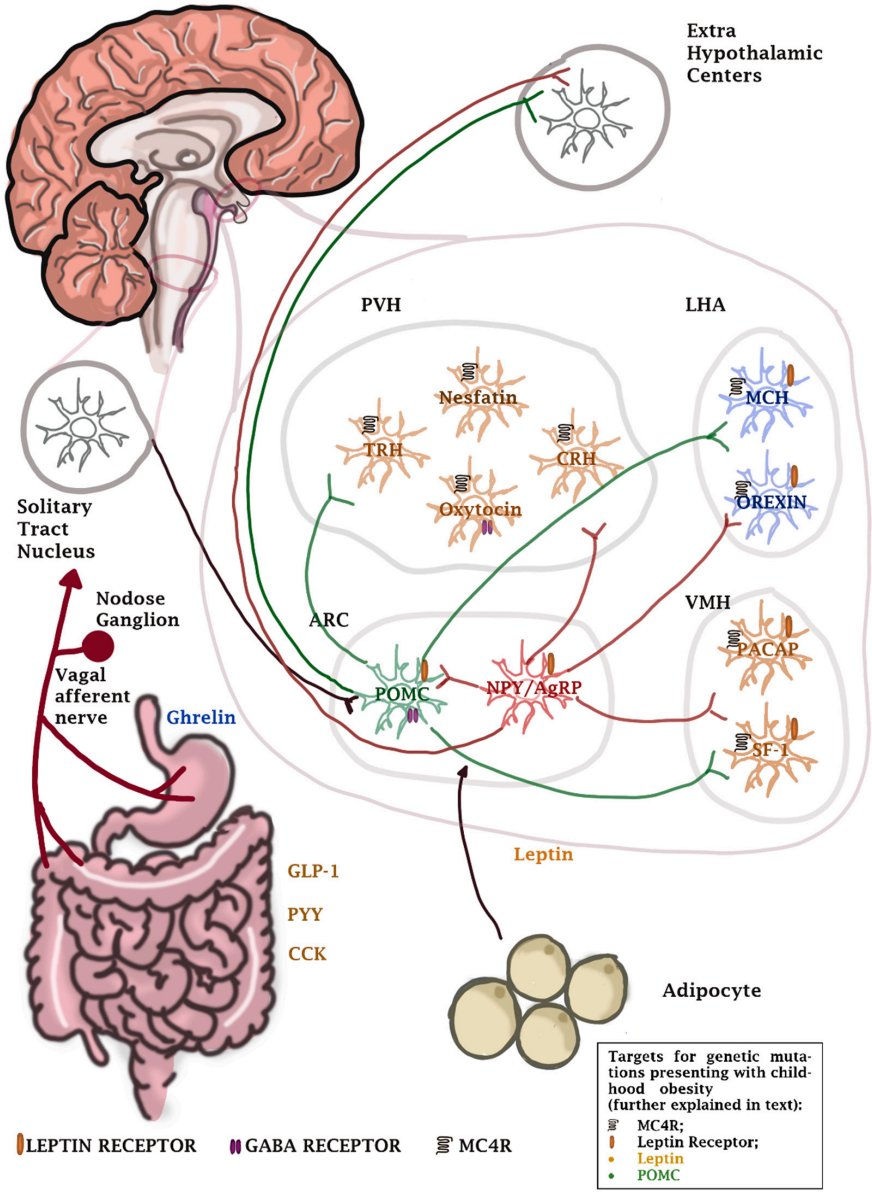


Figure 12. Neurohormonal regulation of appetite [153]. Pro-opiomelanocortin (POMC) neurons in the arcuate nucleus (ARC) suppress appetite by means of secreting a-melanocyte-stimulating hormone (a-MSH) which acts upon melanocortin 4 receptors (MC4R) exhibited by neurons in the paraventricular nucleus (PVH), ventromedial nucleus (VMH), lateral hypothalamic area (LHA), dorsomedial nucleus, and several other non-hypothalamic brain regions. Neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons have an opposite effect and stimulate hunger by acting upon the NPY receptor and by antagonizing the action of a-MSH on MC4R. In addition, AgRP also acts upon the Kir 7.1 potassium channel and induces the hyperpolarization of MC4R-expressing neurons. By projecting both stimulatory and inhibitory appetite signals in the same areas, the neurons within ARC serve as key modulators in this respect, depending on which particular neuron population is activated predominantly. Furthermore, NPY/AgRP neurons inhibit POMC neurons by interacting with the GABA receptor, thus prioritizing the generation of hunger sensation over suppressing it. Leptin secreted by adipocytes acts upon the arcuate nucleus by passing through the blood–brain barrier, while peptides produced by the gastrointestinal tract use the vagus nerve to interact with the hypothalamus. The effects of these peptides on appetite are further detailed in text (Sections 6.1.2 and 6.1.3). Red lines represent inhibitory pathways, while green ones represent stimulatory ones. Hormones and peptides with blue text have an overall effect of stimulating appetite, while those with orange text have an inhibitory effect in this respect. Genetic mutations presenting with obesity in childhood include congenital leptin deficiency, the hypothalamic receptor for leptin mutations, alteration of POMC-aMSH pathway, and loss of function mutations of MC4R receptors [154,155]. Further detailed in Section 6.2.2.

6.1.2. Adipokines

The most significant adipokine implicated in hunger modulation is leptin. The discovery of this peptide has had a substantial impact on the understanding of appetite regulation. Leptin is synthesized within white fat cells. Leptin receptors are exhibited by neurons within the hypothalamic centers responsible for appetite control. By activating POMC neurons and inhibiting NPY/AgRP neurons, leptin inhibits the sensation of hunger and leads to the feeling of satiety, thus reducing food intake and lipid accumulation. Furthermore, leptin also plays a role in modulating energy use and carbohydrate metabolism, reducing weight gain. Several genetic mutations altering the effect of leptin, the function of its receptor, as well as the POMC-aMSH pathway have been described [154,155]. They are further detailed in Section 6.2.2.

