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Review Article

Epigenetic and Metabolic Alterations that Interfere in Human Development and Predispose the Manifestation of Obesity and Other Metabolic Disorders: A Systematic Review

Linda Carla Moraes Lima[1], Angela Civalsci Cubaski[1], Mirian Ueda Yamaguchi[2] and Marcelo Picinin Bernuci[2]*

[1]Department of Medicine, Cesumar University (UniCesumar), Maringá, Parana Brazil

[2]Health Promotion Department, Cesumar University (Uni Cesumar), Cesumar Institute of Science, Technology and Innovation (ICETI), Maringa, Paraná, Brazil

***Corresponding Author:** Marcelo Picinin Bernuci, Department of Promotion of Health, Cesumar University (UniCesumar), Cesumar Institute of Science, Technology and Innovation (ICETI), Maringá, Paraná, Brazil.

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Abstract

Recent studies have demonstrated the multifactorial characteristics of the development of metabolic disorders that have shown the necessity for new research in the area, with the objective of unravelling the factors that could possibly influence critical stages of human development, altering a patient's metabolic programming. This study aims to identify the main elements that endorse the biological incorporation of these events on an intrauterine environment or on the first years of life, assessing the potential epigenetic, endocrinological and metabolic mechanisms responsible for this process. The goal of this analysis is to state which main factors allow broader studies to develop specific intervention models for the prevention of metabolic disorders, particularly obesity. This systematic review was based on the PRISMA-E 2012(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and registered on PROSPERO (Nº CRD42020197344). The research and selection of the articles occurred in June-July 2020 and used the United States National Library of Medicine PubMed – Medline and Cochrane Central Register of Controlled Trials databases, and clinical trials that focused on the analysis of influencing factors on metabolic programming were collected. In this study, we discuss how these elements are capable of influencing critical periods of human development and its potential consequences for the affected individuals, with the objective of identifying possible targets for future interventions. Sixty-two articles were identified and included in this systematic review. Among the selected articles, twelve were directly related to epigenetics, fourteen were related to obesity, sixteen were nutrition related and twelve were focused on diabetes. The data revised showed that stress, excessive weight and maternal malnutrition are potential fetal metabolism modifiers that result in disorders that can predispose to child obesity. It was also demonstrated that gestational diabetes and dyslipidemia are conditions that can influence the fetus' levels of adiposity and that epigenetics can directly alter fetal programming, resulting in significant metabolic alterations, including the predisposition to weight disorders in the child. In conclusion, epigenesis presented itself as an important way for biological incorporation of the heritability of metabolic diseases, through the methylation and deacetylation pathways, becoming an important factor in future studies focusing on possible interventions for the prevention of these disorders.

Keywords: Metabolic Programming; Biological Incorporation; Risk Factors; Metabolic Disorders; Mother-Child Overweight

Introduction

Child obesity is one of the most important issues of the present day and a challenge for health-systems worldwide. Overweight is defined as an exaggerated and abnormal accumulation of fat that is potentially harmful to one's health [1]. This condition substantially favors the risk of chronic disease, disabilities, affects quality of life and increases mortality through the association of excess weight as a risk factor for the development of cardiovascular disease, dyslipidemia and insulin resistance [2]. There are many risk factors for developing child obesity, according to the Obesity Management Guidelines of the Brazilian Health Supplementary (2017), such as the following: prematurity, obese parents, early interruption of breast feeding, diabetic mothers, small-for-gestational-age (SGA) newborns, large-for-gestational-age (LGA) newborns, erroneous food introduction and the consumption of meals containing high levels of sugar and fat during early childhood. Children that show an elevated body mass index (BMI), accelerated and exaggerated weight gain in their first months have higher chances of becoming overweight [3].

The child obesity rate rose considerably among children aged from five to nine years during the 1989-2009 time period. The percentage of overweight boys in that age group rose from 13.8% in 1989 to 51.4% in 2009; the percentage of overweight girls belonging to the same group rose from 10.4% to 43.8% during the same time interval [4]. In 2016, approximately 340 million children and adolescents aged between five and nineteen were overweight [1]. This significant impact justifies the importance of understanding the development of this process and the potential modifiable risk factors, so that specific interventions can be elaborated. Obesity has a multifactorial etiology and is defined as a polygenic condition, the combination of a group of genes that favors adiposity due to its activity on genetic components; its modification of microorganisms that influence energy metabolism, degrees of inflammation and bowel alterations; the endocrinological disorders associating obesity to conditions such as hypercortisolism, hypoparathyroidism, hyperparathyroidism, growth hormone deficiency; neurological and sleep disorders [4].

