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Obesity in children: systematic review over a 6-year period, including the Covid-19 pandemic

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ABSTRACT

Although obesity is a frequently formulated diagnosis at all ages, due to the long-term projection of the consequences of this condition in children it is a real public health problem. The etiology of obesity is multiple and its complexity requires a multidisciplinary medical approach from which the psychological component cannot be omitted. Thus, diseases such as diabetes, dyslipidemias, cardiovascular diseases, sleep apnea syndrome, non-alcoholic fatty liver or neoplasia are encountered with a higher incidence in this category of individuals. During the COVID-19 pandemic, the isolation and, consequently, the reduction of access to ways of performing physical exercise increased the balance between caloric intake and caloric consumption resulting in the accumulation of surplus calories in the form of adipose tissue. The purpose of the present work is to emphasize the interest manifested by the medical scientific world regarding obesity in the pediatric population, in the pre-pandemic period, during the pandemic period and one year after its' end (2018-2023). We performed systematic review of clinical studies on obesity in the pediatric population, including 98 articles published in the PubMed database. The number of studies published during the pandemic period (53) vs the number of studies published ex-pandemic (45), corresponds to a ratio of 1.17:1 in favor of the first. Obesity remains a research topic of major interest in early life, regardless of the coexistence of COVID-19.

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Introduction

The burden of obesity quantified in the Global Burden of Disease study (2017), which used global deaths and disability-adjusted life years (DALYs) as analytical factors, showed that an increased body mass index (BMI) is associated with multiple comorbidities, an increased risk of death, and an increased economic burden on health systems [1]. Considering the long-term consequences of this condition in children, it is a priority to study obesity as an economic and social burden, and also from the perspective of the individual negative consequences. The current descriptive analysis aims to quantify the size of the obesity phenomenon and the scientific interest on this topic whose extent is underestimated [2].

COVID-19 pandemic has impelled weight gain patterns across different age groups. One can thus intuit the concern for finding viable solutions to counteract the immediate and future consequences of this weight burden. On the other hand, it is obvious that the short period of time since the end of the pandemic could not offer the possibility of carrying out studies that would allow drawing relevant conclusions regarding the consequences and the pandemic dimension of obesity [3]. This aspect is supported by the analysis of some studies published post-pandemic that provide data on obesity, also related to the pre-pandemic period [4].

This descriptive analysis aims to describe the size of this burden [5] by comparing the incidence of obesity in three distinct periods of time, and to quantify in the interest

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shown by the medical scientific researchers regarding obesity in the pediatric population, starting from the premise that during the pandemic period there was a decline in interest regarding this phenomenon. Also, another purpose of the research is to highlight the complexity and polymorphism of the factors involved in the etiopathogenesis of obesity and also the complexity of the therapeutic approach in medical practice.

Another secondary objective is to find theoretical models from which the mechanisms of action that contribute to obesity appearance can be deduced. Thus, from the arsenal of existing theoretical models, Bronfenbrenner's theory of ecological systems seems to overlap extremely well with the pandemic situation regarding the determinism and incidence of obesity. According to this model, there are 5 interconnected systems that act on the child's development and the action is bidirectional [6].

During the pandemic, the medical crisis attracted an economic and social crisis that profoundly changed interpersonal relationships and produced transformations in terms of the medical approach to various conditions. Recent research on obesity through a holistic approach has highlighted the fact that the economic status and the role of parents in food choices or children`s lifestyle were major factors in the etiology of obesity [7,8].

Materials and Methods

Two independent reviewers searched for clinical studies on obesity in the pediatric population published in the PubMed database using as search key the words obesity, diet, and children. By that definition, therefore, children are those persons under the age of 14. It is, however, worth noting that Article 1 of the United Nations Convention on the Rights of the Child defines 'children' as persons up to the age of 18. By definition, therefore, children are those persons under the age of 14. It is, however, worth noting that Article 1 of the United Nations Convention on the Rights of the Child defines 'children' as persons up to the age of 18. The mention was made because there are several classifications of the childhood period (some including middle childhood up to 12, 13 or 14 years old). We chose the version up to the age of 14.

We identified 98 articles published in a 3-year period in which there was a pandemic burden, and in an ex-pandemic period, the ex-pandemic period consisting of three years: 2 pre-pandemic years (2018 and 2019) and one year being post-pandemic (2023). The search for articles in the mentioned database was carried out at the beginning of 2024, more precisely starting in January 2024. As a general rule in this review, reference was made to the year of publication of the studies.

