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Genes to the Epigenome: Understanding Childhood Obesity

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Abstract: ***Childhood obesity has become a major public health concern worldwide, with rising prevalence rates and severe long-term health consequences. This review explores the complex interplay of genetic, environmental, and epigenetic factors contributing to childhood obesity. We discuss the role of genes, such as FTO, MC4R, and LEPR, and the impact of epigenetic modifications, including DNA methylation and histone changes, on obesity risk. Environmental factors, including maternal nutrition, exposure to toxins, and socioeconomic and cultural influences, are also examined. We highlight the need for a multimodal approach to prevention and treatment, incorporating personalized medicine, novel therapeutic targets, and evidence-based strategies. Further research is necessary to elucidate the complex relationships between genetic, environmental, and epigenetic factors and to develop effective interventions to combat childhood obesity.***
Keywords: Epigenome, Childhood Obesity, Genetics, Monogenic Obesity, Polygenic Obesity, Gene Environmental Interactions.

I. INTRODUCTION

Childhood obesity has emerged as a major public health concern throughout the world, with prevalence rising at an alarming rate in recent decades. According to the World Health Organization [(1)], childhood obesity has more than quadrupled since 1975, with over 39 million children under the age of five categorized as overweight or obese worldwide. The surge is most noticeable in low- and middle-income nations, where increasing urbanization and the adoption of Westernized dietary habits have resulted in greater intake of processed, high-calorie foods and decreased physical activity [(2)].

In the United States, data from the **National Health and Nutrition Examination Survey (NHANES)** indicate that obesity rates among children and adolescents aged **2–19 years have increased from 5% in the 1970s to nearly 20% in recent years**[(3)]. Similar trends are observed in Europe, Asia, and the Middle East, where childhood obesity rates continue to rise due to shifting dietary habits, sedentary lifestyles, and reduced physical activity [(4)].

Genetic predisposition, environmental variables, socioeconomic inequality, and epigenetic changes are some of the reasons that contribute to this rising prevalence [(5)]. The obesity pandemic has been made worse by the interaction of genetic predisposition and lifestyle choices, including excessive screen time, high sugar intake, and little physical exercise [(6)]. Furthermore, the environment in the early years of life, such as the diet of the mother during pregnancy and the feeding habits of the newborn, has a significant impact on the development of obesity risk through epigenetic processes [(7)].

The long-term consequences of childhood obesity are severe, increasing the risk of metabolic disorders, cardiovascular diseases, and reduced life expectancy [(8)]. Given the growing burden of childhood obesity, urgent public health interventions, including school-based nutrition programs, policies to limit the marketing of unhealthy foods to children, and community initiatives promoting physical activity, are essential to curb this epidemic [(9)].

II. THE ROLE OF GENETICS AND EPIGENETICS IN OBESITY

A complex disorder, obesity is impacted by both hereditary predisposition and epigenetic changes. Numerous genetic variables increase the incidence of obesity; important genes linked to obesity, including FTO, MC4R, and LEP, which control appetite, energy balance, and fat metabolism, have been identified by genome-wide association studies (GWAS).

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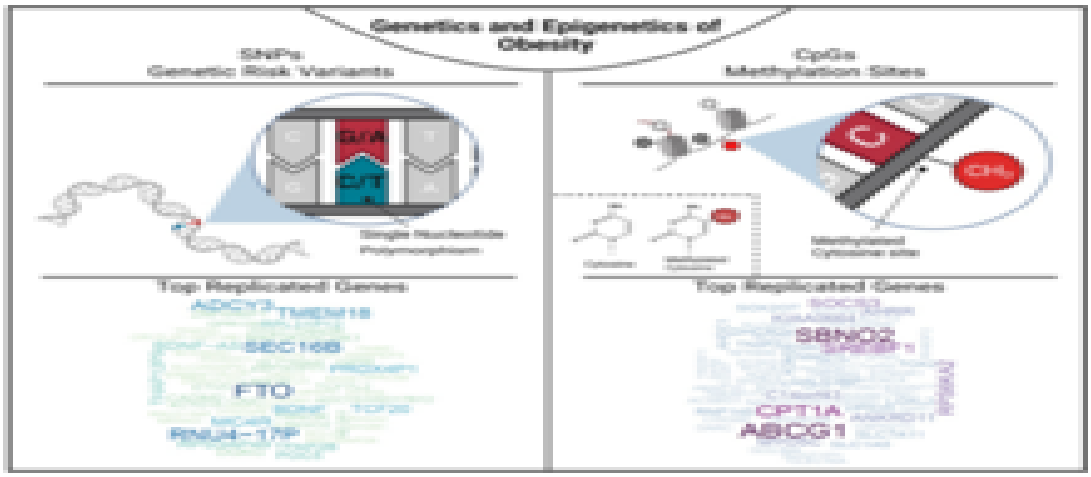

