UNIVERSITATEA LUCIAN BLAGA DIN SIBIU

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DOCTORAL THESIS

CONTRIBUTIONS TO ASSESSING THE IMPACT OF OBESITY ON CARDIOMETABOLIC RISK IN CHILDREN AND ADULTS: A MULTIDISCIPLINARY APPROACH BASED ON CLINICAL, ENVIRONMENTAL STUDIES, AND PREDICTIVE ANALYSES

ABSTRACT

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MOTIVATION FOR TOPIC CHOICE

The myriad advantages of recent astonishing advancements have significantly transformed the world into what we recognize today. However, along with this progress, a profound chasm has emerged between populations that have been integrated into this technological success and those that have not enjoyed the same opportunities.

Medicine, as a discipline, has naturally experienced a similar trajectory. In areas once considered the cradle of our civilization, infectious diseases continue to be the primary causes of mortality. In contrast, developed parts of the world face a different epidemic: that of cardiovascular mortality. The shift in global morbidity/mortality profiles has directed substantial efforts towards new pathological entities that have taken precedence in incidence. Furthermore, there is an increasing emphasis on disease prevention rather than just treatment. Fundamental to this approach is an in-depth understanding of risk factors involved in pathogenesis and controlling them before a disease becomes overt.

In this context, obesity stands out as one of the most alarming risk factors, due to its increasing incidence and its close association with a wide range of cardiovascular ailments. In recent years, the prevalence of obesity has reached alarming levels. Regrettably, this trend is evident even among children – offering a grim perspective on the future global burden of this ailment.

Addressing this issue is imperative and should be a priority in preventive medicine. However, the responsibility for preventative measures doesn't solely lie with individuals. Broad public interventions are needed, capable of significantly influencing the multitude of objective factors that can exacerbate early risks – ranging from familial socio-economic conditions to education, exposure to temptations, and school environments. As Gro Harlem Brundtland, former Prime Minister of Norway, asserted, *“Obesity is a global public health issue requiring global solutions”*.

In essence, these are the primary arguments underpinning the research encompassed in this doctoral thesis. The highly intricate nature of the issue, combined with the multitude of factors and facets involved, has led to the broad diversity of studies presented. The research commenced with an extensive literature review on potential causes of childhood and adolescent obesity and mechanisms leading to cardiometabolic diseases in adults. Socio-economic and educational aspects were then explored by adapting and applying the ISCOLE questionnaires in Sibiu, yielding significant results concerning potential individual and system-level preventive actions. Subsequent clinical-level studies employed advanced statistical techniques and artificial intelligence algorithms, including a risk profile analysis in ischemic coronary disease, exploration of the link between IGF-1 and obesity, an efficiency analysis of adipose tissue segmentation on MRI scans, and an assessment of predictors for glycemic control in children with Type 1 diabetes.

In the author's opinion, the inclusion of these studies aligns with the primary objective of this doctoral research: to objectively demonstrate, backed by advanced statistical techniques, the existence and intricacy of the obesity issue, its measurable risks, and the often-addressable solutions at both individual and societal levels related to this problem.

PART I. CURRENT STATE OF KNOWLEDGE

Cap. 1. Obesity. General Aspects, Etiology and Pathogenesis

1.1 General aspects – Definition and epidemiology

he World Health Organization (WHO) defines obesity as an „abnormal or excessive fat accumulation that presents a risk to health” (1). The quantification of weight status in adults is determined using the Body Mass Index (BMI): $BMI = \frac{\text{Weight}}{\text{Height}^2}$ (2).

Quantifying obesity in children can be problematic for several reasons. Childhood and adolescence, with the latter defined by the WHO as “the phase of life between childhood and adulthood, from ages 10 to 19” (3), are characterized by a series of significant physiological and somatic changes in relatively short time spans. While in adults, establishing normative values through the statistical analysis of anthropometric parameters can provide satisfactory approximations, pediatric populations tend to exhibit greater inhomogeneity in relation to several confounding factors such as age, gender, pubertal stage, and even ethnicity (4,5).

The currently accepted method to determine a child's weight status involves the use of weight charts recommended by both the CDC and WHO, which account for the influence of age and gender. For children under the age of 2, the use of BMI is not recommended. For this age group, body weight evaluation is done using gender-specific weight-for-height curves. A value exceeding two standard deviations above the median for this parameter, appropriate for age, defines overweight, while a value exceeding three standard deviations above the median defines obesity. However, for children aged 2 and above, it is advised to use age- and gender-specific BMI curves to ascertain their weight status. The CDC recommends the 85th and 95th percentiles as thresholds for overweight and obesity, respectively. For children older than 5 years, the World Health Organization defines overweight as a BMI-for-age greater than one standard deviation above the age-specific median and obesity as a BMI-for-age greater than two standard deviations above the median (6,7).

The prevalence of childhood obesity is on the rise globally, especially in urban areas (2). In 2019, it was estimated that 38.2 million children under the age of 5 were overweight or obese. The prevalence of overweight and obesity among children and adolescents aged between 5 and 19 years saw an alarming rise, from 4% in 1975 to approximately 18% in 2016. Both genders were similarly affected by this increase (2,8).

1.2 Ethiology and pathogenesis

The imbalance between energy intake and expenditure is typically cited as the primary factor in the etiology of obesity. When caloric intake exceeds expenditure, the excess is stored as lipids in adipose tissue, and chronic exposure to this imbalance leads to an increase in adipose mass (2). However, the current understanding suggests that the etiology of excess body weight goes beyond this simplistic approach.

1.2.1 Neurohormonal regulation of appetite

The sensation of hunger results from a complex interaction between the central nervous system, which plays a pivotal role due to certain hypothalamic nuclei, and a large number of hormones, many of which are secreted by the gastrointestinal tract (9, 10).

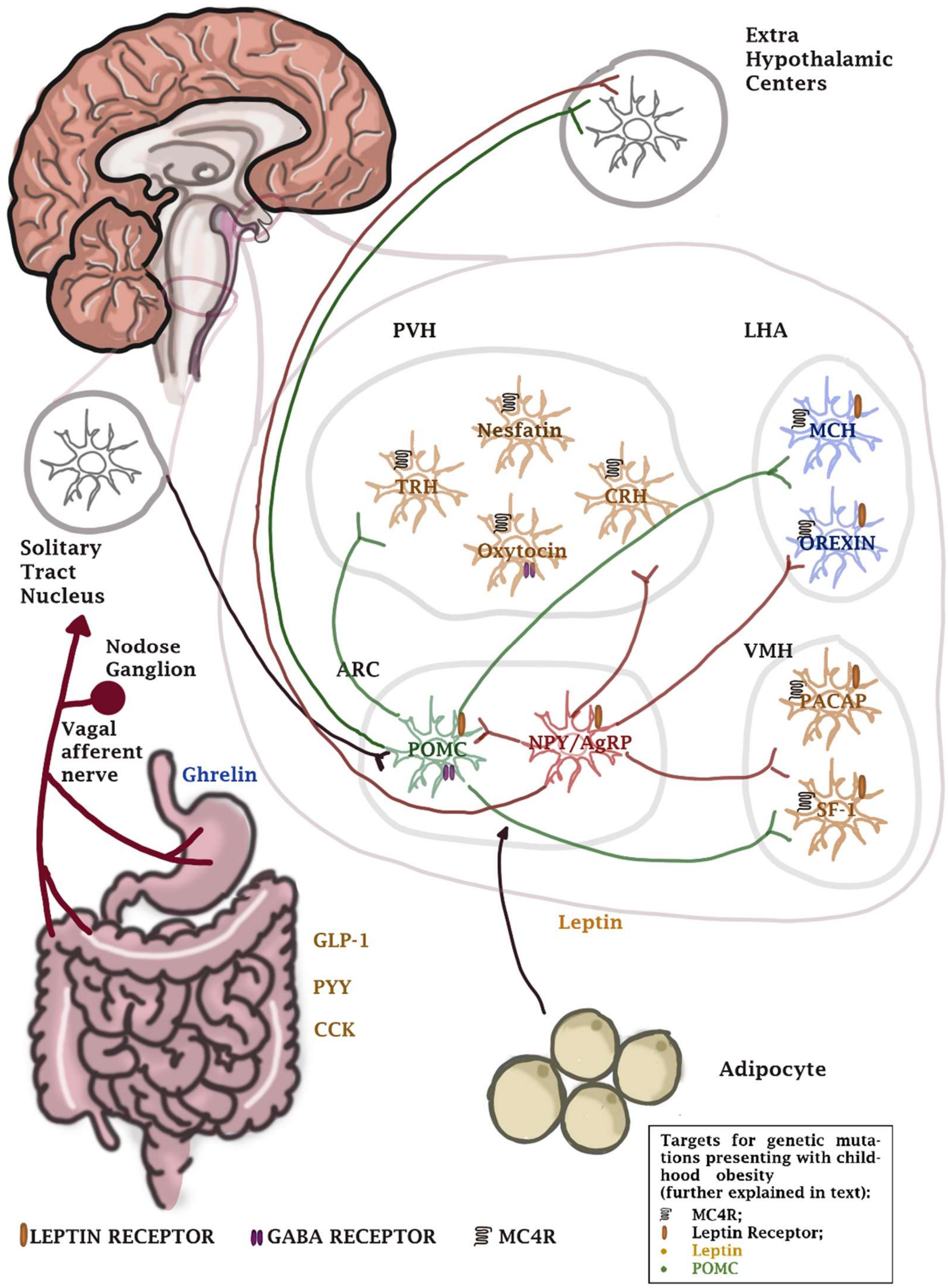


Figure 1 – Neurohumoral regulation of appetite. POMC – proopiomelanocortin, ARC – arcuate nucleus, a-MSH – melanocyte-stimulating hormone, MC4R – melanocortin receptors, PVH – paraventricular nucleus, VMH – ventromedial nucleus, LHA – lateral hypothalamic area. NPY – neuropeptide Y, GLP-1 – glucagon-like peptide-1, PYY – peptide YY, CCK – cholecystokinin, GABA – gamma-aminobutyric acid. Red lines represent inhibitory pathways, and green lines represent stimulatory pathways. Hormones and peptides in blue text have an overall stimulating effect on appetite, while those in orange text have an inhibitory effect in this regard.

1.2.2 Genetics of obesity

Over 500 genetic loci have been associated with obesity-related traits in a genome-wide association study conducted on nearly 700,000 individuals (11,12). Noteworthy examples include genes associated with fat mass and obesity (FTO), which are highly expressed in the arcuate nucleus. The FTO genotype correlates with weight status in children (13), dietary habits (14–16), and may also play a role in the distribution of subcutaneous and visceral adipose tissue, along with the associated cardiometabolic risk (17). Other examples include OLFM4 and HOXB5. These genes impact the development of the gastrointestinal tract and hence can influence the intestine-regulated appetite signaling (18,19). The PCSK1 gene encodes for PCI (prohormone convertase 1) and is involved in the synthesis of aMSH from POMC. Defects at this level may result in a form of early-onset obesity (20,21). It has also been found to be poorly expressed in Prader–Willi syndrome (20). Genes involved in the development of other syndromic forms of early-onset obesity are also pertinent in understanding both the normal weight regulation pathways and the multifaceted components of non-syndromic multifactorial obesity. ALMS1 mutations associated with Alström syndrome, for instance, demonstrated a link between adipose tissue growth and insulin resistance (22,23). In Bardet-Biedl syndrome, genetic defects lead to a ciliopathy which may be involved in impaired leptin signaling, possibly explaining the severe leptin resistance seen in these patients. The primary mechanism leading to obesity in Bardet–Biedl patients relates to appetite disruption (24).

Along with the discovery of genetic diseases with implications on weight excess, there are additional facets emphasizing the significance of genetic predisposition in obesity. The fact that the majority of obese pediatric patients come from families where one or both parents are overweight is a testament to the intricate interplay between genetic and environmental factors (25). Beyond the hereditary influence of obesity, the often-observed familial nature of obesity can be attributed to exposure to risk factors associated with the environment created by cohabiting with family members. Sedentary lifestyles, inefficient time management, and unhealthy eating habits are all accountable for altering the lifestyle of younger family members and are influenced by a plethora of socio-economic and cultural factors (26). However, multiple arguments underscore the importance of genetic determinism in obesity. One such argument pertains to twin studies suggesting that the concurrence of obesity in monozygotic twins seems to be irrespective of environment (27). Another point is brought forth by studies on adopted children who display a weight pattern more similar to their biological parents than to their adoptive ones (28).

Lastly, another hypothesis worth considering is the "thrifty gene" theory. The underlying premise posits that, throughout evolution, a genetic arsenal adapted to create energy stores during times when nutrition sources were scarce was an advantage for survival. This same genetic configuration has become a significant disadvantage in modern times (29).

1.2.3 Vulnerable periods

Exposure to various factors during specific vulnerable periods is crucial. These periods include pregnancy, infancy, early childhood, as well as the preschool, school-age, and adolescent stages. Each of these phases has unique characteristics regarding increased susceptibility to certain environmental factors – from intrauterine exposures to toxins to peer influences in adolescence (30).

1.3 Imbalance between caloric intake and energy expenditure

The adoption of a socio-ecological model for the etiology of obesity not negate the well-established foundation of this pathology related to the imbalance between increased caloric intake and deficient energy expenditure. This balance continues to play a central role in the development of obesity.

One approach to caloric intake can be structured into three main directions: one focused on the quantity of consumed food, a second on its quality, specifically regarding the caloric content of each item and the ratio of macro and micronutrients in the diet, and a third on the rhythm or timing of calorie intake.

Adequate energy consumption is key to maintaining a normal weight. The balance between active and sedentary intervals is essential in this respect, regardless of age. In this context, screen time for non-academic activities represents a significant risk factor for obesity (31–33). Rest is equally important for achieving balanced growth. Among adults, sleep deprivation has been linked to obesity due to reduced circulating leptin levels and increased ghrelin synthesis, thereby elevating appetite and inducing insulin resistance (34, 35). The relationship between obesity and sleep deprivation also holds for children (36–43). Elevated cortisol levels and imbalances in growth hormone associated with insufficient sleep contribute to weight gain (44).

In essence, energy expenditure can be organized similarly to caloric intake, considering the quantity, quality, and rhythm. This pertains to the amount of time spent engaged in physical activity or rest, the quality of both activities, where moderate to high-intensity activity is preferred for physical exertion, and prioritizing sleep over screen time for rest periods. Integrating all these components into a healthy circadian rhythm can be vital for weight balance.

Other significant factors affecting the ability to regulate the balance between intake and energy expenditure include endocrine disorders, iatrogenic interventions and therapies with obesogenic potential, and various psycho-behavioral and socio-cultural aspects that can lead to obesity.

1.4 Obesity fenotypes and distribution

The distribution of body fat plays a crucial role in determining the detrimental effects of excess adiposity on the body. Certain features related to the anatomical location of fat surplus deserve attention. One of the first noticeable aspects when examining an overweight patient is the superficial distribution of body fat, with a particular predisposition towards specific anatomical areas. The most basic categorization of superficial fat distribution distinguishes between android and gynoid obesity patterns. The distinction between the two becomes clear under the influence of sex hormones, typically during adolescence. Android obesity is characteristic of males and involves fat distribution around the central body areas, especially the abdomen. In contrast, gynoid fat distribution predominantly affects the hips and thighs (45). Android obesity is typically associated with a greater accumulation of visceral adipose tissue, linked to a higher cardiovascular risk compared to gynoid obesity (46). Moreover, the excess adipose tissue presents different cardiovascular risk profiles depending on the anatomical depth of the surplus. This relates to the distinction between subcutaneous and visceral fat. The latter is accountable for a stronger correlation with metabolic effects and increased cardiovascular risk due to obesity (47). Visceral adipose tissue seems to play a role in increased leptin resistance and enhanced sympathetic tone, oxidative stress, and vascular calcification, all influencing the development of cardiovascular diseases (48). Central obesity has been found to be a potent risk factor for cardiometabolic disease, not only in adults but also in children and adolescents (49–55). Additionally, it appears to correlate more robustly with cardiovascular risk in children than obesity defined by BMI (56,57). Moreover, the onset of central obesity during childhood seems to persist into adolescence and adulthood (58–60).

The harmful effects of excess adipose tissue manifest both systemically and locally (61). Hence, beyond the general statement concerning the cardiometabolic risk associated with predominant visceral fat in obese individuals, it has become evident that a specific predilection of fat disposition involving certain areas or organs can elevate the risk of developing particular diseases. One example is the mechanical effect of predominant intraabdominal adipose excess, which can precipitate the development of several gastrointestinal diseases, such as gastroesophageal reflux or hiatal hernia. The same conditions can promote chronic venous insufficiency due to venous system compression (62). Besides the mere local mechanical effects of adipose surplus, local functional effects may also be involved in the mechanisms leading to various pathologies. These relate to the secretion of pro-inflammatory and prothrombotic adipokines (63,64), local induction of hypoxia (65), fibrosis (66), and mitochondrial function impairment (67). Several specific sites of adipose tissue excess are known to have heightened harmful effects. Perihepatic adipose tissue excess is also associated with intracellular lipid deposits in hepatocytes, damaging at this level. The resultant pathological entity was recently defined as non-alcoholic fatty liver disease, frequently linked with metabolic syndrome and weight excess (68,69). Another relevant example of local effects of adipose surplus involves epicardial adipose tissue, whose excess is known to correlate with ischemic coronary disease, heart failure, arterial hypertension, left ventricular hypertrophy, dyslipidemia, and insulin resistance (70–75). Another noteworthy location pertains to perivascular adipose tissue, whose abundance around peripheral vessels correlates with increased insulin resistance (76). Another significant site of adipose surplus is around the kidneys. Excess perirenal adipose tissue can induce elevated intrarenal pressure, potentially affecting or exacerbating glomerular filtration function, leading to microalbuminuria. This adipose tissue is involved in various cardiometabolic risk-related processes, including regulating renal vascular tone and inflammatory marker secretion (77).

