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Review Article

Obesity is a Unique Metabolic Disease: An Update

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Received: June 06, 2023; **Published:** July 22, 2023

Abstract

The adiposity, and the risks associated with this altered metabolic state, with acute cardiovascular events are poorly understood, and the relationship is a complex one. Abdominal obesity is known to cause alterations in adipocyte biology, leading to inflammation, dysglycemia, insulin resistance, increased blood pressure, endothelial dysfunction and atherogenesis. Compared with Europeans, people of South Asian and East Asian ethnicity develop type-2 diabetes, with a lower body mass index. Genome Wide Association Studies (GWAS) have identified 400 genetic variations associated with the risks for type-2 diabetes. Adiposity per se, does not explain excess risk for type-2 diabetes. Visceral fat and ectopic fat accumulation in or around the liver, pancreas, and muscle, are causally related to insulin resistance, impaired glucose tolerance and type-2 diabetes. Body fat distribution across the population is not uniform. South Asian phenotype predominantly accumulates fat in the abdominal region, and this type of obesity has been referred as central abdominal obesity, as compared to the increase in the overall body mass index (BMI), observed in western populations. No matter what the pattern of fat distribution, increases in white fat seem to promote weight gain, and leads to the development of obesity. Excess fat is associated with higher concentration of the hormones of the renin-angiotensin system, which may initiate oxidative stress by generating reactive oxygen species. Visceral fat also may play a role in lipid peroxidation and promote damage through production of cytokines. These reactions may further activate nuclear factor kB (NF-kB) and induce inflammation. Such metabolic disturbances, promote increases in blood pressure, insulin resistance, arterial stiffness, and endothelial dysfunction. Some studies have demonstrated the relationship between leptins and adiposity. Leptin resistance elevates cytokines and tumor necrosis factor, promotes inflammation, and increases risk for CVDs. Physical fitness reduces leptin concentrations, increases satiety, lowers inflammation, and improves vascular functions. Obesity in general, childhood obesity in particular, is a global public health crisis. Although there is lots of speculation, there is no single definitive cause of obesity, which means there is no definite cure for this condition. In this overview, we have discussed few novel approaches for the early diagnosis of this metabolic condition, as well as for developing appropriate preventive interventions. Obesity is speculated to emerge as the fastest growing, and leading metabolic risk factor, underlying acute myocardial infarction.

Keywords: *Obesity; Metabolic Disease; Acute Myocardial Infarction; Genome Wide Association Studies (GWAS); Body Mass Index (BMI); Nuclear Factor kB (NF-kB)*

Introduction

Incidence and prevalence of excess weight and obesity has increased to epidemic proportions, worldwide, in the last three decades. Globally, obesity has nearly tripled since 1975, to more than 1.9 billion adults, 18 years and older [1-8]. According to the World Health Organization, 39% of the world's population aged 18 years and older were overweight. Over 340 million children and adolescents aged 15 - 19, were overweight or obese. Obesity-related clinical complications are preventable and treatable. Despite growing recognition worldwide, the obesity epidemic continues to increase in incidence and prevalence and is going to be the most difficult challenge to address by public health officials [2,9]. In a recent article, researchers from the Department of Molecular Epidemiology, German Institute of Human Nutrition, describe that of the 20 leading global risk factors estimated to cause loss of life in 2040, just three metabolic risks, high blood pressure, high BMI, and high fasting glucose, as the top variables [10]. Based on these studies and similar observations, a concept is being developed, which focuses on the aggregation of important risk factors, which allows the identification of sub phenotypes, metabolically unhealthy and metabolically healthy, with differing risk for cardiometabolic diseases [11,12]. Despite several reports describing metabolically healthy individuals being at less risk for cardiovascular events, a metanalysis could not identify any obese group, that was not at increased risk of cardiovascular events, compared with normal-weight healthy participants [11]. A meta-analysis of 41 cohort studies, found that compared to metabolically healthy group, metabolically unhealthy subjects had higher risk of all-cause mortality [12]. Based on their observations, the authors recommended that normal weight population should also be screened, for basic metabolic phenotypes, so that adverse cardiovascular events could be prevented. Kramer and associates reported increased incidences of cardiovascular disease, and all-cause mortality among obese adults, for both metabolically 'unhealthy' and metabolically 'healthy' [13,14].