Figure 01:Genetics and Epigenetics of Obesity

Apart from genetics, epigenetic processes—like DNA methylation, histone changes, and non-coding RNAs—have a significant impact on the development of obesity because they modify gene expression without changing the DNA sequence [(10)]. Epigenetic alterations that predispose people to obesity can result from environmental variables such as physical activity, early-life food, and maternal nutrition [(11)]. According to these findings, obesity is caused by intricate connections between inherited genes and alterable epigenetic modifications, highlighting the necessity of tailored therapies.

III. CHILDHOOD OBESITY: A GLOBAL CONCERN

A. Understanding BMI and Obesity Classifications in Children:

The Body Mass Index (BMI) is a commonly used tool for determining children's weight status. Weight (in kg) divided by height (in meters) squared yields the BMI. BMI in children is age and gender specific, and is given as a percentile rank.

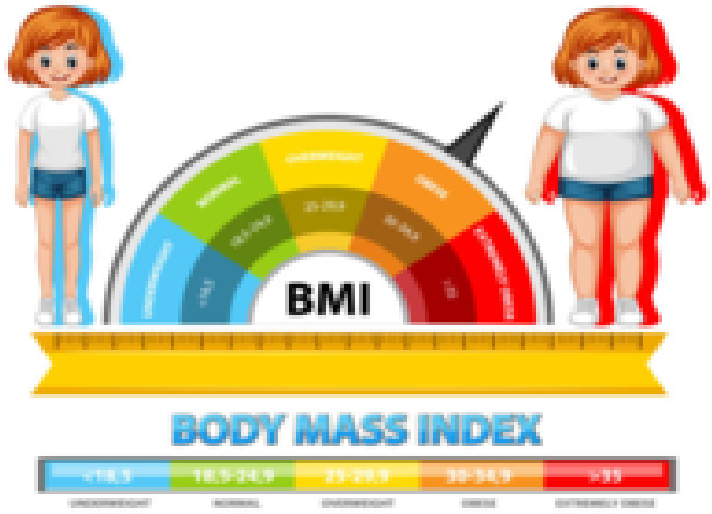

Figure 02: Body Mass Index

Obesity Classifications in Children:

- Underweight: BMI <5th percentile
- Normal weight: BMI 5th-84th percentile
- Overweight: BMI 85th-94th percentile
- Obese: BMI ≥95th percentile
- Severely obese: BMI ≥120% of the 95th percentile [(12)]

Obesity in children must be classified accurately in order to be detected and treated early. Childhood obesity is a major risk factor for a variety of health conditions, including type 2 diabetes, hypertension, and cardiovascular disease [13,14,15].
While BMI is an effective tool for determining weight status, it does have limits. BMI does not distinguish between lean body mass and body fat, and it may not appropriately classify youngsters of muscular build [16,17,18].

B. Global Trends and Public Health Impact:

An estimated 41 million children under the age of five globally suffer from childhood obesity, an increasing global health concern [19]). Both industrialized and developing nations are seeing an increase in the frequency of childhood obesity; the Americas, Europe, and the Eastern Mediterranean have the highest rates [18].
Significant public health consequences of childhood obesity include:
- A higher chance of developing health issues linked to obesity, including cardiovascular -disease, type 2 diabetes, and hypertension [20].
- A lower standard of living and a higher chance of mental health issues such anxiety and depression [21].
- Rising healthcare expenses and financial strain on families and communities [22].
Factors Contributing to Childhood Obesity:
-Lack of physical activity and a sedentary lifestyle [23].
- The use of fast food and sugary drinks, along with an unhealthy diet [24].
- Socioeconomic issues, including those related to poverty, availability to nutritious food, and chances for physical activity [25,26,27].