1.4.1 Histology

The adipocyte is the fundamental cellular unit of adipose tissue. Beyond its storage role, adipocytes operate as part of a system akin to an independent endocrine organ, secreting a broad variety of peptides and metabolites involved in weight regulation. Alongside metabolic functions achieved through enzymatic pathways involved in beta-oxidation and free fatty acid metabolism, many of the adipokines secreted by these cells exert a pro-inflammatory and pro-coagulant influence. Other peptides are involved in insulin resistance and apetite regulation, significantly impacting body weight and the cardiovascular risk associated with obesity. Many substances secreted by adipocytes have yet unexplored roles and are of keen interest to medical research (78).

Adipose tissue is predominantly cellular in nature. The adipocytes conglomerating to form this tissue can respond to external stimuli inducing lipid deposit accumulation either by increasing their individual sizes or by augmenting the physical cell count. The growth in adipocyte size defines their hypertrophy. This response type is typically seen in android obesity characterized by significant visceral fat proportions. Hypercellular obesity, on the other hand, has a more variable character, often identified in individuals who become overweight during childhood. However, it is almost always present in severely obese patients, regardless of age. Hypertrophic obesity usually develops in adulthood and closely correlates with cardiovascular risk. This obesity type generally responds well to weight interventions, which are typically ineffective in hypercellular adiposity. This particular resistance to treatment is one of the principal aspects underlining the need for strong preventive action from childhood (79).

1.5 Obesity-related cardiometabolic complications

In adults, there is a well-documented link between obesity and a wide range of cardiovascular diseases, including coronary heart disease, hypertension, cerebrovascular disease, atrial fibrillation, ventricular arrhythmias, and sudden cardiac death (61,80). Moreover, obesity leads to the development of a number of conditions that are in themselves individual risk factors for cardiovascular diseases, such as type 2 diabetes, dyslipidemia, and obstructive sleep apnea. From this perspective, obesity is more than just an isolated condition and can be better described as an entire dismetabolic and mechanically flawed conglomerate (81–83).

The pathophysiological pathways leading from obesity to cardiovascular impairment involve both direct and indirect mechanisms, with local and systemic actions (80). Hemodynamically, the adaptive changes of the cardiovascular system are synonymous with the structural and functional changes imposed by the increase in circulating volume and the metabolic overload attributable to the excess adipose tissue. The result is a hyperdynamic cardiovascular system constrained to adapt the cardiac output by increasing the ejection volume and heart rate. Peripheral vascular resistance, in turn, increases due to sympathetic hyperreactivity and the systemic pro-inflammatory status associated with obesity. All these changes lead to cardiovascular remodeling, predisposing to the development of a plethora of cardiovascular diseases, including hypertension (84), left ventricular hypertrophy, heart failure (85–87), and even atrial fibrillation (88). The initiation of cardiac remodeling is a relatively early process, as demonstrated in studies identifying manifestations of this type in obese children (89) and may occur well before the clinical onset of cardiovascular diseases.

Among the harmful effects of obesity on the vascular system, atherosclerosis is one of the key mechanisms involved. This process begins in early childhood, as post-mortem studies have shown by the presence of lipid streaks in the coronaries even in the first decade of life (90,91). The initial subclinical vascular deterioration can progress over time to diseases characteristic of advanced atherosclerosis: ischemic coronary disease, peripheral artery disease, and cerebrovascular disease (92,93). Obesity accelerates the process of atherosclerosis (94) and its presence in childhood increases the risk of developing atherosclerosis-related diseases in adulthood (95,96). The risk can, however, be reduced in obese patients who achieve adequate weight loss, a fact that should encourage the development of effective and early prevention programs (97,98).

Metabolically, there are several changes relevant to the interrelationship between obesity and cardiovascular risk. The increase in insulin resistance in children occurs through mechanisms similar to adults and is a fundamental phase in the pathogenesis of type 2 diabetes. Insulin resistance is more common in obese individuals, especially when the onset of weight excess is earlier (99,100).

Dyslipidemia is another metabolic disorder frequently associated with obesity. Obese patients often display a typical pattern of hypertriglyceridemia, hyper-LDL-cholesterolemia, and hypo-HDL-cholesterolemia. Obese children present a similar pattern, though hyper-LDL-cholesterolemia is not as common in this population. In children, hypertriglyceridemia generally responds well to the reduction of refined sugar intake (100,101).

Cap. 2. Diagnosis and Risk Evaluation

2.1 Anamnesis and clinical examination

As in any pathology, a detailed medical history plays a crucial role in identifying the factors that have led to the onset of obesity, existing comorbid conditions, potential secondary causes for obesity, and for an exhaustive characterization of each patient's risk profile. Through this process, any iatrogenic causes of obesity should also be identified.

The symptomatology associated with obesity can be related either to the primary cause of this pathology or to complications resulting from excess weight. Significant family history reveals, on the one hand, a rough estimate of an individual's genetic load, and on the other hand, data related to the environmental factors to which they have been exposed by growing up in a particular family environment. Additionally, through medical history, information can be gathered regarding eating habits, the sleep-wake cycle, sedentary lifestyle or regular physical activity, and non-academic screen times. All these factors can provide insights into the risk of developing various pathologies related to obesity. Furthermore, potential targets for reducing this risk can be identified through the lens of modifiable risk factors (102). Additionally, a more precise picture of obesogenic exposures present in everyday life, including in the school or social environment, can be outlined. An effective method to standardize the process of collecting anamnestic data is based on formulating questionnaires or scales to guide the medical history (103,104).

A comprehensive identification of risk factors for the development of obesity includes, in pediatric patients, an assessment of exposures during pregnancy, birth circumstances, and nutrition in the breastfeeding period (105–110).

The physical examination also plays a significant role in identifying secondary causes of obesity or complications that have arisen as a result of it (102). Assessing pubertal status can provide important information for diagnosis, identifying elements of sexual development often intertwined with the obese status of patients. The systematic physical examination of systems and organs must identify the characteristic signs of comorbidities and complications associated with obesity (111,112).

2.2 Paraclinical investigations, quantifying obesity

Etiological suspicions raised during the anamnesis and physical examination play a significant role in establishing the necessary further specific examinations in cases where the clinical picture is suggestive of an endocrinopathy or a genetic cause. Identifying a secondary cause of obesity requres characteristic therapeutic approaches. In the case of endogenous obesity or through multifactorial determinism, with a significant involvement of the energy-metabolic imbalance between intake and expenditure, a multidisciplinary approach is required. Establishing a complete diagnosis also includes identifying complications or comorbidities present due to or associated with obesity.

The use of the Body Mass Index (BMI) in everyday practice has the advantage of accessibility, as its determination is straightforward. It provides an acceptably comprehensive view of weight status from the perspective of the risk associated with obesity. The relationship of the BMI with cardiovascular risk has been validated in repeated studies, highlighting a U-curve profile, with the existence of an optimal range for this parameter's values. This range is bounded, on the one hand, by underweight, associated with its own spectrum of comorbidities, and on the other, by overweight and obesity (113,114). However, this parameter does not provide information related to body composition, disregarding the contribution of muscle mass and the degree of bone mineralization in the weight determinism of patients, aspects of great significance, especially in the pediatric population where the mentioned variables are continuously changing during the growth process. Moreover, standardized curves for BMI highlight percentiles for its values only in relation to age and sex, without taking into account the significant variability and the wide range considered normal for height at a certain age, which in turn represents an important indicator of developmental status and, consequently, of variable body composition. The same aspect of variable body composition has been identified in different races (115).

In this context, significant efforts have been made in researching methods that better assess obesity in children, with the desire to identify parameters that correlate more closely with the risk associated with obesity, as presented in the following sections, adapted Horan et al (116).

2.2.1 Inferential methods

These methods rely on measurements made with relatively simple instruments, based on which the weight status of a patient can be deduced with acceptable precision. This type of methods includes skinfold thickness measurements and a series of anthropometric indices. The latter category encompasses measurements such as the BMI, waist circumference, waist-hip ratio, waist-height ratio, ABSI (A Body Shape Index (117)), neck circumference, and so forth. Each of these measurements presents certain advantages and disadvantages or stronger associations with certain pathologies. Measuring skinfold thickness in predetermined areas of the body is a technique that can be used in adults to estimate the percentage of adipose tissue at the body level. However, the heterogeneity of the pediatric population poses significant challenges related to the applicability of standardized equations. The method requires particular rigor in conducting measurements and, for this reason, presents a relatively steep learning curve (118–127).

2.2.2 Methods of determining body composition

These methods are useful for determining the percentage of body fat, yet they do not provide data regarding the distribution of adipose tissue. The techniques used for this purpose are succinctly presented in Table 1.

Method	Functioning Principle	Advantages	Disadvantages	Reference
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	(128–130)
Bioelectrical impedance analysis	Variable electrical imped-ance 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	(131–135)

Method	Functioning Principle	Advantages	Disadvantages	Reference
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 patients Problematic adherence to measuring protocol of pediatric patients	(136–139)
Air displacement plethysmography	Determining body density by measuring different parameters obtained during a series of thermodynamic processes.	Non-invasive Very good adherence to measurement pro-tocol 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 pro-cesses involved	(140–148)
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 con-tent 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	(149,150)

Table 1 – Methods of determining body composition

2.2.3 Imaging methods

2.2.3.1 Overview

While the methods enumerated so far provide an overall picture of the adipose tissue content at the body level, the imaging techniques used in defining weight status primarily aim to differentiate between visceral fat tissue and somatic fat tissue. For this reason, the information provided by these two types of methods is complementary in nature. The imaging techniques useful for this purpose are synthesized in Table 2.

Metoda	Principiu	Avantaje	Limite	Referințe
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 meas-urement protocol Insufficient data on pediat-ric patients	(151–155)
Computerized To-mography	Varying absorption of X-rays in different tissues Sectional imaging and 3D reconstruction	High accuracy	Contraindicated in pediatric patients for adiposity eval-uation due to high X-Ray exposure	(156,157)

Metoda	Principiu	Avantaje	Limite	Referințe
Rezonanța magnetică	Sectional imaging technique based on the behavior of pro-tons under the influence of a variable high-intensity elec-tromagnetic field	High accuracy Non-invasive	High cost	(17,158–167)

Table 2 – Imaging methods for quantifying weight status

2.2.3.2 Magnetic resonance imaging for adipose tissue quantification

Among the techniques used to quantify visceral adipose tissue, computed tomography (CT) is recognized as the gold standard (157,168–170). However, its use is limited due to radiation exposure, especially in pediatric patients. Magnetic Resonance Imaging (MRI) has emerged as a viable alternative, demonstrating comparable results (171–174). Several methods for quantifying abdominal visceral adipose tissue using MRI have been described (17,158,160–162, 166, 167, 174–187). Image manipulation generally involves a pre-processing stage, followed by a method for discriminating between adipose and non-adipose tissue, as well as the background (167,178). Examples in this regard include the "thresholding" technique and Fuzzy C-means or K-means clustering analysis algorithm.

2.3 Evaluation of the cardiometabolic effects of obesity

The identification and assessment of clinical, serological, and imaging parameters that can provide information on cardiovascular risk are essential for early intervention and a tailored therapeutic approach in children with obesity. The following subsections detail these parameters, offering an integrated perspective on their complexity and relevance in the management of the pediatric patient with obesity.

2.3.1 Clinical parameters

The assessment of heart rate and blood pressure are clinical elements that may indicate the hyperdynamic status of the pediatric patient with obesity (111). This can be observed even in the preclinical stage, when, although values are still within normal ranges, they are on average higher compared to the normal weight population of the same age (112). Additionally, the clinical examination can reveal aspects related to liver impairment in the context of obesity, which can be clinically manifest in the form of fatigue and discomfort in the right hypochondrial area, sometimes accompanied by hepatomegaly (188).

2.3.2 Serological parameters

A wide range of serological determinations with known relevance for the development of cardiovascular pathologies have been described. The atherogenic lipid profile, identifiable through the determination of total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceridemia, is widely used in clinical settings to predict the cardiovascular risk of examined patients (99,189,190). However, a parameter that has not entered routine practice is the plasma atherogenic index (defined as the base-10 logarithm of the ratio between triglyceridemia and serum HDL-cholesterol). This parameter appears to have a closer correlation with cardiovascular risk compared to its individual components (191). Fasting blood glucose and glycated hemoglobin are determinations used for the diagnosis of diabetes mellitus, but they are also useful in defining the state of prediabetes or impaired fasting glucose - entities that forewarn the development of this pathology with significant and well-known cardiovascular impact (192,193). A parameter that can provide information about the preclinical stages of diabetes mellitus, especially in obese patients, is the insulin resistance index (HOMA-IR – Homeostatic Model Assessment for Insulin Resistance), defined as the product of glucose and basal insulin levels (112,194).

Withinn the context of metabolic impairment preceding cardiovascular pathologies, uric acid has been shown in certain studies to have a role that has been underestimated so far (195). The proinflammatory status also plays a significant role in the development of cardiovascular pathologies. The value of C-reactive protein is commonly used to provide information on the inflammatory status, which correlates with the presence of cardiovascular diseases (196,197). However, this determination (especially in its high-sensitivity form - hsCRP) has certain disadvantages related to costs for use in screening applications (198). For this reason, there have been attempts to define more accessible parameters to quantify chronic inflammation. A pertinent example in this regard is the neutrophil-to-lymphocyte ratio. This ratio correlates with a wide range of cardiovascular diseases, as well as with the outcomes of therapeutic interventions within them, particularly concerning coronary artery disease. A possible explanation lies in the fact that neutrophils play a significant role in the nonspecific inflammatory response, and their increase (even before exceeding the thresholds of normal values) reflects the increase in oxidative stress at the body level, while the decrease in the number of lymphocytes correlates with a more precarious overall status of immunity (199–203). Other factors related to the proinflammatory (and thus protrombotic) status are the platelet-to-lymphocyte ratio and the width of platelet distribution (204).

Regarding the unmasking of liver impairment, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) may show increases between two and five times over the upper normal limit, but values within the normal range do not eliminate the potential presence of MASLD, even with significant impairment (205,206). The ratio between AST and ALT is usually below 1 (207) in MASLD. Alkaline phosphatase can indicate values up to double or triple compared to the upper normal level. Various combinations of clinical and paraclinical parameters are used to predict steatotic liver damage.

2.3.3 Imaging techniques

In recent decades, ultrasonographic techniques have become some of the most accessible resources in everyday clinical practice. Parameters determined through carotid ultrasound (intima-media index) and carotid Doppler examination (arterial stiffness indices) have repeatedly demonstrated their connection with the atherogenic process (208–210).

Arterial stiffness can be measured through the pulse wave velocity (PWV) at the aortic level. This parameter is a reliable surrogate for predicting cardiovascular events (211,212) and is considered the method of choice for estimating arterial stiffness, according to the European Society of Cardiology's guideline for the diagnosis and treatment of hypertension (213). There are non-invasive oscillometric methods that can be implemented for estimating PWV (214).

Cardiac ultrasound plays a crucial role in diagnosing cardiovascular pathologies in everyday practice, and the most modern innovations such as tissue Doppler and speckle-tracking technology have extended the field of applicability beyond usual determinations, with increasingly promising opportunities in the direction of risk stratification from the subclinical phase of cardiac impairment (215,216). Another imaging method used in heart investigation is cardiac MRI. It has a much more limited scope compared to ultrasonographic methods (especially due to reduced accessibility).

Abdominal ultrasound can be used to estimate the distribution of adipose tissue between somatic and visceral types by measuring the thickness of the subcutaneous adipose tissue layer and the preperitoneal fascia. The latter can be considered a surrogate for the visceral distribution of adiposity (151–153). Additionally, abdominal ultrasound can unveil liver impairment in its characteristic form associated with obesity through the presence of hyperechogenicity. The incorporation of more advanced techniques can refine the diagnosis of hepatic steatosis. Elastography (Fibroscan) is a pertinent example in this context (217).

Cap. 3. Data Management - The Role of Advanced Statistical Techniques and Machine Learning Algorithms

Retrospective studies most commonly implement bivariate analysis for exploring connections among collected data. This approach has the advantage of being easy to implement and has a relatively intuitive interpretation. However, it presents certain significant disadvantages, especially when it comes to small sample sizes or when exposed to multicollinearity or confounding factors. Although essential for identifying potential risk factors, bivariate analysis fails to probe the complex interactions among the variables under study.

Certain advanced techniques deserve mention for the role they play in enhancing the utilization of data obtained in studies. Binary regression, for example, can provide relevant information regarding the prioritization of the importance of predictors identified in bivariate analysis. It is used to predict the value of a dichotomous dependent variable based on predictor variables.

Some artificial intelligence algorithms also have a potential role in refining results. Cluster analysis, for example, can identify patient groups where risk factors conglomerate, potentially necessitating specialized therapeutic approaches. The operating principle behind two-step clustering algorithms is based on first applying a pre-clustering stage using the k-means algorithm and then an agglomerative hierarchical clustering stage to classify cases based on similar characteristics, in terms of both categorical and continuous variables. In the first step, the algorithm traverses the dataset to create multiple small subgroups. This is achieved by measuring the distance between observations (218). The hierarchical clustering stage then merges the closest individual points to produce increasingly larger clusters. The final number of clusters and the most accurate model can be selected by calculating the Akaike information criterion (AIC) or the Bayesian information criterion (BIC).