The systematic review of the results of the studies was realized with Microsoft Excel® program.

We consider it more correct to classify our work in the category of systematic reviews (than in the category of descriptive analyses) and we argue this by the fact that it corresponds to the last criteria established for this type of analysis: the academic synthesis of the evidence (the 98 studies on a certain topic - obesity at child) using critical methods of identification, definition and evaluation. In other words, the systematic review extracted and interpreted the data from the studies published on a topic - the one mentioned - subsequently performing an analysis, description, critical evaluation and summary of the data in an evidence-based approach. We appreciate the confusion regarding the study's framing is due to the fact that systematic reviews are closely related to meta-analyses and frequently the terms are considered synonymous (in the literature often appearing framing - systematic review and meta-analysis). We believe that the difference between the two types of classification consists precisely in the fact that a meta-analysis uses statistical methods to induce a single number from the combined data set (such as the effect size), while the strict definition of a systematic review excludes this step. Consequently, a systematic review can be designed to provide a detailed summary of the current literature relevant to a research question, as is the case with the study under your attention. In order to evaluate and minimize the bias of the results we have rigorously approached and transparent research synthesis (requested table) aspects imposed in the case of this type of study. For this reason, we appreciate that our study, which is not based on a quantitative meta-analysis (it only uses a given number of studies as analysis material on the same topic) can be classified as qualitative reviews or a type of mixed analysis that adheres to the standards imposed for the collection, analysis and reporting of evidence. We followed the PRISMA criteria that standardized how to report methods for combining qualitative and quantitative research in systematic reviews. The specialized literature makes a clear mention of the fact that the inclusion of the PRISMA criteria can be limiting and limited only to studies related to intervention research, the present study being research without intervention, more precisely a non-interventional systematic evaluation. Consequently, we opt for inclusion in a systematic (non-interventional) review.

We used the Formulas-Statistical function of Microsoft Excell and the Data Analysis function of the same statistical analysis software for data processing.

We obtained the following data: Average 32.66; SDEV 21.45279; T Confided (for 95%) 0.136244; Median 44.5; Z-score: the test statistic follows the standard normal distribution N (0.1); p-value $\approx$ 0.002318. The result is statistically significant; we can reject the null hypothesis and accept the alternative; this decision is made at significance level $\alpha = 0.05$; the Z-Score: test statistic follows the standard normal N (0.1) distribution.

Our working hypothesis concerning the statistical analysis was that the pandemic period represented a moment of decline in terms of interest in childhood obesity, an aspect possibly determined by the focus on the health crisis determined by the existence of the COVID-19. We opted for this type of analysis because it presents a low risk of bias. We mention the fact that the design of the study took into account the use of some search terms - obesity, diet, and children - in order to comply with the eligibility criteria of a systematic review type study, an aspect that also leads to the minimization of the risk of bias through the selection of some relevant studies for the topic addressed. It also allowed us to easily synthesize the data collected by analyzing the research used as study material [9]. In the selection of studies that we included in this systematic review we used the previously mentioned search terms, each of them being considered representative of a concept. Gathering the conclusions obtained in the case of each individual concept allowed the formulation of the final conclusion of the present study. We mention the fact that for the design of the study we took into consideration the terms - obesity, diet, and children- in PubMed database.

Studies that are not found among the 98 that are the object of the current analysis but the ones that are present in the bibliographic references were used to complete the frame of reference of the subject addressed. The material used in the study was identified in the PubMed database, this being both a database accessible to all professionals and without involving additional costs (for access to medical information).

The articles used in the study were searched in the PubMed database and the results were independently triple-checked through title/abstract and full text stages (Table 1). Included studies were assessed for risk of bias. Of the 161 references analyzed, 98 (Supplementary Material) met the eligibility criteria and were included in the evaluation and 63 were removed from the study for various reasons, mentioned in the flow diagram (Figure 1).

