MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.36478/makrjms.2024.10.436.444

OPEN ACCESS

Key Words
Childhood obesity, genetics, epigenetics, energy metabolism, environment, lifestyle

Corresponding Author
Anamika Chakraborty Samant, Chaitanya Hospital and Obesity Clinic, Virar, Palghar, Maharashtra, India
dranamika-c@yahoo.co.in

Author Designation
[1]Consultant Physician, Bariatrician
[2]Director
[3]Associate Professor

Received: 21 August 2024
Accepted: 30 September 2024
Published: 1 October 2024

Citation: Anamika Chakraborty Samant, Ajoy Tewari and Hemali Jha, 2024. Unraveling Childhood Obesity: An Overview on the Interplay of Genetics, Epigenetics, and Environmental Factors. Res. J. Med. Sci., 18: 436-444, doi: 10.36478/makrjms.2024.10.436.444

Unraveling Childhood Obesity: An Overview on the Interplay of Genetics, Epigenetics and Environmental Factors

[1]Anamika Chakraborty Samant, [2]Ajoy Tewari and [3]Hemali Jha
[1]Chaitanya Hospital and Obesity Clinic, Virar, Palghar, Maharashtra, India
[2]Jai Clinic and Diabetes Care Center, Lucknow, UP, India
[3]Integral Institute of Medical Science and Research Centre, Lucknow UP, India

ABSTRACT
In the last few decades, with advanced modern technology and discoveries in pharmacology, the human life span has increased. However, sedentary lifestyles and easy access to calorie-dense food have resulted in the growth of obesity and a significant rise in non-communicable diseases, resulting in increased morbidities. Though genetic predisposition remains an important contributing factor, epigenetic modifications and environmental factors may play an essential role in the development of obesity in early life, including intrauterine and post-natal stages. Understanding the interaction between these factors is necessary as these are modifiable and can be the target of therapeutic and pharmacological interventions, thus offering hope to combat obesity effectively. While genetic studies identify obesity-linked genes, epigenetic research explores the factors related to lifestyle and environment and how they can alter gene expressions and are passed on to future generations. This article discusses the interplay of these variables in the dysregulation of energy metabolism and the role of current and future therapeutic strategies to intervene in obesity at an early stage.

INTRODUCTION

Childhood obesity is now a topic of significant concern worldwide. Due to its alarming rise and profound impact on the future, it is considered a major health challenge. Obese children are more likely to become obese adults and develop numerous adverse health outcomes such as type 2 diabetes, hypertension, dyslipidemia, atherosclerotic heart diseases, non-alcoholic fatty liver disease and certain malignancies, thus reducing their overall life expectancy. Also, obese children are at a higher risk of developing psychological issues, including low self-esteem, depression and social stigmatization[1].

Definition: Characterized by excessive accumulation of adipose tissue, there are multiple criteria to define childhood obesity.

The WHO Employs Charts that Describe Obesity as Follows:

For Children Under 5 Years of Age: When the child's weight for height is greater than 2 standard deviations above the WHO Child Growth Standards median, it is considered Overweight and when it exceeds 3 standard deviations above the WHO Child Growth Standards median, it is considered Obese[2].

For Children Aged Between 5-19 Years: BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median is considered Overweight and that greater than 2 standard deviations above the WHO Growth Reference median is considered Obese[3].

In many countries including the US, childhood overweight and obesity are defined as BMI above the 85th percentile for age and sex and above the 95th percentile respectively[4].

The International Obesity Taskforce (IOTF) has developed an international standard growth chart that uses age and gender-specific cut points that, on average, correspond to adult criteria[5].

Epidemiology: The WHO, in 2022, reported 37 million children below five years of age as being overweight. Half of these children were living in Asia and a quarter were from Africa[6]. In adolescents aged 5-19 years age, 390 million were overweight and 160 million were obese. 21% of boys and 19% of girls in this age group were found to be overweight. From only 8% in 1990 to 20% in 2022, the prevalence of overweight (including obesity) among children and adolescents aged 5-19 had increased significantly. A report by the WHO Childhood Obesity Surveillance Initiative (COSI) on data collected from 33 countries between 2018 and 2020 indicated that one in every three children in Europe aged 6-9 years was overweight or obese[7].

The countries in the Pacific Islands have the highest rates of childhood obesity. Childhood obesity rates are also high in the United States and Mexico and it's rising significantly in countries like Brazil and Argentina, due to the influence of genetic predispositions and the replacement of highly nutritional traditional diets with high-calorie junk food.

Etiology and Risk Factors: The etiology of childhood obesity is multifactorial, involving an interplay of various elements including genetics, epigenetics and environmental factors[8]. Each of these factors contributes to the likelihood, onset and course of obesity differently.