Another example regards the CART (Classification and Regression Trees) algorithm, which can provide visual representations of complex interactions between variables to define subpopulations with particular characteristics. Decision trees like CART are supervised machine learning algorithms that classify data and reveal patterns of association for user-defined outcomes, also offering a visual representation of the model. This model's construction starts from the main root and advances through branching until no further divisions are possible, correlating all predictor variables with the tested outcome. These bifurcations arise from conditions (internal nodes) established on the predictor variables. The terminal nodes, so-called "child nodes" or "leaves" located at the end of a branch, represent the final resolutions given by the algorithm (219).

PART II. PERSONAL CONTRIBUTIONS

Cap. 4. Introduction

From the analyzed bibliographic sources, it is apparent that obesity plays a significant role in the determinism of multiple cardiometabolic manifestations. The effects seem to be more pronounced in the case of central obesity, particularly in the context of an increase in circulating free fatty acids as a determining factor of cardiometabolic repercussions. This aspect is outlined in Figure 2.

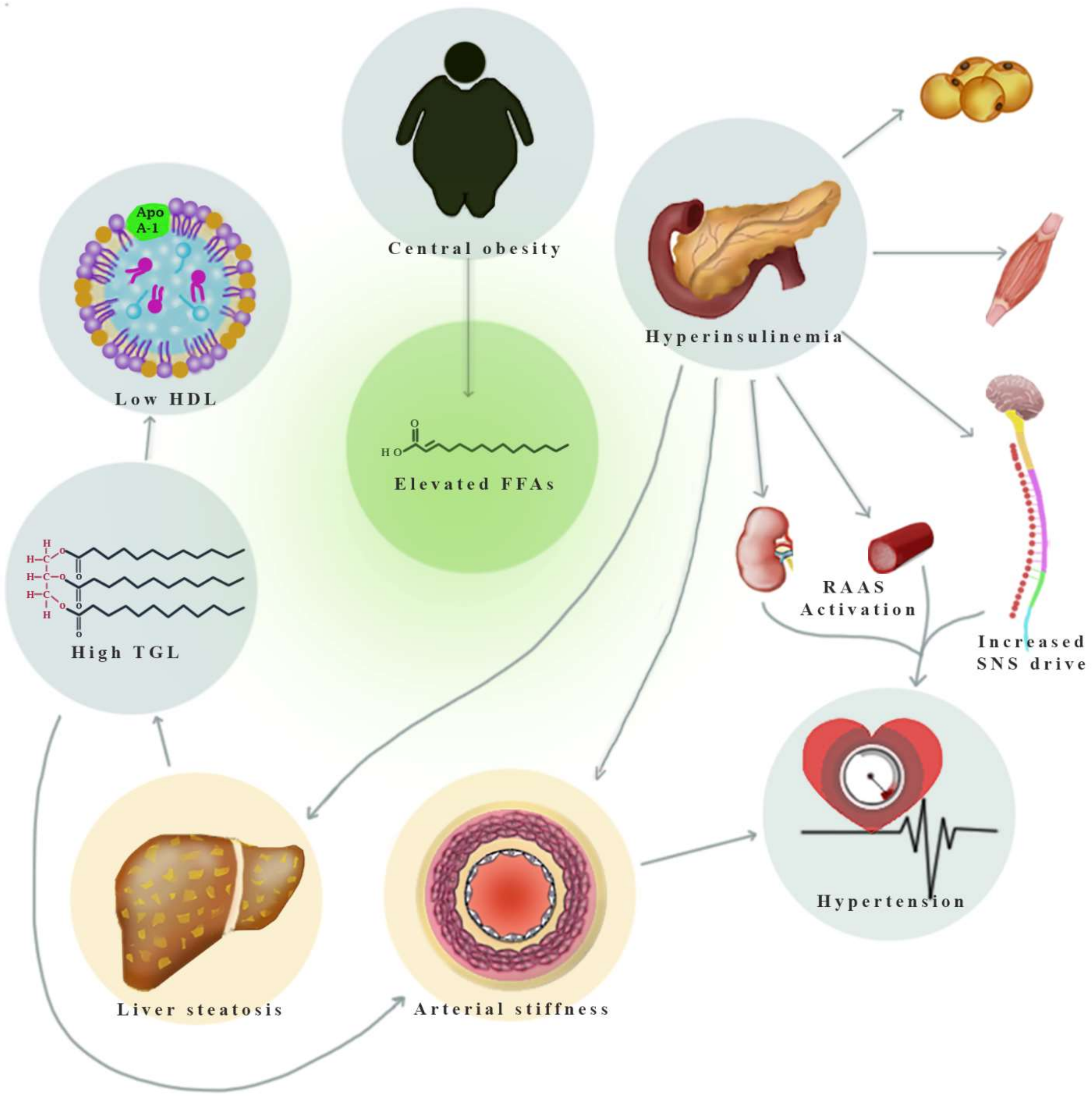


Figure 2 – Central obesity and FFA-mediated cardiometabolic effects (FFA – free fatty acids, TGL – triglycerides, RAAS – renin-angiotensin-aldosteron system, SNS – sympathetic nervous system)

The objective of the research was to explore the impact of obesity within the spectrum of cardiometabolic risks, emphasizing the implementation of advanced statistical techniques and machine learning algorithms where feasible to refine data interpretation. Concurrently, the study sought to explore methods that could enhance the assessment of defining parameters of obesity for a better understanding of this risk factor within its socio-ecological model of etiopathogenesis. In this regard, we investigated parameters related to the environment to which children and adolescents are exposed that could influence weight balance during these developmental periods, with the well-known potential long-term effects, to provide a public health-oriented perspective on the description of modifiable obesogenic factors. We then aimed to quantify the role of obesity within the spectrum of cardiometabolic risk in patients with cardiovascular and metabolic diseases, as well as to develop new perspectives on paraclinical assessment in children and adults with obesity.

4.1 General research methodology

The first step in achieving the objectives was to summarize the literature regarding current knowledge about overweight in children and adolescents as a cardiometabolic risk factor with lifelong effects. From this endeavor, several key aspects emerged, namely:

1) The necessity for comprehensive analyses of environmental factors leading to the onset of obesity, beyond the classic conception of the imbalance between intake and expenditure as the main etiological factor, and interpreting data within the context of the socio-ecological model of obesity's etiology. We chose to address this issue by adapting validated questionnaires to study the effect of exposures within the school environment that may impact students' weight balance. We applied the adapted lifestyle assessment questionnaires in a cross-sectional study of students from a high school in Sibiu. We conducted a second study using the adapted questionnaires to assess the school environment at schools throughout Sibiu county.

2) The necessity to identify the potential role of certain serological parameters that could be of interest in quantifying the cardiometabolic risk associated with obesity. In this regard, we explored the relationship between IGF-1 and weight status in children and adolescents in a retrospective observational study. This parameter has the potential to be used in assessing insulin resistance in children. Our goal was to quantify the relationship between IGF-1 and weight status as a potential confounding factor in children and adolescents at different stages of development.

3) The necessity to improve and increase the accessibility of methods for assessing adipose tissue disposition as a modulating factor of cardiometabolic risk. In this regard, we compared various techniques used in segmenting abdominal adipose tissue based on magnetic resonance imaging in a retrospective study. We pursued the efficiency of these parameters concerning the accurate quantification of the phenotypic expression of obesity in the form of visceral or somatic localization, depending on the demographic and anthropometric parameters of the examined patients.

4) The importance of risk stratification in cardiovascular pathology, regardless of age. In this context, we opted to conduct a retrospective observational study that targeted the exploration of patients with acute coronary syndrome without ST-segment elevation, in which we assessed various risk profiles depending on gender and clinical presentation.

5) The necessity to quantify the impact of obesity within the spectrum of exposures associated with cardiometabolic risk through advanced data processing techniques. This approach aims to provide a nuanced perspective on the clinical interpretation of the interaction among variables quantifying cardiometabolic risk, including weight status. We examined this approach in a retrospective study designed to assess the role of predictors for glycemic control in pediatric patients with type 1 diabetes, among which weight status was also considered.

The specific elements related to the research methodology, data organization, and statistical analyses employed are described in each conducted study in the "Materials and Methods" section.

4.2 Ethical aspects

The studies conducted within the research were in accordance with national and international requirements in the field of medical research on human subjects, adhering to the principles set forth in the Declaration of Helsinki. The study protocols were approved by the ethics committee of the Sibiu Clinical Hospital of Pediatrics (ref. no. 6731/05.10.2021). Patients involved in cross-sectional studies signed study-specific informed consent forms. Patients included in retrospective studies had signed consents at admission regarding the use of their personal data for medical education and research purposes. All personal data that the author had access to during the investigations were handled in strict compliance with the legal provisions in force concerning their protection.

4.3 Statistical analysis

Data analysis and visualization were carried out using Microsoft Excel® and IBM® SPSS® Statistics. Categorical variables were represented by frequencies and percentages, while continuous variables were described using means, standard deviations, and in some studies minimum and maximum values, interquartile ranges, and 95% confidence intervals for means. The normality of continuous variables was assessed using the Kolmogorov-Smirnov or Shapiro-Wilk tests and visual inspection of box-plot diagrams, Q-Q plots, and histograms. To compare groups, chi-square or Fischer's exact tests were used for categorical variables, while the independent t-test was applied to continuous variables with a normal distribution when comparing means between two independent groups. For continuous variables without a normal distribution, the Mann-Whitney U test was used. The degree of association between two continuous variables was investigated using Pearson's correlation coefficient (for normally distributed variables) or Spearman's rho (for variables without a normal distribution). Partial correlation was used to isolate the relationship between two variables of interest, taking into account the potential influence of other variables. When means were compared across three or more categories, the ANOVA test was used for variables with a normal distribution, and the Kruskal-Wallis test for variables that were not normally distributed. Variables from paired samples were compared using the paired t-test for variables with a normal distribution and the Wilcoxon signed-rank test for those that did not follow a normal distribution. The ANOVA with repeated measures or Friedman test was applied to investigate significant differences between the means of variables from paired samples. The significance threshold was set at an α level of 0.05. Linear regression was performed to rank associations between variables. Where linear regression was used, Bootstrapping with 10,000 samples was conducted to adjust the model in light of sample heterogeneity. The BCa method was used to calculate the 95% confidence interval for regression coefficients. To find optimal linear regression models, the successive and exhaustive addition and removal of predictor variables were attempted. Multinomial variables were recoded into dichotomous variables before being introduced into regression models. To check for the presence of multicollinearity, the variance inflation factor (VIF) was calculated. Values under 5 for this parameter were considered indicative of the absence of significant multicollinearity. For cluster-type analyses, the Akaike information criterion was used to select the optimal number of clusters. Successive and exhaustive addition or removal of variables was employed until a good average silhouette of cohesion separation (>0.5) was obtained. Variables with a predictive importance of at least 0.5 (+/- 0.01) were retained in the model. The CART algorithm, where used, was implemented using the "pruning" method to avoid overfitting, which internally uses cross-validation to select the best tree. Variables that did not contribute to prediction were removed to achieve the optimal model. Automatic selection of maximum growth levels (i.e., 5) was allowed, with 5 as the minimum number of cases for parent nodes and 3 for child nodes. Regarding the Gini impurity measure, a minimum change of 0.0001 was established with the maximum accepted difference in standard error risk set at 0.

Cap. 5. Literature review concerning Causative Mechanisms of Childhood and Adolescent Obesity Leading to Adult Cardiometabolic Disease

5.1 Introduction

The past decades have witnessed an alarming escalation in the prevalence of obesity and its associated ailments (220). This phenomenon significantly impacts global mortality and morbidity and also carries substantial economic implications (221,222). This trend is also notably pronounced in pediatric obesity (223), an especially concerning aspect considering the well-established link between cardiovascular diseases and obesity (224,225), as well as the tendency for weight issues in childhood to frequently persist into adulthood (226). Furthermore, the majority of obese adults have a history of weight excess commencing in childhood (227). Additionally, given the cumulative nature of time and the severity of exposure to obesity as a risk factor for related diseases, the repercussions of obesity and associated morbidity could potentially exhibit exponential characteristics over time (228).

Bearing these aspects in mind, it becomes evident that early intervention to prevent obesity and associated diseases is imperative. An accurate understanding of the underlying mechanisms that transition an individual from a state of health to obesity, and from obesity to associated illness, could be pivotal in formulating an effective strategy for action.

The aim of this literature review is to highlight the key aspects concerning current knowledge about obesity in children and adolescents as a cardiometabolic risk factor, as well as the most prevalent etiological pathways involved in the development of excess weight and related cardiovascular and metabolic diseases.

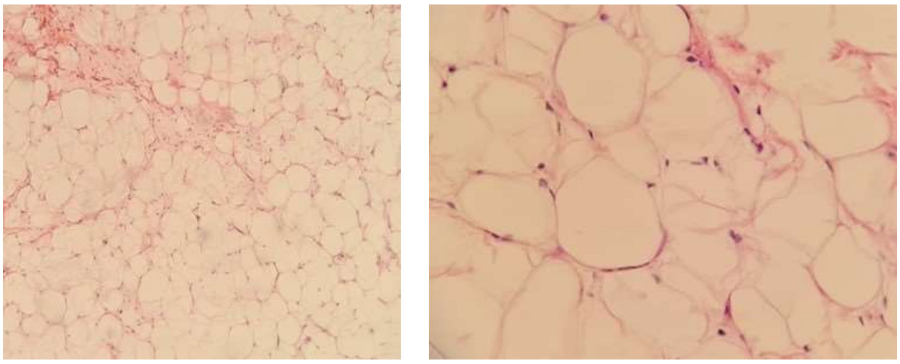
5.2 Materials and methods

Literature searches were conducted using the Medline/PubMed databases, and references were made to international guidelines where appropriate.

5.3 Results

Our search yielded over 300 relevant bibliographic entries, significantly shaping the discourse on the mechanisms inducing overweight conditions from childhood and their dynamics through developmental stages into adulthood, and how this excess weight predicates the emergence of cardiovascular pathology, irrespective of age. The results, materialized in the form of an article (10), the results of which have been pivotal for Part I of this dissertation. What follows is a reference to the sections of the mentioned article, briefly outlining the results obtained.

Our approach initiates by stating the currently accepted definitions for obesity in childhood and adolescence, discussing the limitations inherent in these definitions (Section 2, Defining Obesity). Subsequent is a section covering the prevalence of pediatric obesity, underscoring the severity of this escalating global issue (Section 3, Epidemiology). Section 4 (The Anatomy of Obesity) delves into the nuances of adipose tissue distribution in the body, starting with a macroscopic view and narrowing focus to cross-sectional aspects, peri-organ fat deposits, and, ultimately, the microscopic and metabolic features of the constitutive cells of adipose tissues. The pathways from overweight to pathology are discussed at each level of this exploration. Concerning the overall surface fat distribution, the mechanisms behind the sexual dimorphism characterizing android and gynoid fat distributions are described, as well as their connection with obesity-related disease. This initial perspective also discusses the correlations surrounding central obesity as a a cardiometabolic risk factor. The pathophysiological pathways linking central obesity to cardiometabolic risk are explored, considering the potential role of increased lipolytic activity of visceral adipose tissue altering hepatic and overall metabolism. Furthermore, the distinct role of excess fat situated near specific organs is presented. This includes the discussion on excess perihepatic fat and flawed intracellular triglyceride storage in hepatocytes as a primary factor in non-alcoholic fatty liver disease. Subsequently, the topic also encompasses the excessive disposition of adipose tissue located epicardically, perivascularly, and perirenally, and their deleterious effects on hemodynamics and metabolism. Section 4.4, Central Obesity and Metabolically Healthy Obesity, addresses the conundrum of apparent metabolically healthy obesity, which is ultimately revealed to be merely a precursor state to dysmetabolic obesity. The final subsection provides insights into the mechanisms underpinning obesity-related disease, tracing the connection between various histological aspects of adipose tissue and cardiometabolic diseases. The main subject pertains to the differences between hypercellular and hypertrophic adipose tissue regarding their development in childhood versus adulthood, as well as the distinct cardiometabolic prognoses each entity entails. Figure 3 is a section of adipose tissue stained with hematoxylin and eosin, sourced from the Pediatric Hospital Sibiu's collection, with its permission. The insights from Section 4 emphasize the need for more refined obesity assessment methods, considering its disposition.



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

Figure 3 – 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.

Section 5 (Obesity Assessment) provides an overview of current endeavors regarding the techniques and parameters that more accurately depict weight excess in correlation with the risk of obesity-related diseases. Imaging diagnosis plays a pivotal role in this regard, especially in studying the characteristics of obesity distribution, with significant relevance to the mechanisms leading from obesity to impaired cardiovascular function. Figures 4-13 represent the outcomes of various imaging techniques listed in Section 5, extracted from the Pediatric Clinical Hospital Sibiu's collection, used with its permission.