Despite the beneficial effects of leptin, it seems that circulating leptin levels correlate with BMI. This phenomenon can be explained by the decrease in leptin receptor sensitivity, which leads to an increase in peripheral leptin secretion [156,157]. This mechanism is similar in principle with the hyperinsulinism found in individuals with decreased peripheral insulin sensitivity, a condition which most commonly precedes the development of type 2 diabetes [158].

6.1.3. Gastrointestinal Tract Peptides

The peptides that are secreted by the gastrointestinal tract that increase appetite are glucagon-like-peptide 1, neuropeptide y, cholecystokinin, and amylin [158–161]. Ghrelin has an opposing action, thus stimulating hunger, and is secreted in the area of the stomach fundus [162].

6.1.4. Other Factors

In addition to the mechanisms described, several further factors are involved in appetite regulation. This refers, on the one hand, to several important circulating mediators such as endocannabinoids which, by interacting with specific receptors, will determine an increase in appetite and nutrient absorption and promote lipogenesis [163]. On the other hand, this refers to certain secondary neural circuits which may have an important influence in generating the sensation of hunger. One such example is the involvement of olfactory stimuli in generating hunger. The link between smell and metabolism could be mediated by insulin, an increase in which determines the attenuation of olfactory input, thus reducing appetite [164].

This brief description of the physiology of neuro-hormonal appetite regulation can aid in better illustrating where some of the most common genetic defects intervene in the normal process of food intake. More than 500 genetic loci have been associated with obesity-related traits in a genome-wide association study performed on nearly 700,000 individuals [147,165]. Notable examples include fat mass and obesity-associated (FTO) genes, which are highly expressed in the arcuate nucleus. FTO genotype correlates with weight status in children [166], dietary habits [167–169], and may even play a role in the distribution of somatic and visceral fat and associated cardiometabolic risk [138]. Further examples include OLFM4 and HOXB5. These genes impact the development of the gastrointestinal tract and may therefore influence gut-regulated appetite signaling [170,171]. The PCSK1 gene encodes PCI (prohormone convertase 1), is involved in the synthesis of aMSH from POMC, and defects of the gene can cause early onset obesity [172,173]. It has also been found to be weakly expressed in Prader–Willi syndrome [172]. Genes implicated in the development of other syndromic forms of early onset obesity are also of relevance in understanding both the normal pathways of weight regulation as well as the various components of multifactorial non-syndromic obesity. ALMS1 mutations associated with Alström syndrome, for example, have shown a link between adipose increase and insulin resistance [174,175]. In Bardet-Biedl syndrome, genetic defects lead to a ciliopathy that may be involved in leptin signaling. This could explain the severe leptin resistance in these

patients. The main mechanism leading to obesity in Bardet–Biedl patients is related to the dysregulation of food-seeking activity [176].

An interesting aspect linking genotype to phenotypical expression regards the different relationships between certain anthropometric measurements and specific gene loci. In particular, loci associated with WHRadjBMI seem to be mainly comprised of genes influencing adipose tissue biology [177], while BMI-associated loci show a stronger connection to genes related to appetite regulation, predominantly expressed in the brain regions with functions attributable to this purpose [178].

6.2. Obesity as a Symptom

Understanding diseases that often present with obesity can aid in the understanding of the mechanisms involved in generating this ailment. A brief description of the most common of such diseases can be structured as follows.

6.2.1. Genetic Syndromes

Several genetic syndromes intervene in obesogenic mechanisms and lead to weight excess [179].

Prader–Willi syndrome (PWS) is one such example, where an anomaly involving the partial disappearance of oxytocin neurons [180] within the hypothalamus leads to the impossibility of achieving satiety. The resulting hyperphagia leads to severe obesity, which in turn leads to limitation of physical activity and corresponding energy expenditure, thus intensifying weight gain and leading to loss of muscle mass. Obesity in Prader–Willi syndrome commonly has a central predisposition (abdomen, hips, thighs) in both genders and is usually the main causative factor behind morbidity and mortality associated with this disease. The current literature reports higher levels for orexigenic hormone (ghrelin) in PWS children than in other obese children. In PWS, children starting with nutritional phase 3 (8 years of age) ghrelin levels increase before the meal but also after the meal, pointing to a hypothalamic pathway dysfunction related to appetite regulation [181].

Bardet–Biedl syndrome is associated with a prevalence of obesity of 72–86%. Children with Bardet–Biedl syndrome are typically born with a normal weight, a third of which will however develop weight excess by the age of 1. Individuals with Bardet–Biedl syndrome are prone to developing diabetes mellitus, hypertension, and metabolic syndrome [182,183].

Carpenter syndrome is a rare genetic disease that frequently associates obesity involving the proximal regions of the limbs, the face, neck, and thorax [184]. It is an acrocephalopolysyndactyly type II associating craniosynostosis, learning disability, cardiac defects, obesity, and polysyndactyly. A mutation in the gene RAB23 gene leads to subsequent RAS dysfunction and impaired intracellular vesicular transport. The encoded GTPase is a negative regulator for hedgehog (HH) family signaling; however, it is not yet clear how these pathways can be linked with obesity. It is known that HH signaling inhibits adipose tissue hypertrophy and hyperplasia [185].

Cohen syndrome (CS) is a recessive autosomal disease defined by the presence of multiple congenital malformations and intellectual disability. In this disease, obesity predominantly affects the torso and has a characteristic disposition, characterized as "truncal obesity". CS was described in the Finnish population and is due to mutations in a vacuolar protein sorting 13 homolog B(VPS13B) gene. This protein is necessary to the Golgi network and endosomal transport [186,187].