According to British and German researchers, there is no 'obesity survival paradox', when better ways of measuring body fat was used [15,16]. Excess weight and obesity is defined as body mass index (BMI). This generally accepted index comes originally from the Adolph Quetelet index named after a Belgian astronomer, who used height and weight to assess individuals in French and Scottish armies in 1832 [17]. The Framingham heart study was one of the earliest, to identify obesity as an independent risk factor for cardiovascular disease [18]. In 1972, Prof Ancle Keys an epidemiologist from the University of Minnesota, coined the term 'body mass index' in a paper titled "indices of Relative Weight and Obesity," originally published in the *Journal of Chronic Diseases* [19]. Although, BMI is used as the gold standard for measuring obesity, the lack of a suitable 'gold standard' has made it difficult to evaluate alternative measures of obesity. For instance, 45% of obese White women are misclassified as non-obese, using BMI and this will be much greater for South Asian and East Asian populations [20]. Fat distribution patterns vary considerably across various ethnic populations, independent of obesity. Asians (East and South) have more, and Africans less visceral fat, compared to Europeans and North Americans. Consequently, those populations with excess visceral fat, tend to be more susceptible to develop diabetes even with lower BMIs, compared with European and American populations.

Three decades ago, Dr Bela Shah of Indian Council of Medical Research (ICMR), and Paul M McKeigue of London School of Hygiene and Tropical Medicine, studied South Asian population in London, and reported that South Asian group had a higher prevalence of diabetes, higher blood pressure, higher plasma triglyceride and lower HDL cholesterol. Based on their findings, they concluded, that within this ethnic group, waist-hip ratio (WHR) was correlated with glucose intolerance, insulin resistance, triglyceride and associated with a pronounced tendency to central abdominal obesity [21]. According to Aaron Kelly of University of Minnesota, who has two decades of experience in conducting clinical trials in the treatment of pediatric obesity, this metabolic abnormality leads to endothelial dysfunction, and progression of metabolic diseases such as hypertension, excess weight, diabetes, and vascular diseases. His studies have demonstrated, that even as short as eight weeks of exercise, improved fitness, HDL cholesterol and endothelial function [22]. Compared to the US., the waist-weight ratios are significantly higher in men and women from Chennai, India. Based on their findings the authors concluded that South Asian Indians are particularly predisposed toward central adiposity [23]. In a later study, Bajaj and associates demonstrated the importance of waist circumference (WC), as measurement for mortality, diabetes, and CVD risk prediction, and suggested that obesity specific interventions targeting WC in addition to traditional risk factor management, may favorably impact the outcomes [24].

Since the time Framingham Heart Group described risk factors for the development cardiovascular diseases, body mass index (BMI) has been the gold standard and popular marker to define obesity index. In recent years, there are suggestions to use lower BMI cutoffs, compared to standard BMI cutoffs, to reduce the risk of obesity-related co-morbidities. Kali and associates from Kazakhstan, claim to be the first group, to explore new BMI and WC cut-offs in this ethnic population. These authors concluded, that for central Asian populations, the current recommended BMI and WC cutoffs may not be suitable and suggested that further work is needed to establish specific cut-offs for this population [25]. Patel and associates questioned, as to whether the "South Asian Phenotype" is unique to South Asians? They compared the cardiometabolic risk factors in the CARRS study representing Chennai, New Delhi, India; Karachi, Pakistan; and the United States, Asians, Blacks, Hispanics, and Whites. They concluded that individuals with "South Asian Phenotype" were 5 to 9 times more likely, to exhibit dysglycemia and dyslipidemia in the 'healthy' BMI range, compared with any other race/ethnic group [26]. Using Body Mass index alone, as a screening tool for cardiovascular risk assessment, fails in populations that are characterized by higher prevalence of central abdominal obesity, and reminds us of a seminal observation made by Professor Yajnik, the lead investigator of Pune Maternal Nutrition Studies (PMNS), in his article "Y-Y paradox", which demonstrated the limitations of BMI as a measure of adiposity across populations [27]. These studies led to the conclusion, that small Indian babies have small abdominal viscera and low muscle mass but preserve body fat during their intrauterine development. This body composition may persist postnatally and predispose to an insulin-resistant state [28].