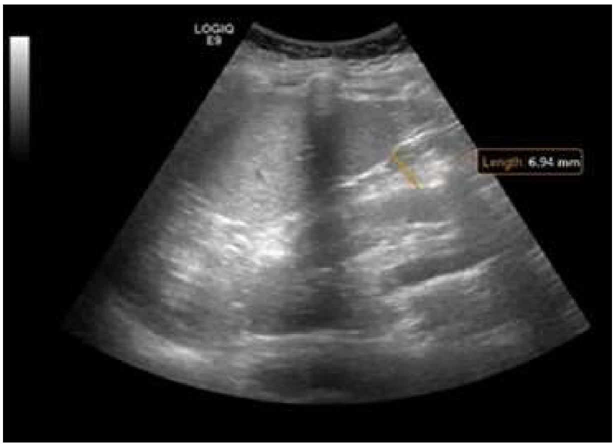


Figure 4 – Ultrasound image showing the thickness of the inter-spleno-renal adipose tissue corresponding to the inferior renal pole = 6.94 mm

Figure 5 – Ultrasound image showing the thickness of the subcutaneous adipose tissue of the abdominal wall = 45.12 mm, approximately 2 cm below the navel.

Figure 6 – MRI T2 HASTE, T5 transversal section showing the measurement of abdominal wall subcutaneous adipose tissue thickness (46.85 mm).

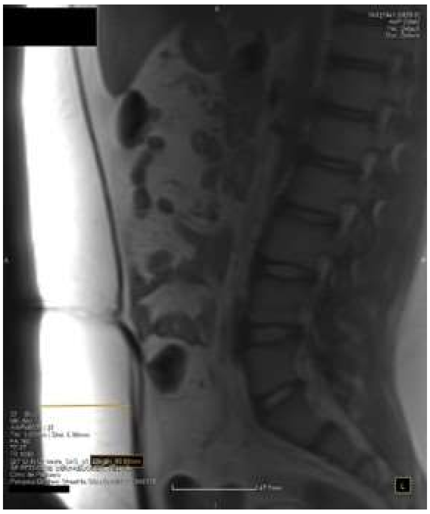


Figure 7 – MRI T2 HASTE, sagittal section tangent to T5 showing the measurement of abdominal wall sub-cutaneous adipose tissue thickness (49.85 mm).

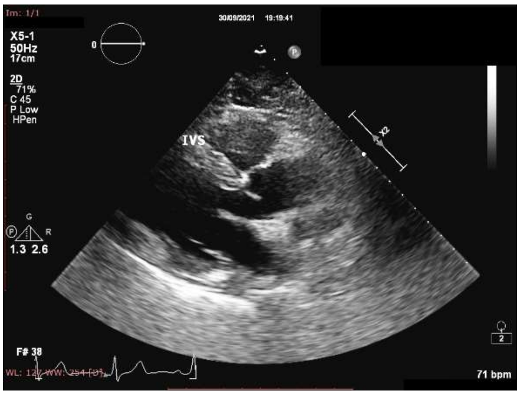


Figure 8 – 2D Echocardiography, parasternal long-axis view showing concentric left ventricle hypertrophy.

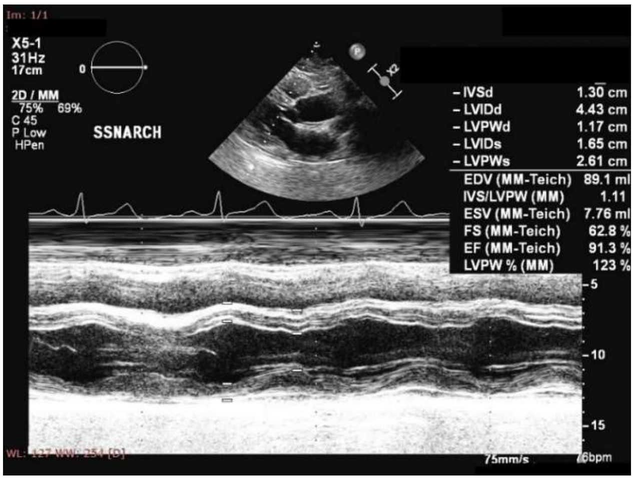


Figure 9 – M-Mode Echocardiography of the same patient showing cardiac chamber and wall measurements.

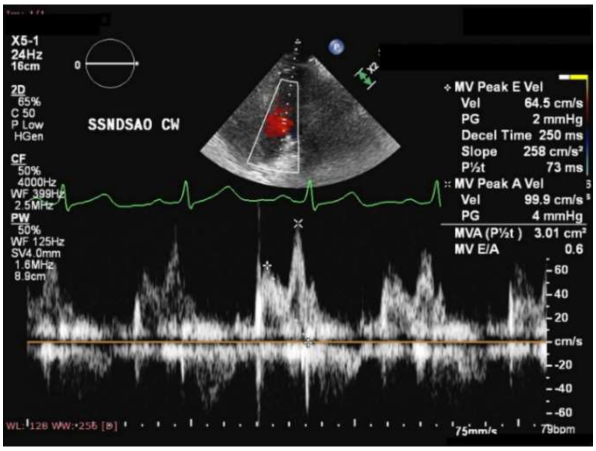


Figure 10 – PW Doppler Echocardiography of the same patient showing grade I diastolic dysfunction (impaired relaxation).

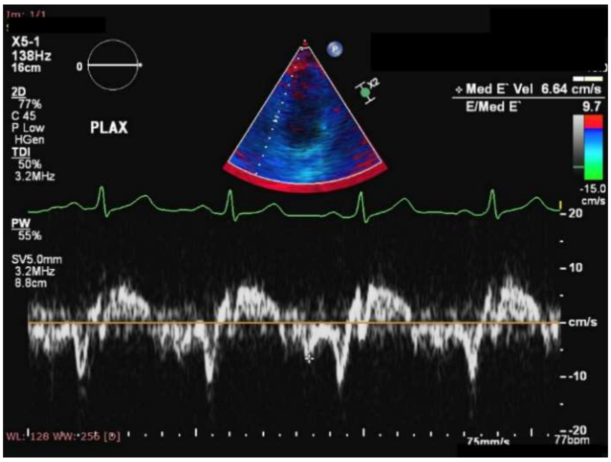


Figure 11 – Tissue Doppler Echocardiography, four chamber view, tissue Doppler, estimation of LV filling pressures by measuring E/E'.

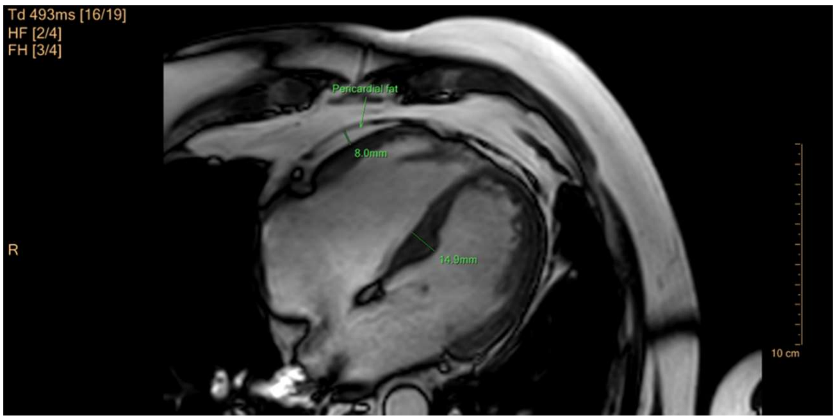


Figura 12 – Cardiac MRI, BTFE sequence, cine four chamber view, 8 mm, telediastolic measurement of inter-ventricular septum exhibiting hypertrophy (14.9 mm), epicardial fat thickness of 8 mm lateral of the right ventricle.

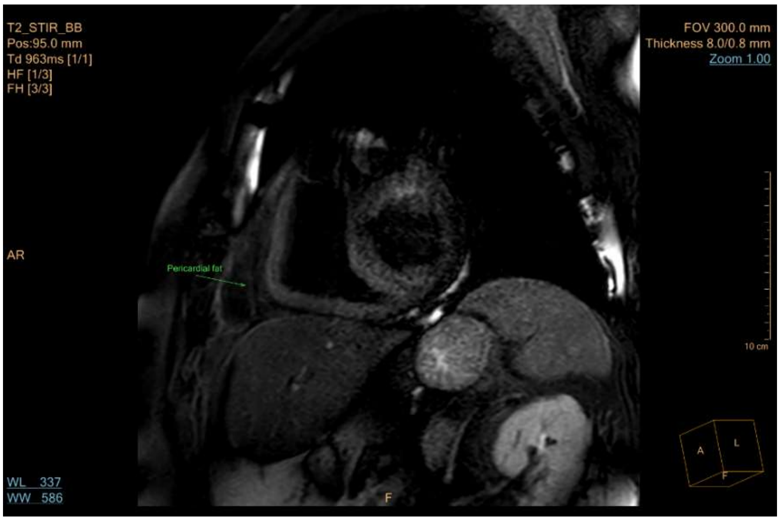


Figura 13 – Cardiac MRI Philips Ingenia 3Tardiac T2-STIR sequence, short-axis view, 8 mm, showing hy-pointensity lateral of right ventricle signifying adipose tissue.

Section 6 (Determinant Factors of Obesity) commences with a concise presentation of the physiological aspects of appetite regulation. Subsequent subsections describe factors that interfere with this schematic representation and can be implicated in the transition from physiological to pathological. The rationale of this section follows the interaction between genetic causality and environmental factors, focusing on pediatric populations from conception through puberty and adolescence.

Section 7 (Childhood Obesity as an Adult Risk Factor) offers a brief description of observational evidence that demonstrates the link between obesity developed in childhood and the emergence of associated pathologies in adulthood.

Section 8 (Mechanisms of Obesity-Related Cardiometabolic Disease) aims to delineate the mechanisms behind these associations. These two sections primarily refer to cardiovascular and metabolic diseases and the mechanisms implicated in their development in obese patients, including 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) endeavors to address topics concerning known and novel markers associated with obesity and its related diseases, with an emphasis on pediatric populations. Section 10 concludes this review, underscoring its main objective of providing pertinent data regarding the pathophysiology of diseases associated with obesity originating in childhood.

5.4 Discussions/Conclusions

The complex mechanisms establishing the link between obesity and cardiovascular risk develop from the early years of childhood and contribute to the formation of a conglomerate of harmful features that include physical inactivity, unhealthy dietary habits, and an altered metabolism, defined by increased insulin resistance and dyslipidemia. It is reasonable to assume that there is a high likelihood that today's obese children will become tomorrow's cardiovascular patients. The intricate interactions between environment and genotype may reveal a series of pivotal points at which preventive actions could have a significant impact on reducing the burden of obesity.

Cap. 6. Assessing Obesogenic School Environments in Sibiu County, Romania: Adaptation of the ISCOLE School Environment Questionnaire

6.1 Introduction

The obesogenic impact of school environments has garnered significant attention in recent years. To understand this influence in Romanian schools, we adapted and validated the ISCOLE questionnaire regarding the school environment (229,230).

6.2 Materials and methods

A multidisciplinary committee consisting of experts in teaching, school administration, clinical research, linguistic adaptation, and public health was assembled to oversee the progressive and regressive translations of the questionnaire, thereby ensuring the accuracy of the content. Subsequently, we analyzed responses from schools in Sibiu County, differentiating between urban and rural environments, and conducted a two-stage cluster analysis to identify potential intervention targets. To assess the validity of our adapted tool, we evaluated the questionnaire's construct validity and internal consistency.

6.3 Results

We achieved a response rate of 71.19% from the schools approached in Sibiu County. Of the 84 respondents in our sample, 37 (44%) were from rural areas.

Figures 14-16 and Table 3 summarize some of the results obtained, detailed within the content of the doctoral thesis.

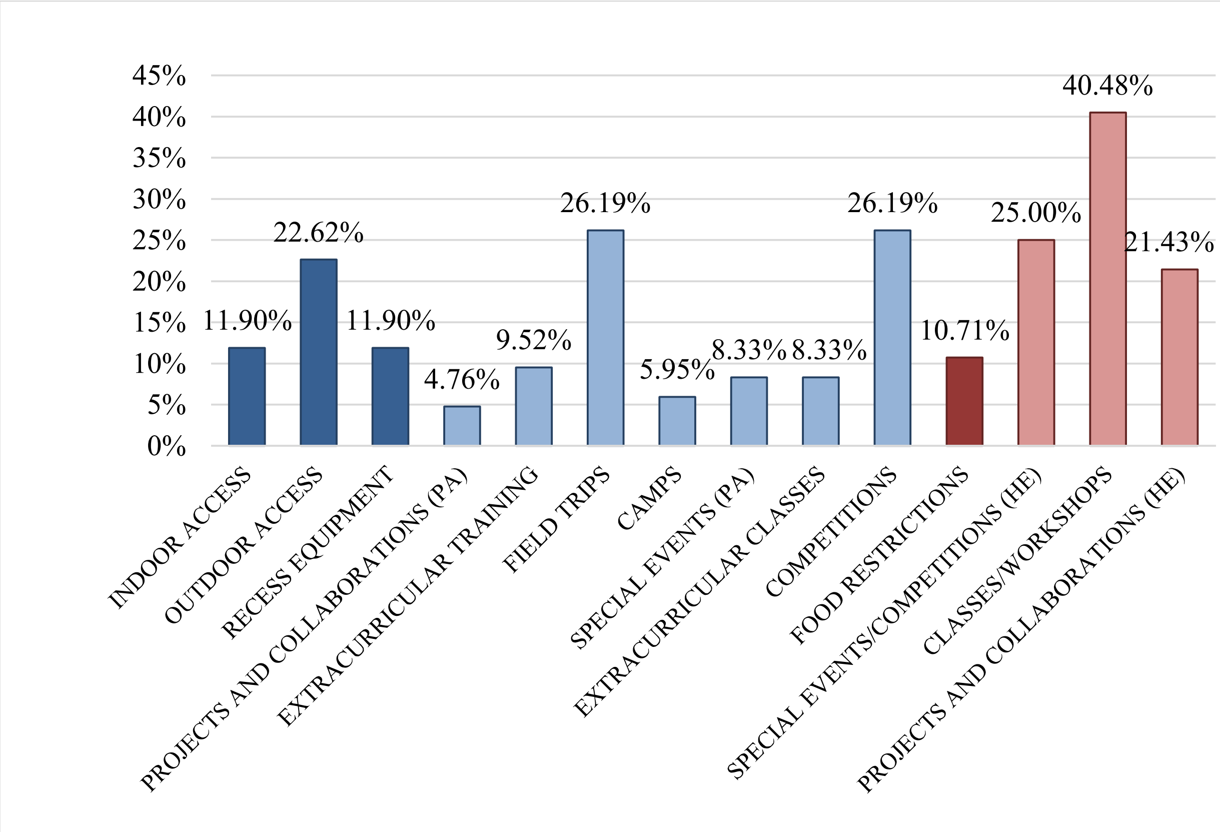


Figure 14 – Policies and practices regarding physical activity and healthy eating. PA – physical activity, HE – healthy eating

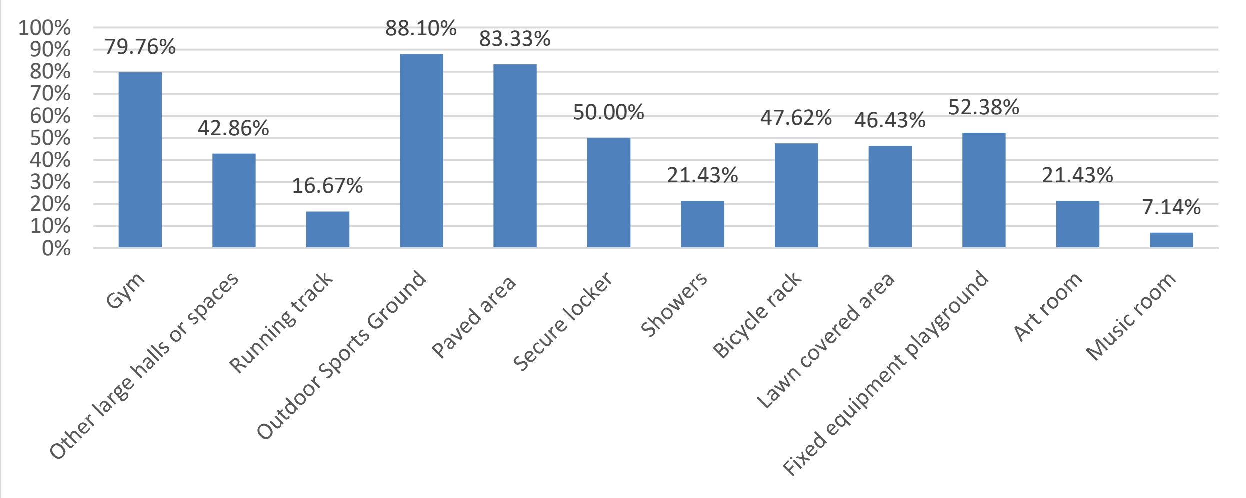


Figure 15 – School physical activity facilities available during school hours

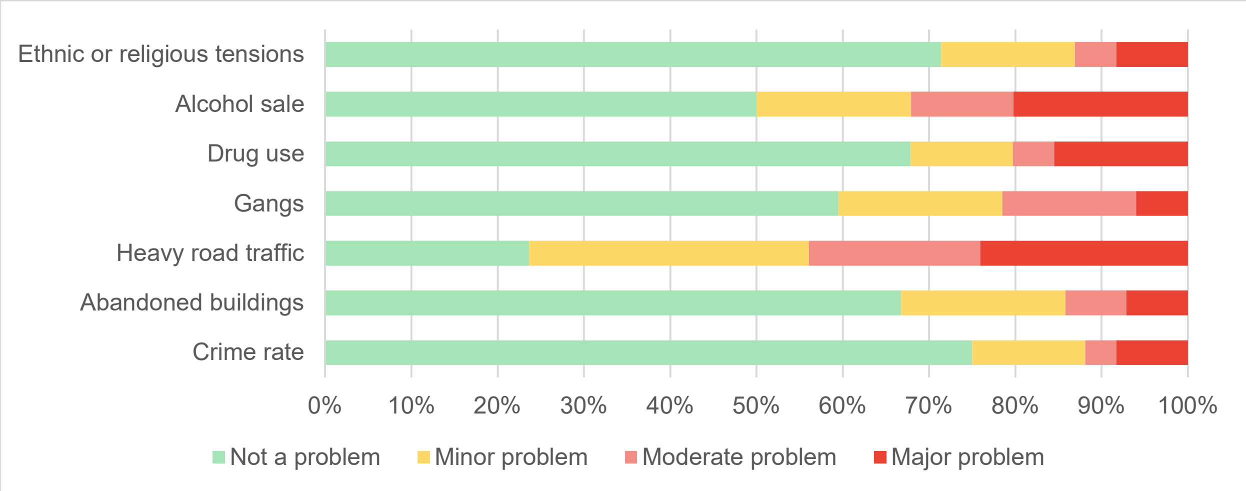


Figure 16 – Problems regarding school surroundings

Problem intensity	Environment		*p*
	Rural (%)	Urban (%)	
Not a problem	7 (18.9%)	24 (51.1%)	<0.01
Minor	10 (27%)	12 (25.5%)	
Moderate	9 (24.3%)	8 (17%)	
Major	11(29.7%)	3 (6.4%)	

Table 3 – Garbage in the school surroundings

Our results highlighted the differences between rural and urban schools, especially concerning the presence of facilities that promote physical activity, as well as aspects related to the size of the schools and the type of education provided. The two-step cluster analysis identified specific categories of schools based on their size, infrastructure, and policies.