Alström syndrome is a recessive autosomal disease involving the mutation of ALMS1, defined by the presence of obesity, type 2 diabetes, and neurosensory degeneration [188]. Recent data presents ALMS as a ciliopathy due to mutation in the ALMS1 gene (located in the centromeres) along with another ciliopathy, Bardet–Biedl syndrome, which is polygenic. However, in ALMS patients, obesity is more severe and ensues in the first years of life (until the age of 5). ALMS gene has its location in the centrosomes and is involved in the microtubules' functions. It has important roles in both visual and auditory analyzers, lungs, heart, liver, and kidneys' function and, most importantly, in metabolic regulation. It seems

that not only the subcutaneous adipose tissues' function is severely deregulated, but also the skeletal and hepatic ones with subsequent insulin resistance. These patients have large dysfunctional adipocytes [189].

6.2.2. Monogenic Causes

The discovery of several diseases that involve a single gene has aided in better understanding both the normal function of weight regulation, as well as some of the genetic factors involved in weight excess. Most of the mutations affect elements within the leptin/melanocortin-hypothalamic axis involved in appetite regulation. Mutations in the genes that code for leptin or the leptin receptor are pertinent examples [190].

Congenital leptin deficiency is a recessive autosomal disease caused by a series of possible mutations of its coding gene. It is characterized by the presence of severe obesity, hyperphagia, and a series of metabolic, neuroendocrine, and immune dysfunctions. It typically responds well to the parenteral supplementation of leptin, with significant weight reduction after treatment and a decrease in voluntary food ingestion. Mutations involving the hypothalamic receptor for leptin have a similar clinical presentation but do not respond to treatment involving leptin [191].

Alteration of POMC production (including mutations of the enzymes responsible for the cleavage of POMC and production of aMSH) or loss of function of MC4R receptors fit into this category as well. Due to the pigmentation effects of MSH, patients with POMC deficit or abnormal MC4R function will frequently associate obesity with red hair and pale complexion. Some studies have shown a prevalence of up to 5% of these types of mutations in morbidly obese children [192–194].

Another example concerns the activity of PPAR-gamma, a transcription factor involved in adipocyte differentiation. Patients with mutations affecting the receptor for PPAR-gamma will invariably be severely obese [195].

6.2.3. Endocrine Disorders

Hormonal imbalance, due to the implications on energy metabolism, will most often tip weight balance in one direction or the other, by affecting either the basal metabolism or the general capacity of managing energy expenditure. Examples of endocrine diseases that often associate obesity include growth hormone deficit or resistance, hypothyroidism, Cushing syndrome, and polycystic ovary syndrome [196–198].

6.2.4. Iatrogenic Obesity

Obesity caused by therapeutic intervention is a common side effect of certain medications. The most frequently incriminated agents are antipsychotics, antiepileptics, sedatives, antidepressants, anxiolytics, mood stabilizers, antimigraine drugs, some oral antidiabetics, insulin, corticosteroids, thyroid hormone replacements, oral contraceptives, diuretics, and even some antibiotics [199]. The latter may be involved in inducing obesity by acting upon the intestinal microbiota. Additionally, it may be plausible that probiotic treatment could aid weight loss in certain individuals [200].

6.3. Genetic Predisposition

Along with the discovery of genetic diseases with implications on weight excess, several further aspects bolster the importance of genetic predisposition in obesity.

The fact that most obese pediatric patients come from families where one or both parents have excess weight is an expression of the complex interaction between genetic and environmental factors [201]. In addition to the hereditary influence of obesity, the often-encountered familial character of obesity is related to the exposure to risk factors associated with the environment created by cohabitation with family members. Sedentarism, inefficient time management, and unhealthy dietary habits are all responsible for altering the lifestyle of the youngest members of a family and are influenced by a large variety

of socio-economic and cultural factors [202]. There are, however, several arguments that underline the importance of genetic determinism in obesity.

One such argument is in relation to studies on twins. Type 2 diabetes and obesity are more frequently simultaneously encountered in monozygotic twins than in dizygotic twins. Furthermore, some studies have even shown a correlation between the percentages of adipose tissue in monozygotic twins raised in different environments. The simultaneous character of obesity in monozygotic twins seems to take little regard to family environment. In addition, monozygotic twins tend to have similar mechanisms of adapting their weight to the environmental factors they are exposed to [203].

A further argument is brought forth by studies on adopted children. Frequently, adopted children exhibit a weight pattern more similar to their biological parents rather than the adoptive ones [204]. The importance of epigenetic mechanisms has also been outlined by studies that have shown a strong correlation between the presence of adiposity in males and their descendants [205].

Finally, another hypothesis worth taking into consideration is the theory of "thrifty" genes. The fundament behind it states that across evolution, a genetic arsenal tailored towards creating energy storages, in a time when sources of nutrition were scarce, was a survival advantage. The same genetic configuration has become a major disadvantage in modern times. This theory could explain the puzzling differences in obesity between certain races, as well as the variable influence of the same environmental factors on different ethnicities of people. A relevant example of where this theory could provide an explanation regards the development of weight excess in migrating populations from areas where the prevalence of obesity is low, to locations where it is higher. The prevalence of obesity frequently becomes greater in the migratory population when compared to natives [206].

6.4. Vulnerable Periods

From the point of conception onwards, human organisms are under the continual influence of external factors. Certain timeframes are particularly important, however, with regard to the susceptibility towards obesogenic factors.

