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Obesity, intergenerational programming, and epigenetics: emerging concepts and challenges

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Thesis

OBESITY, INTERGENERATIONAL PROGRAMMING, AND EPIGENETICS:
EMERGING CONCEPTS AND CHALLENGES

by

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ABSTRACT

One of the most important medical and public health issues of today is obesity, defined as abnormal and excess fat accumulation. Obesity is linked to many health problems including metabolic syndrome (MS), hypertension, type II diabetes mellitus (T2DM), and cardiovascular disease (CVD). Recently, the incidence of these conditions has surged to epidemic proportions, especially in Western societies. Research has also linked obesity to cancer and osteoarthritis.

Preventing, diagnosing, and treating obesity is challenging. The diagnosis of obesity is often unclear when it is made with generalized criteria such as the Body Mass Index (BMI). Obesity interventions generally include the often difficult lifestyle change to healthy diets and adequate exercise, which depends heavily upon patient compliance and discipline.

Today’s society is pushing for the discovery of a shortcut or of a “magic pill” to cure obesity. Consequently, many studies aim to identify therapeutic targets. The majority of current obesity research is focused on discovering and revealing the underlying mechanisms and genetic risk factors. Certain stages of development, such as childhood, are especially susceptible times to be exposed to stressors that lead to obesity.
A developing concept is the intergenerational transmission of risk of obesity through epigenetics. Epigenetics is the study of the heritable changes in gene regulation and expression not caused by mutations or changes in DNA sequence. A person’s genes may increase or decrease his or her susceptibility to obesity. In addition to genetic inheritance, parents may pass non-genetic alterations to their children. Changes can be mediated through methylation of deoxyribonucleic acids (DNA) and modifications to histones. These epigenetic changes may alter gene expression patterns and “program” offspring towards developing chronic metabolic disease. Many models have begun to show the effects of environmental perturbations on individuals and on several generations of future descendants.

This review will analyze the current literature on obesity and evaluate this rapidly evolving field. Current obesity preventions and treatments will be surveyed. In addition, the relative impact of different contributors to obesity risk will be examined. The crossover between obesity and epigenetics may provide a deeper understanding of disease risk and developmental origins. Future directions of study will be proposed such as large-scale prospective studies to further characterize intergenerational transmission of risk.
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<tr>
<td>ACS</td>
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<td>ADP</td>
<td>Adenosine diphosphate</td>
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<td>AF</td>
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<td>AMA</td>
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<td>ATPIII</td>
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<td>BMI</td>
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<td>CAD</td>
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<td>cAMP</td>
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<td>GDM</td>
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<td>GIP</td>
<td>Gastric inhibitory polypeptide</td>
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<td>GLP-1</td>
<td>Glucagon-like peptide 1</td>
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GWAS ...................................................... Genome-wide association studies
GWG ........................................................ Gestational weight gain
HDL ........................................................... High-density lipoprotein
HFD ............................................................. High fat diet
HHS ......................................................... U.S. Department of Health and Human Services
IL6 ............................................................. Interleukin 6
IR ............................................................... Insulin receptor
IRS ............................................................ Insulin receptor substrate
IUGR .......................................................... Intrauterine growth restriction
LBW ............................................................ Low birth weight
LDL ............................................................. Low-density lipoprotein
MAPK ........................................................ Mitogen activated protein kinase
MS ............................................................. Metabolic syndrome
MHO .......................................................... Metabolically healthy obese
miRNA ........................................................ Micro-ribonucleic acid
mRNA ........................................................ Messenger ribonucleic acid
mtDNA ........................................................ Mitochondrial deoxyribonucleic acid
NCI ............................................................. National Cancer Institute
NHLBI ......................................................... National Heart, Lung, and Blood Institute
NIAMS ....... National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIDDK ............ National Institute of Diabetes and Digestive and Kidney Diseases
NIH .......................................................... National Institutes of Health
PET .............................................................. Positron emission tomography
PI3K ............................................................... Phosphatidylinositol 3-kinase
RNA .................................................................. Ribonucleic acid
T1DM .................................................................. Type I diabetes mellitus
T2DM .................................................................. Type II diabetes mellitus
TNF $\alpha$ ........................................................... Tumor necrosis factor $\alpha$
UCP1 ................................................................. Uncoupling protein 1
USDA ................................................................. United States Department of Agriculture
WAT .................................................................. White adipose tissue
WHO ................................................................. World Health Organization
INTRODUCTION

Famine and food shortages have challenged almost every generation until recently. Agricultural and industrial advances in technology have allowed surplus amounts of food to be produced around the world. Unfortunately, a lot of this food contains high amounts of calories and saturated fats. The increase in accessibility of food with high amounts of calories and saturated fat has led to eating habits also known as “The Western Diet” (Cordain et al., 2005). Modern society now faces a new form of malnourishment; unhealthy eating and reduced physical activity have resulted in overweight and obese populations (Caballero, 2007).

Obesity is defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that negatively impacts health (WHO, Health Topics, Obesity). Obesity occurs when caloric intake exceeds energy expenditure (Khandekar et al., 2011). Both genders and all age groups are affected by obesity, although it is more common in women and in people of older age. Obesity is also more prevalent in developed countries with high median incomes. Paradoxically, within these rich countries, obesity disproportionally affects the poor (WHO, Health Topics, Obesity).