Endocrine disorders like hypothyroidism, growth hormone deficiency or resistance, hypercortisolism, and polycystic ovarian syndrome (PCOS) are either consequences or contributors to obesity. Hypothalamic disorders have been linked to severe obesity in children and adolescents. Besides these, factors responsible for obesity in adults, like depression, certain medications and eating disorders may also contribute to childhood obesity.

Genetic Influences: In 1923, Davenport was the first to publish about the inheritable nature of obesity[9]. Following this, several family, twin and adoption studies have provided valuable insights into the role of genetics. It is well established that children with obese parents are more likely to be obese themselves. This elevated risk is due to a mix of genetic predisposition and shared environmental factors including eating choices and physical activity levels. According to studies, having one or both parents who are obese increases the likelihood of childhood obesity substantially. A child with one obese parent is two to three times more likely and one with two obese parents is five to six times more likely to become obese[10].

The inheritability of body mass index (BMI) is reported to range between 40% and 70%. Twin studies comparing the prevalence of obesity among monozygotic and dizygotic twins consistently demonstrate that monozygotic twins have greater obesity concordance rates than dizygotic twins[11-13].

Adoption studies have shown that the BMI of adopted children more strongly correlates with the BMI of their biological parents than with that of their adoptive parents[14].

Childhood obesity cases can be either syndromic or non-syndromic[15].

Syndromic obesity is caused by chromosomal abnormalities or genetic mutations and is associated with multiple clinical symptoms, such as developmental delays, dysmorphic features and other health problems. A few examples of Syndromes associated with obesity are listed in the table below[16-22].

Table 1: Few Examples of Syndromes Associated with Obesity are Listed in the Table Below

Name of syndromes	Clinical features	Mechanism
Prader-Willi Syndrome (PWS)	hypotonia, hyperphagia, cognitive disabilities and obesity.	loss of function of specific genes on chromosome 15.
Bardet-Biedl Syndrome (BBS)	Retinitis pigmentosa/ retinal dystrophy, polydactyly, kidney abnormalities, and obesity	mutations in various BBS genes
Alström Syndrome	Photophobia/ nystagmus and hearing loss, cardiomyopathy, type 2 diabetes and obesity	mutations in the ALMS1 gene.
Cohen Syndrome	developmental delay, microcephaly, characteristic facial features, neutropenia and obesity	mutations in the VPS13B gene.
Albright Hereditary Osteodystrophy (AHO)	short stature, brachydactyly, intellectual disability, and obesity	mutations in the GNAS gene, leading to resistance to the hormone parathyroid hormone (PTH).
Fragile X Syndrome	intellectual disability and behavioral issues, obesity	mutations in the FMR1 gene.
WAGR Syndrome	Wilms Tumor, Aniridia, Genitourinary Anomalies and Intellectual Disability with obesity	deletions in the BDNF gene located in the WAGR region on chromosome 11.

Table 2: Few Examples of Genes Associated with Obesity are Listed in the Table Below

Gene involved	Mechanism
Single-minded 1 (SIM1) Deficiency	This gene has a role in hypothalamic development, necessary for energy homeostasis and appetite control, hence deficiency causing obesity
LEP (Leptin) Gene Mutations	Leptin deficiency causing obesity
LEPR (Leptin Receptor) Gene Mutations	Mutations can disrupt leptin signaling, leading to early-onset obesity.
PCSK1 (Proprotein Convertase Subtilisin /Kexin Type 1) Gene Variants	affects the processing of prohormones, impacting appetite and metabolism, thus causing obesity
POMC (Proopiomelanocortin) Gene Mutations	Role in melanocortins production, plays a role in regulating food intake and energy homeostasis, mutations lead to obesity
Melanocortin 4 Receptor (MC4R) gene mutations	increased appetite and food intake, causing obesity

Table 3: Few Examples of Genes Associated with Obesity are Listed in the Table Below

Genes involved	Mechanism
FTO (Fat Mass and Obesity-Associated) Gene	influences appetite regulation and energy balance, associated with higher BMI and increased obesity risk
GNPDA2 (Glucosamine-6-Phosphate Deaminase 2) Gene	associated with higher BMI and an increased risk of obesity
TMEM18 (Transmembrane Protein 18) Gene	through effects on brain regions that regulate appetite and energy balance, associated with higher BMI and increased obesity risk
SH2B1 (SH2B Adaptor Protein 1) Gene	linked to obesity and insulin resistance. SH2B1 plays a role in leptin and insulin signaling.
NEGR1 (Neuronal Growth Regulator 1) Gene	NEGR1 is involved in brain development and function, influencing energy balance, associated with increased BMI and obesity.
BDNF (Brain-Derived Neurotrophic Factor) Gene	can influence eating behaviors and obesity risk.
ADRB3 (Beta-3 Adrenergic Receptor) Gene	involved in the regulation of fat breakdown and energy expenditure.
NPC1 (Niemann-Pick Disease, Type C1) Gene	affecting lipid metabolism and energy homeostasis, associated with increased BMI and obesity.
KCTD15 (Potassium Channel Tetramerization Domain Containing 15) Gene	exact mechanism not known

Non-Syndromic cases of obesity can be either monogenic obesity or polygenic obesity.