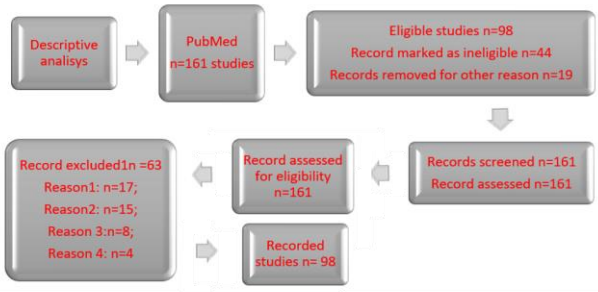

Figure 1. Flow diagram according to the PRISMA criteria (2020)

Flow diagram according to the PRISMA criteria 2020 (Figure 1) also defines the 4 terms of exclusion from our study: reason 1 for exclusion: Without obesity - obesity prevention, reason 2 for exclusion: Key term - physical exercise, reason 3 for exclusion: Key term – family and reason 4 for exclusion: Adults.

Table 1. PRISMA guidelines table according to our study (2020 version)

Articles (98)	Systematic review
Objectives	Has the pandemic period led to an increase in the incidence of childhood obesity and hence its study, quantified by the number of published studies?
Motivation	The importance of diagnosing and managing obesity in children due to the inclusion of this condition in the category of public health problems
Eligibility criteria	Children (under 14 years of age) with obesity and aspects related to their diet
Source of information	Data base PubMed, accessed in January 2024
Search strategy	Keywords: obesity, diet, and children.
Selection process	Manual search in the database - 3 of the authors searched independently in the same database, in the same interval and using the same search keywords
Data	Free full text; associated data; classical article; clinical study, clinical trial, comparative study, pragmatic clinical trial, randomized controlled trial. The results were double-checked independently through title/summary and full-text steps by 3 of the authors. Included studies were assessed for risk of bias. Of the 161 references reviewed, 98 met the eligibility criteria and were included in the assessment.
Effect measures	They are only mandatory in the case of meta-analyses; Tabulation of study intervention characteristics Comparison with planned groups; The study is not included in the category of meta-analyses and for this reason does not require the evaluation of the risk of bias
General interpretation in the context of other evidence	It is possible that measures taken in connection with the limitation of the spread of SARS CoV-2 (mainly isolation) have contributed to favoring a positive dynamic in terms of weight gain in children, especially in obese children. We are talking about a childhood obesity pandemic that is evolving in parallel with the Covid-19 pandemic
Limitations of the review process (limitations arising during any research process)	The limits of the research process; Limited access to information (in this case by accessing a single database) Language fluency; Time constraints; Methodological limitations High heterogeneity due to multiple variables like the variability of the participants, the methodological diversity, the differences between the studies, the differences between the evaluations of the results. Limitations of the review process; Limitation to studies in English; Difficulties in the selection process
Implications of results for practice, policy and future research. Obesity is a public health problem, especially in the pediatric population. Knowing the etiology and implications of obesity in the health economy can facilitate better management and limiting its consequences.	

Results

Systematic review of distribution of studies

We observed the distribution of the data represented by the number of studies in the periods described before. There was a homogeneous distribution of the number of studies, but we appreciate a high heterogeneity due to multiple variables like the variability of the participants, the methodological diversity, the differences between the studies, the differences between the evaluations of the results. The validity of this systematic review lies in the fact that each study/type of analyzed studies presents the same type of intrinsic medical interest based on the same core study characteristics – obesity-children-diet. In addition, we presented the information using a mixed qualitative and quantitative approach for easier understanding by the clinicians.

Analyzing the data related to the distribution of studies by year, we noticed that the largest number of studies were published in 2020 (25 studies representing 25.51% of the total number of studies) [10-20]. Next are the years 2019 [21-25] and 2021[26-30] that are equal: 22 completed studies that represent 22.44% of the total number of studies analyzed. A drop in the number of studies can be observed in the post-pandemic period (the ratio between 2022 and 2023 being 3.66:1 in favor of 2022). Thus, in the year 2022 [31,32] in which the pandemic officially ended, a number of 6 studies were found. In 2023, the number of studies were equal to half of the previous year, meaning only 3 studies [33-35] (a decrease of 50%) as shown in Figure 2 (distribution of studies by years).