The prevalence of obesity worldwide has risen dramatically from 1980 to 2008. The percentage of obese men worldwide has gone from 5% to 10% and
the percentage of obese women worldwide has gone from 8% to 14%. In 2008, almost 1.5 billion adults worldwide were obese. (WHO, Health Topics, Obesity).

In the United States, more than two thirds of the population is considered obese or overweight. Although this number has been rising for the past few of decades, recent data suggests that the incidence of obesity in children is leveling off (Flegal et al., 2012). Figure 1 depicts data collected by the Center for Disease Control and Prevention (CDC) and illustrates the massive increase in percentage of obese individuals living in the United States over the past twenty years. This rapid increase underscores the seriousness of this public health crisis.

Figure 1. Obesity trends among U.S. adults. 1990, 2000, 2010. BMI ≥ 30, or about 30 lbs, overweight for 5’4” person. (CDC, Overweight and Obesity, Data and Statistics).
The traditional method of measuring obesity in adults is the Body Mass Index (BMI). A BMI is calculated by dividing the person’s weight in kilograms by the square of the person’s height in meters. The normal (healthy) range for an adult BMI is between 18.5 and 25. A BMI of 25 or more is considered overweight, a BMI of 30 or more is considered obese, and a BMI of 40 or more is considered morbidly obese. In children, different BMI cut-offs are used. A child’s height and weight is plotted on a growth chart for his or her age and sex to obtain a percentile. A BMI percentile of 85-95% is considered “overweight” and a BMI percentile greater than 95% is considered “obese.” (CDC, Healthy Weight, BMI).

Excess weight increases a person’s BMI and is thus considered a reflection of a person’s increased adiposity. An increase in adiposity may contribute to an increased risk of obesity and other health problems. Although early research suggested that overweight BMIs did not detrimentally affect mortality, these studies were often poorly controlled because they included patients that smoked or who had disease related weight loss (Berrington de Gonzalez et al., 2010). These studies also had large age distributions or small sample sizes. Pooled prospective studies have recently shown that, when controlled for confounders, BMI is associated with all-cause mortality in Caucasians (Berrington de Gonzalez et al., 2010). Similar findings have also been established in Asian populations (Chen et al., 2012).

The BMI is often criticized as inaccurate or misleading in terms of adiposity. Much debate exists about the usefulness of BMI due to the simplicity of
its formula (Ahima and Lazar, 2013). BMI may be appropriate for use in population studies, but may be inappropriate for use in diagnosing individual patients. Differences in ethnicity, gender, age, fat percentage, and fat distribution are not taken into consideration.

The amount of muscle mass a person has affects their weight and BMI. Athletes and those with a lot of muscle will have higher BMIs that overestimate body fat. Older people and those with less muscle will have lower BMIs that may underestimate body fat.

Ethnicity also affects obesity. People of African descent typically have higher BMIs, but relatively few health problems. In contrast, people of Asian and Hispanic descent are often more susceptible to obesity and many develop obesity related complications at lower BMIs. Consequently, several international health organizations, predominately in Asia, have established lower thresholds for being considered overweight and obese. (WHO, Health Topics, Obesity).

Recently, there has been increased recognition of a unique subgroup of obese and overweight individuals that have metabolically normal phenotypes, termed “metabolically healthy obese” (MHO). MHO patients have increased adiposity compared to non-MHO patients, but the increased adiposity does not seem to be detrimental to their health (Karelis et al., 2005). In addition, some obese patients with diabetes, end stage renal disease, and hypertension have surprisingly been shown to have reduced mortality compared to normal weight individuals. In contrast, a different subgroup of normal weight individuals has
been shown to have poor metabolic status. These populations may seem paradoxical at first, but studies continue to demonstrate that obese individuals have a higher risk of adverse outcomes when compared to normal weight individuals. A recent study analyzed the results from two large prospective cohorts and concluded that the data refuted the notion of lower mortality or better health in obese patients. (Tobias et al., 2014).

It is hypothesized that the studies with the paradoxical populations may have failed to establish controls properly (Kramer et al, 2013). Normal populations may have been classified solely based on BMI without considering other metabolic parameters. Additionally, smoking substantially increases cardiovascular risk and is a likely confounder. Better experimental controls should include both BMI and metabolism measurements. When comparing obese individuals without metabolic complications to normal weight individuals without metabolic complications, obese individuals still have a higher risk for death, CVD, and cancer (Kramer et al, 2013). This suggests that BMI is, at the very least, a good indicator of health.

The American Medical Association (AMA) did not officially begin to recognize obesity as a disease until June 2013 (AMA, June 18, 2013 Press Release). The AMA is the largest organization of physicians and medical students in the United States. Although the decision to recognize obesity as a disease was not without controversy, it is hoped that the decision will bring more attention and resources to the disease.
SPECIFIC AIMS

Obesity is an epidemic in the United States and around the world. Its associated comorbidities are detrimental to health and life expectancy. Studies continue to correlate more and more maladies every year to obesity.