Monogenic Obesity is caused by mutation of a single gene. Only 5% of the obese have non-syndromic monogenic obesity, while about 95% have common polygenic obesity. (Selum).

A few examples of genes associated with obesity are listed in the table below[23-29].

Polygenic Obesity is caused by the combined effect of multiple genes.

A few examples of genes associated with obesity are listed in the table below[30-38].

Genome-wide association studies (GWAS) have helped in discovering genes involved with obesity. The first discovery made in 2007 was genetic variants in the fat mass and obesity-associated gene (FTO)[39,40]. Many polymorphisms in FTO and MC4R have been identified so far. One revolutionary discovery was that of the ectonucleotide pyrophosphatase/phosphodiesterase 1 gene (ENPP1), located on chromosome 6q, which plays a significant role in many biological processes. There are more than 1000 loci-carrying variants including single nucleotide polymorphisms (SNPs) associated with BMI and other factors like neuro-circuits of appetite and satiety regulation (BDNF, MC4R and NEGR), energy and lipid metabolism (FTO, RPTOR and MAP2K5, insulin secretion and action (TCF7L2, IRS1) as well as adipogenesis[41-48]. Variations in TMEM18, GNDPA2, MC4R, NEGR1, BDNF, INSIG2 and KTCD15 are associated with early-onset obesity (49-52). Effects of some SNPs seem to be more prominent in children and decline later in life.

The genetic risk of obesity is assessed using polygenic risk scores (PGS), which are based on several genetic variants located at various sites throughout the genome. The outcome of polygenic risk scores (PGS) can be improved by combining it with other factors such as environmental or epigenetic indicators[53].

Epigenetic Influences: Epigenetics is the study of changes in gene expression that can be brought about by environmental influences, dietary choices and lifestyle choices but do not involve changes to the underlying DNA sequence[54]. The three main mechanisms of epigenetic changes include DNA methylation, histone and chromatin modification and post-translational regulation, including that by micrornas (mirnas)[55].

DNA Methylation: The act of incorporating a methyl group into DNA, usually at CpG sites, can suppress gene expression. Changes in DNA methylation patterns have been observed in genes involved in appetite regulation, fat storage and energy metabolism. Methylation of the appetite-regulating POMC gene has been connected to elevated childhood body mass index (BMI). Hypomethylation of the leptin gene promoter has been linked to obesity and metabolic issues. A similar link has been found with altered methylation of genes like IRS1, PIK3R1 which are involved with insulin signaling. DNA methylation can be influenced by the maternal consumption of folate, methionine and vitamin B12 during pregnancy[56].

Histone Modifications: Gene expression is impacted by chemical changes to the histone proteins encircling DNA, thus affecting how loosely or securely DNA is packaged. Histone acetylation and methylation changes can affect genes linked to inflammation and adipogenesis, two processes that are essential to the development of obesity[57]. Increased acetylation of specific histone residues, associated with a high-fat diet can cause obesity and interestingly, calorie restriction can reverse these modifications.

Non-Coding Rnas (MicroRNAs (miRNAs) and long Non-Coding RNAs (lncrnas): Tiny non-coding RNAs can attach to messenger RNAs (mRNAs) and prevent them from being translated into proteins. Specific miRNAs have been found to regulate genes involved in lipid metabolism, insulin signaling and inflammation. miRNAs are already being studied in cancer and type 2 diabetes. Elevated levels of miR-21 and miR-221 have been associated with obesity-related inflammation in children[58]. lncRNAs like GYG2P1 RP11-20G13.3 are also associated with obesity and metabolic dysfunctions.

An example of epigenetic dysregulation is Prader-Willi syndrome, which is characterized by obesity with hyperphagia and neurodevelopmental delay. Though caused by a genomic deletion in chromosome 15, a subset of sporadic Prader-Willi cases has been reported from inappropriate epigenetic silencing of the same chromosomal region[59].

Epigenetic changes induced by environmental factors can sometimes be passed from one generation to the next, potentially predisposing the offspring to obesity[60].

The Dutch Famine Study and the Pima Indian Study strongly support the theory of Intergenerational Epigenetic Effects. Pregnant women with severe malnutrition during the Dutch Hunger Winter of 1944-1945 had children who showed higher rates of obesity, diabetes and cardiovascular diseases later in life[61,62].