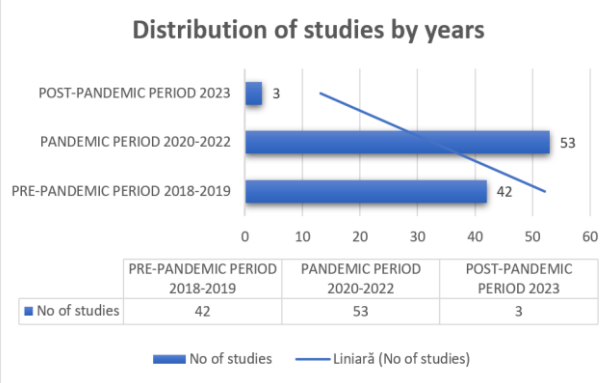

Figure 2. Distribution of studies by year

We compared the number of studies in subjects with obesity related to the presence of the SARS-CoV2 virus infection versus controls. We observed that the pandemic period did not represent an impediment to the study of obesity, in which its multifactorial etiology was the reason for the study. The number of studies on obesity unrelated to the presence of COVID-19, referring to the number of studies analyzed, was 65.44 times higher than the one in subjects with COVID-19 (a single study being published during 2021) [36].

The comparative analysis of the number of studies published during the pandemic period (53) relating to the subject addressed versus the number of studies with the same subject published ex-pandemic (45), shows a numerical advantage in favor of the pandemic period (1.17% more studies conducted during pandemic) (Figure 2). During the pandemic period (2020-2022) we observe that it is a downward tendency, with a sharp decrease of 3.66 times in 2022 compared to 2021, and 4.16 times compared to 2020.

In 2019 there was the largest number of ex-pandemic studies (22) on the subject addressed. The comparative analysis of the pre-pandemic vs post-pandemic period reveals a number of 44 studies in 2018 and 2019 and only 3 studies in 2023 (more precisely 14.66 times less than in the two years, 6.66 times compared to 2018, respectively 7.33 times compared to 2019) (Figure 3).

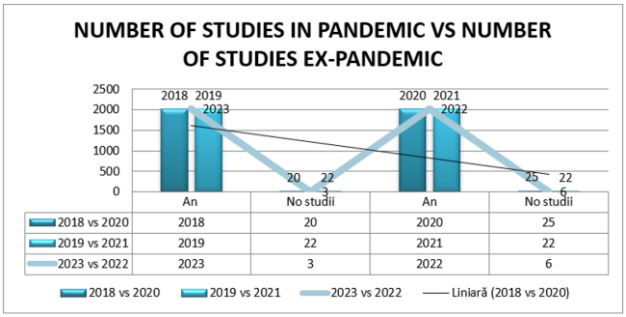

Figure 3. Comparative graphic: studies published in the pandemic period vs. studies published in the after the pandemic period.

With reference to the number of studies published in the PubMed database during the pandemic period (53) vs. the number of studies published ex-pandemic (45), a ratio of 1.17:1 can be observed in favor of the number of studies published in the first period.

Searching for the studies in which the term "diet" appears as a reference index, we found that only a number of 28 studies (28.57%) containing this term; the percentage is significant, thus making it almost 1/3 of the number of studies [37-44].

Factors involved in the pathogenesis of obesity

We analyzed the factors involved in the etiology [43,44] of obesity that appear in the mentioned studies and found that a number of 4 studies had as reference the genetic factors (4.08%) [41-49], 2 studies considered the epigenetic factors (2.04%), 1 study focused on behavioral factors (1.02%), 3 studies on psychological factors (3.06%), 2 studies on educational factors (2.04%), 60 studies on general factors (61.22%) and 26 studies included a polymorphism of these factors (26.53%) [50]. We found that the multifactorial etiology of obesity is considered in the majority of studies and researchers chose different approaches to complete the missing pieces of this complex puzzle as shown in Figure 4.

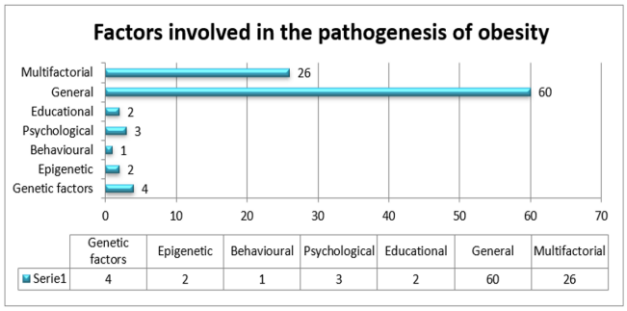

Figure 4. Factors involved in the pathogenesis of obesity

The classic theories regarding the etiology of obesity incriminate a number of "traditional" factors, namely diet [51,52], sedentary lifestyle, the genetic factor [53], transgenerational or cultural habits, and education. Newer studies, including some of those addressed in this descriptive analysis, bring into discussion other factors such as the microbiome, metabolomics [54] or up to date perspectives of a classic factors, like maternal obesity. A number of 14 (14.28%) of the total studies discuss modern factors in the study of obesity [55]. Of the 14 studies that involve these factors, three (21%) study maternal obesity [56-58], three (21%) involve the microbiome in the genesis of obesity, and eight studies (56%) bring in the metabolomic discussion as a factor incriminated in the etiopathogenesis of obesity.