6.4 Discussions/Conclusions

Our efforts led to the adaptation and validation of the ISCOLE questionnaire on the school environment for use in Romanian schools. We observed significant differences between schools located in rural areas compared to those in urban settings. Regarding school characteristics, institutions in rural areas tend to have a smaller number of students and teaching staff and are primarily oriented towards primary and lower secondary education.

There was a low prevalence of specialized committees concerning the implementation of practices and policies on physical activity and healthy eating, especially in the rural environment. Other discrepancies between rural and urban schools were highlighted regarding access to a gym, secure changing rooms, showers before and after physical activity, and bicycle racks. In all the cases mentioned above, rural schools were significantly less likely to benefit from these facilities. Another concerning issue was the improper waste disposal around schools, which was significantly more common in rural areas. Additionally, the accessibility of unregulated food in both rural and urban schools is alarming, as two-thirds of the surveyed schools were in proximity to such a source. These findings have underscored several potential areas where government program-type interventions could be beneficial.

We conducted a two-step analysis to further refine the identification of potential targets for such interventions. We based our algorithm on school size, the adoption of practices or policies regarding physical activity, and access to the school's gym facilities. This approach resulted in four distinct groups of schools within our sample. Groups 3 and 4 consisted of either large schools or schools of small to medium size, characterized by having access to an indoor gym as well as established policies or practices regarding physical activity. We referred to these schools as "willing and able."

Of particular interest, however, were two groups that highlighted clear opportunities for initiative. Group 1 included smaller schools that lacked a gym, although they had proactive practices or policies regarding physical activity. In contrast, Group 2 consisted of larger schools with access to a gym but without the implementation of policies or practices related to physical activity. We named Group 1, primarily located in rural areas, as "willing but unable," while Group 2, mainly composed of urban schools, was termed "able but unwilling." A minor segment from Group 1 had neither access to indoor facilities nor implemented policies or practices, being classified as "unwilling and unable." Our differentiation underscores specific areas where efforts in proposing governmental measures can be most efficiently channeled. This aspect particularly refers to investments in infrastructure in "willing but unable" schools on the one hand, and promoting physical activity by initiating programs for promoting a healthy lifestyle in schools that are "able but unwilling."

The limitations of our study refer to the absence of objective measurement methods that other studies have used to assess students' weight status and quantify sedentary durations or MVPA (231–234), such as anthropometric measurements or accelerometry. Additionally, our study did not implement an on-site audit-based evaluation of school facilities, as was the case in the original study (229,230). However, our methodology offers the advantage of being easy to apply and cost-effective. Moreover, it provides directions for interventions based on existing literature, which has established positive correlations between weight status, students' activity levels, and the improvement of policies, practices, and school facilities related to physical activity and healthy eating.

Cap. 7. Assessing the Lifestyle of Students from a High School in Sibiu: Adapting and Applying ISCOLE Specific Questionnaires

7.1 Introduction

This study aimed to analyze the prevalence of overweight and obesity among adolescents in a high school in Sibiu, Romania, and identify associated factors using questionnaire-based assessments (229,230).

7.2 Materials and methods

The questionnaires incorporated a selection of translated and adapted questions from the *"ISCOLE Diet and Lifestyle Questionnaire"* and the *"ISCOLE Demographic and Family Health Questionnaire"* used for assessing family influences (230). The sample consisted of 119 adolescents, aged between 15 and 17 years. Variables such as parents' education level, sedentary behavior, screen time exposure, sleep duration, and academic performance were analyzed.

7.3 Results

Out of 314 ninth and tenth-grade students at the "Gheorghe Lazăr" National College in Sibiu, 119 (37.9%) participated in the study, providing complete information in the questionnaires. The cohort consisted of 68 girls (57.1%) and 51 boys, with ages ranging from 185 to 211 months (mean ± standard deviation (SD): 197.52±6.54). There were no significant differences between genders regarding the age of the participants. The prevalence of overweight and obesity was 15.13%.

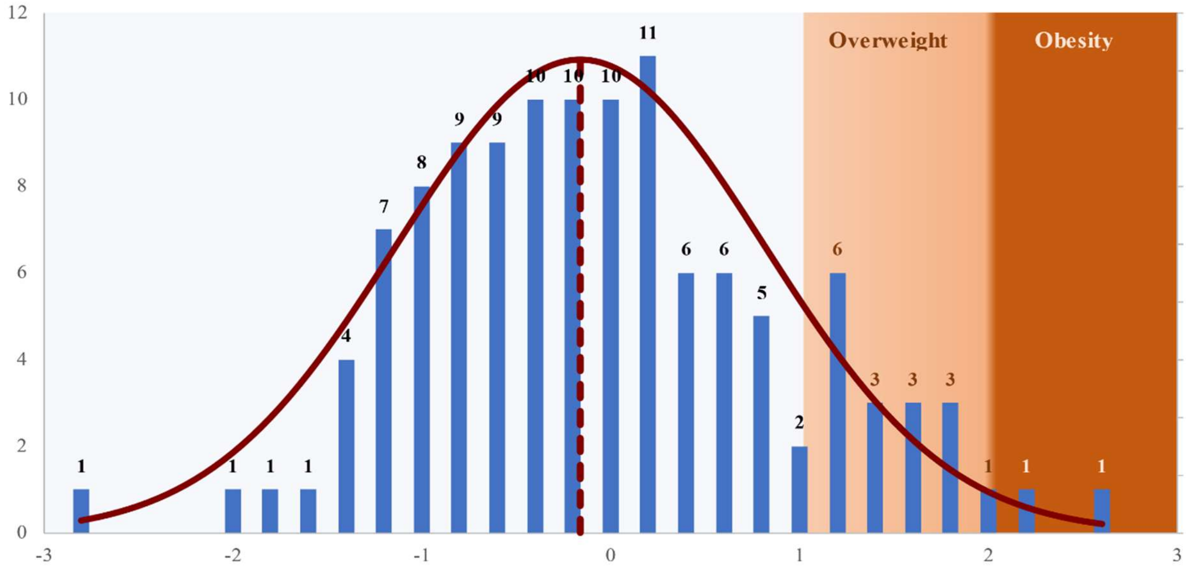


Figure 17 – The distribution of the BMI Z-score for the participating students, overlaid on the normal curve at the same mean and SD

Among the biological parents of the students, maternal obesity was present in 10.4% of cases, maternal overweight in 27%, paternal obesity in 23.2%, and paternal overweight in 50.9%. Excess weight among students was associated with sedentary behavior, a lower educational level of the mother, and maternal obesity. The majority of adolescents reported a sleep deficit, correlated with lower academic performance compared to those who slept more than 8 hours during school days.

The Cronbach's alpha indices for questions using the same response scale are presented in Table 4.

Question number in the ISCOLE questionnaire	Crohnbach's alpha
13-20	0.856
21-25	0.538
39-45	0.740
46-55	0.801

Table 4 – Questionnaire internal consistency

Question number represents the count of corresponding questions from the original *"ISCOLE Diet and Lifestyle Questionnaire"*. Questions 21, 23, 48, and 49 were reverse-coded for the computation of Cronbach's alpha.

7.4 Discussions/Conclusions

The study conducted at the "Gheorghe Lazăr" National College in Sibiu highlighted significant associations regarding the influence of the mother's education level and sedentary behavior on overweight, as well as the correlation between sleep deficit and academic performance. This latter aspect raises a red flag, given that the majority of adolescents fail to meet current sleep recommendations. Moreover, the prevalence of overweight was strikingly high among the responding parents.

Thus, the study underscores the need to address these health issues within the community. Due to the low costs and accessible data collection methods, the implemented methodology and the results obtained can serve as a foundation for educational initiatives and health promotion in schools. The applicability of the results in developing effective strategies for improving the health and well-being of adolescents represents a significant potential of this approach.

Cap. 8. Exploring the Link Between IGF-1 and Obesity

8.1 Introduction

The intersection between the pathways involved in growth, glucose metabolism, and lipid metabolism might play a crucial role in the imbalances leading to the dysmetabolic changes observed in obese children and subsequently in adults. The growth hormone/insulin-like growth factor 1 (GH/IGF-1) axis is a prime example in this context (235), with IGF-1 levels proven to correlate with insulin resistance (236,237). The aim of this study is to examine whether there is a relationship between circulating IGF levels and weight status in children as an independent association, irrespective of insulin sensitivity.

8.1 Materials and methods

We retrospectively collected data from patients aged 5 to 12 years, referred to the Clinical Hospital of Pediatrics in Sibiu between January 2010 and May 2023, for whom IGF-1 levels were documented. We excluded patients with pathologies or medication that could influence weight status, glucose and lipid metabolism, or growth hormone secretion, as well as those with short stature or a growth rate of less than 5 cm per year. Anthropometric measurements were retrieved, and the BMI Z-score was calculated.

8.2 Results

Our study included 66 patients (32 females and 34 males) with an average age of 100.09 months (SD: 24.754 months). The initial bivariate analysis showed a significant negative correlation between the BMI Z-score and IGF-1 values.

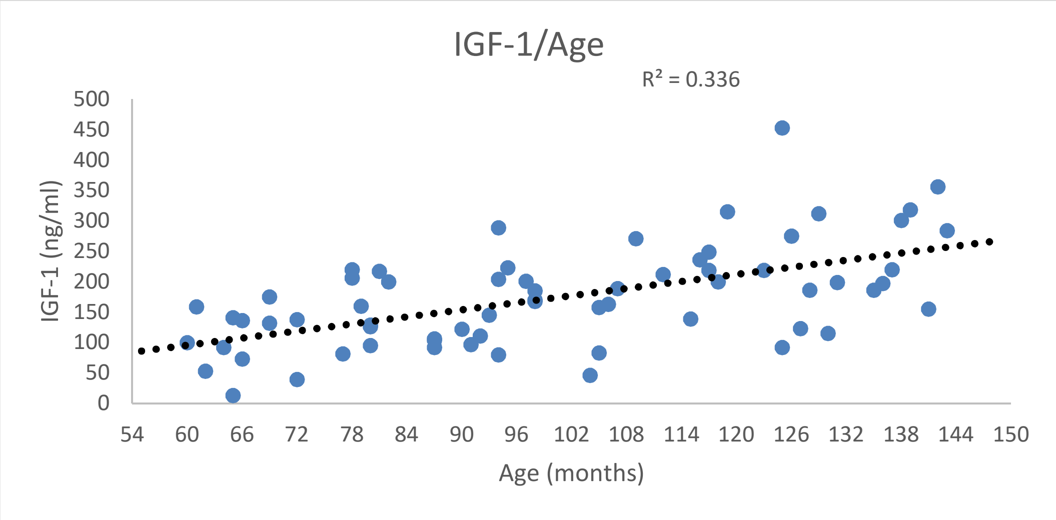


Figure 18 – Relationship between IGF-1 and age

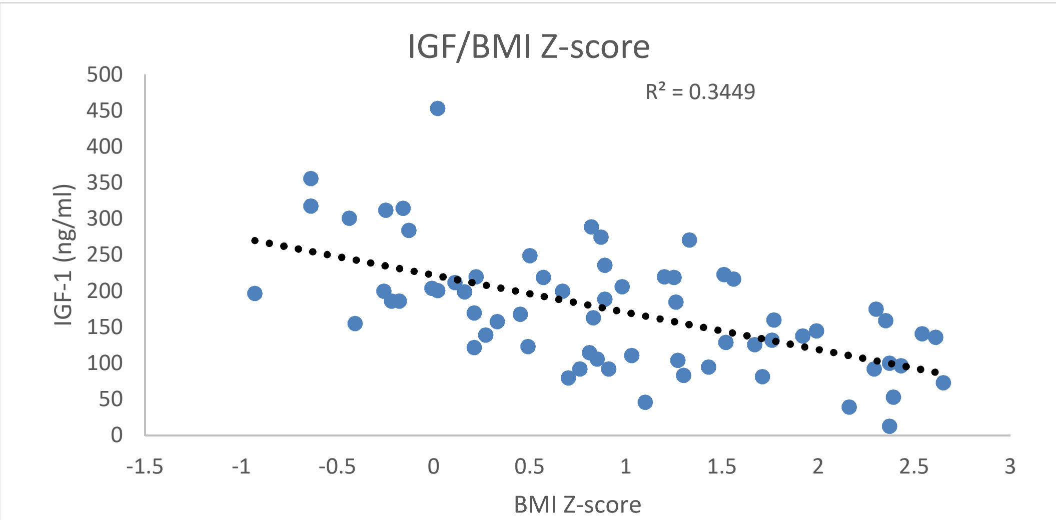


Figure 19 – Relationship between IGF-1 and BMI Z-score

However, after adjusting for age, it was indicated that there is actually no significant relationship between these two parameters (partial correlation coefficient=-0,226; p=0,071). Nonetheless, insulin-like growth factor 1 levels varied significantly depending on the patient's age.

8.3 Discussions/Conclusions

IGF-1 levels exhibited an age-dependent variation that should be considered in data analysis. Our study did not find a correlation between weight status and IGF-1 levels when adjusted for age-dependent variation. Further studies could clarify the potential role of IGF-1 in distinguishing between obese children with or without increased insulin resistance.

Cap. 9. Analyzing the Efficiency of Abdominal Adipose Tissue Segmentation in MRI Sections Using Otsu, K-means, and Fuzzy C-means Methods

9.1 Introduction

Obesity is acknowledged as a cardiovascular risk factor, particularly in the context of excessive visceral adipose tissue accumulation. The primary objective of this study was to evaluate the efficiency of three distinct image processing algorithms (Otsu, K-means, and Fuzzy C-means) in quantifying abdominal adipose tissue based on magnetic resonance imaging (MRI), by comparing their performance with a reference value obtained through a previously validated manual technique (167,238). We integrated these algorithms with a novel approach for the automated differentiation between visceral and subcutaneous adipose tissue. Our aim was to identify the most efficient algorithm capable of delivering satisfactory results, regardless of the patients' demographic characteristics, weight status, or diagnoses. Additionally, we explored the demographic and anthropometric variables that might influence the accuracy of the implemented methods.

9.2 Materials and methods

We conducted a retrospective study by retrieving abdominal MRI images from the database of the Pediatric Clinical Hospital of Sibiu, Romania, performed between November 2015 and May 2023. The study included patients aged 8 years and older, regardless of their weight status or underlying diagnosis. Patients who had undergone extensive abdominal surgeries or had significant space-occupying intraabdominal pathologies were excluded from the study. Additionally, we excluded repeated examinations for the same patient, examinations lacking opposed-phase images, as well as those with images heavily distorted due to breathing artifacts or improper selection of the field of view.

Examinations missing sections at the L2 vertebra level, either entirely or due to apparent communications between subcutaneous and visceral adipose tissue, were also excluded, as were those where the presence of substantial intestinal content could have been mistakenly interpreted as adipose tissue. Furthermore, patients with missing data and those who did not consent to the use of their personal data for scientific purposes were not included in the analysis.

Demographic data (age, gender), anthropometric data (weight, height), and information regarding the diagnosis established after MRI interpretation were documented for each patient.

The research team, coordinated by the author, included pediatricians, faculty members from the engineering department of the "Lucian Blaga" University of Sibiu, and independent researchers with expertise in the use of programming languages.

The sequence regarding the selection and processing of images is illustrated in Figure 20 and data analysis workflow is presented in Figure 21.