In addition to these factors, the epigenetic modulations also present considerable relevance for child obesity and, possibly, for overweight in adults and adolescents. There is current evidence that sustains the idea that there are processes through which the initial life factors can influence the child's health. This concept is named programming and it originated from a great number of epidemiological and experimental observations. The concept of Developmental Origins of Health and Disease (DOHaD), also known as fetal programming, originated initially as an explanation for a definite response generated in an organism against certain expositions during critical periods of human development. The concept of programming was then improved and defined as the process through which the pre-conceptional environment, intrauterine environment and early-childhood longitudinality shapes the physiological control and the homeostasis of the human organism [5].

Recent evidence has pointed to a significant impact of certain early exposures in life – for example: maternal obesity, diabetes, perinatal and neonatal malnutrition – on the child's metabolic risk, creating a transgenerational amplification of metabolic alterations. This epigenomic programming is widely established in the intrauterine period, and is specifically sensitive to prenatal stress factors, resulting in potential singular mutations during one's lifetime, thus influencing the health-disease process [6]. Considering all possible metabolic alterations that can be created through epigenetics and comprehending the existence of a clear relationship with the development of child obesity through influences in embrionary life and early childhood (where the involvement of epigenetic modifications – DNA methylation, histone tails and microRNA modifications – are evidently more related to the development of obesity [7] it is necessary to study and elucidate which are the main influencing factors of this process, with the aim of understanding how to identify successful interventions.

Regarding the formation process of this metabolic programming, the maternal influences are fundamental. Through understanding that preconceptional, gestational and postgestational factors can create alterations or adaptations in the child's metabolic profile, it is possible to comprehend the predisposition to certain diseases such as diabetes, obesity and metabolic syndrome, among others that can be presented by the child. Based on that information, it is understood that the mother's nutritional state, the intrauterine environment, the feto-placental unit development and dietary intake, affect not only the maternal metabolic modification during pregnancy but also the capacity of programming the fetus [8]. Therefore, the main goal of the present study is to analyze the potential environmental and genetic influences that affect preg-

nant individuals and result in alterations on human development that can happen from the embrionary period to early childhood, making children susceptible to metabolic disorders, especially obesity.

Materials and Methods

This article is a systematic review, written based on the PRISMA-E 2012(Preferred Reporting Items for Systematic Reviews and Meta-Analyses) report guide [9]. It was registered on PROSPERO (Nº CRD42020197344). The methods are schematized in Figure 1.

Database and research methods

The research was conducted in the United States National Library of Medicine PubMed – Medline and Cochrane Central Register of Controlled Trials electronic databases between the period of June 01st - August 05th 2020. The following describers were used in the research: "epigenetics and obesity", "maternal influences related to obesity" and "maternal influences and metabolic programming".

Eligibility criteria

The PICO (Population, Intervention, Comparison and Outcomes) system was followed, described in table 1.

Population	Pregnant women presenting gestational diabetes mellitus or overweight.
Intervention	Lifestyle changes, physical exercise, dietary supplementation and pharmacological treatment for gestational diabetes mellitus.
Comparison	Obese pregnant women with comorbidities compared to healthy pregnant women.
Outcomes	Overweight, diabetes and supplementation alter the child's metabolism and influence it to develop obesity.

Table 1: Detailed eligibility criteria following the PICO system. Source: Authors (2020).

Clinical trials, randomized clinical trials, books and documents were included. These were included based on four questions of the main analysis: Are there embrionary development factors that corroborate for the development of dyslipidemia in the future? What are the possible genetic and epigenetic factors that can interfere in embrionary development? How do these factors, including environmental influence, endorse the development of metabolic disorders, particularly obesity? In which phases do these determinant factors act? From this were selected articles published in the last 10 years, with no language restriction. Excluded: doubled articles, articles published before 2010, high risk of bias and systematic reviews.

Data extraction

The article extraction was done in duplicate by the two main authors and stored in a digital table in Excel.

Risk of bias assessment

The following categories were assessed: bliding of the participants, professionals and evaluators; creation of random sequences; concealment of allocation; uncomplete conclusions and selective reports or other potentially biased sources. The risk of bias determined for each domain was: (1) high risk; (2) unknown risk; (3) low risk.