Recognized as a period of psychobiological crisis, the adolescent period represents a crossroad in the life of each individual with major implications in the health status determined by the eating and living habits of the future adult. Thus, the need for a quality diet is emphasized, exemplified by the Mediterranean-type diet in children and adolescents with abdominal obesity, the consequences being represented by the significant reduction of the BMI standard deviation score (BMI-SDS) accompanied by the reduction of blood glucose and serum cholesterol levels [59]. In the same registry, a series of studies show the presence of metabolic syndrome in children and adolescents, with its cardiovascular implications and the role of diet and physical exercise in its management [60,61]. There are studies that refers to that refer to the obesity-child-diet triad [59-62]. This scourge of obesity is found in various geographical areas and it is an example of the burden of obesity for the public health system and the consequences for the health status of children through the comorbidities due to obesity. This aspect correlates with the findings of the previously mentioned study in which the metabolic syndrome with cardiovascular consequences in children and adolescents is spreading in Europe, Asia and America [61]. The „Australian Burden of Disease Study", from 2018 is an example of the burden of obesity for the public health system and the consequences for the health status of children through the comorbidities due to obesity (placed in a certain geographical area. It was cited due to the complexity of the approach, being able to be extrapolated to any pediatric population on the Globe. The analysis of the studies reveals the fact that a number of 13 studies (13.26%) were carried out on adolescent subjects [62-68].

The analysis of the relationship between childhood obesity and its associated comorbidities showed that metabolic disorders, in which glycoregulation disorders prevail, are the most numerous. Thus, from studies in which the comorbidities of obesity were investigated, the analysis of the relationship between childhood obesity and its associated comorbidities showed that metabolic disorders, in which glycoregulation disorders prevail, are the most numerous. From our research there were studies in which the comorbidities of obesity were investigated and 11 (11.22%) studies associated glycoregulation disorders [69], 14 studies (14.28%) associated metabolic disorders (glycoregulation and other disorders) and an equal number of 3 studies (3.06%) associated asthma [70] and non-alcoholic fatty liver - 3 [71-73] and 2 studies (2.04%) neoplastic diseases, endocrine disorders 3, urinary stone 1, sleep disorders 1, density bone 1, affective disorders 2 (Figure 5).

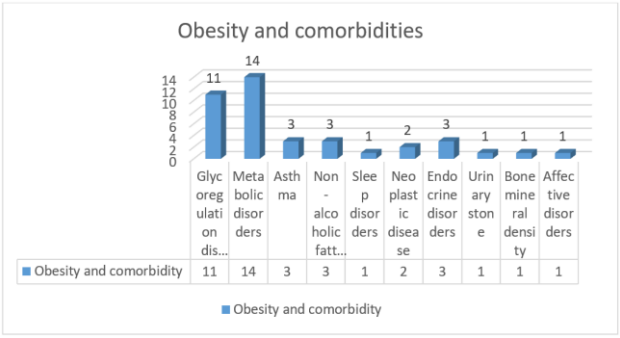

Figure 5. Comorbidities associated with childhood obesity

As it results from Figure 6, the treatment of obesity requires intricate, complementary factors [74]. Among the factors involved, we note that the most significant is the quality of the diet [75], which is mentioned in 41 studies (41.83%), followed by the nutritional intervention [76-81] factor found in 34 studies (34.69%) [82].