Between 1993 and 2001, a bilateral study between the Medical Research Council Environmental Epidemiology Unit, University of Southampton, UK., and Mission Hospital, Mysore, India, used the birth records at Mission Hospital, Mysore (MHM), India, to trace people born in the hospital between 1934 and 1966. This is the largest birth cohort in India, in which surviving members are still living late in life. The study data are freely available [29]. Based on the findings of PMNS, MHM, and at the UK Epidemiology group, Professor Barker, a British Epidemiologist, developed his hypothesis, that revealed a significant association between low birth weight and adult metabolic diseases [30-34]. The Barker hypothesis, proposed that adverse nutrition in early life, including prenatally as measured by birth weight, increased susceptibility to the metabolic syndrome, which includes obesity, diabetes, insulin insensitivity, hypertension, hyperlipidemia and complications that include coronary heart disease and stroke. The underlying causes for metabolic diseases are multifactorial since the microenvironment during the fetal growth is derived from maternal source. In addition to various epigenetic factors, it is possible that many DNA and RNA sequences and a variety of genes may influence the fetal programming of future adult cardiometabolic diseases. According to Professor Baker, "both the fetus and conditions for birth and its mothers' conditions for birth" matter [35].

A news release from the Children's National Hospital, Washington, DC, reported a 'game changer' for the management of adiposity-related disorders. Since we have been working on the development of various strategies for the reduction, reversal, or prevention of metabolic diseases, I was very much interested in this news release. I contacted the lead investigator, Dr. Robert Freishtat and discussed the possibilities of collaborating with researchers of Pune Maternal Nutrition Study group at King Edward Memorial (KEM) Hospital, Pune, India. He readily agreed to discuss the possibilities and together we contacted the researchers at KEM, Pune, India. These discussions led to the development of a National Institute of Health (NIH) funded research grant [36]. According to Dr Freishtat the lead investigator, "A novel possibility of this research is, that an adiposity-related maternal factor crosses the placenta, to reprogram fetal cardiometabolic pathways. Preliminary studies by this group, have identified adipocyte-derived exosomes, as the maternal factor, capable of driving abnormal fetal cardiometabolic development. As nanoparticle-sized endocytic vesicles, 'exosomes' can cross the placenta, their microRNA contents are predicted to alter developmental pathways and gene expression" [37,38]. We have come a long way since the Baker Hypothesis was proposed. A professional society, developmental origin of health and adult diseases (DOHaD) has been started, and it organizes annual meetings to discuss areas related to this topic. Having said that, I would like to remind the readers that, this problem, like the studies related to central abdominal obesity, is of great interest to researchers especially, in the developing countries.

Pathophysiology of adiposity

We have already briefly discussed, that compared to Europeans and Americans, South Asians as well as East Asians, develop central abdominal obesity and develop type-2 diabetes with a lower body mass index. Advances in high throughput genotyping technologies, have facilitated genome-wide association studies (GWAS), which has resulted in uncovering hundreds of genetic risk loci, for BMI and Waist Hip ratios (WHr) for European populations. The problem with such large studies is the large number of genes, that associate with the specific risk in question. A large meta-analysis of GWAS for BMI-associated single-nucleotide polymorphisms (SNPs), revealed over 750 SNPs, representing susceptibility genes and specific genes [39]. One of the strongest genes, FTO alpha-ketoglutarate dependent dioxygenase, seems to be a significant contributor, to polygenic obesity. The authors of this seminal study concluded that, "Despite a large number of studies reporting known obesity loci, the molecular mechanisms underlying this complex disease are not fully explained yet, and neither is the variation across human diversity in terms of obesity. Obesity is the single most public health problem throughout world, yet we do not know why half of the global population have a distinctly different pattern of fat distribution. It is believed that central abdominal obesity leads to the development of type-2 diabetes. If one looks at the so called 'endocrine crisis'- number one ranking for type-2 diabetes prevalence, goes to the United States of America, followed by China and India. Therefore, it is not just the pattern of fat distribution but many other factors such as poor eating habits, quality of nutrition, lifestyle, physical activity or the lack of it, and other socio-economic features that contribute to the development of metabolic diseases.

Obesity; cellular and molecular mechanisms

A brief review of literature reveals that obesity is multifactorial, and largely preventable disease. Yet we have not seen any major public health program, aimed at preventing this metabolic disorder.