It has been challenging to pinpoint the exact cause of obesity. There are many elements that influence susceptibility to obesity and the relative impact of each is unknown. Elements that may contribute to obesity include genetics, environment, and intergenerational programming.

The goal of this review is to perform a systematic analysis of current literature and the assess factors that may contribute to obesity. The emerging concepts of intergenerational transmission of risk and epigenetics will be discussed in detail.

It is hoped that this report will identify the elements that increase or decrease a person’s likelihood of developing obesity. If human intervention and control is a factor, then ways to reduce the incidence of obesity will be proposed. Suggestions for future directions of study in the field of obesity will also be made.
ASSOCIATED HEALTH RISKS

Obesity is associated with many health risks. Common health risks among obese individuals are metabolic syndrome (MS), type II diabetes mellitus (T2DM), cardiovascular disease (CVD), and cancer. Many of these comorbidities are also among the leading causes of death in the United States (CDC, National Center for Health Statistics).

Metabolic Syndrome

Metabolic syndrome (MS), also known as Syndrome X, is the name for a group of risk factors that increases one’s risk for developing health problems such as heart disease, diabetes, and stroke. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) stipulates that a diagnosis of MS is appropriate if a patient has at least three of the following five metabolic risk factors: large waistline, high triglyceride level, low high-density lipoprotein (HDL) cholesterol level, hypertension, and high fasting blood sugar (Grundy et al., 2005). The specific categorical cutpoints for MS are listed in Table 1. The chances of developing MS are associated with being overweight or obese, being older, having an inactive lifestyle, having insulin resistance, and having a genetic predisposition (NIH, Metabolic Syndrome).
Table 1. Criteria for clinical diagnosis of metabolic syndrome. NCEP/ATPIII guidelines last updates by the NHLBI and AHA in 2005. (Adapted from Grundy et al., 2005).

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<tr>
<th>RISK FACTOR</th>
<th>CATEGORICAL CUTPOINTS</th>
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<td>Large waist circumference</td>
<td>≥ 102 cm (≥ 40 inches) in men</td>
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<td></td>
<td>≥ 88 cm (≥ 35 inches) in women</td>
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<td>High triglycerides</td>
<td>≥ 150 mg/dL</td>
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<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>On drug treatment for elevated triglycerides</td>
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<tr>
<td>Low HDL cholesterol</td>
<td>&lt; 40 mg/dL in men</td>
</tr>
<tr>
<td></td>
<td>&lt; 50 mg/dL in women</td>
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<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>On drug treatment for reduced HDL</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>≥ 130 mm Hg systolic blood pressure</td>
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<tr>
<td></td>
<td>or</td>
</tr>
<tr>
<td></td>
<td>≥ 85 mm Hg diastolic blood pressure</td>
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<td>or</td>
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<tr>
<td></td>
<td>On antihypertensive drug treatment in a patient with a history of hypertension</td>
</tr>
<tr>
<td>High fasting blood sugar</td>
<td>≥ 100 mg/dL</td>
</tr>
<tr>
<td></td>
<td>or</td>
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<td></td>
<td>On drug treatment for elevated blood sugar</td>
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The diagnosis of MS is controversial. A person who has MS has a higher risk for developing CVD and T2DM. However, the presence of even one risk factor raises a person’s risk for developing disease. The more metabolic risk factors a patient has, the more likely he or she is to develop obesity related diseases. The diagnostic utility is unclear because it is uncertain whether having the full syndrome is more risky than having each of the criteria (Beltran-Sanchez et al., 2013).
In the United States, approximately 22% of the population has MS (Beltran-Sanchez et al., 2013). It does not affect all sexes, races, and ethnic groups equally. For example, Mexican Americans have the highest rate of MS followed by Caucasians and then African Americans. A higher percentage of female Mexican Americans and African Americans have MS than male Mexican Americans and African Americans. By contrast, an equal percentage of Caucasian females and males have MS. (Beltran-Sanchez et al., 2013).

**Diabetes**

Diabetes mellitus is a metabolism disorder characterized by a very high blood sugar level. In the United States, almost 8% of the population has diabetes. Rates of diabetes have been projected to reach much higher levels over the next several decades with escalation of the obesity epidemic (NIDDK, Diabetes Overview). Diabetes is one of the leading causes of death and disability. It is estimated to be responsible for almost $175 billion each year in medical costs, reduced productivity, lost time from work, and disability payments (NIDDK, Diabetes Overview).

Diabetes is diagnosed with a blood glucose test. A patient has diabetes if his or her blood glucose level is 200 mg/dL or higher and he or she has symptoms of diabetes, his or her fasting blood glucose level is 126 mg/dL or higher, or if his or her blood glucose level is 200 mg/dL or higher after an oral glucose tolerance test. (NIDDK, Diabetes Overview).
It is important for glucose to be absorbed by the cells because it is the body’s main source of energy. Carbohydrates are broken down after they are eaten and digested into simple sugars such as glucose. The glucose is readily absorbed into the bloodstream by the gut. In non-diabetics, the pancreas produces insulin in response to ingestion in order to move glucose from the blood into systemic cells. In people with diabetes, the pancreas produces no insulin, it does not produce enough, or the cells do not appropriately respond to the insulin. (NIDDK, Diabetes Overview).