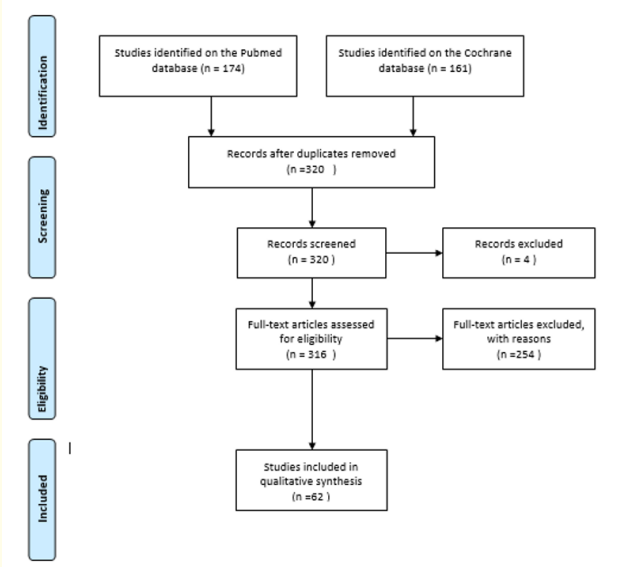

Figure 1: Flow diagram showing the identification, screening, eligibility and inclusion of the articles. Source: Authors (2020).

Results and Discussion

Sixty-two articles were identified and included in this systematic review. There was great heterogeneity in the studies regarding the size of samples, length and assessing methods. Four main fac-

tors were determined following the analysis of the articles, these being: epigenetics, nutrition, obesity and diabetes. Among the selected articles, twelve were directly related to epigenetics, fourteen were related to obesity, sixteen were nutrition related and twelve were focused on diabetes. In the end, only the most important studies were selected, which are presented in table 2, where a brief description of the selected articles is directly related to the previously mentioned topics.

Epigenetics

According to studies, the excessive calorie storage through fat was of extreme importance for our ancestors, it guaranteed higher

Author/Year	Study Model	Sampling Design	Findings
Arianas., *et al*. 2017. [10]	Human model	Comparison between the behavior of overweight mothers and average weight mothers and their respective children, analyzing the mother's interpretation of their children satiety signs.	It was concluded that overweight and obese mothers identified the child's satiety signs and didn't have the tendency to overfeed them, suggesting that the child's potential overweight in the future might occur because of other metabolic influences.
Altmae., *et al*. 2017. [11]	Human model	Comparative analysis between plancentary transcriptomas from obese and non-obese women.	It was concluded that maternal obesity is a factor that causes intrauterine harm due to modifications on the maternal transcriptoma, originating a localized inflammatory process and unregulating the lipid metabolism, creating a lipotoxic environment in the placenta.
Bouret G., 2017. [12]	Human model	Analysis of specific hypothalamic lesions and conditioning situations in order to observe the neural circuits adaptation.	After exposure to the lesions or conditioning situations, a hypothalamic regulation regarding the organism's energy balance that involved a specialized neural network in certain hypothalamic nuclei was observed.
Casei., *et al*. 2015. [13]	Human model	Analysis of the treatment of women with gestational diabetes mellitus and its consequences on the size and weight of the child.	It was concluded that there was a great benefit for the weight and size of the child of those overweight and slightly obese mothers who were treated for GDM. In spite of this, the children of women with adequate weight and of those suffering from excessive obesity did not benefit from the treatment.
Demetrious., *et al*. 2015. [14]	Human model	Bibliographical research in order to identify studies that demonstrate the relationship between early exposition and changes in DNA methylation.	It was concluded that epigenetics, mainly from DNA methylation, is an acceptable mechanism for explaining how children exposure in early life suffer a biological incorporation process.
Grimes, A.B., *et al*. 2018. [15]	Human model	Assessment study comparing the lipid levels in newborn children from healthy mothers and hypercholesterolemia mothers.	It was seen that the maternal lipid status can program cardiovascular disease in the adult, confirming that maternal hypercholesterolemia is associated to the augmented risk of thermogenesis during childhood. It also demonstrated a faster progression of the atherosclerotic process in children born from hypercholesterolemia mothers.