C. Health Risks Associated with Childhood Obesity:

A serious public health concern that has both immediate and long-term effects is childhood obesity. It raises the chance of getting long-term conditions such cardiovascular disease, type 2 diabetes, and high blood pressure [28]. Furthermore, respiratory conditions including asthma and sleep apnea are more common in obese kids, which has an impact on their general health [29].
In terms of psychology, obesity is associated with anxiety, depression, and low self-esteem, frequently as a result of bullying and social stigma [30]. Additionally, juvenile obesity is a powerful indicator of adult obesity, which raises the risk of heart disease, stroke, and a shorter lifeexpectancy [31].
Healthy dietary practices, frequent exercise, and a decrease in sedentary behaviour are examples of preventive strategies. To combat childhood obesity, public health programs emphasizing education and family involvement are essential [32].

IV. THE GENETIC BASIS OF CHILDHOOD OBESITY

A. Key Obesity-Related Genes and Their Role:

A variety of environmental and genetic variables contribute to the complicated condition known as obesity. Numerous genes have been found to play a significant role in the development of obesity. Some of the most important genes linked to obesity and their functions are listed below.

1) FTO (Fat Mass and Obesity-Associated Protein)

- Role: Controls energy expenditure and food intake.
- Mechanism: Modifies the expression of genes related to energy metabolism and appetite control.
- Association: In some populations, variations in the FTO gene have been reliably linked to obesity [33].

2) Melanocortin 4 Receptor, or MC4R

- Role: Controls body weight and energy homeostasis.
- Mechanism: Initiates signaling pathways that raise energy expenditure and decrease food intake.
- Mechanism: Initiates signaling pathways that raise energy expenditure and decrease food intake[34].

3) LEPR (Leptin Receptor)

- Role: Controls body weight and energy homeostasis.
- Mechanism: Attaches itself to the hormone leptin, which increases energy expenditure and inhibits appetite.
- Leptin resistance and obesity have been linked to variations in the LEPR gene [35].

4) POMC (Proopiomelanocortin)

- Role: Energy homeostasis and body weight are regulated.
- Mechanism: Melanocortins are produced, which activate MC4R and control energy balance.
- Association: The POMC gene has been linked to both obesity and adrenal insufficiency [(36)].

5) PCSK1 (Proconvertase Subtilisin/Kexin Type 1)

- Role: Controls body weight and energy homeostasis.
- Mechanism: Generates active hormones by breaking down prohormones, such as POMC.
- Association: Obesity and metabolic diseases have been linked to variations in the PCSK1 gene [(37)].