Environmental Influences: Environmental influences like diet, physical activity, cultural and societal norms, and socioeconomic status play crucial roles in childhood obesity. These factors are influential based on the life stages of a child.

A faulty maternal diet including overeating of a high-calorie diet or deficiency of essential elements are both linked to an increased risk of obesity in the offspring. Obese mothers are more likely to have children who develop obesity later in life[63]. Gestational diabetes mellitus (GDM) can lead to higher birth weight and increased adiposity in the offspring[64]. Exposure to tobacco during pregnancy, elevated stress, and cortisol levels during pregnancy may impact fetal development and metabolism, thus raising the likelihood of childhood obesity[65,66].

Early Fetal Influences like Intrauterine Growth Restriction (IUGR) can result in a compensatory rapid growth pattern postnatally, which is associated with a higher risk of obesity and metabolic syndrome later in life[67]. Abnormalities in placental function can affect nutrient and oxygen delivery to the fetus, impacting growth and metabolic programming[68]. Studies have shown that breast fed infants are less likely to grow into obese individuals compared to formula-fed infants. Early introduction of solid foods before four to six months of age can increase the risk of obesity[69]. Rapid infant weight gain in the first few months of life is a strong predictor of childhood obesity[70]. Parental feeding practices can contribute to the development of unhealthy eating behaviors and obesity in children[71]. Limited physical activity and sedentary behaviors, excessive screen time, inadequate sleep length and poor sleep quality during infancy and early childhood are associated with a higher risk of obesity[72,73]. Early exposure to chemicals like phthalates and bisphenol A (BPA) that can interfere with hormonal function, may increase the risk of obesity[74].

Socioeconomic differences make it difficult for the unaffordable to achieve adequate physical activity and a nutritious diet, which can lead to obesity and chronic illnesses in children. Poor food literacy results in wrong dietary decisions. Lack of space, inadequate facilities,

decreased security and lack of awareness of the benefits of exercise may prevent parents from encouraging their children to engage in daily outdoor games and activities. Parental conduct and the home environment may encourage sedentary behaviors and unhealthy eating patterns. The social media and advertising industry also have a big impact on what children eat thus misguiding them to make wrong choices.

Genetic Epigenetic and Environmental Interactions: Environmental factors such as nutrition, physical activity, stress, exposure to toxins and socioeconomic factors can cause epigenetic alterations that affect metabolic processes, appetite regulation and fat storage, increasing an individual's risk of obesity.

Stress and food can influence hormonal pathways that control appetite, metabolism and energy balance, which can then interact with genetic predispositions to determine obesity risk. Individuals with particular variants of the FTO gene are more likely to be obese, although studies have shown that those who engage in regular physical exercise have a lower BMI than inactive individuals with the same gene variant[75].

Studies have shown that a high-fat, high-sugar diet might worsen the effects of MC4R variations, resulting in increased weight gain[76].

A study discovered that children with a high genetic risk score for obesity were more likely to be obese if they lived in low-income neighborhoods[77]. Also reported that children who endure early-life stressors such as abuse or neglect are more likely to develop obesity and metabolic diseases[78].

Prevention and Interventions: The interplay between genetics, epigenetics and environmental factors is complex. Genetic predispositions can interact with environmental influences to either exacerbate or diminish the risk of obesity. Understanding these interrelations is crucial for developing effective strategies for the prevention and intervention of childhood obesity. Early intervention initiatives can reduce long-term health concerns, especially for children with a family history of obesity.

The modifiable environmental influences can be tackled with interventions to prevent and manage childhood obesity at various stages of development and multiple aspects of a child's environment.

Nutritional Counseling of the mother for adequate intake of healthy nutrients and avoidance of excessive weight gain in pregnancy, management of gestational diabetes, encouraging regular exercise, cessation of smoking and stress reduction are examples of interventions during pregnancy for healthy outcomes[63].

Early fetal and postnatal interventions include the promotion of breast feeding and guiding parents on infant feeding practices. Teaching parents about monitoring the growth and development of the child and promoting physical activity at an early age can prevent the development of obesity[69].

Interventions that can influence changes in policy regulation and legislation by creating awareness and education about childhood obesity need to be implemented. These include promoting healthy behaviors, setting nutritional standards for foods and beverages and creating safe, accessible environments that encourage physical activity[79]. Socioeconomic disparities can be lessened with interventions like providing subsidies for healthy foods, educating communities to make better decisions about nutrition, and the advantages of physical activity and providing sports and leisure activities for children after school.