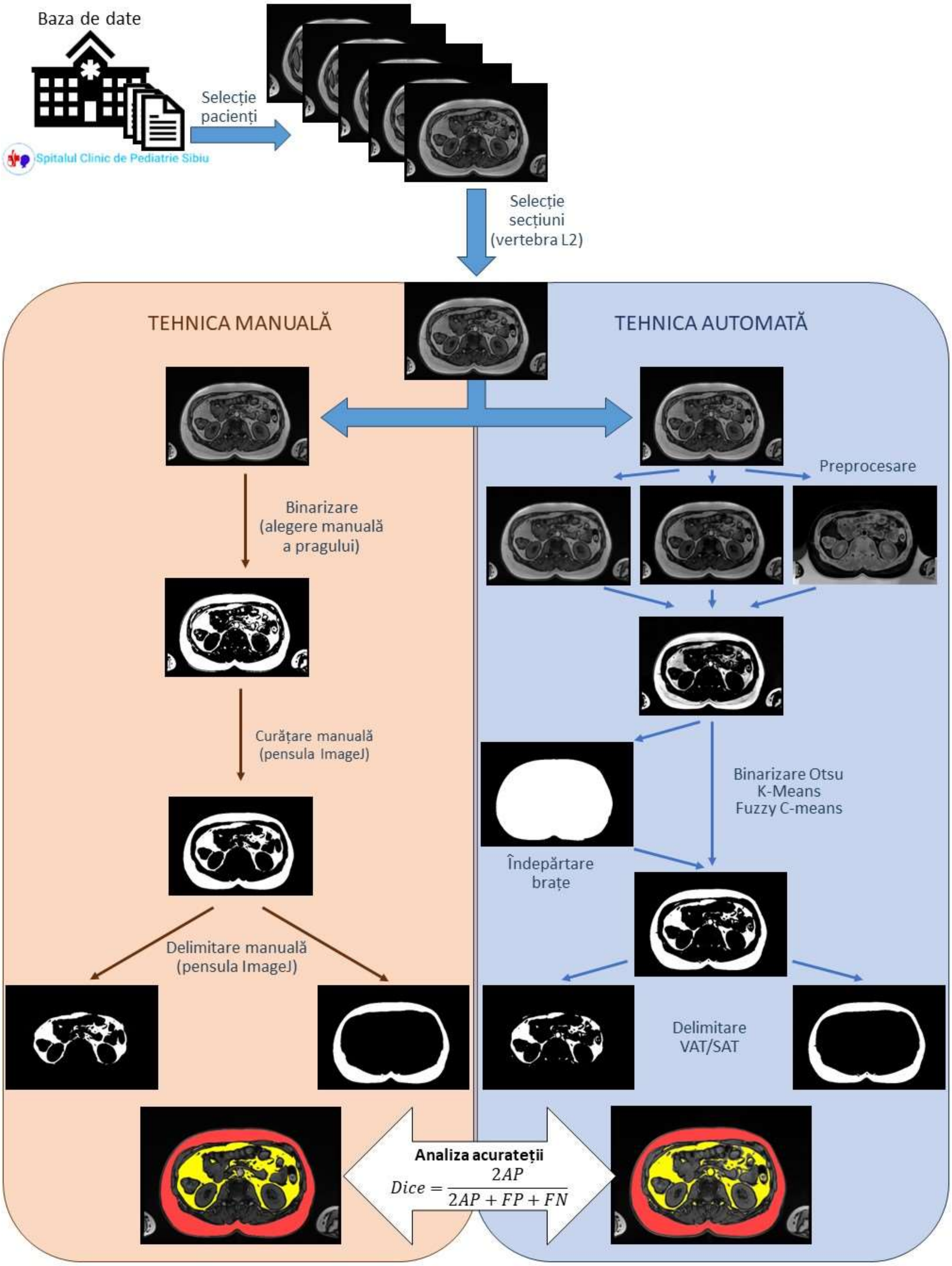


Figure 20 – Image selection and processing

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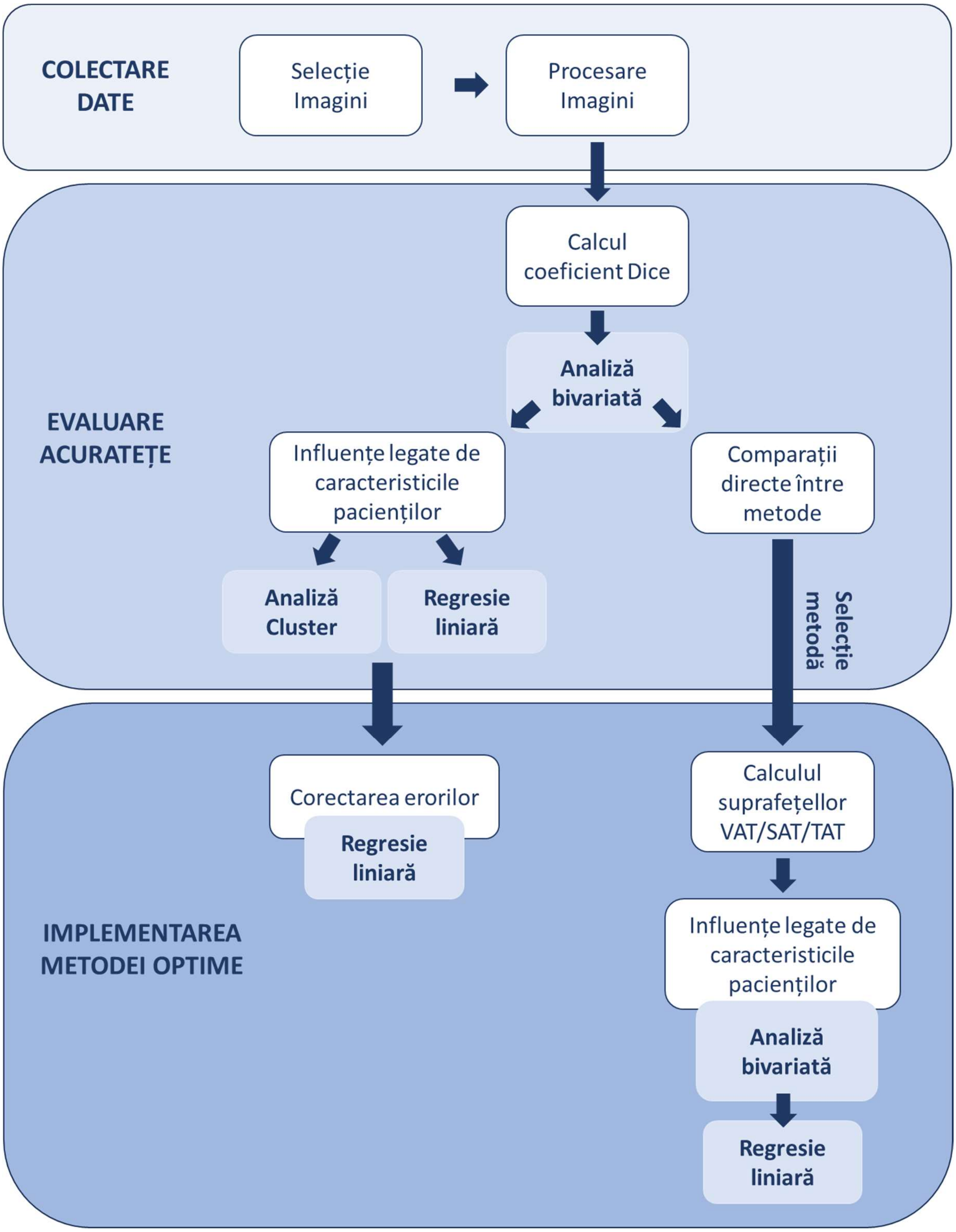

Figure 21 – Data analysis workflow

9.3 Results

9.3.1 Patient characteristics

Between November 2015 and May 2023, there were 173 patients who underwent abdominal MRI examinations at the Pediatric Clinical Hospital of Sibiu. Of these, 68 patients were included in our study (30 males and 38 females).

The patients' ages ranged from 8 to 84 years, with an average of 40.69 years (SD: 22.179 years). Males in our study were significantly younger than females (mean age ± SD of 33.5 ± 23.212 years versus 46.37 ± 19.83 years; p=0.015). Obesity was more prevalent among children and males. Regarding the interpretation of the MRI results, 17 patients had no detectable pathologies, 8 patients suffered from malignant pathologies, and 43 patients were diagnosed with various benign processes. Malignant pathologies were more prevalent among adults but did not show any correlation with weight status or gender.

The accuracy of the implemented algorithms is presented in Table 5 as the value of the Dice coefficient ± SD.

Tissue	Otsu	K-means	Fuzzy C-means	*p*
TAT	0.9152±0.0333	0.9099±0.0368	0.9082±0.0368	<0.01
SAT	0.9647±0.015	0.9646±0.015	0.9637±0.0152	<0.01
VAT	0.7863±0.107	0.7856±0.107	0.7807±0.107	<0.01

Table 5 – Performance (Dice coefficient) of all three algorithms

The Otsu method consistently outperformed the K-means and Fuzzy C-means algorithms. Additionally, the K-means algorithm was superior to the Fuzzy C-means in all cases. We compared the performance of the algorithms on patient groups, divided by gender, age category, weight status, and type of diagnosis. Table 6 succinctly highlights the investigated differences and the statistically significant results obtained.

Variabila	Eficiență mai mare la categoria..	Eficiență mai mare pentru..
Gender	Male > Female	VAT, TAT
Age category	Children > Adults	SAT
	Adults > Children	VAT
Weight status	Obesity > Overweight > Normal weight	TAT, SAT, VAT
Diagnosis type	-	No correlations found

Table 6 – Performance of algorithms across various patient groups

We conducted a two-stage cluster analysis to capture the complex interactions among parameters influencing the accuracy of visceral adipose tissue quantification. We employed the Akaike Information Criterion for the automatic determination of the optimal number of clusters and used as variables the Dice scores for visceral adipose tissue quantification obtained using the Otsu method (since this method consistently provided more accurate results in our study population), gender, age category, and dichotomized weight status (overweight or obese versus normal weight). This approach led to a model comprising 5 distinct, well-defined clusters, with an average silhouette measure of cohesion and separation of 0.6 - indicating a good fit of the model. Cluster 5 primarily consisted of overweight or obese adult males. Cluster 4 exclusively included adult females characterized by either overweight or obese status. Cluster 3 was composed of boys identified as overweight or obese. In contrast, Cluster 2 primarily encompassed normal-weight adult females, and Cluster 1 was predominantly populated by normal-weight girls.

Dice scores showed a significant progressive increase from Cluster 1 to Cluster 5. Figure 22 graphically illustrates the distribution of these Dice values for VAT surfaces, as calculated by the Otsu method, expressing the medians along with the 25th and 75th quartiles.

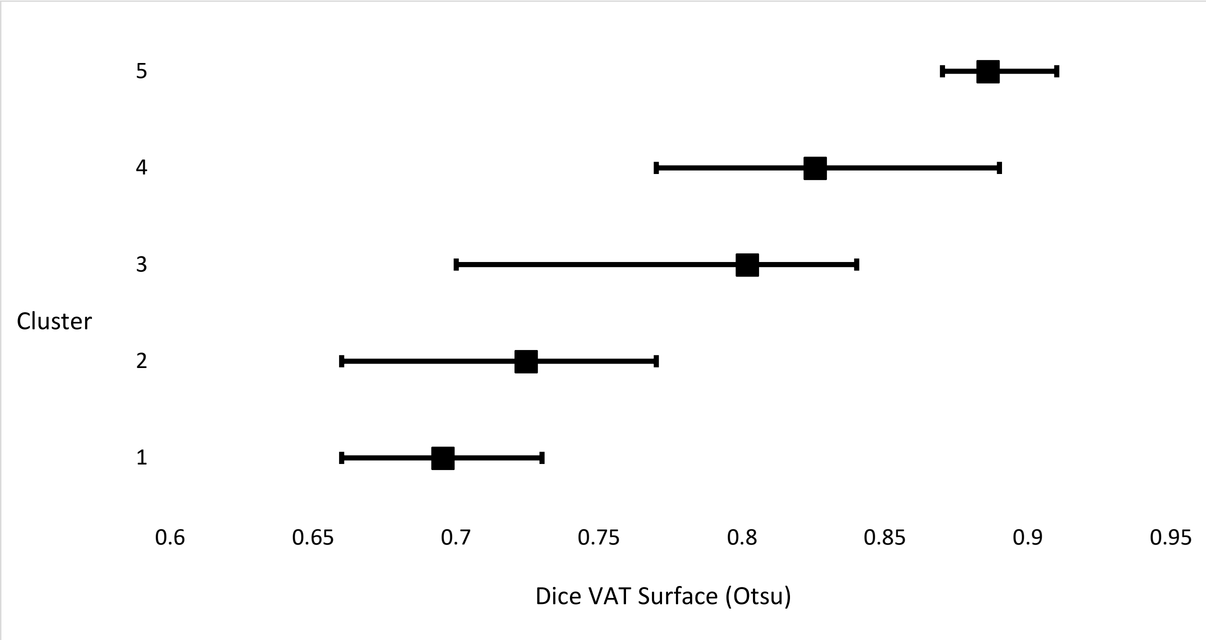

Figure 22 – Dice value distribution (VAT/OTSU) across clusters

9.3.2 Linear regression for accuracy predictors

We investigated whether variables affecting the precision of the Otsu method exerted their influence independently, adjusting for variations in gender distribution according to weight and age categories. For this purpose, we employed linear regression analysis, with the Dice coefficient for VAT measurement based on the Otsu method selected as the outcome variable. Binary dummy variables were encoded for gender, age category, and weight category. Females, childhood, and normal weight served as reference categories. These variables were subsequently incorporated as independent variables in the regression. The regression was statistically significant: $R^2=0.289$; $F=8.683$ (df Regression=3; df Residual=64); $p<0.01$. The VIF values were under 5 for gender, weight status, and age category, indicating no multicollinearity. Thus, the selected variables proved to be independent predictors of the efficacy of the Otsu method. The details of the regression model are presented in Table 7.

Variabila	Parametru	Valori
Constant	B	0.647
	BCa 95%CI	0.592-0.697
	p	<0.01
Gender	B	0.076
	BCa 95%CI	0.027-0.121
	p	<0.01
	VIF	1.29
Age category	B	0.093
	BCa 95%CI	0.047-0.138
	p	<0.01
	VIF	1.16
Weight category (dichotomized)	B	0.062
	BCa 95%CI	0.012-0.117
	p	0.02
	VIF	1.12

Table 7 – Linear regression model for VAT Dice coefficient using Otsu threshold method

9.3.3 Method agreement and error correction

The automated methods implemented in this study significantly underestimated the values calculated through the manual method for both SAT (subcutaneous adipose tissue) and VAT (visceral adipose tissue). Utilizing the Otsu threshold method, VAT was consistently underestimated by an average of 20.03 cm^2 (StdDev = 14.06 cm^2), and SAT by 9.22 cm^2 (StdDev = 5.81 cm^2). The differences displayed a normal distribution in both cases. To compensate for these discrepancies, we conducted a linear regression analysis. In this model, the VAT area calculated through the reference manual method was selected as the dependent variable. The independent variables were the VAT area calculated through the Otsu algorithm and the presence of obesity. The regression was statistically significant ($R^2 = 0.978$; F = 1465.649 (df Regression = 2; df Residual = 65); $p < 0.01$), and the adjusted regression model was as follows (Table 8):

$$VAT_{manual\ (cm^2)} = 7.224 + 1.112 \times VAT_{Otsu\ (cm^2)} + 7.583 \times [Obesity]$$

Variable	Parameter	Values
Constant	B	7.224
	BCa 95%CI	3.5-11.6
	p	<0.01
VAT Surface (Otsu)	B	1.112
	BCa 95%CI	1.063-1.157
	p	<0.01
Obesity	B	7.583
	BCa 95%CI	1.978-13.035
	p	0.014

Table 8 – Regression model for VAT surface correction using Otsu Thresholding

The method allowed for the adjustment of errors with appropriate correction of the underestimation. The values calculated based on the model showed an excellent correlation with the manually determined VAT area (Spearman's rho correlation coefficient = 0.986; $R^2 = 0.978$). Bland-Altman analysis indicated that estimating the VAT area value by applying the regression model to the results obtained through the Otsu threshold method provided agreement limits between -21.46 and 21.51 cm^2.

To adjust the errors in the automatic determination of the SAT area, we performed a linear regression using the SAT area calculated through the manual reference method as the dependent variable, while the SAT area calculated through the Otsu algorithm and the age category (with the children's category as reference) were selected as independent variables. The regression was statistically significant ($R^2 = 0.998$; F = 13902.99 (df Regression = 2; df Residual = 65); $p < 0.01$). The regression model was:

$$SAT_{manual\ (cm^2)} = 0.67 + 1.037 \times SAT_{Otsu\ (cm^2)} + 3.337 \times [Age\ Category]$$

Variable	Parameter	Values
Constant	B	0.67
	BCa 95%CI	-2.116-3.179
	p	0.622
SAT Surface (Otsu Threshold)	B	1.037
	BCa 95%CI	1.020-1.056
	p	<0.01
Age Category	B	3.337
	BCa 95%CI	1.134-5.674
	p	<0.01

Table 9 – Regression model for SAT surface correction using Otsu Thresholding

The model demonstrated excellent correlation with the manually determined SAT area (Spearman's rho correlation coefficient=0.999; R^2=0.998). Subsequently, a Bland-Altman analysis was conducted after applying the regression model to the results obtained using the Otsu method. The estimation of the SAT area provided limits of agreement ranging between -9.22 and 9.31 cm^2.