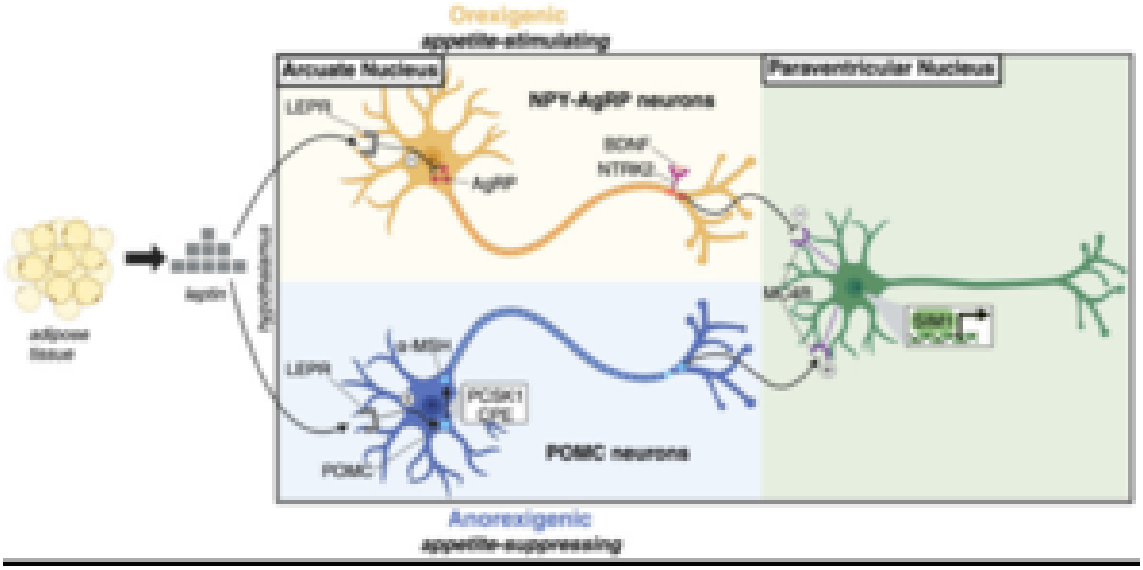

Figure 03: Orexigenic Appetite-Stimulating and Anorexigenic Appetite-suppressing

B. Heritability and Family History of Obesity:

Obesity is a complicated illness influenced by genetic, environmental, and lifestyle factors. According to heritability estimates, genetic variables account for 40–70% of the variation in body mass index (BMI) [(38)].

1) Heritability of Obesity:

- Heritability of obesity has been estimated by twin studies to be between 50 and 80 percent [(39)].
- Family studies have demonstrated that obesity tends to run in families, with first-degree relatives of obese people having a 2-3 times higher likelihood of being fat themselves [(40)].

2) Family History of Obesity:

- A child's chance of becoming obesity is increased if one or both of its parents are obese (40).
- A person's chance of developing obesity is also increased if they have an obese sibling [(41)].

3) Genetic Factors Influencing Obesity:

- Genetic variants: Several genetic variations, such as those in the FTO, MC4R, and LEPR genes, have been found to be risk factors for obesity (42).
- Epigenetic factors: Obesity development is also influenced by epigenetic mechanisms, including histone modification and DNA methylation [(43)].

C. Monogenic vs. Polygenic Obesity:

A complicated illness, obesity is impacted by both environmental and hereditary factors. Based on the hereditary component, it can be roughly divided into two categories: monogenic obesity andpolygenic obesity.

1) Monogenic Obesity:

A single gene that is essential for controlling hunger and maintaining energy balance can get mutated, leading to monogenic obesity. Leptin-melanocortin, which regulates hunger and metabolism, is frequently impacted by these mutations [(44)]. Important genes implicated include:

- Mutations in the leptin gene (LEP) result in leptin insufficiency, which causes severe early-onset obesity.
- Hyperphagia is the outcome of defects in the leptin receptor gene (LEPR), which affects leptin signaling.
- Melanocortin-4 receptor gene (MC4R) mutations are the most frequent cause of monogenic obesity because they interfere with appetite regulation.

Rarely occurring monogenic obesity typically presents as extreme childhood obesity, frequently accompanied by developmental problems and hormonal imbalances [(45)].

2) Polygenic Obesity:

Multiple genetic variations (single nucleotide polymorphisms, or SNPs) combined with environmental factors including nutrition and lifestyle lead to polygenic obesity [(46)]. Polygenic obesity is prevalent and makes up the bulk of obesity cases, in contrast to monogenic obesity.

- The most extensively researched obesity-associated gene affecting hunger and metabolism is FTO (Fat mass and obesity-associated gene).
- Common kinds of obesity are caused by certain SNPs in the MC4R gene, which is also implicated in polygenic obesity.
- Peroxisome proliferator-activated receptor gamma, or PPARG, controls the metabolism and storage of fat.

Due to its progressive development and lifestyle choices, polygenic obesity is more amenable to behavioral, dietary, and exercise therapies [(47)].

Polygenic obesity is more prevalent and arises from the interaction of several genetic changes with environmental circumstances, while monogenic obesity is a rare and severe kind of obesity brought on by single-gene alterations. Knowing the hereditary causes of obesity can help with the creation of individualized therapies and preventative measures[(44,45,46,47)].

D. Epigenetics and Its Role in Childhood Obesity:

Since epigenetics controls gene expression without changing the DNA sequence, it is essential in the fight against childhood obesity. Histone modifications, non-coding RNAs, and DNA methylation are important epigenetic factors that affect metabolism, appetite regulation, and fat storage and are implicated in obesity [(48)].