6.4.1. Pregnancy

One theory regarding the genome-environment interaction postulates that most pathologies are the result of a genetic preconditioning of disease which becomes phenotypically apparent under the influence of environmental factors [207]. From this perspective, pregnancy represents the earliest period in which an individual is exposed to potentially disease-inducing environmental conditions. Obesity is one such disease. The hypothesis that in utero exposure is the fundamental event leading to the genesis of adult disease has been proposed by Dr. DJ Barker in his studies [208,209]. The fetal origin of disease hypothesis is based on the concept of phenotypic plasticity, which embodies the concept that living organisms can have different phenotypical expressions of the same genetic code under the influence of different environmental exposures. In this respect, fetal exposure to inadequate nutrition may have a role in "programming" the individual towards developing a significant array of cardiovascular diseases and risk factors, including obesity [210,211].

When viewed from the traditional standpoint of the etiology of obesity as the result of an altered balance between energy intake and expenditure, it is the mother's behavior that establishes the quantity and quality of nutrients the fetus receives. Increased refined sugars intake and inadequate dietary polyunsaturated fatty acid ratio (i.e., high omega-6 fatty acid and low omega-3 fatty acid intake), for example, are associated with an increase in developing excess weight in childhood [212,213]. With regard to energy expenditure, few mothers follow the recommendations for physical activity during pregnancy. Some studies have shown that less than 15% of interviewed pregnant women participated in moderate physical activity at least 3 times a week for 20 min or more [214,215].

All the aforementioned factors influence one of the most important predictive parameters of childhood obesity: mother's weight status during pregnancy. The mother's weight

at the beginning of pregnancy can be regarded as a partial representation of the genetic material available to the child, as well as an insight into the family environment to which the mother had been exposed and in which the child will be integrated. Both the BMI before pregnancy, as well as weight gain during pregnancy can influence the child's weight status after birth [216–218]. During the first two trimesters, weight gain is predominantly attributable to an increase in the mother's adipose tissue, and not fetal mass. It is plausible that excessive weight gain of the mother during this period could lead to an increase in child adiposity after birth, due to an increase in available nutrients in utero [216,219].

One of the most pertinent arguments sustaining the link between mother and child in respect of weight status derives from studies on obese mothers that have given birth to children both before and after gastric bypass surgery. Children born after such an intervention and, implicitly, after a significant correction of excess weight in mothers, have shown an improved weight status as compared to children born before the mother's surgery [220–222].

Malnourishment is, however, also a risk factor for childhood obesity. Although malnourished mothers more frequently give birth to children who are small for gestational age [221], they are at risk for developing an excessive body weight during childhood [209]. A possible explanation for this phenomenon could be connected to the aforementioned intrauterine "programming" which leads to childhood and adult obesity along with a wide range of metabolic disorders and cardiovascular diseases [223].

Similarly, intrauterine injury caused by tobacco smoke, alcohol ingestion, or other toxins can lead to the birth of small for gestational age children, with the same predisposition of developing obesity during childhood [224–226]. Iatrogenic exposure to certain medications, such as hormonal treatments or antibiotics, can have a similar effect [227–230].

Of the most relevant metabolic disorders during pregnancy, gestational diabetes is a dysmetabolic entity with significant repercussions on metabolic health well beyond pregnancy, both for the mother and the child. Gestational diabetes is yet another potential exposure that can create a predisposition towards early obesity [231,232].

The end of pregnancy is the point in which environmental factors no longer pass through the mother as a filter. Some studies have shown that even the way in which this process occurs can influence childhood weight status. A prospective study on more than 20,000 subjects has found a correlation between cesarian birth and the risk of developing obesity. This association was even stronger in mothers that did not have a clear indication for cesarean birth [233].

6.4.2. New-Born Period and Infancy

In the first 6 months of life, exclusive breastfeeding is the nutrition of choice for infants, preferably on demand, according to the AAP, ESPGHAN, and WHO [234–236]. Deviating from this ideal has been linked to an increase in the risk of developing obesity [237–239].

6.4.3. Early Childhood, Preschool, and School-Age Periods

Initiation of solid foods is essentially synchronous with the onset of exposure to the day-to-day dietary habits within a child's environment. The conditions created for the child, initially by the family or legal guardians, followed by kindergarten or other means of social integration and school, as well as the general cultural background of the society they are brought into (i.e., development status of the place of birth, urban versus rural area, ethnic, social, and cultural background, family education level, etc.) to which the addition of the influence of mass media is not negligible—all of these factors have significant implications on establishing whether or not the child will be exposed to the unhealthy influences which lead to obesity.

Furthermore, this developmental time frame contains one of the most vulnerable periods in respect to weight balance, around the age of 4 to 7 years, due to BMI rebound. In this interval, the BMI will reach a nadir value from which, under physiological conditions, it will continue to rise during childhood, extending into adulthood as well. Early BMI rebound

is a risk factor for obesity and reveals a period of significant vulnerability to unhealthy behavior concerning energy balance, with potentially long-term implications [240].

6.4.4. Puberty and Adolescence

In a similar fashion to pregnancy and the BMI rebound time span, adolescence defines an individual period of vulnerability to obesogenic factors [240]. In addition to the aforementioned external influences on lifestyle, which continue to stay relevant during adolescence, this period is marked by a series of distinct particularities relevant to the matter.

Puberty is responsible for a wide range of homeostatic and somatic alterations, with significant psychological and behavioral implications. The beginning of sexual maturation leads to diverging modifications in body composition and adipose disposition between boys and girls. In girls, there is a typical increase in adipose tissue percentage and the disposition in specific areas due to sexualizing hormones. In contrast, boys usually present an increase in muscle mass and a reduction in adipose tissue percentage [241–243]. Partly due to these significant changes and the adaptive necessary coping mechanisms, adolescence is regarded as a very demanding growth stage [244].

The influence of peers also becomes more potent during adolescence, as well as potentially harmful behaviors promoted in society. Transitioning from the childhood environment to adult independence, characterized by the need for social acceptance, exposes the vulnerability to the aforementioned influences. Marginalization of overweight teens leads to lowering of self-esteem and burdens social interaction, potentially leading to anxiety and depression. The same stigma around teenage obesity can lead to a situation where unhealthy eating and sedentary behavior lead to weight excess, which leads to social isolation and further lack of activity due to fear of judgment.