Studies in recent years have shown that, in brief, central nervous system detects metabolic needs of the adipose tissues, and in response releases hormones such as cholecystokinin, glucagon like peptide (GLP-1), insulin, and leptin to decrease the food intake. On the other hand, when nutritional deficiency is detected, different neurons become sensitive to leptin, ghrelin, insulin, and glucose, which are the molecules signaling the availability of energy [40]. In individuals with unhealthy obesity, adipocyte hyperplasia develops, mainly driven by the recruitment of adipogenic progenitors, such as insulin-like growth factor-1, tumor necrosis factor-α, angiotensin 11, and macrophage colony stimulating factor. Oxidative stress, proinflammatory cytokines, non-coding RNA interference and changes in gut microbiota, are some of the other molecular mechanisms associated with obesity-related disorders, including endothelial dysfunction [41]. Furthermore, low grade inflammation, and insulin resistance, are the common features that promote the development of type-2 diabetes. Several recent studies have shown, that 'resistin' is the key hormone linking insulin-resistance to obesity [42]. Just like the variation in body fat distribution, there are different types of fat in the body. Most of the fat in the body is white fat, and excess of this fat leads to obesity [43]. Discovery of metabolically active brown fat has encouraged scientists and dieticians for the development of novel anti-obesity treatments [44]. A new study published just this month, revealed the molecular structure of a protein called 'Uncoupling Protein 1 (UCP1)', which allows brown fat tissues to burn of calories as heat [45]. In a short overview like this, it is hard to cover all aspects of the basic mechanism involved in the development of obesity and its relationship to adiposity-related disorders. Readers are urged to refer to the original articles and comprehensive reviews on this topic [36-46].

Metabolic diseases: Risk stratification and prevention

Metabolic diseases such as hypertension, excess weight, obesity, type-2 diabetes, and vascular diseases, have increased in incidence and prevalence, to epidemic proportions worldwide in the last three decades [47-53]. According to the WHO, an estimated 1.28 billion adults aged 30 - 79 years worldwide, have hypertension, most (two-thirds) living in middle-income countries. Excess weight and adiposity, whether abdominal or overall, leads to insulin resistance and development of type-2 diabetes [53]. Since by definition metabolic syndrome refers to known cardiovascular risk factors, such as insulin resistance, obesity, atherogenic dyslipidemia and hypertension,

modern medicine focuses on management of these identified risks. Many major clinical studies have demonstrated that management of modifiable risks for CVD and a healthy lifestyle, significantly lowers premature mortality, due to myocardial infarction [54-56]. Despite such encouraging reports, multiple global disease burden studies, have shown that cardiovascular disease burden has increased in incidence and prevalence. Prevalence of total cardiovascular disease nearly doubled from 271 million to 523 million in 2019, while the number of deaths from CVD increased from 12.1 million in 1990 to 18.6 million in 2019. Since obesity of children and adolescents are increasing rapidly, this metabolic condition, will lead to higher CVD morbidity and morality in the coming years. We are of the opinion, that instead of just focusing on the management of modifiable risk factors for CVD, it is time, we develop a robust holistic prevention strategies, to manage risks for metabolic diseases, which are the primary drivers of the progression of CVDs.

Discussion

Vascular diseases are the leading cause of morbidity and mortality worldwide. However, according to public health experts, the greatest burden of CVD is in low-and middle-income countries (LIMICs), with approximately 80% of the cardiovascular deaths occurring in LIMICs [57-59]. There is yet another difference between CVD deaths in the Western countries versus LIMICs. In higher-income countries, CVD deaths occur in populations aged > 60 years, whereas in LIMICs, 3 times as much death occurs affecting males and females of working age. Because of such observations, the intervention strategies should be developed, considering the ethnic specific variations in the CVD risks. We have already discussed that children with low birth weight are prone to develop metabolic diseases in adult life. Therefore, interventions related nutritional deficiency, for both mothers and the growing fetus should be addressed. Appropriate nutritional supplements should be recommended for women prior to conception and should be continued during the pregnancy. Nutritional supplements should be recommended to neonates during the first 1000 days of life. Nutritional interventions during the early life (preconceptionally, prenatal, and early postnatal) period, are increasingly recognized as playing important role [60-63].