1) DNA Methylation:

A methyl group (CH_3) is added to cytosine residues in DNA, a process known as DNA methylation, which typically suppresses gene expression. Increased fat storage and poor appetite control are caused by the hypermethylation of genes that affect hunger and energy balance, such as POMC (pro-opiomelanocortin) and LEP (leptin) [(49)].

2) Histone Modification:

Gene accessibility for transcription is affected by chromatin structural changes caused by histone modifications like acetylation and methylation. Obesity-related genes such as FTO (Fat mass and obesity-associated gene) have higher histone acetylation, which can worsen metabolic dysfunction and fat accumulation [(50)].

3) Non-Coding RNAs (ncRNAs):

Post-transcriptional regulation of gene expression is accomplished by non-coding RNAs, specifically long non-coding RNAs (lncRNAs) and microRNAs (miRNAs). Dysregulated expression of miR-33 and miR-122 has been linked to childhood obesity by influencing lipid metabolism and adipogenesis [(51)].

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Children are predisposed to obesity thanks to early-life variables like the mother's diet, environmental pollutants, and lifestyle choices that can cause epigenetic changes. Gaining insight into these processes can aid in the creation of focused therapies for the treatment and prevention of obesity.

V. ENVIRONMENTAL INFLUENCES ON THE EPIGENOME

A. Maternal Nutrition and Foetal Programming:

Pregnancy-related maternal nutrition has a significant impact on fetal development and programming, which can affect the likelihood of childhood obesity. Pregnancy-related maternal nutrition affects fetal growth and development; intrauterine growth restriction (IUGR) is caused by inadequate nutrition [(52)]. A higher chance of developing chronic illnesses later in life, such as obesity, type 2 diabetes, and cardiovascular disease, has been associated with fetal programming [(53)]. Pregnancy-related maternal nutrition may affect the offspring's epigenetic markers, possibly predisposing the risk of child obesity[(54)].

Studies have demonstrated that maternal folic acid supplementation during pregnancy can affect fetal programming and lower the risk of childhood obesity [(55)]. Pregnancy-related protein intake has been associated with fetal growth and development; insufficient protein intake causes IUGR [(56)].

A serious public health concern, maternal nutrition during pregnancy has an impact on childhood obesity and other illnesses. To minimize the risk of childhood obesity and maximize maternal nutrition during pregnancy, personalized nutrition strategies might be required[(57,58,59)].

B. Early-Life Stress And Its Impact On Obesity Risk

Childhood obesity can be significantly influenced by early-life stressors, such as prenatal and postnatal stress. Stress during pregnancy can alter fetal programming, changing the fetus's development and raising the chance of obesity in later life [(60)]. Childhood obesity has been associated with postnatal stress, which includes childhood trauma and adversity [(61)]. Early-life stress can affect how the hypothalamic-pituitary-adrenal (HPA) axis develops, changing how cortisol is regulated and raising the risk of obesity [(62)]. Early-life stress (ELS) is becoming more widely acknowledged as a major cause of childhood obesity. ELS encompasses negative experiences like abuse, financial difficulties, dysfunctional families, and exposure to violence. These stressors have the potential to cause long-term changes in behavioural and physiological pathways, which raises the risk of obesity.

1) Dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) Axis - Long-term stress causes the HPA axis to be continuously activated, which raises cortisol levels. Excess cortisol increases the appetite for high-calorie foods and encourages fat accumulation, particularly in visceral adipose tissue [(63)].
2) Changes in Eating Behaviours - Stress can cause children to develop emotional eating habits, using foods high in energy as a coping strategy [(64)]. Leptin and ghrelin, two hormones that control appetite, are altered by stress, which also leads to an increase in caloric intake.
3) Epigenetic Modifications - Negative childhood experiences might cause epigenetic modifications in genes related to metabolic regulation, making people more likely to become obese later in life [(65)].
4) Gut Microbiome Disruptions - Changes in gut microbiota composition brought on by stress may affect metabolic processes, raising the risk of obesity and adiposity [(66)].
5) Reduced Physical Activity and Sleep Disruptions – Stress can result in poor sleep and a reduction in physical activity, both of which are risk factors for obesity [(67)].