Medical and Clinical Interventions like regular screening and assessment of school children for obesity and related health conditions such as type 2 diabetes and hypertension should be promoted. There should be a multidisciplinary approach collaborating with pediatricians, dietitians, psychologists and other healthcare professionals to provide comprehensive care for children with obesity.

Extensive research and studies are required to slow down the impact of the complex interactions between genetics, epigenetics and the environment responsible for childhood obesity. The GWAS results indicate that although hundreds of loci associated with obesity have been discovered to date, they only explain 6% of the variation in BMI[80]. Polygenic risk scores and methylation risk scores combined with greater sample sizes and better weighting statistics may prove to be useful tools in future therapeutic settings.

The ultimate goal from a therapeutic perspective will be to create incredibly accurate and exact prediction scores that will allow physicians to forecast obesity as well as patient's responses to medicines specifically designed to help them lose weight.

CONCLUSION

Addressing childhood obesity requires a holistic strategy that acknowledges its genetic, epigenetic and environmental roots. Early intervention is critical for reducing long-term health implications. By fostering supportive environments and promoting healthy lifestyles from an early age, children should be empowered to lead healthier lives. Healthcare providers, policymakers and communities must work together to implement effective strategies that prioritize the well-being of our children and help reduce the prevalence of obesity in future generations.

REFERENCES

1. Bray, G.A., 1996. Health hazards of obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, End Metab Clin North Am., 25: 1-10.0.

2. WHO Multicentre Growth Reference Study Group. 2006. WHO Child Growth Standards based on length/height, weight and age. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Acta Paediatr Supp, 450: 1-10.0.
3. de Onis, M., A.W. Onyango, E. Borghi, A. Siyam and C. Nishida,et al., 2007. Development of a WHO growth reference for school-aged children and adolescents. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Bull. World Health Org.ization, 85: 1-10.0.
4. Ogden, C.L. and K.M. Flegal, 2010. Changes in terminology for childhood overweight and obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Natl Health Stat Rep, 1: 1-10.0.
5. Cole, T.J., M.C. Bellizzi, K.M. Flegal and W.H. Dietz, 2000. Establishing a standard definition for child overweight and obesity worldwide: International survey. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, BMJ, 320: 1-10.0.
6. Rohde, K., M. Keller, L.L. Poulsen, M. Blüher, P. Kovacs and Y. Böttcher, 2019. Genetics and epigenetics in obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Metabolism, 92: 1-10.0.
7. Davenport, C.B., 1923. Body Built and Its Inheritance. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, 0 1-10.arnegie Institute of Washington.
8. Whitaker, R.C., J.A. Wright, M.S. Pepe, K.D. Seidel and W.H. Dietz, 1997. Predicting Obesity in Young Adulthood from Childhood and Parental Obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Engl. J. Med., 337: 1-10.0.
9. Silventoinen, K., B. Rokholm, J. Kaprio, and T.I.A. Sørensen, 2010. The genetic and environmental influences on childhood obesity: A systematic review of twin and adoption studies. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Int. J. Obesity, 34: 1-10.0.
10. Bouchard, C. and A. Tremblay, 1997. Genetic Influences on the Response of Body Fat and Fat Distribution to Positive and Negative Energy Balances in Human Identical Twins. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J. Nutr., 127: 1-10.0.
11. Stunkard, A.J., J.R. Harris, N.L. Pedersen and G.E. McClearn, 1990. The Body-Mass Index of Twins Who Have Been Reared Apart. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Engl. J. Med., 322: 1-10.0.
12. Sorensen, T.I., C. Holst and A.J. Stunkard, 1992. Childhood body mass index--genetic and familial environmental influences assessed in a longitudinal adoption study. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Intern Jou Obe Rela Meta Dis., 16: 1-10.0.
13. Littleton, S.H., R.I. Berkowitz and S.F.A. Grant, 2020. Genetic Determinants of Childhood Obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Mol. Diagnosis amp Ther., 24: 1-10.0.
14. Cassidy, S.B., S. Schwartz, J.L. Miller and D.J. Driscoll, 2012. Prader-Willi syndrome. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Genet. Med., 14: 1-10.0.
15. Forsythe, E. and P.L. Beales, 2013. Bardet–Biedl syndrome. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Eur. J. Hum. Genet., 21: 1-10.0.
16. Marshall, J.D., S. Beck, P. Maffei and J.K. Naggert, 2007. Alström Syndrome. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Eur. J. Hum. Genet., 15: 1-10.0.
17. Kolehmainen, J., G.C. Black and A. Saarinen, 2003. Cohen syndrome: interval mapping and identification of a locus on chromosome 8q22.1-q22.2. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Am J Hum Genet., 73: 1-10.0.
18. Weinstein, L.S., S. Yu, D.R. Warner and J. Liu, 2001. Endocrine manifestations of stimulatory G protein alpha-subunit mutations and the role of genomic imprinting. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Endocr Rev., 22: 1-10.0.
19. Kogan, C.S., J. Turk, R.J. Hagerman and K.M. Cornish, 2008. Impact of the Fragile X-associated tremor/ataxia syndrome on intellectual functioning, daily living skills, and quality of life. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Am J Med Genet A., 14: 1-10.0.
20. Yang, P., Y. Yang, A. Nie and X. Zhang, 2020. WAGR syndrome: From phenotype to diagnosis and treatment. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Eur J Med Genet., Vol. 3 .0 1-10.0.
21. Salum, K.C.R., J.D. Rolando, V.M. Zembrzuski, J.R.I. Carneiro and C.B. Mello et al., 2021. When Leptin Is Not There: A Review of What Nonsyndromic Monogenic Obesity Cases Tell Us and the Benefits of Exogenous Leptin. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Front. Endocrinol., Vol. 12 .10.3389/fendo.2021.722441 1-10.0.
22. Hung, C.C., J. Luan, M. Sims, J.M. Keogh and C. Hall et al., 2007. Studies of the SIM1 gene in relation to