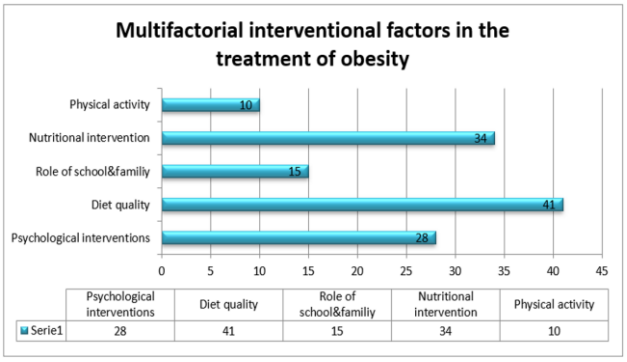

Figure 6. Multifactorial interventional factors in the treatment of obesity

On the third place is the psychological factor mentioned in 28 studies (28.57%) [83], followed by the role of school and family in 15 studies (15.30%) with multiple components: parents perception of the child's overweight/obesity, eating habits in the family, the type of food offered to children, socio-economic status of the family, the school's interest in children with weight problems, the diet plan adopted in the school, the collaboration between parents and the school in the case of obese/overweight children [84-88]. In last place is the physical exercise mentioned in 10 studies (10.20%) [89-91].

Discussions

The systematic review carried out regarding the number of published studies during the COVID-19 pandemic period rejects the hypothesis from which the present descriptive analysis started. There could be multiple factors explaining the equal number of studies in the two periods. First, the short period of time that passed since the end of the pandemic and the procession of comorbid conditions. Second, COVID-19 has reduced the time available for data collection and for conducting studies on large population samples at that time. Thus, the ongoing studies that due to the complexity of the situation were difficult to complete, were published immediately after the pandemic, creating the illusion of a concern still focused on the pre-pandemic period [92,93]. On the contrary, the present systematic review demonstrates an increase in the interest shown by the medical scientific world regarding obesity. Through the theoretical analysis of the general risk factors of obesity, an increase in obesity among children was predicted during the period of isolation, knowing the pandemic restrictions. This fact is supported by the numerous studies published both during 2020-2022 and after the end of the pandemic.

It can also be observed that medical studies regarding obesity were not diverted from its multifactorial origin. In essence, the pandemic context has emphasized a series of factors that contribute to the appearance of obesity, namely sedentary lifestyle and higher calorie consumption determined by the refuge "in food" as a consequence of isolation and anxiety [94]. Regarding the comorbidities of obesity, a significant association with metabolic diseases was found (14.28%). The remote risks of death at a young age or major complications for affected individuals are exponential given the life expectancy of a child [95]. For this reason, sustained interventions are needed to counteract the effects of obesity in children from the prenatal period through the education of future mothers. This education is also necessary in the gestational and postnatal period, being a team work, interdisciplinary, with the participation of doctors from different specialties (gynecologists, neonatologists, pediatricians, nutritionists, psychologists) [96,97].

An identification of the interventional factors involved in obesity therapy and the quality of the diet [98-100] bring this study in the foreground [101,102]. On the second place are nutritional interventions, closely followed by psychological interventions. In the case of this last factor, we mention that the psychological factor plays a double role, that of a co-factor that acts synergistically with the diet and as a protective factor for the appearance of the anxiety disorder depression, substance addiction or eating disorders. The pandemic period has brought multiple changes both in the way and type of children's food and to an equal extent it has changed the attitude and expectations that individuals have from the medical world, in solving this health problem with long-term and very long-term implications when referring to the pediatric population [103,104], but during pandemic there were no statistical modifications for appetite in adults [105].

All the mentioned factors mutually increase the action, contributing positively to obesity therapy, which represents a personalized treatment adapted to contextual-situational factors. In this case, the pandemic context determined an unexpected turn in the evolution of obesity as a condition per se, as well as the factors involved in its determinism. The situational uncertainty, isolation and anxiety generated by the pandemic have contributed to increasing the significance of the psychological factor in the genesis of obesity [98].

A comparative analysis with studies previously published in the literature confirms the multifactorial etiology of obesity in which diet occupies an important place. It is also emphasized in these studies the need to access new branches of interest – proteomics [106], epigenetics, genetics, metabolomics, to decipher still unknown mechanisms involved in the determinants of obesity, which can provide valuable information regarding the clinical management of this condition [107].

Our systematic review has several limits represented by the small number of articles (98 articles) and consequently by the comparative reporting to large trials taken into the study. Moreover, it represents an indirect method of analyzing the sphere of interest for this subject. By studying in depth, the relationship between all the variables found in the published articles in a meta-analysis would be useful. There is a risk of bias which is due to the risk of bias of the individual studies considered. The advantages of a multifactorial study (Multiple factor analysis/ MFA) like this one are represented by: the idea of a starting point for future studies regarding significant correlations between obesity and psychological, behavioral and educational factors with relevance in the etiology and management of obesity [108]. In addition, it offers the possibility for a comparison between the ex-pandemic and pandemic periods regarding both the frequency and the interest shown by researchers on a worrying phenomenon with medical, economic and social repercussions. It also offers a comparative perspective between the classic and the modern approach to obesity, regarding the possibilities of diagnosis [109-112].