Reducing the risk of childhood obesity requires addressing early-life stress through supportive interventions, mental health services, and socioeconomic policies. Targeted interventions that lower stress-related obesity pathways and enhance long-term health outcomes should be the main focus of future research.

C. Influence Of Endocrine Disruptors And Pollutants

A major contributing factor to the rising incidence of childhood obesity is environmental factors. Among these, pollutants, and endocrine-disrupting chemicals (EDCs) have been linked to changes in metabolic regulation that raise the risk of obesity. These drugs affect adipogenesis, energy balance, and hormone signaling, which causes children to gain weight.

1) *Bisphenol A (BPA):* BPA, which is frequently present in food packaging and plastics, interferes with normal endocrine function by mimicking estrogen. Children are at risk for obesity because it changes insulin sensitivity and encourages adipocyte differentiation [(68)].

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2) *Phthalates:* Phthalates disrupt adipogenesis and thyroid hormone regulation when they are used in plastics and personal care products. In children, a higher body mass index (BMI) has been associated with higher exposure to phthalates [69].
3) *Persistent Organic Pollutants (POPs):* POPs that upset metabolic homeostasis include dioxins and polychlorinated biphenyls (PCBs), which build up in adipose tissues. These pollutants have been linked to increased childhood obesity rates because of their impact on lipidmetabolism[70].
4) *Pesticides (Organochlorines & Organophosphates):* Some pesticides change the metabolism of glucose and the storage of fat, which makes them obesogens. Exposure during pregnancy and the early years of life has been associated with a higher risk of fat accumulation and obesity[71].
5) *Heavy Metals (Lead, Arsenic, Cadmium):* Heavy metal exposure impairs mitochondrial and endocrine signaling, which causes children to accumulate more fat and have a slower metabolism [72].

EDCs alter thyroid, androgen, and estrogen hormones, which impacts appetite control and fat storage. Long-term metabolic changes can result from gene expression changes brought on by pollution exposure. Because of their detrimental effects on energy metabolism, some pollutants contribute to obesity by lowering energy expenditure.

D. Gene-Environment Interactions In Childhood Obesity

Genetic and environmental factors interact in complex ways to influence childhood obesity. Although genetics contribute to the risk of obesity, environmental and lifestyle changes can have a big impact on weight outcomes. By better understanding these gene-environment interactions, interventions may become more successful, lowering childhood obesity rates, and enhancing long-term health results.

1) The Impact of Socioeconomic and Cultural Factors

Particularly in the context of childhood obesity, socioeconomic and cultural factors significantly influence people's health and well-being.Low-income families have a higher risk of having obese children because they have less access to opportunities for physical activity and nutritious food [73].Cultural norms and values regarding food, exercise, and body image can affect the risk of obesity; certain cultures place more value on these aspects than others [74].The socioeconomic and cultural factors that impact obesity risk can have a significant impact on the accessibility and availability of healthy food options [75].

Socioeconomic Factors:

- Families with low incomes may find it difficult to pay for physically active opportunities and nutritious food, which raises the risk of obesity[76].
- Gooder lifestyle choices and a decreased risk of obesity are linked to higher levels of education[77].
- Prolonged sitting or restricted access to nutritious food options are two factors that can increase the risk of obesity in some occupations[78].

2) Epigenetic Changes Across Generations in Childhood Obesity

Gene expression and disease risk, including childhood obesity, can be influenced by epigenetic marks that are passed down from one generation to the next, according to research [79]. Maternal nutrition during pregnancy may have an impact on the offspring's epigenetic changes, raising the risk of childhood obesity [80].Paternal factors like diet and lifestyle can also affect the offspring's epigenetic changes, raising the risk of childhood obesity[81].

The significance of environmental factors in determining health outcomes is underscored by the fact that epigenetic modifications can impact disease risk, including childhood obesity, and be transmitted to future generations[82].The development of epigenetic therapies to prevent or treat childhood obesity may result from a better understanding of how epigenetic changes occur across generations[83].

3) Prevention and Intervention Strategies

Several stakeholders, including families, communities, schools, and healthcare professionals, must be involved in a comprehensive strategy to prevent and treat childhood obesity[84].