6.5. Energy Balance

6.5.1. Caloric Intake

One way to describe the characteristics of caloric intake is to view it from the perspective of quantity, quality, and rhythm of nutrition.

The aspect of quantity of nutrition refers to the ideal absolute value of calorie intake corresponding to each age group. There is no general consensus in this regard, however, the optimal strategy most probably takes into account the level of activity for each individual and establishes optimal caloric intake accordingly. Several guidelines provide a detailed description in this respect [245,246].

The quality of nutrition refers to achieving an optimal proportion of macro and micronutrients through dietary intake. Foods with an excessive amount of lipids and carbohydrates accompanied by a reduced proportion of protein, vitamins, minerals, and micronutrients are particularly harmful to maintaining a normal weight. The WHO recommends reducing the intake of free sugars to a value under 10% of total caloric intake, regardless of age. This refers mostly to mono and disaccharides added to food and drinks, as well as naturally occurring sugars in honey, syrups, and fruit juices. An additional reduction to under 5% of caloric intake can be warranted in certain conditions. Elevated free sugars intake frequently implies an increased overall caloric intake, which leads to weight gain. A dietary reduction in free sugars with the purpose of reducing total caloric intake leads to significant weight loss, regardless of the initial values. In studies where complex carbohydrates have been exchanged with other nutrients while maintaining the same overall caloric intake, weight reduction was not achieved [247,248]. It is therefore most probable that the weight-reducing efficiency of free sugar intake reduction is due to the high caloric density of such foods. In consequence, a relatively modest reduction in free sugars can imply a significantly lower overall daily energy intake [249]. To this avail, sweetened beverages and "fast-food" should be avoided in children before reaching school age [250,251]. On the opposing side, the consumption of fruit and vegetables provides an

optimal nutrient composition, along with preferentially searching for foods with a low glycemic index to provide sources for carbohydrates, such as whole-grain foods [245].

When regarding lipid intake, lipid-rich foods such as high-fat dairy should generally be limited and an optimal ratio between saturated and unsaturated fats should be sought after. Saturated fats have a detrimental effect on weight status and cardiovascular risk. They are generally found in animal-origin foods. For this reason, it may be preferable to achieve optimal lipid intake using vegetal oils, a good source of essential fatty acids, and vitamin E. A further aspect worth considering relates to the intake of trans fats, which can increase the risk of weight excess and cardiovascular disease. Partially hydrogenated oils are the main source of trans fats. Protein intake should be achieved mostly through animal source foods with low lipid content and vegetal foods with high protein content such as beans, peas, soy, nuts, and seeds. Limitation of sodium intake should also be taken into account when considering the optimal diet [245].

When regarding the rhythm of energy intake, dividing daily calorie consumption into three main meals and 1–2 snacks is the recommended strategy starting from age two. Replacing main meals or omitting one of them with subsequent compensation, as well as frequent dining out have all been incriminated in increasing the risk for obesity [252]. Eating at irregular intervals (particularly during the night), and binge eating are typical examples of a maladjusted eating rhythm that can lead to weight excess [198,250,253]. A possible explanation concerning the deleterious effects of nocturnal calory intake refers to the inversed disposition of circadian energy expenditure versus intake. Most of the calories consumed during the day should be spent during daily activity in order to avoid energy storage in the form of adipose tissue. Calorie intake during the night will tip the balance towards the creation of energy reserves in the absence of physical activity. Although this pattern is more common in adults, it may be prudent to avoid late meals in children, in particular those at risk of becoming obese [254–256].

Finally, one aspect worth mentioning is the general recommendation of avoiding recompense through food. This conduct usually implies an alteration of all three of the described elements of a healthy diet. It can increase the total caloric intake above the recommended quantity, it alters the optimal nutrient proportion, as these types of rewards are usually high in rapidly absorbed free sugars, and it alters the adequate rhythm of food intake, as they are usually offered between meals or planned snacks [250].

6.5.2. Energy Expenditure

Adequate energy expenditure is a key element in maintaining a normal weight. The proportion of active and sedentary intervals is essential in this respect, regardless of age. In this respect, unrestrained non-academic screen time is an important risk factor for obesity and should be avoided completely until the age of 2 [257–259]. Between the age of 2 and 4, non-academic screen time should be reduced to a minimum. The habits acquired in this age interval may resonate even into adult life. From the age of 5 and onwards, children can be encouraged to participate in team sports and to achieve a minimum of 60 min of moderate to intense physical activity every day.

Rest is just as important in achieving a balanced development. In adults, sleep deprivation has been linked to obesity by reducing circulating leptin and increasing ghrelin synthesis, thus increasing appetite and inducing insulin resistance [260,261]. The association of obesity with lack of sleep applies to children as well [262–270]. Cortisol levels and growth hormone imbalances associated with insufficient sleep are contributory to generating weight excess [271].

In essence, energy expenditure can also be described similarly to caloric intake, by taking into consideration its quantity, quality, and rhythm. This refers to the quantity of time spent engaged in physical activity or rest, the quality of both physical activity (preferably moderate to high intensity) and rest, where prioritizing sleep over screen time may be beneficial, as well as the rhythm of physical activity through establishing a healthy circadian rhythm.

6.6. Psychological Aspects

Psychological stress has been linked to obesity in children. One of the proposed mechanisms that leads to this connection could include inflammation and the interference in the hypothalamic-pituitary-adrenal axis with a subsequent increase in cortisol levels and increased appetite. Several major stress-generating events such as abuse or divorce have been linked to excess weight [272].

The mental status of caretakers is also an important determinant factor in forming the basis of a healthy lifestyle for children. Maternal depression can have a significant impact on this matter. Post-partum depression, for example, is associated with adverse postnatal feeding practices, including early cessation of breastfeeding. In older children, parental depression is associated with a lack of physical activity and an increase in screen time, both of which could translate into similar behavior in children [273].