According to the World Health Organization, over 340 million children and adolescents aged 5 - 19 are overweight or obese. Dietary factors that contribute to childhood obesity, include consumption of energy dense food [64,65]. Authors of this study in an earlier study demonstrated, that in overweight children and adolescents, C-Reactive Protein (CRP) is independently associated with fasting insulin. Just eight weeks of aerobic exercise improved fitness, HDL cholesterol, and endothelial function in this group. In a recent review, these researchers concluded that. “First line of approaches should include family-based behavioral obesity interventions addressing diet, physical activity, sedentary behaviors, and sleep quality, underpinned by behavior change strategies”. In our opinion, these suggestions are hard to implement. Discussions around weight management are focused on personal responsibility for weight. As though the weight gain/loss is entirely in the hands of the individual. Stigma attached to this altered metabolism, may indeed result in adverse emotional responses such as, depression, low self-esteem, and anxiety. Because of these observations, the use of web-based technology, may be one of the better choices that can provide more personalized intervention, to reduce obesity in school aged children and adolescents [66].

In a recent study, Professor Anurag Agrawal, and associates from New Delhi, India, used anthropometric measurements in school children, to develop predictivity of metabolic risks [67]. It is worth noting, that these researchers found unexpected high prevalence of pre-hypertension and hypertension in this cohort. They also found the benefits of mid-day meal program in providing adequate nutrition to these growing children. These observations indicate, that first of all, simple non-invasive measurements could be used to assess CVD risks at schools. Secondly, such measures could be used for not only screening for stratification of CVD risks, but also for developing preventive strategies. For instance, this study noticed the benefit of mid-day meals programs in schools. The largest such program in India, a centrally sponsored scheme serves 120 million children in over 1.27 million schools and is the world’s largest school meal program. What’s interesting is to note, that some of these school lunch programs are served in economically weak countries. Access to nutritious food in school is rising up in the UK. Both Wales and Scotland have committed to providing school food for all primary school children. One way to take advantage of this ‘healthy diet’ movement is, to say YES to School Food For All. We further recommend, that simple non-invasive diagnostic

tests be introduced in schools, for the early diagnosis of metabolic risks and their interventions. Global Nutrition data base shows that more than 139 countries participate in mid-day meal program for school children, serving 330 million meals. As mentioned earlier, we do have access to a huge population of school going children and adolescents, and these cohorts could be effectively used for stratification of metabolic risks and development of appropriate interventions [68].

Prevention of prehypertension, pre-obesity and prediabetes is a great strategy for the overall prevention of CVD deaths [69-75]. Pre-diabetes, prehypertension, and pre-obesity/overweight are considered as intermediate health sates, between ideal health and clinically diagnosed altered metabolic conditions indicating elevated levels of risk to vascular health [74]. Nearly 61% of the U.S adult population has a BMI > 25 kg/m^2. The National Heart Lung and Blood Institute guidelines suggest a waist circumference above 102 cm (40 in) for men, and above 88 cm (35 in) in women, indicates high risk. These trends have led member states of the WHO, to endorse a target of no increase in obesity in childhood by 2025, as well as 30% reduction in low birth weight. It is a great decision, and both are worthwhile goals. The major question is can we achieve such ambitious goals? Knowing the past record of the WHO/UN member states in 'achieving the sustainable goals', it is just about impossible, to fulfill the goals of WHO and achieve substantial reduction in the incidence and prevalence of obesity worldwide by 2025. Discussing the prevalence of childhood obesity worldwide, a multicountry study concluded that, "To be successful, the obesity epidemic must be a political priority, with these issues addressed both locally and globally. Work by governments, civil society, private corporations, and other key stake holders must be coordinated" [73-75]. Rise in obesity as a risk factor for metabolic disease morbidity is more predominant in younger and middle-aged groups, whereas metabolic disease mortality for older populations is driven by hypertension and hyperlipidemia. Because of this difference, we need to develop appropriate interventions on the basis of ethnic and age specific risk factors.