There are three main types of diabetes – type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM).

T1DM affects approximately 5-10% of the population with diabetes in the United States, but overall only affects 0.5% of the total population. In T1DM, the immune system attacks and destroys the pancreas’ insulin-producing beta cells. Since the pancreas is unable to produce adequate insulin, patients with T1DM must take insulin injections. Failure to treat will cause ketoacidosis and ultimately death. Symptoms usually develop relatively quickly and include increased thirst, increased urination, constant hunger, weight loss, blurred vision, and extreme fatigue. T1DM is most common in children, young adults, and Caucasians. (NIDDK, Diabetes Overview).

The majority of diabetics in the United States have T2DM. T2DM is characterized by insulin resistance because, although the pancreas produces insulin, the body is unable to use the insulin effectively. Insulin resistance is the
result of disruptions in the cell signaling of insulin, the insulin receptor, or downstream pathways of insulin. Symptoms may develop slowly and include fatigue, frequent urination, increased thirst, increased hunger, weight loss, blurred vision, and slow healing of wounds. Similar to T1DM, long term complications in T2DM include CVD, renal failure, retinopathy, and edema. T2DM is common in people who are overweight or obese, older, physically inactive, have a family history of diabetes, or had GDM during pregnancy. Certain ethnicities are more likely to have T2DM, including African Americans, American Indians, Asian Americans, Native Hawaiians, Pacific Islander Americans, and Hispanics. (NIDDK, Diabetes Overview).

Interestingly, a small percentage of adults who have T2DM exhibit the “obesity paradox.” This refers to the observation that normal weight adults have a higher mortality than overweight and moderately obese adults. Although there is a well-established positive correlation between BMI and many chronic conditions, studies have shown that normal weight adults with T2DM have a higher mortality than heavier adults with T2DM (Carnethon et al., 2012). Many people who have extremely poor diabetes control lose weight because they lose so much glucose in their urine. Glucose is normally completely reabsorbed in the kidneys, but the kidneys are not able to handle extremely high levels of glucose. Consequently, excess glucose is not reabsorbed by the kidney and is excreted through the urine. Other theories suggest that the paradox is the result of inflammation, body fat distribution, or adipose tissue action. (Carnethon et al., 2012).
Around 3-8% of the population of pregnant women in the United States develops GDM (NIDDK, Diabetes Overview). Higher maternal BMI is strongly associated with higher risk for GDM (Chu et al., 2007). GDM is caused by pregnancy hormones that trigger insulin resistance or by a shortage of insulin. Usually GDM goes away after the woman delivers the baby. However, women with prior GDM have a high risk of developing T2DM. Certain ethnic groups and women with a family history of diabetes are more likely to develop gestational diabetes. (NIDDK, Diabetes Overview).

Diabetes increases risk of CVD. Many conditions and risks are shared between the two diseases. It is important for people with diabetes to reduce cardiovascular risk factors such as diet, smoking, high cholesterol, and blood pressure. More than 65% of those with diabetes die from heart disease or stroke. (NIDDK, Diabetes Overview).

**Cardiovascular Disease**

CVD is the leading cause of death in the United States. Obesity related CVD includes myocardial infarction, coronary artery disease (CAD), angina, aortic aneurysm and dissection, arrhythmias, atrial fibrillation, cardiomyopathy, heart failure, and peripheral artery disease. (CDC, Heart Disease).

The most common type of cardiovascular disease is CAD. This occurs when cholesterol deposits build up in the arteries that supply blood to the heart, causing atherosclerosis. If the heart muscle does not get enough blood, then
angina may result. Prolonged CAD weakens the heart and makes a patient more susceptible to heart failure and arrhythmias. (CDC, Coronary Artery Disease).

The diagnosis of CAD is made by evaluating a patient's blood pressure, cholesterol, blood sugar, and family history of heart disease. Electrocardiograms (EKG), echocardiograms, exercise stress tests, chest x-rays, cardiac catheterizations, and coronary angiograms may also be performed. (CDC, CAD).

Extreme obesity is associated with CVD and heart failure. It was thought that these correlations were indirectly related to each other through covariates such as dyslipidemia (abnormal lipid and cholesterol levels), hypertension, high blood sugars, and T2DM. However, recent studies have shown that increased BMI is directly associated to increased risk of heart failure independent of other factors. Not only is this true for the morbidly obese, but it is also true for people in all BMI categories. There is no threshold for association; risk for CVD increases with higher BMI. (Kenchaiah et al., 2005).

Cancer

Cancer occurs when abnormal cells grow out of control due to DNA damage. There are more than a hundred different types of cancer. Half of all males and a third of all females in the United States will develop at least one cancer during their lifetimes (ACS, Cancer Basics). The NIH estimates that cancer costs over $200 billion every year (NIH, Cancer).
Obese individuals have an increased risk of developing certain types of cancer including: esophagus, pancreas, colon/rectum, post menopause breast, endometrium, kidney, thyroid, and gallbladder. In 2007, it was estimated that 4% of new cancers in men and 7% of new cancers in women were due to obesity (NCI, Obesity and Cancer Risk). In fact, 40% of new endometrial and esophageal cancers are due to obesity alone (NCI, Obesity and Cancer Risk).