9.3.4 Clinical correlations

Through the implementation of regression models to adjust the VAT and SAT surface values obtained by the Otsu method, we calculated the areas in cm2 for each patient and determined the VAT/SAT ratios, as well as the VAT percentages of TAT. We also investigated the differences between these variables based on gender, weight status, and diagnostic categories.

The VAT percentage of TAT followed a normal distribution across the entire sample, and this pattern persisted in distinct age groups, diagnostic types, gender classifications, and weight status categories.

Analyzing the group as a whole, adults presented significantly higher percentages of VAT/TAT and VAT/SAT ratios compared to children. Additionally, overweight patients had the highest percentages of VAT/TAT and VAT/SAT ratios, followed by patients with normal weight. Obese patients displayed the lowest values for these parameters. Further details on these aspects can be found in Table 10.

Variable	Categories	VAT/TAT %	*p*	VAT/SAT	*p*
Gender	Female	34.03±12.06	0.122	0.57±0.33	0.208
	Male	40.01±17.87		0.85±0.64	
Age category	Copii	24.72±8.62	<0.01	0.35±0.17	<0.01
	Adulți	42±14.31		0.85±0.53	
Weight status	Normal weight	36.99±13.79	0.026	0.68±0.45	0.042
	Overweight	43.59±16.51		0.95±0.65	
	Obesity	31.52±13.46		0.53±0.36	
Diagnosis type	Normal	33.48±13.8	0.210	0.58±0.39	0.302
	Benign	36.4±15.18		0.69±0.52	
	Malignant	44.88±16.02		0.96±0.6	

Tabel 10 – Adipose tissue proportions across patient categories (media±SD)

Considering strictly the adult population of the study, the VAT, SAT, and TAT surfaces showed significantly higher values with the increase in weight categories. However, no correlation was found between the VAT/TAT percentage or the VAT/SAT ratio and the weight category, as presented in Tables 11-12.

Variable	Categories	VAT (cm2)	*p*	SAT (cm2)	*p*	TAT (cm2)	*p*
Gender	Female	102.1±75.9	<0.01	171±89.1	0.465	273.1±148.2	0.115
	Male	177.8±59		142.6±49.9		320.4±84	
Weight status	Normal weight	74±52.9	<0.01	103.5±43.7	<0.01	177.5±83.2	<0.01
	Overweight	137.9±75		147.5±47.8		285.4±86.2	
	Obesity	179.5±73.7		257.1±59.9		436±80.7	
Diagnosis type	Normal	144.2±43.4	0.176	214.6±80.4	0.049	358.8±86.1	0.03
	Benign	113.5±85.3		141.6±71.6		255±136.3	
	Malignant	153.9±80.8		179±83.8		333±126	

Table 11 – Adipose tissue surfaces across patient categories in adults

Variabilă	Categorii	VAT/TAT %	*p*	VAT/SAT	*p*
Gender	Female	35.75±11.42	<0.01	0.61±0.32	<0.01
	Male	55.34±10.21		1.35±0.54	
Weight status	Normal weight	39.39±13.89	0.385	0.75±0.47	0.444
	Overweight	45.84±15.78		1.02±0.65	
	Obesity	40.40±12.75		0.75±0.4	
Diagnosis type	Normal	41.63±13.08	0.829	0.79±0.42	0.891
	Benign	41.35±14.59		0.83±0.55	
	Malign	44.88±16.02		0.96±0.6	

Table 12 – Adipose tissue proportions across patient categories in adults

Among adults, males demonstrated significantly larger VAT areas, as well as higher VAT/TAT percentages and VAT/SAT ratios compared to their female counterparts. Regarding the type of diagnosis, adult patients with benign pathologies showed significantly lower values for SAT and TAT areas.

In adult patients, there was a statistically significant positive correlation between the absolute values of VAT, SAT, TAT areas, and BMI.

Correlation	**Pearson correlation coefficient**	*p*	R^2
TAT Surface & BMI	0.792	<0.01	0.62
VAT/TAT% & BMI	-	0.539	-
Corelație	**Spearman's Rho**	*p*	R^2
VAT Surface & BMI	0.623	<0.01	0.36
SAT Surface & BMI	0.782	<0.01	0.52
VAT/SAT ratio & BMI	-	0.480	-

Table 13 – Correlations between adipose tissue quantifiers and BMI in adults

However, no significant correlation was identified between BMI and adipose tissue proportions measured by the VAT percentage of TAT and the VAT/SAT ratio.

9.4 Discussions/Conclusions

The study was based on MRI images obtained through standard clinical protocols from a diverse group of patients with varying demographic, anthropometric, and clinical parameters. The primary objective was the development and validation of a freely available algorithm capable of performing fully automated segmentation of adipose tissue at the L2 level.

We conducted a comparative analysis of the efficiency of the Otsu, K-means, and fuzzy C-means algorithms for image binarization. A validated reference method based on manual segmentation (463) was used to evaluate the performance of the mentioned algorithms. With the algorithm developed in this research, we achieved precise delineation between visceral and somatic adipose tissue, applicable to all three distinct segmentation methods.

Moreover, we investigated the impact of patient-related characteristics on the accuracy of the algorithms. Our results aligned with those reported in the literature for similar approaches (239). Our models demonstrated increased accuracy with higher BMI and showed superior results for adults and males. However, it's essential to acknowledge that women tend to be underdiagnosed and undertreated for cardiovascular diseases, partly due to the perception that the female sex offers cardioprotective characteristics in the pre-menopausal years. Nonetheless, women remain susceptible to increased cardiovascular mortality and a more unfavorable prognosis following cardiovascular events (240).

These observations underscore the importance of developing effective diagnostic and prevention strategies specifically tailored to women's needs. Furthermore, investigating the quantification of adipose tissue in children could provide valuable insights for developing prevention strategies aimed at reducing the adult cardiovascular burden associated with early exposure to cardiovascular risk factors (241).

In our study, the Otsu method provided the most accurate results. We used the most efficient algorithm to quantify and assess the disposition of abdominal adipose tissue in the included patients. Our study population encompassed a broad range of ages, similar to Shen et al. (242) and Kuk et al. (243). Additionally, we included patients with various pathologies, including malignant ones. Previous studies have explicitly explored adipose tissue quantification in this patient category (244,245). The study aimed to explore a method capable of reliably segmenting adipose tissue in MRI sections under the most varied and diverse circumstances possible.

Within the studied population, VAT, SAT, and TAT areas increased with the weight category based on BMI, and in adults, showed a positive linear correlation with BMI. However, adipose tissue disposition, quantified by the VAT/TAT percentage and the VAT/SAT ratio, did not demonstrate correlations with BMI in adults. Examining the group as a whole, overweight patients showed the highest values for the VAT/TAT percentage and the VAT/SAT ratio. This heterogeneous result may represent a well-known disadvantage of using BMI as an obesity quantification parameter, as it lacks the ability to assess different body compositions (246).

Male patients in our study exhibited a higher susceptibility to obesity, and for adult patients, they displayed a significant trend towards predominantly visceral fat accumulation. This outcome is consistent with findings obtained in other current studies (247). Furthermore, the adult age category in our study was more prone to increased visceral adipose tissue disposition, even though obesity defined by BMI was significantly more prevalent in children than in adults in our study. This could provide useful insights regarding the exact point when obesity starts to shift towards its visceral form, the most harmful cardiometabolic phenotype, encouraging future research in this direction. The results concerning adipose tissue distribution in relation to pathology type showed decreased TAT and SAT areas in patients with benign pathologies. This aspect may be due to the limitations of our study concerning sample size and distribution and could be elucidated in more extensive research.

Cap. 10. Risk Profiles in Ischemic Coronary Disease – Gender Particularities and Clinical Presentation

10.1 Introduction

Despite the significant recent advances in managing cardiovascular diseases, they continue to pose a significant health issue globally. Conditions related to ischemia are chiefly responsible for this, profoundly impacting quality of life and mortality (248). Acute coronary syndromes (ACS) stand among the most dramatic and life-threatening entities within this spectrum and are recognized medical emergencies due to the critical nature of their timely management (249,250). Atypical clinical presentations can affect the speed of treatment, leading to delays in both pre-hospital and in-hospital phases. There's also heightened interest in the gender disparities concerning the presentation, diagnosis, and treatment of these conditions. For instance, women may more frequently exhibit atypical symptoms and may receive less invasive treatments. The mechanisms underpinning these disparities continue to be a research subject.

This study's aims are to explore the gender-related differences in patients presenting with Non-ST-Elevation Acute Coronary Syndromes (NSTEACS) in the context of well-known cardiovascular risk factors: history of atherosclerotic disease, type 2 diabetes mellitus, smoking, hypertension, and overweight. Secondary objectives include investigating the variances between genders regarding implemented treatment strategies and assessing the prevalence of NSTEACS's atypical clinical presentations in the entire study group. Additionally, distinctions between the two entities that define NSTEACS: Unstable Angina (UA) and Non-ST-Segment Elevation Myocardial Infarction (NSTEMI), were elucidated.

10.2 Materials and methods

We collected data retrospectively, utilizing the discharge records of patients admitted to the cardiology department of the Clinical Recovery Hospital in Cluj-Napoca with NSTEACS between January 2014 and December 2015. The data encompassed demographic information, medical history, weight status, presenting symptoms, laboratory analyses, and results of coronary angiography, as well as the treatment strategies employed. Typical and atypical angina was identified post hoc (after examination of the medical records of the included patients).

10.3 Results

Women in our study group were more frequently hypertensive than men (89.5% versus 75.4%; *p*=0.043), had a higher mean value of serum HDL cholesterol (43 versus 38 mg/dL; *p*=0.022), were more frequently diagnosed with microvascular coronary heart disease (32% versus 9.8%, *p*=0.036), and were more often treated conservatively (49.1% versus 30.8%, *p*=0.038), while men were significantly more prone to smoking than women (30.8% versus 14%, *p*=0.028) and had higher mean values of serum creatinine (1.2 versus 0.8 mg/dL; *p*=0.022) and uric acid (6.9 versus 6.2 mg/dL; *p*=0.048). Of the 122 patients included, 109 had documented information regarding symptoms. The prevalence of atypical presentation was 4.6% (95% CI 0.7-8.5%). In our study group, patients with UA had a more frequent history of atherosclerotic diseases (77.4% versus 56.7%, p=0.015), the mean value for BUN was higher in patients with NSTEMI compared to those with UA (47 versus 39 mg/dL, *p*=0.038), and patients with NSTEMI received interventional treatment more frequently compared to those with UA (60% versus 41.9%; *p*=0.046).

10.4 Discussions/Conclusions

There is growing interest in the causality of gender differences in cardiovascular disease. Studies have indicated that women are more prone to vascular damage due to pathological vasoreactivity, vascular spasm, and endothelial dysfunction (251). Most patients with microvascular disease are female (252,253). Women develop cardiovascular diseases later than men and exhibit differences in risk factors (254,255). The conducted study analyzed gender disparities concerning risk factors, highlighting, among others, lower HDL-cholesterol levels, and a lower prevalence of smoking and overweight but higher hypertension in women. One area of interest is the clinical presentation of angina, where women are more susceptible to atypical symptoms (256,257). The study had limitations such as its retrospective nature, the limited geographical origin of the patients, and the sample size. Future prospective studies could provide further clarification about gender differences in cardiovascular disease.

Based on the information presented, it can be concluded that, despite limitations related to data collection and sample size, the results obtained in this study provide pertinent insights. The methodology outlined could assist in designing further studies exploring the gender-specific characteristics of patients with coronary disease or clinical aspects related to this entity. The ultimate aim would be to avert potential delays in administering optimal therapeutic management to these patients, especially in the context of atypical symptomatology.

Cap. 11. Predicting Glycemic Control in a Small Cohort of Children with Type 1 Diabetes Using Machine Learning Algorithms

11.1 Introduction

Type 1 diabetes (T1D) is a chronic condition characterized by an insulin deficit due to the autoimmune depletion of pancreatic β-cells, and it follows a course laden with various complications, associating with reduced life expectancy (258–261). Its prevalence is on the rise, reaching approximately 425 million cases globally, with 58 million in Europe. Demographic, clinical, biological, and socio-economic factors influence glycemic control, particularly in children. Although there are varied recommendations for target HbA1C levels depending on patients' ages, the American Diabetes Association (ADA) suggests a common target value of <7.5% for all pediatric age groups. With this in mind, our retrospective study sought to identify risk factors that affect glycemic control, initially through bivariate analysis and then using advanced statistical methods, including binary regression, two-step cluster analysis, and a CART decision tree, focusing on maintaining the same threshold value for all age groups. These advanced analyses aimed to enhance clinical interpretation and management of patients with type 1 diabetes, even within a small sample.

11.2 Materials and methods

The study was based on a retrospective analysis of data from the Pediatric Clinical Hospital of Sibiu, encompassing the period from January 2010 to August 2023, focusing on patients aged between 0 and 18 years, diagnosed with type 1 diabetes. The diagnosis was made following the recommendations of the American Diabetes Association, and data collection was oriented towards demographic, socio-economic aspects, and disease progression. In the data analysis process, various methods were employed, such as bivariate analysis to assess correlations, logistic regression to identify patterns of correlation significant with glycemic control, and cluster analysis for data grouping. Additionally, the CART algorithm was used to develop predictive models, evaluating their performance with the AuROC parameter and measuring agreement with the results of the cluster analysis usng the Kappa coefficient. Ultimately, the management of outlier values was considered to ensure the robustness and reliability of the results.

11.3 Results

In total, 79 patients were included in the study. Of these, 46 (58.2%) had an average HbA1C value of ≥7.5 g/dl, indicative of inadequate glycemic control. Bivariate analysis highlighted correlations between inadequate glycemic control and an extended duration of the disease, a higher Z-score of the BMI, an HbA1C at onset of ≥7.5 g/dl, lower family income, rural living environment, lower maternal education level, episodes of ketoacidosis following the onset of the disease, total cholesterol levels >200 mg/dl, and triglyceride levels >150 mg/dl.

The variables utilized in the regression model were the HbA1C category at onset, the presence of at least one episode of ketoacidosis during the course of the disease (excluding the onset of the disease), the Z-score of the BMI (centered around the mean), low or medium family income (a dichotomous variable derived from the initial categorical variable), and the last documented value for total cholesterol over 200 mg/dl. The outcome was an adequate binary logistic regression model for predicting glycemic control (Hosmer-Lemeshow p-value = 0.655). The model had an overall efficiency of 83.5% (87.9% for predicting good glycemic control and 80.4% for predicting inadequate glycemic control). The statistical significance of the included parameters, as well as the 95% confidence intervals for the regression coefficients, calculated using the BCa method, are presented in Table 14.

Variable	B	Sig.	BCa 95% CI pentru B	
			Limita inferioară	Limita superioară
Ketoacidosis episodes	21.1	<0.01	17.62	39.2
HbA1C at onset ≥ 7.5g/dl	3.12	<0.01	0.38	30.25
Family income low or average	2.73	0.018	0.32	57.02
Cholesterol ≥200 mg/dl	2.43	0.029	0.15	38.74
BMI Z score (mean-centered)	0.58	<0.01	0.1	1.94
Constant	-5.57	<0.01	-24.84	-5.08

Tabel 14 – Binary logistic regression model

Regarding the cluster analysis, the variables included were maternal education, living environment, family income, episodes of ketoacidosis, and the presence of elevated serum triglycerides. The resulting model defined four clusters with an average silhouette of cohesion-separation of 0.6, indicating good model quality. A visual representation of the cluster characteristics is depicted in Figure 23.

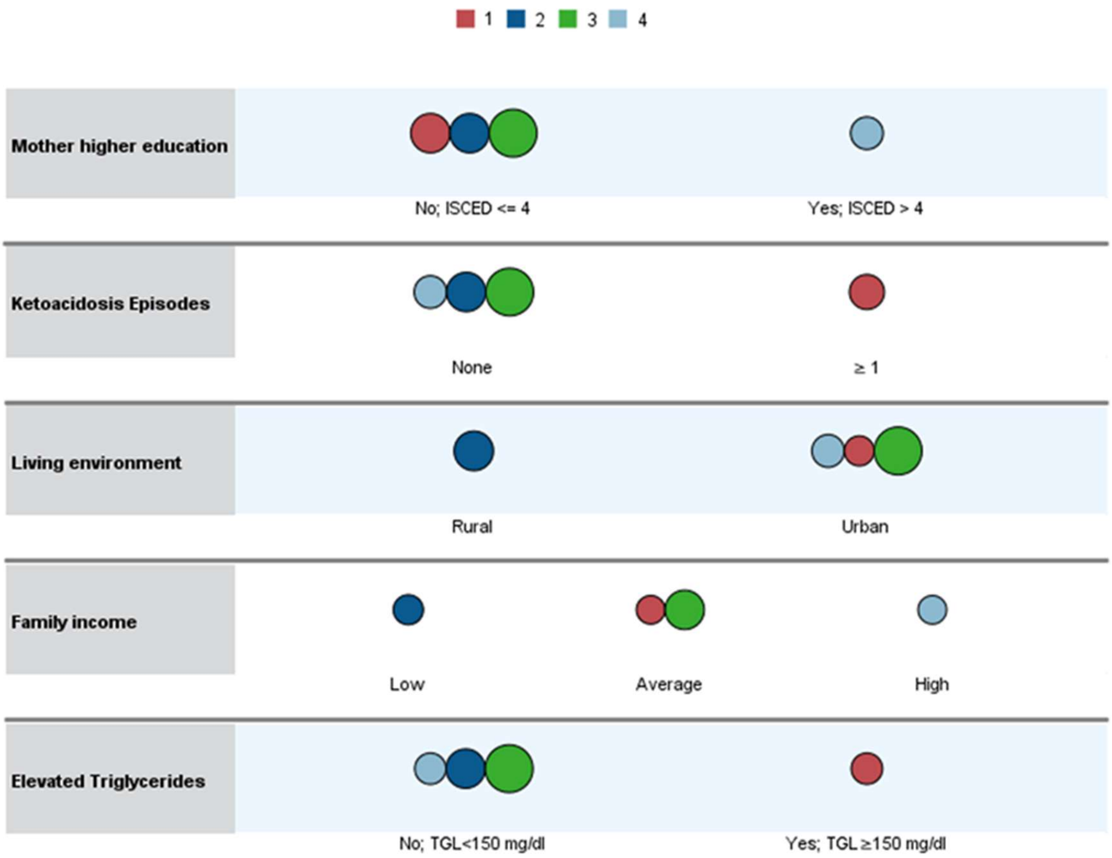

Figure 23 – Visual representation of cluster characteristics

The frequency of inadequate glycemic control within the clusters is presented in Figure 24. The observed differences are statistically significant (p<0.01).