Multiple weight loss interventions have been developed during the past two decades, including lifestyle and behavioral changes and anti-obesity medications (AOMs), orlistat, phentermine, topiramate, naltrexone, bupropion, liraglutide and semaglutide. Semaglutide, a glucagon like peptide-1 receptor agonist (Ozempic once a week injection of 2.4 mgs) is approved for treating type-2 diabetes and is also approved for achieving weight loss. The semaglutide treatment effect in people with obesity trials have shown efficacy of this drug for the treatment of obesity [76]. A recent clinical trial showed that a daily 50-mg dose of oral semaglutide, induced greater weight loss than those who received placebo pills [77]. In a review and a meta-analysis, UK and US researchers found, that when cardiometabolic risks factors were assessed, AOMs reduced or had no impact on blood pressure, lipids, or glycemia. They also noticed a pattern of poor adherence and large gaps in the evidence base [78]. In addition to the use of AOMs, research over last two decades also has provided evidence to support the role of bioactive dietary components in the prevention and treatment of obesity and associated metabolic disorders. Dietary components shown to promote activation, leading to white adipose tissue browning and enhancing energy burning, include capsaicin, capsinoids, resveratrol, curcumin, green tea, menthol, and fish derived omega-3 fatty acids [44]. Three decades ago, we posed a question, will antioxidants prevent atherogenesis? [79]. Even to this day, there is no conclusive evidence that daily intake of antioxidants will reduce, reverse, or prevent atherogenesis. Similarly, we are of the opinion, that dietary effect of various bioactive molecules on the browning of fat is a great topic for further research, and at the time of this writing, it lacks evidence as a therapeutic option, for obesity-related disorders.

Conclusion

According to the World Health Organization, a new study from the Imperial College London reports a tenfold increase in childhood and adolescent obesity in the last four decades. The study which was published in the journal of *Lancet* ahead of the World Obesity Day 2022, is one of the largest ever in number of participants (31.5 million aged 5 to 19 130 million; 97.4 million aged 20 and older). These observations and the data published by the Global Burden of Diseases study, highlight that overweight and increases in white fat mass is a global health crisis, will worsen, unless the public health professionals take drastic action. Genome wide association studies (GWAS) have revealed 300 loci that are robustly associated with Type-2 diabetes and over 500 loci with body mass index, waist-hip ratio, and other

obesity traits. Despite availability of such information, potential for risk profiling, the potential for clinical utility and therapy, remains elusive. Irrespective of the pattern of fat distribution (abdominal/body mass. Waist-hip ratio), increases in white fat mass seem to initiate and promote metabolic risks such as oxidative stress, inflammation, insulin resistance, and vascular dysfunction. We have discussed the difference in fat distribution across different ethnic populations, fetal origin of obesity-related disorders in low-and middle- income countries, and the excess burden of metabolic diseases in this part of the world. Though this condition is unique to South Asian and East Asin phenotypes, because of the large populations involved, it still represents a significant global healthcare burden. We are of the opinion, that with better maternal, fetal, and neonatal nutrition programs, the fetal origin of adult disease could be effectively reduced, reversed, or prevented. A recent report in the *Lancet* (2023), on the global Burden of Obesity (territories), places malnutrition and obesity as independent pathologies, along the same spectrum. Because of this observation, newer policies have been put forward to tackle the burden of malnutrition and obesity, with a more holistic approach. One of the salient findings of this study was at the same BMI, men seem to have greater incidents of diabetes, insulin resistance, and ectopic fat levels, which may contribute to higher rates of obesity related morbidity and mortality. In the United States, obesity is the second leading cause of preventable disease and death. The Member countries of the United Nations have discussed this very important topic and recommended prevention of obesity in children and adolescents as a top public health priority. In this brief overview, we have discussed some novel approaches to reduce, reverse, or prevent this trend in the increased incidence, prevalence, of childhood and adolescent obesity. Readers are urged to refer to guidelines provided by various professional societies (AHA, ADA, and the Obesity Society) for information about the management of adult adiposity.

I started this article with a title, "Obesity is a Unique Metabolic Disease". What is so unique about this adiposity? Just think about why half of the global population store excess white fat in the abdominal region, while the rest of the population, has a general distribution of fat in their body. Obesity is different in Asia; the people have lower body mass index (BMI) but have a central abdominal adiposity for a given body weight when compared to matched white populations. Is so called 'thrifty gene' responsible for this kind of fat distribution? Other possibilities include, peroxisome proliferator activated receptor gama (PPARr), a nuclear receptor that is involved in adipogenesis. Yet another genetic factor that is thought to be involved is Apolipoprotein E (APOE) which is involved in transport of lipids within the tissues. There is considerable interest in studying the effect of low-birth weight on the development of adiposity in later life and the molecular mechanisms that are responsible for fetal programming of future lipogenesis, and possible epigenetic factor that 'trigger' these events decades later. These are some of the thoughts, that I would like to leave with your readership, so that debate on this very important but poorly understood area continues and results in new discoveries.

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