Increased BMI is correlated to increased death rate from all cancers combined. Studies estimate that in 2000 in the United States, 14% of all cancer deaths were attributable to overweight and obese men and 20% of all cancer deaths were attributable to overweight and obese women (Calle and Thun, 2004).

It is hypothesized that obesity and cancer are linked for several reasons. Fat tissue is known to produce excess estrogen and high levels of estrogen are associated with breast and endometrial cancers (Calle and Thun, 2004). Fat is also known to produce leptin, which may promote cell proliferation (Choi et al., 2005). Adiponectin, which is reduced in obese people, has been suggested to inhibit tumorigenesis (Khandekar et al., 2011). Fat cells may affect tumor growth regulators. Hyperinsulinemia and hyperlipidemia may promote the development of certain types of tumors. Chronic low-level inflammation due to macrophage infiltration, which is common in adipose tissue, is associated with increased cancer risk. (NCI, Obesity and Cancer Risk; Calle and Thun, 2004).
Osteoarthritis

Arthritis is inflammation of the joints. Common types of arthritis include osteoarthritis, rheumatoid arthritis, and juvenile arthritis. Osteoarthritis is the most prevalent type of arthritis afflicting around 27 million people in the United States (NIH, Osteoarthritis; AF, Osteoarthritis).

Osteoarthritis occurs when the cartilage that normally cushions bones breaks down and wears away. This causes bones to rub against each other. Eventually the joint may change shape or may grow small bone deposits. Broken bone and cartilage may float in the joint space. This results in pain, swelling, and loss of movement in the joint. It is generally a slowly progressing disease. The most common body parts affected by osteoarthritis are the finger, thumb, neck, lower back, knee, and hip joints. (NIAMS, Osteoarthritis).

Osteoarthritis is most common in older people and in women (Cross et al., 2014). Risk factors for osteoarthritis include increasing age, obesity, previous joint injury, overuse of joint, weak thigh muscles, and genetics (AF, Osteoarthritis). Increased weight harms joints because it puts added pressure on them (NIAMS, Osteoarthritis). Recent studies also suggest that osteoarthritis is affected by the chronic low-grade inflammation associated with obesity (Griffin and Guilak, 2008).
There are many established obesity treatments and prevention methods, including healthy diets and daily exercise regimens. Other treatments include drugs and surgery.

**Diet**

The primary obesity prevention and treatment method is following a healthy diet such as low-fat and low-calorie diets. It is well established that diet affects adiposity and weight. Obese people typically have poor dietary habits and consume more calories than they burn (HHS, Physical Activity Guidelines). A person’s ideal daily calorie need is calculated by taking into account age, gender, and physical activity level. In order to lose one pound of body fat, a person needs to consume 3,500 calories below his or her calorie needs (HHS, Calories). In addition to consuming too many calories, unhealthy eating habits that often lead to weight gain include eating too quickly, eating when not hungry, eating mindlessly, and skipping meals. Poor dietary habits also include eating fast-food and drinking sugar-sweetened beverages. (CDC, Eating Habits).

The United States Department of Agriculture’s (USDA) current nutrition guide, called “MyPlate,” debuted on June 2, 2011. The circular plate is divided into four sections corresponding to 30% grains, 30% vegetables, 20% fruits, and 20% proteins. A smaller circle represents one serving of dairy. Additional
guidance includes switching to skim or 1% milk, making at least half of your grains whole grains, varying protein food choices, and cutting back on foods with high levels of solid fat, sugar, and salt. The USDA also recommends being aware of your personal daily calorie limit and limiting your intake of alcohol to 1 drink per day for women and 2 drinks per day for men. (USDA, MyPlate).

Saturated fats and trans fats from food have a more negative impact on health than unsaturated fats. Solid fats increase low-density lipoprotein (LDL) cholesterol levels, triglyceride levels, and promote CVD. Excessive consumption of solid fats is also associated with insulin resistance and inflammation. Unsaturated fats are not generally associated with such unhealthy consequences. (Lottenberg et al., 2012; Rosqvist et al., 2014).

In western societies, the Mediterranean diet is highlighted as an ideal healthy diet. This diet is based on the foods frequently prepared and consumed around the Mediterranean Sea. For example, most of the grains in the Mediterranean region are whole grains and bread is usually dipped in olive oil (mainly unsaturated fat). This diet features many fruits, vegetables, grains, olive oil, beans, nuts, seeds, herbs, and spices. Seafood is a staple eaten a little less frequently. Nuts and red wine are consumed in moderation. Red meats, dairy and sweets are consumed very infrequently. Studies have shown that adherence to a Mediterranean diet is correlated with a decreased likelihood of becoming obese (Mendez et al., 2006; Shai et al., 2008).
Other popular diets that have been studied for obesity prevention or treatment are low calorie diets and low carbohydrate diets. There are many low carbohydrate, high protein, and high fat diet plans such as the Atkins diet. Although low carbohydrate diets have been shown to be effective in weight reduction in the first 6 months of implementation, there is no significant difference compared to other diets after one year (Foster et al., 2003). At the same time, low carbohydrate, high protein, and high fat diets have a positive effect on lipid metabolism (Shai et al., 2008).