Haschke, F.., *et al*. 2019. [16]	Human model	The study longitudinally followed the anthropometric evolution of children that presented with previous morbidity risk, associating health progression to the use of exclusive breastfeeding or just formulas.	At the end of the study, it was found that children that received exclusive breastfeeding during a 4 - 6month period or those who received infant formulas with low protein concentrations had a slower development in comparison to children that were fed with high protein concentration formulas. The anthropometric measurements during the 5 - 8 years of age period demonstrated that breastfeeding and low-protein infant formulas are related to lower weight gain and fat storage in the future.
Hawkins., *et al*. 2017. [17]	Human model	Comparative study among adequate, overweight and GDM women.	It was proved that adequate weight women that suffered from GDM have greater probabilities of presenting weight gain after pregnancy and of giving birth to overweight children. Besides that, GDM was associated with higher risks of child obesity and cardiovascular disease.
Lillycrop, K.., *et al*. 2017. [18]	Human model	Analysis of the long non-coding RNA ANRIL methylation levels and their relationship with the probable risk of developing obesity.	The association between perinatal methylation in important loci for the ANRIL gene function and higher prevalence of child obesity rates were proved. This statement offers support for the assumption that epigenetic processes are important during fetal programming development.
Litwin., *et al*. 2019. [19]	Human model	Observational study conducted on pairs of mothers and children in which mothers that presented normal weight during pregnancy were compared to mothers that suffered from overweight and GDM.	It was demonstrated that weight gain associated with GDM directly affects the child's weight gain, although this relationship is only detectable in individuals that present >30kg/m2 BMI. It was proved that the higher incidence of overweight in children from mothers that suffered from GDM during pregnancy is due to a failure in glycemic regulation.
Larnkjaer., *et al*. 2018. [20]	Human model	Comparison study on children born from obese mothers and those born from non-obese mothers. The assessed criteria were the hormones related to growth and appetite.	The study showed that children born from obese mothers were larger, heavier and presented high levels of insulin, adiponectine and leptine explaining their larger weight and height; nevertheless, the children presented lower IGF-1 levels, indicating that their growth might be related to high insulin levels.
Mustila., *et al*, 2018. [21]	Human model	Interventional study applied to pregnant women with high risk of GDM and overweight women with the goal of preventing child obesity.	The research showed that early interventions in pregnant women with high risk of developing GDM helps to prevent that condition and consequently reduces the chances of overweight children.

Rosenbaum, M. 2018. [22]	Human model	Comparative study between monozygotic and dizygotic twins. Also presents nutritional analysis that analyzed the obesity prevalence in children exposed to a malnutrition environment.	The study showed that the heritability of adiposity levels is more significant in monozygotic twins, even when exposed to different environments during early childhood. An increased obesity prevalence was seen in children born from mothers who were malnourished during pregnancy, despite the fact that a lower prevalence of child obesity was observed in children born from mothers that were in a state of malnutrition after giving birth. Therefore, the creation of the hypothesis that intrauterine malnutrition can affect the hypothalamus development, altering the appetite control. In cases of postnatal malnutrition, it was theorized that the anti obesity effects might be related to adipocyte formation suppression.
Uebel., *et al*. 2014. [23]	Human model	Adipocyte, insulin and lipid profile analysis on pregnant women and the assessment of the child's anthropometrical data.	It was concluded that obese mothers that suffer from GDM promote neonatal hyperinsulinemia and consequently increase the child's adiposity levels. Increased levels of maternal C-peptide result in higher levels of adiponectine in children, thereby creating a risk of cardiovascular diseases and future obesity.
Wang., *et al*. 2018. [6]	Human model	The study demonstrated the prevalence of genetic variants related to adult life that are associated to childhood conditions. Genetic studies that explain nutritional interference were also presented.	The study proves that the genetic risk from pre-existent maternal obesity is strongly related to higher risks of fetal overweight and elevated child adiposity. It also demonstrates that nutritional regulation can occur through DNA methylation and unmethylation and that the process can be influenced by nutrients such as: vitamin B12, vitamin B6 and folate, among other bioactive components derived from food ingestion.

Table 2: Brief description of the main points associated to the four main topics chosen on the present systematic review. Source: Authors (2020).

chances of survival during long periods of calorie restriction and created a reproductive advantage through the increment of female fertility, allowing them to have greater breastfeeding capacities. Therefore, it is possible that through natural selection, the human genome was enhanced with genes that favor the storage of adipose tissue. In the majority of cases (except for the cases where rare mutations on a single gene are able to greatly increase body fat), body fat has a quantitative character that shows the interaction between development and associated environmental factors to the inherited genome. Cohort studies that analyzed twins indicate that the heritability rate of body fat and its distribution in adult life is of 50 - 80%. Research has already identified significant genetic influence, around 30%, on the rest metabolic rate, food preferences, eating behavior and alterations in energy consumption that occur in response to a nutritional excess. The genetic influence was also evident in studies conducted on twins, in which the heritability calculation assumes that members of each pair (monozygotic or dizygotic) are raised in the same environment and that the level

of similarity is greater among monozygotic twins due to a greater genetic similarity [22].