- *Prevention strategies include: -*

➢ Encouraging children to eat a balanced diet that includes a lot of fruits, vegetables, whole grains, and lean protein sources; this will help them develop healthy eating habits [85].

- Encourage kids to participate in moderate-to-intense physical activity for at least 60 minutes each day in order to increase their physical activity levels [86].
- Children should not spend more than two hours a day on screens[87].

- *Family-based interventions:*
- Parents and other caregivers in initiatives to prevent and treat obesity [88].
- Put in place school-based initiatives that support physical activity and a healthy diet [89].
- Involve local residents in initiatives to prevent and treat obesity[90].

- *Effective Intervention Components: -*
- Behavioral counselling: To encourage healthy lifestyle choices, offer behavioral counselling to kids and families [91].
- Nutrition education: Teach families and kids how to eat healthily [92].
- Physical activity: Encourage kids to be physically active on a regular basis [93].

Since childhood obesity is a complicated public health concern, prevention and treatment must be approached holistically and from multiple angles.

- Population-based approach: Instead of treating individual cases of obesity, concentrate on preventing obesity in the general population [94].
- Multi-sectoral collaboration: Encourage the participation of various sectors in obesity prevention initiatives, such as community organizations, healthcare, and education [95].
- Evidence-based strategies: Research has demonstrated that these strategies are successful in both preventing and treating childhood obesity [95].

E. Future Perspectives and Research Directions

With rising prevalence rates and related long-term health effects, childhood obesity continues to be a serious worldwide health concern. A multimodal strategy including prevention, early intervention, policy implementation, and research improvements is needed to address this issue. The viewpoints listed below highlight important avenues for future research in the fight against childhood obesity.

F. Advances in Epigenetic Research and Childhood Obesity

Understanding the intricate relationships between genetic and environmental factors that lead to childhood obesity has advanced significantly thanks to epigenetic research.Research has linked epigenetic markers, including histone modifications and DNA methylation, to a child's risk of obesity[96].Environmental factors like maternal nutrition and exposure to toxins can affect epigenetic marks and raise the risk of childhood obesity [97]. Epigenetic processes, including gene activation and silencing, are essential for controlling gene expression and causing childhood obesity [98].

- Next-generation sequencing technologies: Early interventions that affect epigenetic markers, like dietary changes and lifestyle changes for mothers, may help prevent childhood obesity [97].
- Personalized medicine:Personalized medicine strategies for childhood obesity that are based on each person's distinct epigenetic profile may be made possible by epigenetic research [96].
- Novel therapeutic targets:Research on epigenetics may reveal new therapeutic targets for childhood obesity, including transcription factors and epigenetic enzymes [98].

Potential for Personalized Medicine in childhood Obesity Management:

Personalized medicine has the potential to significantly improve childhood obesity management by customizing interventions according to behavioral, metabolic, and genetic characteristics. Nutritional, pharmaceutical, and lifestyle modifications can be tailored thanks to developments in genetics, microbiome research, and digital health tools. This method takes individual differences in metabolism, appetite management, and response to interventions into account, increasing therapy efficacy and reducing side effects. Children's obesity-related comorbidities can be decreased and long-term weight control enhanced using personalized approaches[99].

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G. Ethical Considerations in Genetic and Epigenetic Research of childhood

Children's genetic and epigenetic research presents a number of ethical issues, such as informed permission, privacy, possible prejudice, and the psychological effects of genetic results. It is unclear if children will consent to the use of their genetic information in the future, but parental or guardian consent is necessary because youngsters are incapable of giving fully informed consent. Additionally, employers or insurers may misuse genetic data and stigmatize people. In addition to minimizing injury and protecting data confidentiality, researchers must think about how genetic results may affect a child's long-term wellbeing. The child's best interests should come first in ethical frameworks that promote scientific advancement[(100)].

VI. CONCLUSION

Childhood obesity is a complex and multifactorial issue, influenced by genetic, environmental, and epigenetic factors. Understanding the interplay between these factors is crucial for developing effective prevention and treatment strategies. Research has highlighted the importance of early-life factors, such as maternal nutrition and exposure to toxins, in shaping epigenetic marks and increasing the risk of childhood obesity. Furthermore, socioeconomic and cultural factors, as well as exposure to endocrine-disrupting chemicals, also play a significant role in childhood obesity. A comprehensive approach, incorporating personalized medicine, novel therapeutic targets, and evidence-based strategies, is necessary to address this growing public health concern. By acknowledging the complexity of childhood obesity and addressing its multiple determinants, we can work towards reducing its prevalence and improving the health and well-being of children worldwide.