Considering the implications of obesity in the etiology of diabetes and the subsequent need in many situations of insulin therapy, it also has repercussions on the weight status of patients on insulin therapy. For this reason, it is important to increase adherence to pharmacological treatment and equally to increase adherence to hygienic-dietary treatment indications [113]. In this context, the use of some work tools, among which we mention the motivational interview, could increase adherence to both diet and therapy [114]. Another aspect of the management of honesty in children involves maintaining a positive affective status that is sometimes difficult to manage, especially in children. In this sense, intuitive eating could offer advantageous alternatives for children's diet, the barrier determined by their food relativity being known [115]. In the absence of adherence to diet and pharmacological therapy, children will honestly become future candidates for some radical therapy methods in order to counteract the harmful effects of obesity [116]. Studies show that overweight and obesity are risk factors for the occurrence of thromboembolic accidents in a significant proportion, in patients with honesty and DM, the age of their occurrence being lower and lower. For this reason, it was necessary to implement new therapy methods that could benefit this category of patients [117].

Limitation of the study

The current study, as we stated, does not aim to provide data on the incidence of obesity in children, nor did it aim to discover new therapeutic methods. We have carried out a systematic review of new obesity therapy attempts, starting from the identification of the etiology and risk factors presented in the studies included in the study.

In the design of the study, we did not start from hypotheses or research questions, the purpose of the study being to demonstrate the interest in a subject belonging to public health, namely, obesity in children, and to highlight the interest shown by the scientific world with reference to three periods having as a reference, the known pandemic period being the moment of medico-social crisis represented by it. For this reason, it does not require Forest diagrams. We believe that any article that discusses a collection of data organized by levels of interest (age, comorbidities, etiology, etc.), depending on the data analyzed, can be the starting point for new studies by being able to make correlations that are easier to made by studying an article that synthesizes the data. The material used in the study was identified in the PubMed database, this database being accessible to all professionals without involving additional costs.

It is recognized that life expectancy is deeply affected by the presence of obesity due to the procession of comorbid conditions. This is one more reason to decipher the genetic, transgenerational and psychological mechanisms involved in the genesis of obesity and, implicitly, the discovery of therapeutic methods and especially methods of intervention and countering the triggering factors.

Conclusions

Obesity remains a research topic of major interest at all ages. Its implications at the pediatric age and even starting from the intrauterine life constitute a priority considering the long-term and very long-term projection related to children's life expectancy. We showed there was a homogeneous distribution of the number of studies related to obesity in children in the pandemic and ex-pandemic period. We observed a high heterogeneity of the studies due to multiple variables including the variability of the participants, the methodological diversity, or the differences between the evaluations of the results.

Our systematic review represents a starting point for future studies regarding significant correlations between obesity and psychological, behavioral and educational factors with relevance in the etiology and management of obesity. In addition, it offers the possibility for a comparison between the ex-pandemic and pandemic periods regarding both the frequency and the interest shown by researchers on a worrying phenomenon with medical, economic and social repercussions. It also offers a comparative perspective between the classic and the modern approach to obesity, regarding the possibilities of diagnosis.

Although the present study does not provide information regarding the discovery of therapeutic possibilities, it can be considered an original approach by analyzing a complex phenomenon such as obesity starting from the etiological factors, incidence, comorbidities and ending with its medico-social implications. The comparative analysis, taking as a benchmark a period of global social crisis - the pandemic, allows a paradigm shift regarding the reporting of medical systems to the needs and consequences of turning points in the evolution of mankind, especially when we refer to a population sample as is the one represented by the pediatric population.

Contributions

Conceptualization: CC, AV and LAM, methodology: CC, AV, LAM and APS, analysis and interpretation of the data: CC, LAM, visualization: CM, RAS and FG, authenticity of the data: RAS and FG writing original draft: CC and LAM, writing the final draft: CM, RAS and AV. All authors read and approved the final manuscript.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript. Informed consent was obtained from all subjects involved in the study.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

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