Epigenetic mechanisms are essential for normal human development and play a great role in complex human diseases [24-26]. Animal and human models show that the intrauterine period is susceptible to the establishment of epigenetic variability [27-31], and consequently influences the risk of future development of various deseases [6]. Epigenetics is extremely important for understanding obesity, through the comprehension of the existence of epigenetic interference in the predisposition of obesity. It was possible to analyze the intrauterine environment effects, the histone acetylation process and microRNA expression, which are of great importance for obesity gene expression. Related to this process, the increase in DNA methylation will decrease the transcription of relevant genes and demonstrate that it can be influenced by parental obesity, maternal diet, gestational diabetes and the use of medication during pregnancy. Research showed that the loss of histone demethylaze is responsible for the manifestation of obesity through decreased expression of PPARα and UCP1 and the deacethylation of GLUT4 histone tail that causes a deficiency in the use and transportation of serum glucose [22].

In a different study, evidence also favored the confirmation of epigenetic interference in human development. Here, the differences in interindividual DNA methylation on distinct human tissues associated with child obesity were examined and a new association between CpG methylation levels at birth inside the long noncoding RNA ANRIL (coded at CDKN2A) and child obesity at the age of 6 years. A relationship between ANRIL methylation and adiposity was also seen in three additional populations: in the analysis of ethnically different newborns, in adolescent's peripheral blood and in adult adipose tissue. Finally, CpG methylation was associated with ANRIL expression in vivo: CpG's in vivo mutagenesis inhibits ANRIL-promoter activity. Hence, the results demonstrated that perinatal methylation in relevant loci for that gene's function can be a fundamental posterior adiposity marker, aiding the epigenetic processes in the development of long-term consequences for human life [18].

Nutrition

It is widely known that presently, nutrition is a biological science with physiological, genomic, social, medical and environmental components. Through time, researchers gathered important evidence that food ingestion, from preconception, afterbirth and even in later years was essential for the health-disease process throughout life and for subsequent generations [32]. The process in which there are phenotypical changes, with no DNA sequence alterations but alterations in gene expression is known as epigenetics. Nutritional epigenetics defines nutrition as one of the main environmental factors that has a continuous interaction with the individual's health, being capable of influencing epigenetic changes and consequently alterations in health development [33].

Epigenetic regulation happens through methylation and demethylation processes that alter the DNA conformation, and this regulation is dependent or influenced by nutrients such as folate, betaine, vitamin B12, vitamin B6, iron, selenium and methionine, among other bioactive components obtained from food ingestion [26]. Therefore, evidence is becoming stronger and pointing towards a relevant relationship between eating regulation and gene expression with multiple health consequences [6].

Prenatal malnutrition is the reflex of maternal malnutrition or a fetal nutritional support malfunction, usually originating in failures in the placenta. From that, the hypothesis that malnutrition during intrauterine life can affect hypothalamic development, altering the pathways that control appetite, was created [22]. The hypothesis that deficient nutrition during the perinatal development period creates a "economical phenotype", in which the individual adapts to a certain environment where food is scarce and develops a lower stature, a lower metabolic rate and demonstrates less activities in order to conserve energy. If the same individuals were posteriorly exposed to an environment with a richer nutritional supply, they would have a greater risk of developing type 2 diabetes, obesity and other metabolic disorders due to an incongruence between the real and idealized environment. The concept of perinatal programming derived from nutrition was associated to other nutrional stimuli, including maternal overnutrition and/or afterbirth overnutrition [12].

There is growing evidence that the development programming of the neurological pathways involved in energy metabolism through the perinatal environment is a potential cause of obesity and other metabolic alterations, one of them being diabetes. A special component of this neural pathway contains a neuron network located in the hypothalamus. Experiments that were based on physical lesions in specific hypothalamic regions and, more re-

cently, conditioning studies using directioning strategies of specific neuron genes, found that hypothalamic regulation of energy balance involves a neural network containing special neurons located at the arcuate nucleus (ARC), the ventromedial nucleus (VMH), the dorsomedial nucleus (DMH), the paraventricular nucleus (PVN) and the lateral hypothalamic area (LHA) [12].

Long term screening studies were conducted, assessing small-for-gestational-age children that showed clinical signs of prenatal malnutrition; at the end of the study, it was reported that even after the adult adiposity levels were corrected, the birth weight was strongly related to the morbidity incidence associated with obesity, including type 2 diabetes, arterial hypertension, stroke and cardiovascular disease in adult life. This association statement reinforces the preconception of interaction between prenatal environment and life-long development, influencing the pancreatic beta cells and the function of other organs related to the energy and cardiovascular regulation processes in the adult, such as the hypothalamus, liver and kidneys. Thus, the main hypothesis would be that the cardiovascular, endocrinological and metabolic basis that explains the development of conditions related to adiposity in adults originates through a fetal adaptive process in response to malnutrition, particularly when the calorie access in the environment where the child is born is no longer limited [22].