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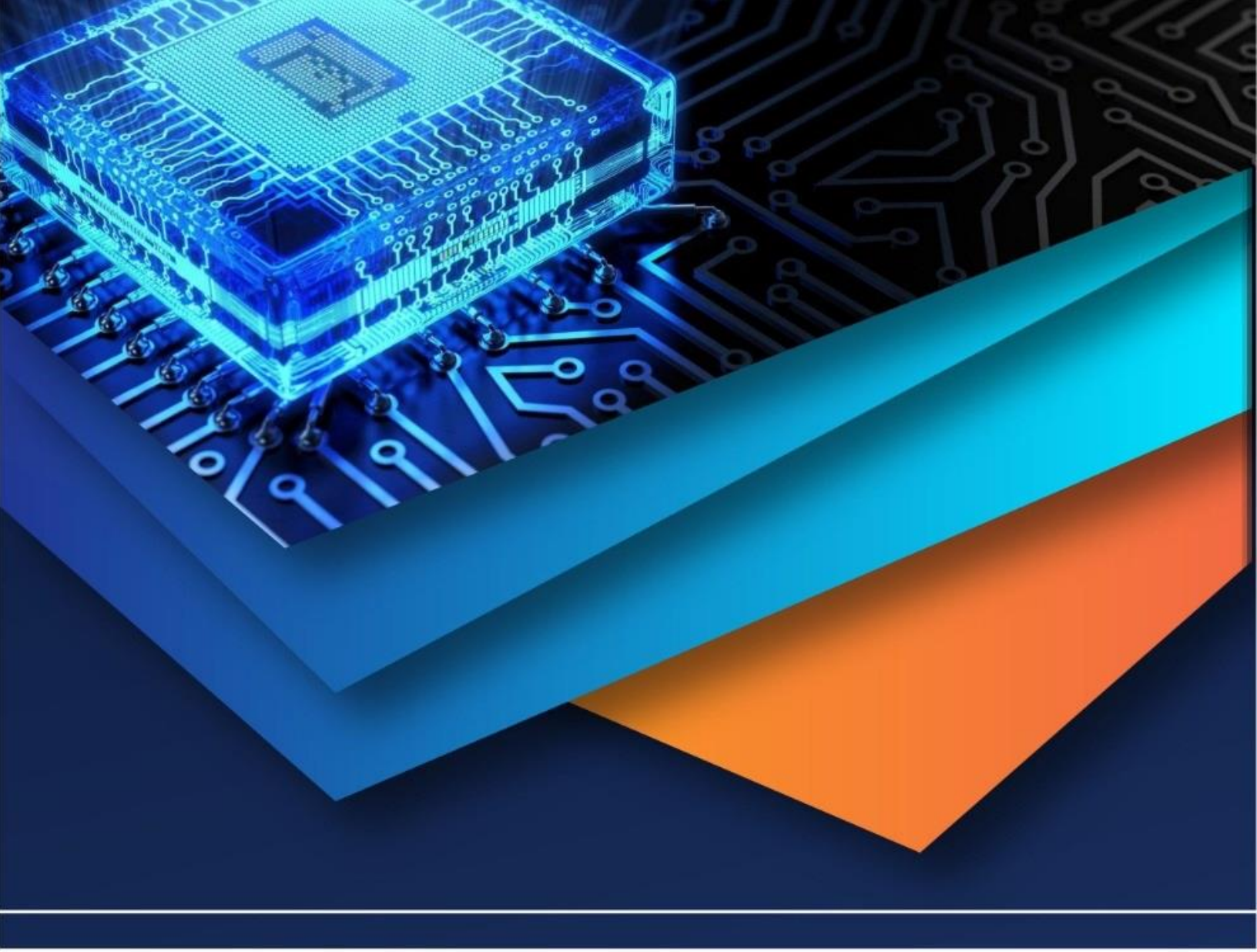

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