**Exercise**

Physical activity is very important to weight loss because exercise consumes energy and results in a negative caloric balance. Sedentary lifestyles and activities, such as excessive television watching, are correlated to weight gain (Mozaffarian et al., 2011). Insufficient exercise is also linked to co-morbidities including obesity, pulmonary disease, neurological disorders, and immune dysfunction (Handschin and Spiegelman, 2008). Along with diet, exercise substantially prevents risk for obesity, T2DM, and CVD (Tuomilehto et al., 2001; Stampfer et al., 2000).

The United States Department of Health and Human Services (HHS) and CDC recommends that people get at least 150 minutes of moderate aerobic exercise each week. This includes walking briskly, water aerobics, and gardening. The equivalent in vigorous aerobic physical activity each week would
be 75 minutes. This includes running, swimming, dancing, bicycling, and hiking. Additionally, HHS recommends that people do muscle strengthening activities at least twice a week such as resistance training and weight lifting. (HHS, Physical Activity Guidelines).

Long-term increases of physical activity and reduction of sedentary activity have a positive effect on weight loss (Cote et al., 2013). Exercise programs consistent with these guidelines prevent increased adiposity and exercise programs in excess of these guidelines result in fat reduction (Slentz et al., 2005). According to HHS, many people need to do more than 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity activity a week in order to meet weight control goals (HHS, Physical Activity Guidelines). Increased intensity of physical activity has been show to reduce the risk factors of MS and CVD (Rennie et al., 2003).

**Pharmaceuticals**

If a patient is not successful in reducing their weight and metabolic risk factors with diet and exercise alone, he or she may be prescribed drugs to help. Pharmaceuticals are intended as a supplementation to lifestyle changes and not as substitutions. Nearly all drugs come with risks and side effects that need to be balanced with the potential benefits.

In the United States, the Food and Drug Administration (FDA) is the agency that controls pharmaceutical regulation. Currently, there are only three
long-term drugs approved by the FDA to treat obesity and weight control: orlistat, loraserin, and phentermine-topiramate (NIDDK, Prescription Medications).

Orlistat is sold both as a prescription drug (Xenical) as well as an over the counter drug (Alli). As a lipase inhibitor, it prevents digestive enzymes from breaking down dietary fat, thereby decreasing absorption of fat from food. Most patients lose 3 to 5 pounds per year on Alli or 5 to 7 pounds per year on Xenical. Since a lot of fat is undigested, complications include abdominal pain, flatulence, loose stool, and diarrhea. It is recommended that no more than 30% of the calories that patients consume while taking orlistat are from fat. It is highly recommended that patients taking orlistat also take a multivitamin supplement because of the decrease in absorption of fat-soluble vitamins from food. (NIDDK, Prescription Medications).

Lorcaserin (Belviq) and phentermine-topiramate (Qsymia) were recently approved by the FDA in 2012. Lorcaserin acts on serotonin receptors to quickly generate satiety. Phentermine is an appetite suppressant and it is combined with topiramate, which is an appetite suppressant as well as an antiepileptic. (NIDDK, Prescription Medications).

Both lorcaserin and phentermine-topiramate have side effects, including dizziness, dry mouth, and constipation (NIDDK, Prescription Medications). There are also risks of adverse tumorigenic, teratogenic, psychiatric and cognitive effects (NIDDK, Prescription Medications). Patients may be wary to take either drug due to slight risk of adverse cardiac events such as serotoninergic
valvulopathy, regurgitation, and valve insufficiency. The FDA has ordered both
drugs to undergo continued clinical studies to determine strength of associations
(FDA, Consumer, Medications, Target Long Term Weight Control). Studies have
not demonstrated that locaserin and phentermine-topiramate have greater
efficacy than orlistat (Colman et al., 2012).

Other weight loss drugs include appetite suppressants such as
benzphetamine, diethylpropion, phendimetrazine, and phentermine. However,
these drugs are only approved by the FDA for short term use due to potential for
abuse. Side effects range from mild dizziness to serious cardiovascular
complications.

Some drugs are used “off-label” to treat obesity. Although not FDA
approved to treat obesity, metformin, which is approved for T2DM, is used to
lower blood sugar, high LDL levels, and high triglyceride levels (NIDDK,
Prescription Medications). Some studies have shown that even in the absence of
T2DM, metformin reduces weight, which suggests that it may be used to help
reduce obesity (McDonagh et al., 2012).