6.7. Social Background

As children grow and become more and more conscious of their surrounding environment, they also become more susceptible to certain elements that define the background of society and day-to-day life which can influence all behavioral aspects, including those linked to dietary habits, physical activity, and weight control.

One relevant example relates to the increased availability of nutritionally inadequate foods, both financially, as well as concerning the ubiquity of such foods in fast-food restaurants and vending machines in public spaces including schools, most often in large quantities and with a significant detrimental potential regarding caloric intake and weight status [274]. Even in facilities used to fulfill daily nutritional necessities such as supermarkets, the proportion of foods rich in free sugars, lipids, and sodium has become worrisome [275]. Marketing techniques that promote such foods are also to be incriminated in the obesogenic tendencies of today's society. Commercials often depict unhealthy foods as palatable, financially accessible, and easy to prepare, appealing both to adults, also exposing the children they are caring for to the same products, and directly to children, sometimes even by associating a favorite cartoon character with unhealthy, sugar-laden products [276,277]. A further example refers to promoting impulse-buying by placing products with a high caloric content in front of cash registers or in waiting zones [278]. All of these methods are rooted in carefully studied manipulative techniques meant to increase the consumption of products that are scientifically proven to be inherently harmful. The filter through which the available information reaches the mind of a child can also be altered due to the social and economic status of their caretakers, the cultural and ethnic aspects that shape their perception of the world, as well as the tolerance towards noxious behaviors of the micro-environment they pertain to [198].

7. Childhood Obesity as an Adult Risk Factor

In adults, there is a well-documented link between obesity and a wide array of cardiovascular diseases, including ischemic heart disease, hypertension, cerebrovascular disease, atrial fibrillation, ventricular arrhythmia, and sudden cardiac death [38,279]. Furthermore, obesity promotes the development of a series of afflictions which are themselves individual risk factors for cardiovascular diseases, such as type 2 diabetes, dyslipidemia, and obstructive sleep apnea. In this view, obesity appears to be more than a standalone ailment and can be better described as a complex dysmetabolic and mechanically dysfunctional condition [280–282].

Considerable efforts have been made to study whether the link between adipose excess and cardiometabolic disease finds its origin during childhood. Table 4 summarizes some of the available observational evidence showing childhood obesity leading to adult disease.

Table 4. Observational evidence showing childhood obesity leading to adult disease.

Reference	Obesity Parameter	Investigated Association	Subject Ages (Childhood)	Subject Ages (Adulthood)	Parameter	Result (95%CI)
Llewellyn et al. * [283]	BMI	Diabetes type 2	6 and under	19–73	OR/StdBMI	1.23 (1.10–1.37)
			7 to 11			1.78 (1.51–2.10)
			12 to 18			1.70 (1.30–2.22)
		Coronary heart disease	7 to 11			1.14 (1.08–1.21)
			12 to 18			1.30 (1.16–1.47)
		Hypertension	7 to 11			1.67 (0.89–3.13)
			12 to 18			1.29 (1.19–1.40)
Juonala et al. *[284]	BMI	Diabetes type 2	3 to 19	23–46	RR (O)	2.4 (1.6–3.6)
		Hypertension				1.8 (1.5–2.1)
		High-risk LDL cholesterol				1.4 (1.2–1.8)
		High-risk HDL cholesterol				1.4 (1.2–1.6)
		High risk triglycerides				1.6 (1.3–1.9)
Owen et al. * [285]	BMI	Coronary heart disease	7 to 18	25–77	OR/StdBMI	1.09 (1–1.20)
Kindblom et al. [286]	BMI	Heart failure	8 vs. 20	Mean FUP = 37.7yrs after age 20	HR(Nw/O)	3.14 (2.25–4.38)
					HR(O/O)	2.85 (1.83–4.45)
Heiskanen et al. [287]	BMI	Eccentric LV hypertrophy	6 to 18	34–49	OR(O/Ob)	2.04 (1.35–3.07)
Adelborg et al. [288]	BMI (>90th percentile of study population)	Atrial fibrillation/flutter	7 Boys	>25	HR	1.35 (1.25–1.45)
			7 Girls			1.26 (1.14–1.38)
			10 Boys			1.42 (1.32–1.53)
			10 Girls			1.32 (1.20–1.45)
			13 Boys			1.46 (1.36–1.56)
			13 Girls			1.38 (1.27–1.51)

Studies marked with an asterisk * are meta-analyses. The following notations refer to the characteristics of the study subgroups: Nw = normal weight, Ov = overweight, Ob = obese, O = Overweight or obese. When more than one BMI measurement was carried out during the study, the first value represents the group category on initial determination, while the second refers to the later measurement. Childhood age refers to the age at which the obesity parameter was determined. Entries containing "vs" describe the ages of BMI measurement when more than one determination of this parameter was carried out during the study. Adulthood ages represent the ages at which the investigated associations were explored. OR/StdBMI = odds ratio/increase of 1 standard deviation of BMI, RR = relative risk, and HR = hazard ratio.