Another nutritional risk factor that is associated with a child's future risk is hypercholesterolemia, which is a risk factor for the development of atherosclerosis that usually happens in adult life. However, evidence shows that the atherosclerotic process can start during uterine development. The first suspicion that maternal lipid profile has the capacity to program cardiovascular disease in the adult began from observations in which maternal hypercholesterolemia, even when restricted to the pregnancy period, was strongly related to an increase in size of the fatty stripes on the fetal aorta. It was also stated that the progression of atherosclerosis is significantly faster in children born from hypercholesterolemic mothers. Yet, comprehension of the mechanisms responsible for the effects of maternal dyslipidemia on fetal development and atherosclerosis risk is still incomplete and needs more research. Observational studies have already proved the harmful effect of maternal hyperlipidemia on metabolic programming; the control of this condition is essential during pregnancy. The baseline treatment is composed of multifactorial actions including adequate diet, exercise and weight control. That is because the pharmacological treatment of dyslipidemia during pregnancy requires great caution [15].

A well-established point is that nutrition during the first 1,000 days of life may have a long-time influence on growth, metabolism and health during adult life. Some studies observed that children that are exclusively breastfed for a period of 4 - 6 months or the ones that receive infant formulas with a low protein concentration have a slower growth rate in comparison to children fed with high protein concentration infant formulas during the first 3 years of life. Measurements of bodily compositions conducted with 5 - 8-year-old children showed that breastfeeding and low protein concentration infant formulas are related with a higher adiposity gain [16].

Gestational diabetes

Child obesity can be related to the prenatal environment, presence of GDM, diet and maternal physical activities. Thus, studies that assess interventions in these aspects during pregnancy evaluate how influential maternal metabolic factors are on the child's metabolic alterations.

Gestational diabetes is defined as the diabetes first diagnosed during pregnancy, more specifically during the 24–28-week pregnancy period and can predispose risks to both mother and child [17]. It is possible to associate GDM to fetal over nutrition because there is an increase in local glucose, lypogenesis, fetal hyperinsulinemia and consequently fetal macrossomy (birth weight greater than 4 kilograms) [22].

Through epigenetic alterations caused by GDM, children born from mothers suffering from this condition have greater chances of developing metabolic diseases or becoming obese adults. On a study conducted with obese pregnant patients it was possible to observe that children born from mothers that were overweight and suffered from GDM had alterations in DNA methylation. This alteration suffered great reduction when the diabetes treatment was initiated, proving the direct influence of maternal metabolic modulation on the child's epigenetic development [18].

In a study conducted with women that suffered from high risk GDM or with BMI ≥ 30 kg/m^2, it was observed that children exposed to a maternal environment with gestational diabetes or with BMI ≥ 30 kg/m^2 have greater overweight rates when compared to chil-

dren born to mothers with an adequate glycemic control. Around 20% of the assessed children presented with excessive weight and 14% were defined as obese [19]. Another study that associated interventions with the goal of preventing GDM showed that adequate care resulted in lesser incidence of diabetes during pregnancy. That being so, low glucose levels and lower risk of developing GDM is related to a smaller chance of child weight gain and lower risk of developing type 2 diabetes [21].

Children of mothers that suffer from GDM have greater fat and insulin secretion levels until 5 - 10 years of age regardless of the individual's BMI and are more likely to develop obesity, type 2 diabetes mellitus and cardiovascular disease in the future [17]. This happens because of a compensation mechanism existent on pancreatic beta cells that increase insulin secretion in order to compensate the greater concentration of glucose in the bloodstream of a mother that suffers from GDM. Increased insulin secretion raises fetal adiposity.

A large number of pregnant women that suffer from GDM are also overweight or obese, and that makes it difficult to distinguish the cause of the metabolic dysfunction that makes children overweight or obese. In these cases, it is not known if the child is overweight due to maternal metabolic consequences or because of genetic inheritance [22].

Obesity

Body fat reflects interactions with the environment, life habits, genetic heritage and human development conditions related to epigenetics. Various studies have tried to prove the association between fetal exposure to maternal obesity during pregnancy and its consequences on children's weight gain. Women that were obese during pregnancy presented 2 - 5 times higher incidence of large-for-gestational-age children. Related to that is the fact that children born of mothers that underwent bariatric surgery and lost weight, themselves presented children with reduced body fat [22].

Pre-pregnancy BMI can be associated with child body fat gain, although weight gain was only evident in children born of mothers with BMI ≥ 30 kg/m^2 [19].