Surgery

Surgery is the final option for weight loss in obese people. Surgery has
many potential risks and complications including death, excessive bleeding,
sepsis, and blood clots (Inge et al., 2014). Therefore, it is only recommended for
very obese patients who had not had success with diet and exercise alone.
Bariatric surgery changes the digestive system and reduces how much can be eaten and reduces the absorption of nutrients. Gastric bypass is the most common type of bariatric surgery. Roux-en-Y involves reducing the stomach to the size of a walnut and connecting it directly to the middle part of the small intestine. Biliopancreatic diversion with duodenal switch consists of removing 80% of the stomach and connecting the remaining stomach to the end of the intestines. During laparoscopic adjustable gastric banding, an inflatable and adjustable band is placed at the top of the stomach to limit the stomach’s size. In vertical banded gastroplasty, the stomach is stapled to create a small upper stomach. Finally, sleeve gastrectomy involves altering the stomach to be shaped like a tube. (Mayo Clinic, Gastric Bypass Surgery).

After bariatric surgery, a special diet and exercise regimen will need to be conscientiously followed. This involves very small and frequent healthy meals and vitamins because there is a high risk of micronutrient deficiency. There are new spatial constraints in the gut and surgery may have removed or decreased the efficacy of absorption. (NIH, Weight Loss Surgery).

Studies have shown that bariatric surgery improves and normalizes obesity related comorbidities including CVD, T2DM, cancer, and overall mortality (Sjöström, 2013; Adams et al., 2007). The mechanisms of action may extend beyond decreases in caloric intake (Laferriere et al., 2008). Recent studies have demonstrated that bariatric surgery resulted in improved glycemic control compared to traditional medical therapies (Mingrone et al., 2012; Schauer et al.,
2012). Also, alterations in gut signaling from incretins, microbiota, and bile salts may be potential drivers of weight loss (Patti et al., 2009).

Lifestyle changes, pharmacotherapy, and surgery offer a wide range of treatments for obesity. Lifestyle modifications in diet and exercise should always be the first treatment due to accessibility and efficacy. It is important and effective to continue following a healthy diet and exercise regiment in addition to any other obesity treatment. Progression to more intensive treatments such as drugs and surgery involves considering the additional benefits and risks as well as qualifications and cost (Kushner, 2014). Surgery, the most invasive intervention, continues to be the most effective and long-lasting treatment.
GENETICS OF OBESITY

Human metabolism is an incredibly complex energy homeostasis. It involves the balance of numerous metabolic signaling pathways and systems. Healthy individuals generally balance the amount of energy that goes into their bodies with the amount of energy that comes out of their bodies. Reducing obesity to simply excess energy intake versus energy output may be an oversimplification. The complexity of concurrent dysfunctions makes it difficult pinpoint a single cause of obesity.

Obesity is a relatively recent problem. The thrifty gene hypothesis attempts to explain why obesity is so prevalent in modern society (Hales and Barker, 2001). The thrifty gene hypothesis proposes that we are genetically programmed to conserve energy. The thrifty genotype exhibited positive natural selection by numerous generations due to its benefits during famines. When food was in abundance, individuals with the thrifty genotype efficiently stored and utilized energy by adding fat to their bodies. Individuals with the thrifty genotype were evolutionally favored when food was scarce because they were able to rely on their stored fat for survival (Hales and Barker, 2001). In today’s society, however, food is more abundant. The historical transition from cycles between times of feasts and famines to a constant time of excess food rendered the thrifty gene no longer beneficial. Without famines, excessive energy translates to excessive adiposity and obesity (Hales and Barker, 2001).
Some researchers critique the thrifty gene hypothesis because it puts too much emphasis on the role of famines in human mortality (Speakman, 2007). Natural selection dictates that the stronger genotype survives and the weaker genotype dies. Some suggest that famines in the past were not frequent enough to cause such a large genetic shift. Otherwise, everyone would be obese (Speakman, 2007).

An alternative to the thrifty gene hypothesis is the drifty gene hypothesis (Speakman, 2007). Today’s wide range of phenotypes may be the result of genetic drift. The drifty gene hypothesis suggests that after the threat of predation by large carnivores was removed, the upper limit of human body fatness drifted upwards unbounded because selective pressure to maintain a competitive maximum amount of body fatness no longer existed. Individuals with poor fitness did not survive the early days of human life. The discovery of fire and the invention of weapons released the constraints on obesity (Speakman, 2007).

The drifty gene hypothesis has been critiqued because it makes illogical assumptions about the number of gene mutations, gene mutation functions, and population size. The drifty gene hypothesis also fails to explain the extremely high prevalence of unfavorable obesity related traits in modern society – much higher than simply random mutation. Additionally, it does not factor the effect of cognitive dietary restraint to maintain BMI below the natural level or the effect of famines on fertility (Prentice et al., 2008).
**Genetic/Molecular Features**

Nearly all organ systems and cells in the body affect the molecular and genetic features of obesity. Many genes and molecules have a role in metabolism and homeostasis. Genetic transmission from parent to offspring plays a key role in risk for obesity. Studies on twins and people who were adopted indicate that anywhere from 40-70% of variability in body mass may be attributed to genetic predisposition (Calle and Kaaks, 2004).

Before recent discoveries and completion of the human genome, genetic studies on obesity were mostly limited to Mendelian diseases linked to single genes (Fall and Ingelsson, 2014). Restriction fragment length polymorphism was used to study a single target at a time. Monogenic traits associated with obesity were primarily found in deficiencies in appetite regulation such as leptin, leptin receptor, pro-opiomelancortin, and melanocortin 4 receptor. New developments in genome mapping and DNA sequencing have led to more comprehensive and unbiased techniques such as genome wide association studies (GWAS). These advances have allowed researchers to scan the entire genome for changes that correlate to a specific phenotype, like obesity (Fall and Ingelsson, 2014).