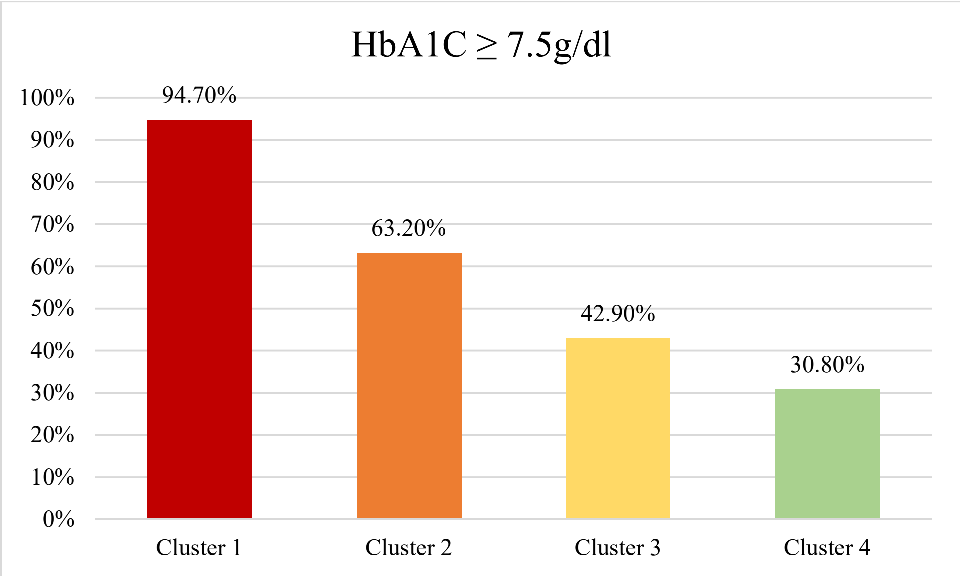

Figura 24 – Frequency of inadequate glycemic control across clusters

The CART decision tree model, depicted in Figure 25, was generated using the following variables: disease duration (continuous variable); low family income (dichotomous variable); residential environment (dichotomous variable); HbA1C at onset (dichotomous variable); episodes of ketoacidosis (dichotomous variable); and elevated cholesterol (dichotomous variable). It demonstrated an overall accuracy of 88.6% (91.3% in predicting poor glycemic control and 84.8% in predicting adequate glycemic control). The decision paths identified by our algorithm differentiated separate risk categories, delineated by sets of distinct characteristics. The AuROC for CART was 0.954, while the value for binary regression was 0.916.

Regarding the comparison of results obtained through cluster analysis and those from the CART decision tree analysis, we examined the distribution of terminal nodes and the clusters within the risk classes they represented. Risk classes were defined based on the proportion of patients exhibiting inadequate glycemic control within the node or cluster. Thus, high risk was characterized by a proportion of 66.6-100%, moderate risk was defined as 33.3-66.5%, and low risk was categorized as 0-33.2%. A visual representation of the patients' distribution within the terminal nodes and clusters is presented in Table 15.

Risk class / cluster		**High risk**				**Moderate risk**			**Low risk**	
		Node 4	**Node 6**	**Node 10**	**Node 15**	**Node 14**	**Node 16**	**Node 13**	**Node 8**	**Node 9**
High risk	**Cluster 1**	**6 (100%)**	**9 (52.9%)**	**2 (40%)**	**1 (16.7%)**	1 (7.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Moderate risk	**Cluster 2**	0 (0%)	4 (23.5%)	3 (60%)	0 (0%)	**5 (38.5%)**	**3 (100%)**	**2 (11.1%)**	2 (25%)	0 (0%)
	Cluster 3	0 (0%)	2 (11.8%)	0 (0%)	4 (66.7%)	**7 (53.8%)**	**0 (0%)**	**9 (50%)**	5 (62.5%)	1 (33%)
Low Risk	**Cluster 4**	0 (0%)	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	0 (0%)	7 (38.9%)	**1 (12.5%)**	**2 (66%)**

Table 15 – Patient distribution across clusters and terminal nodes with corresponding risk class – percentages across column categories

The Kappa coefficient of agreement between the cluster analysis and the CART algorithm in categorizing patients into the three aforementioned risk classes was 0.363 (p<0.01).

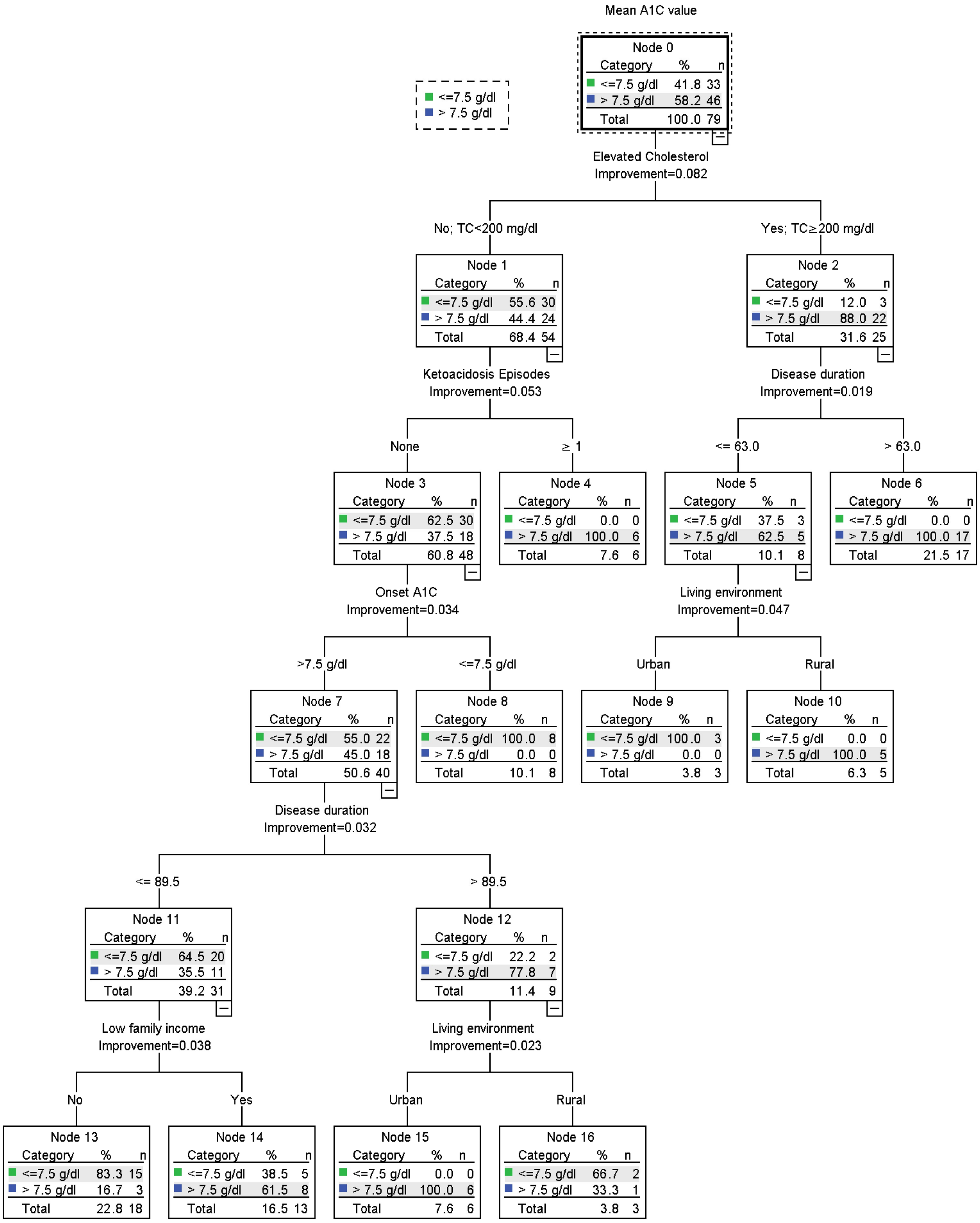

Figure 25 – CART decision tree

11.4 Discussions/Conclusions

The exploration of pediatric patients with type 1 diabetes requires a holistic understanding of the determinants of glycemic control. We approached this by utilizing a range of advanced statistical methods and artificial intelligence algorithms. Binary logistic regression quantified the role of predictive factors, the two-step clustering algorithm underscored the importance of socioeconomic and clinical attributes and their aggregation, while the CART decision tree revealed intricate interactions among variables. Together, these methodologies emphasized the concept of complementarity, considering that no single approach can fully capture the complete picture of such complex interactions.

GENERAL CONCLUSIONS

The comprehensive approach to the mechanisms that lead from pediatric obesity to cardiometabolic diseases in adults, conducted through a literature synthesis, has highlighted the profound connections between these two elements and guided the objectives of the current research. The general conclusions corresponding to each targeted objective can be summarized as follows:

1) In the comprehensive analysis of environmental factors leading to the onset of obesity, beyond the classic conception of the imbalance between intake and expenditure as the primary etiological factor, and interpreting data within the socio-ecological model of obesity etiology, studies focusing on exposures within the school environment that may affect students' weight balance have identified elements such as the presence of policies or practices related to healthy eating and physical activity, or the availability of sports facilities, that could play a crucial role in influencing students' weight balance. Adapted questionnaires for assessing the school environment in Sibiu underscore the profound impact of environmental exposures on student weight, highlighting the need for targeted interventions in schools. It was emphasized that a student's exposures within the family and school, including socio-economic status and parental education, potentially play an important role in determining weight balance.

2) Regarding the identification of the potential role of certain serological parameters of interest in quantifying the cardiometabolic risk associated with obesity, the study focused on evaluating the link between IGF-1 and obesity suggested an initial correlation between IGF-1 levels and weight status. However, this correlation dissipated upon adjusting for age, underlining age-dependent variations in relation to IGF-1. Being independent of BMI, IGF-1 may play a role in quantifying insulin resistance in children and adolescents, thereby providing a promising means of early detection of signs of diabetes and other metabolic complications.

3) To improve and increase the accessibility of methods for assessing adipose tissue disposition as a modulating factor of cardiometabolic risk, we identified the Otsu algorithm to be the most efficient for adipose tissue segmentation. The results highlighted an efficiency proportional to BMI, particularly for adult males. These individuals exhibited a higher predisposition to obesity and a predominant accumulation of visceral fat.

4) Regarding the importance of risk stratification in cardiovascular pathology, irrespective of age, the investigation of patients with NST-ACS revealed differences based on gender and mode of clinical presentation. This underscores the necessity for treatment and monitoring tailored to the individual characteristics of each patient.

5) Stratification methods, such as those based on HbA1C levels, have proven essential for understanding and anticipating the cardiometabolic risks associated with various clinical presentations and weight statuses.

6) The quantification of obesity's impact within the spectrum of exposures associated with cardiometabolic risk through advanced data processing techniques was approached in the study on predictors of glycemic control in children with type 1 diabetes. Binary logistic regression hierarchically quantified the role of predictive factors, the cluster-type algorithm emphasized the importance of socioeconomic and clinical attributes and their aggregation, while the CART decision tree revealed intricate interactions among variables.

ORIGINAL CONTRIBUTIONS

In the majority of studies conducted within the doctoral research included in this thesis, advanced statistical techniques and, where appropriate, machine learning algorithms were employed. Methodologically, this approach can lead to valuable outcomes that are objectively, mathematically confirmed and confirmable, with multiple possibilities for interpretation and further development in subsequent studies. The methodological approach of the thesis resulted in graphical elements that, in the author's opinion, provide new methods for showacsing the mechanisms involved in the onset of obesity and associated cardiometabolic impairments, with the possibility of extension for other medical research.

Within "Ch. 6. Assessing Obesogenic School Environments in Sibiu County, Romania: Adaptation of the ISCOLE School Environment Questionnaire" and "Ch. 7. Assessing the Lifestyle of Students from a High School in Sibiu: Adapting and Applying ISCOLE Specific Questionnaires," an adaptation and validation according to literature standards were conducted for the use of ISCOLE questionnaires in Romania. The two studies presented were conducted on a relatively small scale compared to the original studies, but the author regards the results obtained as remarkable, statistically significant, and notably, with the possibility of annual repetition, including on a much larger scale, on statistically significant samples for the school population in Romania across different age groups. Through the reduced costs and accessible methods of data collection, the implemented methodology and results obtained can serve as a foundation for educational initiatives and health promotion in schools. The application and interpretation of the ISCOLE questionnaires, as adapted by the author at such a level and periodically, open significant opportunities for the objective, scientific identification of necessary preventive interventions, even becoming a tool to support decision-making within the educational system.

"Ch. 8. Exploring the Link Between IGF-1 and Obesity" offers an intriguing opportunity in assessing insulin resistance in children, considering this parameter's independence from the body mass index.

In "Ch. 9. Analyzing the Efficiency of Abdominal Adipose Tissue Segmentation on MRI Sections Using Otsu, K-Means, and Fuzzy C-Means Methods," a new and original method is presented for delineating somatic abdominal adipose tissue from visceral fat based on MRI sections. The manual segmentation method presented in the study has been validated, including for use in children. The described research contributes to the advancement of adipose tissue quantification techniques and could have valuable implications for clinical applications. Similarly, one of the study's objectives was to provide open access to the code developed by the team coordinating the study, available online for those interested at https://github.com/maenstru56/MRI-VAT-SAT-Segmentation. The source code was developed by team members with expertise in programming.

In "Ch. 10. Risk Profile in Ischemic Coronary Disease – Gender Particularities and Clinical Presentation," new perspectives are presented on gender differences in cardiovascular pathology. The presented methodology can assist in designing further studies exploring the gender-specific characteristics of patients with coronary disease or the clinical aspects related to this entity.

"Ch. 11. Predicting Glycemic Control in a Small Cohort of Children with Type 1 Diabetes Using Machine Learning Algorithms" highlights the significant contribution of advanced statistical methods and machine learning algorithms in gaining a holistic understanding of the determinants of glycemic control in pediatric patients with type 1 diabetes. The binary logistic regression used in the study quantified the role of predictive factors, the cluster-type algorithm emphasized the importance of socioeconomic and clinical attributes and their aggregation, while the CART decision tree revealed intricate interactions among variables. Together, these methods underscored the concept of complementarity, considering that no single approach can fully capture the complete picture of such complex interactions. The variations observed in stratifications between cluster-type analysis and CART underline the need for an integrated analytical framework. Future research should consider combining these techniques, delving deeper into the nuances and seeking to further explore qualitative and quantitative outcomes. Such an integrated approach could be beneficial in providing individualized, evidence-based therapeutic guidance in managing type 1 diabetes in children.

FUTURE RESEARCH DIRECTIONS

1) Optimization of Questionnaire-Based Studies

The current methodology based on questionnaires can be enhanced in subsequent research by incorporating students from a variety of educational institutions. Additionally, instead of exclusively relying on self-reporting, the employment of objective methodologies for ascertaining weight status and levels of physical activity—such as the direct measurement of BMI and accelerometry, or the gathering of information from schools through audits—would bolster the reliability and precision of the data. Furthermore, longitudinal data collection might provide additional insights concerning the temporal progression of characteristics pertaining to the investigated communities, as well as the efficacy of interventions implemented to ameliorate the obesogenic environment in schools.

2) The Potential of IGF-1 in Guding Insulin Resistance Therapy

Investigations into the serum levels of IGF-1 present intriguing prospects for quantifying insulin resistance. As its connection with insulin resistance is unveiled, a deeper understanding of these mechanisms may serve as targets for potential innovative treatments.

3) Examining the Impact of Diets on Adipose Tissue Distribution

The methods employed to quantify adipose tissue distribution hold the potential to deepen our understanding of the effects of lifestyle interventions or even various therapies on adipose tissue disposition.

4) Developing Accessible Alternatives for Quantifying Adipose Tissue Disposition

Although the widespread application of magnetic resonance imaging for adipose tissue segmentation may be constrained due to costs and accessibility, research aimed at defining accessible predictive parameters for adipose tissue distribution is crucial. Correlating simpler tools with the findings obtained through the described investigations may offer new perspectives on the validity of such instruments.

5) Implementations of Artificial Intelligence Algorithms

The remarkable evolution of artificial intelligence algorithms and their versatile potential, ranging from population analysis to medical image segmentation, underscores the imperative of their integration into clinical practice. These techniques have the potential to revolutionize the diagnosis and treatment of a wide array of conditions.

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