8. Mechanisms of Obesity-Related Cardiometabolic Disease

The physio-pathological pathways leading from obesity to cardiovascular disease involve both direct and indirect mechanisms with both local and systemic action [279]. From a hemodynamic standpoint, the adaptive changes of the cardiovascular system are due to the structural and functional alterations imposed by the increase in circulating volume and metabolic strain attributable to excess adipose tissue. This generates a hyperdynamic cardiovascular system constrained to adapt the cardiac output by increasing stroke volume and heart rate. Peripheral vascular resistance increases due to sympathetic hyperreactivity and the systemic proinflammatory status associated with obesity. The most direct consequence of these modifications is an increase in blood pressure, which partly explains the causation behind the higher prevalence of arterial hypertension in obese patients [289]. The left ventricle is under the direct effect of the strain induced by the aforementioned processes and adapts by altering its geometry and remodeling its structure in an attempt to manage the increased load. Beyond a certain point, the adaptive mechanisms of the cardiac muscle become dysfunctional, leading to progressive dilation and cardiac hypertrophy, eventually impeding the function of the cardiac pump [290–292]. The initiation of cardiac remodeling is a relatively early process, as demonstrated by studies identifying its presence in obese children [293]. A recent study conducted by Esanu et al. found signs of LV remodeling in up to one third of obese children investigated. The most common pattern was that of concentric left ventricular hypertrophy [294].

The hemodynamic changes in obesity have an effect on the other chambers of the heart as well. The left atrium is also affected in obesity [295]. A possible mechanism is related to the increase in the filling pressures of the left ventricle, which can lead to the progressive distension of the left atrium. This process might aid in explaining why obese patients have an increased prevalence of atrial fibrillation [291]. The increases in pressure on the right heart can be objectified by increased pulmonary artery systolic pressure, a frequent finding among obese patients [296].

The characteristic hemodynamic reshaping in obesity may develop long before the clinical debut of cardiovascular disease. Already in obese children, a circulatory hyperdynamic status can become apparent as demonstrated by an increase in central aortic pressure when compared to children with a normal weight, regardless of the presence of clinically manifest hypertension, dyslipidemia, or sedentarism [297]. The repercussions of this status also affect the morphology and function of the myocardium in obese children. Morphologically, obese children frequently exhibit larger cardiac cavities, thicker ventricular walls, and an increased total cardiac mass. Functionally, even in the absence of a significant modification in left ventricular ejection fraction when compared to children with normal body weight, obese children show important differences in the parameters measured by tissue Doppler and speckle-tracking echocardiography, as well as a comparative decrease in diastolic function [298].

In addition, despite the rare occurrence of clinical hypertension in pediatric populations, when this pathology is identified, it is most frequently identified in obese children [299–301]. The relationship between these two entities is further strengthened by the fact that assertive intervention upon weight excess frequently leads to substantial reductions in systolic arterial pressure [6]. Similar to obesity, if arterial hypertension is developed during childhood, it frequently continues to affect individuals into adulthood [82,302,303]. These children often have a characteristic pattern of subclinical hypertension-related organ damage [304]. Excess weight in children is also associated with decreased diastolic function, microalbuminuria, and increased intima-media index, as well as an increase in vascular rigidity [305–308].

Amongst the ill effects of obesity on the vascular system, atherosclerosis is one of the key mechanisms involved. This process begins during early childhood, as demonstrated in postmortem studies by the presence of lipidic striae on coronary arteries even in the first decade of life [309,310]. The initial lesions are progressive in nature and lead to the formation of atherosclerotic plaques, sometimes even reaching the form of advanced lesions

such as fibrotic plaques as early as adolescence [309]. The inceptive subclinical vascular deterioration can in time lead to the illnesses typically linked to atherosclerosis: coronary heart disease, peripheral artery disease, and cerebrovascular disease [311,312]. Obesity accelerates the process of atherosclerosis [313] and its presence in childhood increases the risk of developing atherosclerosis-related diseases in adulthood [314,315]. The risk can, however, be reduced in obese patients who manage to achieve adequate weight loss, which acts as an incentive for the development of efficient and timely preventive programs [316,317].

From a metabolic standpoint, there are several modifications relevant to the interrelation between obesity and cardiovascular risk. The increase in insulin resistance in children shows similar pathways with adults and is a fundamental phase in the pathogenesis of type 2 diabetes and is more frequent amongst obese individuals, even more so the sooner the onset of weight excess [318,319].

Dyslipidemia is yet another metabolic disturbance frequently associated with obesity. Obese patients frequently manifest a typical pattern of hypertriglyceridemia, hyper-LDL-cholesterolemia, and hipo-HDL-cholesterolemia. Obese children exhibit a similar pattern, however, hyper-LDL-cholesterolemia is not as frequent in this population. In children, hypertriglyceridemia generally responds well to the reduction in artificially sweetened foods and beverages [319,320].

9. Obesity Biomarkers and Risk Assessment

The use of biomarkers can mitigate risk assessment in obesity and provide useful information regarding the mechanisms that generate weight excess and how the latter can negatively influence health. A brief overview of such biomarkers follows.

9.1. Genetic and Epigenetic Biomarkers

Messenger RNA (mRNA) levels corresponding to the genes coding the receptor for leptin, insulin, and CPT1A (Carnitine Palmitoyl transferase 1 A) have shown increased levels in obese children compared to children with a normal weight, while the mRNA levels of SLC27A2 (very long-chain acyl-CoA synthetase) had lower values in overweight individuals [321].

MicroRNA(miRNAs) are molecules of noncoding RNA nucleotides that regulate the genes' expression post-transcription. The literature is scarce regarding these biomarkers in obese children compared to current reports in adults. Nevertheless, in a recent systematic review, Oses M et al. identified six mi-ARN overexpressed in obese children and associated with other adiposity biomarkers: (1) miR-34a, miR-122 (obese children with insulin resistance or nonalcoholic fatty liver disease), (2) miR- 140-5p,142–3143 (obese children). All of them had a significant correlation with BMI values; however, miR-122 seems to play a crucial role in cholesterol and fatty acids regulators in the liver [322].

The expression of specific genes in epiploic adipose cells that code for microtubule-associated protein tau (MAPT), destrin (actin depolymerizing factor–ADF or DSTN), spectrin β non-erythrocytic 1 (SPTBN1), Rho/Rac Guanine Nucleotide Exchange Factor 2 (ARHGEF2), and spindle and kinetochore-associated protein 1 (SKA1) have been linked to childhood obesity [323].