Women that were obese before pregnancy and had GDM were more likely to present children with hyperinsulinemia and an increase in adiposity levels until the sixth week. This study also reports that the relationship between hyperinsulinemia and the impact of intrauterine hyperinsulinemia in raising fetal adipose tissue fat disappears during the first year of life. Associated with this insulin and glucose level dysfunction, the increase in maternal C-peptide raises adiponectine levels favoring the growth of preperitoneal adipose (PPA) tissue in newborns. Consequently, there is a greater risk of child obesity and future cardiovascular disease (2014). Besides the fact that maternal obesity stimulates high insulin levels and hormones like adiponectine suggesting an adipocyte and leptine increase, despite presenting low levels of IGF-1, suggesting that the exacerbated growth occurred because of insulin excess. Despite this, the elevated fetal growth is not related to adult consequences, but from having an accelerated growth rate due to hormone concentration [20].

Cholesterol metabolism is essential for fetal growth, but pregnant women with any dyslipidemia associated with weight excess can be a predisposing factor for fetal size deregulation and future obesity [15].

Studies also report the dysfunction existent in the placental transcriptome that promote adverse effects due to deregulation in molecular pathways responsible for the development of the placenta in obese mothers. In this way, it is possible to observe the unregulated lipid metabolism that creates a lipotoxic environment in the placenta, with augmented oxidative and inflammatory stress markers associating them to metabolic disorders such as hyperlipidemia and atherosclerosis [11]. Inflammation derived from maternal obesity is also associated to changes in fetal mesenchymal cells, resulting in newborn muscular cell alterations, increasing the fetal size. This fetal growth mechanism is not related to glucose metabolism deregulation [13].

Children with obese parents are four times more likely to develop obesity during early childhood. Mothers predisposed to weight gain due to genetic risk, environmental exposure to poor diets or a sedentary lifestyle will have children exposed to these same conditions, raising the risk for the development of obesity [17]. Contrastingly, obese mothers don't have the tendency to overfeed their children during the first months of life, which suggest that other factors could add to the ones previously mentioned and predispose excessive weight gain [10].

Figure 2 shows the relationship between maternal metabolic alterations, maternal overweight, gestational diabetes mellitus (GDM) and consequences for the affected children.

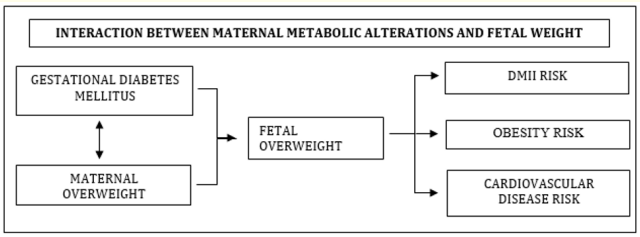

Figure 2: Relationship between gestational diabetes mellitus and maternal overweight. Source: Authors (2020).

The goal of this systematic review was to analyze the main factors that influence human development, identifying the factors that can interfere in critical periods of this process, either in the preconception phase, pregnancy or afterbirth, bearing in mind that the embrionary, prenatal and perinatal periods are highly plastic periods and that is why the fetus is sensitive to environmental and intrauterine alterations. The main factors that were identified through the analysis include paternal stimuli, events that happen in the intrauterine environment and afterbirth environmental stimuli, in a way that the combination of these factors affect metabolic programming. These factors are demonstrated in figure 3.

Regarding the epigenetic analysis, despite the heterogeneity of the presented studies, sample sizes, exposition and results, the final conclusions support the hypothesis that overweight and obesity in childhood are associated to epigenetic alterations, endorsing the preconception of biological incorporation. This proves the hypothesis that the epigenome can influence obesity patterns, either because of direct influences of the involved genes in the metabolic pathways that predispose to future obesity or reflected in one or more factors that influence both DNA methylation and the patterns responsible for obesity in the afterbirth period and nutrition during early childhood [14].

After analyzing all the studies related to nutrition, we observed that a nutritional conduct on critical periods of human development have a strong influence over the affected child's metabolic programming, either through epigenetics or endocrinological pathways. This demonstrates the need for attention and detailed research, specially focused on breastfeeding and low-fat diets as nutritional interventions that could possibly help pregnant women avoid these alterations on their offspring.

Metabolic disorders associated to obesity have been important to the identification of factors that influence children to become obese. Therefore, besides dietetic and behavior factors, it is possible to associate child obesity to the metabolic influences present during the time spent in the intrauterus environment. Maternal overweight can directly or indirectly influence the fetal metabolism, predisposing the individual to a great number of inflammatory alterations on lipid, glucose and hormone metabolism that endorse the accumulation of adipocytes and weight gain during pregnancy or early childhood.