human obesity and obesity-related traits. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Int. J. Obesity, 31: 1-10.0.

23. Montague, C.T., I.S. Farooqi, J.P. Whitehead, M.A. Soos and H. Rau et al., 1997. Congenital leptin deficiency is associated with severe early-onset obesity in humans. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nature, 387: 1-10.0.
24. Clément, K., C. Vaisse, N. Lahlou, S. Cabrol and V. Pelloux et al., 1998. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nature, 392: 1-10.0.
25. Farooqi, I.S., K. Volders, R. Stanhope, R. Heuschkel and A. White et al., 2007. Hyperphagia and Early-Onset Obesity due to a Novel Homozygous Missense Mutation in Prohormone Convertase 1/3. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J. Clin. Endocrinol. amp Metab., 92: 1-10.0.
26. Krude, H., H. Biebermann, W. Luck, R. Horn, G. Brabant and A. Grüters, 1998. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Genet., 19: 1-10.0.
27. Farooqi, I.S., G.S.H. Yeo, J.M. Keogh, S. Aminian and S.A. Jebb et al., 2000. Dominant and recessive inheritance of morbid obesity associated with melanocortin 4 receptor deficiency. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J. Clin. Invest., 106: 1-10.0.
28. Frayling, T.M., N.J. Timpson, M.N. Weedon, E. Zeggini and R.M. Freathy et al., 2007. A Common Variant in the FTO Gene Is Associated with Body Mass Index and Predisposes to Childhood and Adult Obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Science, 316: 889-8940.0.
29. Willer, C.J., E.K. Speliotes, R.J.F. Loos, S. Li and C.M. Lindgren,et al., 2009. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat Genet., 41: 1-10.0.
30. Thorleifsson, G., G.B. Walters, D.F. Gudbjartsson, V. Steinthorsdottir and P. Sulem et al., 2009. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Genet., 41: 1-10.0.
31. Bochukova, E.G., N. Huang, J. Keogh, E. Henning and C. Purmann et al., 2010. Large, rare chromosomal deletions associated with severe early-onset obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nature, 463: 1-10.0.
32. Yeo, G.S.H., C.C.C. Hung, J. Rochford, J. Keogh and J. Gray et al., 2004. A De novo mutation affecting human TrkB associated with severe obesity and developmental delay. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Neurosci., 7: 1-10.0.
33. Walston, J., K. Silver, C. Bogardus, W.C. Knowler and F.S. Celi et al., 1995. Time of Onset of Non-Insulin-Dependent Diabetes Mellitus and Genetic Variation in the ß3-Adrenergic–Receptor Gene. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Engl. J. Med., 333: 1-10.0.
34. Epelman, S., J.D. Morrow and P. Hornsby,et al., 2016. Niemann-Pick type C1-like 1 gene and obesity risk in children and adolescents: findings from the CHOP-Boston collaboration. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J Pediatr, 168: 1-10.0.
35. Meyre, D., J. Delplanque, J.C. Chèvre, C. Lecoeur and S. Lobbens et al., 2009. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Genet., 41: 1-10.0.
36. Dina, C., D. Meyre, S. Gallina, E. Durand and A. Körner et al., 2007. Variation in FTO contributes to childhood obesity and severe adult obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Genet., 39: 1-10.0.
37. Boender, A.J., A.J.V. Rozen and R.A.H. Adan, 2012. Nutritional State Affects the Expression of the Obesity-Associated Genes Etv5, Faim2, Fto, and Negr1. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Obesity, 20: 1-10.0.
38. Ho, E.V., S.J. Klenotich, M.S. McMurray and S.C. Dulawa, 2016. Activity-Based Anorexia Alters the Expression of BDNF Transcripts in the Mesocorticolimbic Reward Circuit. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Plos one., Vol. 11 .10.1371/journal.pone.0166756 1-10.0.
39. Voight, B.F., L.J. Scott and V. Steinthorsdottir,et al., 2007. TCF7L2 variants associate with increased risk of type 2 diabetes and impaired insulin secretion. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat Genet., 39: 1-10.0.
40. Horstmann, A., P. Kovacs, S. Kabisch, Y. Boettcher and H. Schloegl et al., 2013. Common Genetic Variation near MC4R Has a Sex-Specific Impact on