9.2. Inflammatory Markers

The most common inflammatory markers associated with obesity include tumor necrosis factor alpha (TNFα), interleukin-6 (IL-6), and c-reactive protein (CRP). In obese children, elevated CRP levels correlate with insulin resistance and intima-media thickness. CRP, IL-6, and TNFα are frequently elevated in obese children with risk factors for atherosclerosis. IL-6 has been associated with hyperinsulinism, insulin resistance, BMI, and abdominal circumference values. These correlations serve to quantify the known link between inflammation and obesity within the spectrum of cardiovascular risk [81,324].

The neutrophil to lymphocyte ratio (NLR) can serve as a marker for cardiovascular risk. NLR has shown a particularly strong relationship to the evolution of coronary heart disease, including response to treatment. The implicated mechanisms that provide a rationale to using the NLR refer on the one hand to the contribution of neutrophils in nonspecific inflammatory response, with a value that correlates with oxidative stress in the organism even before reaching cut-off values for neutrophilia. Lymphocyte number, on the other hand, provides a good image of the overall immune responsiveness of the body, and their reduction can indicate a hindrance of the capacities of the immune system [325–329].

The NLRs value correlates with vascular parameters in children and is indicative of the inflammatory processes involved in the initial phases of atherosclerosis [325,326].

A further argument that strengthens the parallel nature of the evolution of weight excess and inflammatory state is that dietary measures implemented to reduce adipose surplus may have a beneficial effect on relieving the proinflammatory status associated with obesity as well [330].

9.3. Serological Markers

Given the key implications of leptin in the mechanisms governing appetite and weight regulation, it becomes evident that measuring its circulating levels could aid in tracking the evolution of weight excess. Leptin levels may also aid in evaluating an individual's responsiveness to weight reduction programs [331].

In addition to leptin, adipocytes secrete a wide array of biologically active factors, or adipokines. FABP4 falls into this category. FABP4 has been linked to weight control, metabolism, and formation of atherosclerosis, and has demonstrated increased circulating levels in patients with obesity, cardiovascular diseases, or metabolic syndrome [130,332]. Adiponectin is an adipokine with antiatherogenic, anti-inflammatory, insulin-sensitizing, and cardioprotective effects. Its serum concentration can provide details regarding the atherosclerotic process in children, as its decrease correlates with premature thickening of carotid walls in pediatric subjects, as well as regarding insulin sensitivity assessment, due to its relation to circulating insulin levels and the HOMA-IR [333].

HOMA-IR, defined as: $\frac{\left(\text{Serum glucose}\left(\frac{\text{mmol}}{\text{L}}\right)\right)\cdot\left(\text{Serum insulin}\left(\frac{\mu\text{UI}}{\text{mL}}\right)\right)}{22.5}$ can, in and of itself, provide information on the initially subclinical stages of diabetes, particularly in obese patients [334].

The atherogenic index of plasma (AIP), defined by the following formula:

$\text{AIP} = \lg\frac{\text{Serum Triglycerides (mmol/L)}}{\text{Serum HDL cholesterol (mmol/L)}}$, is a good measure of the balance between the harmful effects of hypertriglyceridemia and the cardio-protective properties of HDL-cholesterol. AIP has shown a potentially stronger correlation to cardiovascular risk when compared to its individual components, and may aid in the quantification of treatment response [335–337].

Certain markers for hepatic injury also foretell the ill effects of obesity on metabolism. An increase in ALT (alanine aminotransferase) levels has been linked to insulin resistance and altered glucose tolerance as well as to increased levels of circulating free fatty acids and triglycerides [338]. The AST/ALT (aspartate aminotransferase/ALT) ratio has been proposed as a potential marker for screening adolescents with increased cardiometabolic risk. Gama-glutamyl peptidase (GGT) may also provide useful information regarding hepatic involvement in obesity [339].

Other potential biomarkers for obesity include isoleucine, glyceric acid, serin, 2,3,4-trihydroxybutyric acid, and phenylalanine [301].

10. Conclusions

Given the points presented in this review, one can conclude that obesity is much more than just a simple disproportion between weight and height. A thorough understanding of the epidemiology and the mechanisms involved in the genesis of this illness is necessary in order to identify potential key points in which preventive or therapeutic action can be

implemented. The collection of information summarized in this review may hopefully be of aid in providing a structured approach to the current knowledge on this subject.

Author Contributions: Conceptualization, M.O.N. and B.N.; methodology, M.O.N. and B.N.; validation, C.D.D.; formal analysis, M.O.N. and B.N.; investigation M.O.N., B.N., I.D., C.R.S., R.M.C., B.I.C., C.D.D. and M.T.; resources, M.O.N., B.N., I.D., C.R.S., R.M.C., B.I.C., C.D.D. and M.T.; data curation, M.O.N.; writing—original draft preparation, M.O.N., B.N. and I.D.; writing—review and editing, M.O.N., B.N., I.D., C.R.S., R.M.C., B.I.C., C.D.D. and M.T.; visualization, M.O.N., B.N., C.R.S. and M.T.; supervision, C.D.D.; project administration, M.O.N. and B.N.; and funding acquisition, M.O.N., B.N., I.D., C.R.S., R.M.C., B.I.C., C.D.D. and M.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethics Committee) of the Pediatric Clinical Hospital Sibiu (protocol code 6731/05.10.2021).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the paraclinical investigations displayed.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to data protection legislation.

Acknowledgments: This work is part of the Ph.D. thesis of candidate Mihai Octavian Negrea under the supervision of Domnariu Carmen at the Lucian Blaga University. We would like to acknowledge the work of Irina Ioana Negrea for her contribution regarding the design of Figure 12. All rights for this figure have been transferred to the authors.

Conflicts of Interest: The authors declare no conflict of interest.

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