Maternal weight variation is also a risk factor for the development of gestational diabetes mellitus that is defined as a failure in the glucose regulation during pregnancy. This maternal organism alteration also creates changes that favor fetal weight gain. Hyperglycemia and insulin resistance are conditions that alter the fetal nutrition and promote a greater growth rate, resulting in large for gestational age (LGA) newborn that predispose the development of cardio metabolic disorders on the mother and offspring over the years.

It was possible to confirm the previously established multifactorial hypothesis that involves the development of metabolic disorders. The relationship between epigenetics, maternal nutrition, preexistent metabolic disorders in pregnant women, stress among other topics mentioned on this review presented capable of directly influencing fetal adaptation, modulating one's metabolic response. We were able to confirm, through the analysis of child obesity development, the interference of the maternal organism and environmental factors on this process, which surpass the commonly accepted hypothesis that bad eating habits and sedentarism are the only responsible.

Conclusion

In conclusion, epigenetic presented itself as an important way for biological incorporation of the heritability of metabolic diseases, through the methylation and deacetylation pathways, becoming an important factor in future studies focusing on possible interventions for the prevention of these disorders. The nutrition factor also appeared to be an influencer that endorse the modulation of fetal and child response, either on the intrauterine period where maternal malnutrition or over nutrition can alter the phenotype developed through neurological and endocrinological pathways or on the first years of life, a period when the nutritional support of-

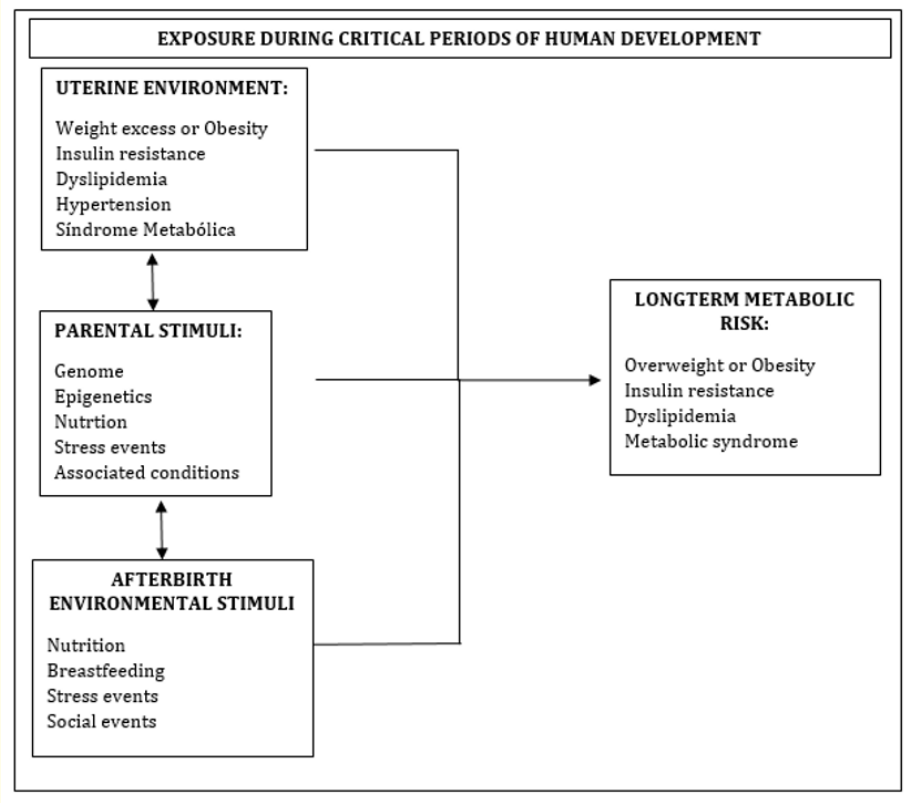

Figure 3: Summary of the main factors that affect human development. Source: Authors (2020).

fered by the environment shapes an individual's energetic profile. Maternal overweight appears to have great influence on the offspring future weight, through promotion of metabolic alterations on fetal development mainly due to a lipid metabolism disequilibrium. At last, gestational diabetes mellitus was also identified as a direct influence on fetal metabolism due to high maternal blood glucose levels that creates an endocrinological disequilibrium. When identifying the potential risk factors that affect critical stages of human development and influence on the appearance of metabolic disorders, obesity in particular, it is important to understand the necessity of new prevention politics. We understood that investments on new research areas specialized on the main topics presented in this review are fundamental, in order to create specific multi factorial intervention protocols that cover the whole process, from the preconceptional period to post natal period.

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Conflict of Interest

The authors declare no conflict of interest.

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