Human Brain Structure and Eating Behavior. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, PLoS ONE, Vol. 8, No. 9 .10.1371/journal.pone.0074362 1-10.0.

41. Locke, A.E., B. Kahali and S.I. Berndt,et al., 2015. ,Genetic studies of body mass index yield new insights for obesity biology. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nature, 518: 1-10.0.
42. Lango, H., T.C. Peakman and A. Mulas,et al., 2008. Macronutrient intake and obesity: data from a UK population-based cohort study. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Obesity, 16: 1-10.0.
43. Kilpeläinen, T.O., M.C. Zillikens, A. Stancákova, F.M. Finucane and J.S. Ried et al., 2011. Genetic variation near IRS1 associates with reduced adiposity and an impaired metabolic profile. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Genet., 43: 1-10.0.
44. Shungin, D., T.W. Winkler and C.D.C. Croteau,et al., 2015. New genetic loci link adipose and insulin biology to body fat distribution. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nature, 518: 1-10.0.
45. Zhao, J., J.P. Bradfield, M. Li, K. Wang and H. Zhang et al., 2009. The Role of Obesity-associated Loci Identified in Genome-wide Association Studies in the Determination of Pediatric BMI. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Obesity, 17: 1-10.0.
46. Bressler, J., M. Fornage, C.L. Hanis, W.H.L. Kao and C.E. Lewis et al., 2009. The INSIG2 rs7566605 genetic variant does not play a major role in obesity in a sample of 24, 722 individuals from four cohorts. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, BMC Med. Genet., Vol. 10 .10.1186/1471-2350-10-56 1-10.0.
47. Campa, D., A. Hüsing, J.D. McKay, O. Sinilnikova and U. Vogel et al., 2010. The INSIG2 rs7566605 polymorphism is not associated with body mass index and breast cancer risk. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, BMC Cancer, Vol. 10 .10.1186/1471-2407-10-563 1-10.0.
48. Herbert, A., N.P. Gerry, M.B. McQueen, I.M. Heid and A. Pfeufer et al., 2006. A Common Genetic Variant Is Associated with Adult and Childhood Obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Science, 312: 1-10.0.
49. Loos, R.J.F. and G.S.H. Yeo, 2022. The genetics of obesity: From discovery to biology. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Rev. Genet., 23: 1-10.0.
50. Pinel, C., B. Prainsack and C. McKevitt, 2019. Markers as mediators: A review and synthesis of epigenetics literature. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, BioSocieties, 13: 1-10.0.
51. Al Aboud, N.M., C. Tupper and I. Jialal, 2023. Genetics, Epigenetic Mechanism. 0, 0, 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, 0 1-10.0.
52. Lima, R.S., J.D.S. Gomes and P.R. Moreira, 2020. An overview about DNA methylation in childhood obesity: Characteristics of the studies and main findings. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J. Cell. Biochem., 121: 1-10.0.
53. Xu, L., M.H.Y. Yeung, M.Y.C. Yau, P.P.Y. Lui and C.M. Wong, 2019. Role of Histone Acetylation and Methylation in Obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0 0, ISBN-1: 0, Curr. Pharmacol. Rep., 5: 1-10.0.
54. Rottiers, V. and A.M. Näär, 2012. MicroRNAs in metabolism and metabolic disorders. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Nat. Rev. Mol. Cell Biol., 13: 1-10.0.
55. Mendiola, A.J.P. and J.M. LaSalle, 2021. Epigenetics in Prader-Willi Syndrome. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Front. Genet., Vol. 12 .10.3389/fgene.2021.624581 1-10.0.
56. Panera, N., C. Mandato, A. Crudele, S. Bertrando, P. Vajro and A. Alisi, 2022. Genetics, epigenetics and transgenerational transmission of obesity in children. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Front. Endocrinol., Vol. 13 .10.3389/fendo.2022.1006008 1-10.0.
57. Lumey, L.H., A.D. Stein and E. Susser, 2011. Prenatal Famine and Adult Health. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Annual Revi Pub Health, 32: 1-10.0.
58. Hales, C.N. and D.J. Barker, 2001. The thrifty phenotype hypothesis: Type 2 diabetes. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, British Med Bulletin, 60: 1-10.0.
59. Sanli, E. and S. Kabaran, 2019. Maternal Obesity, Maternal Overnutrition and Fetal Programming: Effects of Epigenetic Mechanisms on the Development of Metabolic Disorders. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Curr. Genomics, 20: 1-10.0.
60. Gillman, M.W., S. Rifas-Shiman, C.S. Berkey, A.E. Field and G.A. Colditz, 2003. Maternal Gestational Diabetes, Birth Weight, and Adolescent Obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Pediatrics, 111: 1-10.0.
61. Rayfield, S. and E. Plugge, 2017. Systematic review and meta-analysis of the association between

maternal smoking in pregnancy and childhood overweight and obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J. Epidemiol. Comm Health, 71: 1-10.0.

62. Lamichhane, N., N.J. Olsen, E.L. Mortensen, C. Obel, B.L. Heitmann and M.N. Händel, 2020. Associations between maternal stress during pregnancy and offspring obesity risk later in life-A systematic literature review. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Obesity Rev., Vol. 21 .10.1111/obr.12951 1-10.0.
63. Morrison, J.L., J.A. Duffield, B.S. Muhlhausler, S. Gentili and I.C. McMillen, 2010. Fetal growth restriction, catch-up growth and the early origins of insulin resistance and visceral obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Pediatr. Nephrology, 25: 1-10.0.
64. Fajersztajn, L. and M.M. Veras, 2017. Hypoxia: From Placental Development to Fetal Programming. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Birth Defects Res., 109: 1-10.0.
65. Gillman, M.W., S.S.L. Rifas and C.A. Camargo,et al., 2001. Risk of Overweight Among Adolescents Who Were Breastfed as Infants. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, JAMA, 285: 1-10.0.
66. Dennison, B.A., L.S. Edmunds, H.H. Stratton and R.M. Pruzek, 2006. Rapid Infant Weight Gain Predicts Childhood Overweight. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Obesity, 14: 1-10.0.
67. Wardle, J., S. Carnell and L. Cooke, 2005. Parental control over feeding and children's fruit and vegetable intake: How are they related? 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, J. Am. Dietetic Assoc., 105: 1-10.0.
68. Molnár, D. and B. Livingstone, 2000. Physical activity in relation to overweight and obesity in children and adolescents. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Eur. J. Pediatr.s, 159: 1-10.0.
69. Skjåkødegård, H.F., Y.S. Danielsen, B. Frisk, S.W. Hystad and M. Roelants et al., 2021. Beyond sleep duration: Sleep timing as a risk factor for childhood obesity. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Pediatr. Obesity, Vol. 16 .10.1111/ijpo.12698 1-10.0.
70. Hemati, Z., M. Heidari-Beni and R. Kelishadi, 2022. Exposure to Endocrine Disrupting Chemicals, Part of Lifestyle Factors Related to Growth Disorders in Childhood and Chronic Diseases in Adulthood. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Integr. Sci., 2022: 1-10.0.
71. Kilpeläinen, T.O., L. Qi, S. Brage, S.J. Sharp and E. Sonestedt et al., 2011. Physical Activity Attenuates the Influence of FTO Variants on Obesity Risk: A Meta-Analysis of 218, 166 Adults and 19, 268 Children. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, PLoS Med., Vol. 8, No. 11 .10.1371/journal.pmed.1001116 1-10.0.
72. Qi, Q., and F.B. Hu, 2012. Genetics of obesity and dietary intervention. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Public Health Nutr, 15: 1-10.0.
73. Wardle, J., S. Carnell, C.M. Haworth and R. Plomin, 2008. Influence of genetic and environmental factors on obesity-related phenotypes in a reared-apart adoption study., 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Intern Jou Obe, 32: 1-10.0.
74. Tyrka, A.R., L.H. Price, H.T. Kao, B. Porton, S.A. Marsella and L.L. Carpenter, 2012. Childhood Maltreatment and Telomere Shortening: Preliminary Support for an Effect of Early Stress on Cellular Aging. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Bio. Psychiatry, 67: 1-10.0.
75. Novak, N.L. and K.D. Brownell, 2012. Role of Policy and Government in the Obesity Epidemic. 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Circulation, 126: 1-10.0.
76. Müller, M.J., C. Geisler, J. Blundell, A. Dulloo and Y. Schutz et al., 2018. The case of GWAS of obesity: Does body weight control play by the rules? 0 0, January 01-01, 1970, In: 0, 0 (Ed.)., 0 Edn., 0, 0, ISBN-1: 0, Int. J. Obesity, 42: 1-10.0.