The use of GWAS has led to a greater understanding of the genetics of obesity. The first single nucleotide polymorphism to be associated with BMI was the FTO (fat mass and obesity associated) gene (Fall and Ingelsson, 2014). FTO is implicated in the regulation of appetite as well. Subsequently, it has been established that numerous specific loci are directly associated with obesity,
ranging from appetite regulation to growth factors to glucose homeostasis. Obesity is a polygenic disease with genetic variants throughout the body (Fall and Ingelsson, 2014).

Systemic body regulation is commonly studied in relation to hormone control. The most characterized hormones in regard to obesity risk are insulin, leptin, adiponectin, ghrelin, and incretins.

Insulin has a role in glucose uptake in tissues such as liver, muscle, and fat. However, insulin signaling is far more complex than simply glucose uptake. Figure 2 is a simplified model depicting the involvement of insulin and its receptor in gluconeogenesis, glucose synthesis, protein synthesis, and cell growth and differentiation.
The insulin receptor (IR) is a receptor tyrosine kinase that phosphorylates insulin receptor substrates (IRS) that activate two major pathways when insulin is bound. The first activated pathway is the mitogen activated protein kinase (MAPK) via Ras. The MAPK family, also known as extracellular signal regulated kinases (ERK), are responsible for regulating the cell cycle, growth, differentiation, and apoptosis. The other activated pathway is the phosphatidylinositol 3-kinase (PI3K) pathway, which performs the majority of insulin’s metabolic activities. All of these proteins have different isoforms; each has a different specificity and role in the complex signaling network. (Taniguchi et al., 2006).
Insulin signaling also has cell specific roles. All of its specific function in each tissue is not yet fully known. Various roles have been elucidated by studying insulin resistance and action in obesity and in tissue-specific IR knockout models in mice (Rask-Madsen and Kahn, 2012). Figure 3 shows the different physiological features of insulin signaling in obesity and in MS. Impairment of insulin signaling leads to insulin resistance, elevated glucose levels, dyslipidemia, fat accumulation, inflammation, and impaired appetite regulation (Rask-Madsen and Kahn, 2012).
Figure 3. Tissue specific action of insulin in a patient with obesity and metabolic syndrome. (Rask-Madsen and Kahn, 2012).
Tissues

Defects in many different types of tissues are linked to obesity. Collectively, these defects cause metabolic dysfunction. In order to understand the big picture, it is important to examine the impact of each defect.

Adipose Tissue

Adipose is an endocrine tissue that directly secretes hormones into circulation. It allows humans to store energy in the form of fat for future energy needs. It plays a central role in energy balance and nutritional homeostasis (Rosen and Spiegelman, 2014). Fat tissue is composed of many different cell types, but mostly of adipocytes, from which it derives its name.

In adults, the number of adipocytes generally remains the same with constant turnover; an equal number are created and are destroyed each year (Spalding et al., 2008). During overnutrition, however, the body needs to store excess energy from increased food intake. Overnutrition causes adipose depots to expand initially in size by hypertrophy and eventually in number by hyperplasia (Rosen and Spiegelman, 2014). Hyperplasia occurs mostly in childhood and number of adipocytes becomes set. Even after reduction of weight and BMI, the adipocyte number remains fairly constant. Consequently, adipocyte number gained in childhood becomes a major determinant of fat mass in adulthood (Spalding et al., 2008).
Fat tissue is not all the same; its composition and effect vary from place to place in the body. As illustrated in Figure 4A, individuals with excess adipose concentrated in the hip and thigh areas (pear-shaped obesity) have a lower risk of obesity than individuals with excess adipose tissue concentrated in the abdominal area (apple-shaped obesity) (Gesta et al., 2007). These types of tissue are referred to by their depth and superficiality: subcutaneous and visceral. Large amounts of abdominal and visceral fat are associated with increased waist circumference. Waist circumference is an important measure of obesity. In fact, several studies have shown that waist circumference explains obesity related health risks independent of BMI (Janssen et al., 2004).

Figure 4A. Fat distribution influences risks associated with obesity in humans. (Gesta et al., 2007).
One hypothesis for the different health risks of subcutaneous fat and visceral fat is that different depots have unique innervations and relationships with circulation. For example, visceral fat may have increased lipolytic rates and release free fatty acids into the portal circulation. However, the leading hypothesis is that cell-autonomous mechanisms dictate depot-specific difference in adipocyte physiology. (Rosen and Spiegelman, 2014).

Besides differences in fat location, there are two different types of adipose tissue: white (WAT) and brown (BAT). As seen in Figure 4B, BAT is often found in the interscapular, cervical, supraclavicular, and paravertebral areas. In contrast, WAT is located in the subcutaneous, intra-abdominal, and other areas. (Gesta et al., 2007).
WAT is an energy storage tissue and it is the primary site of triglyceride storage. BAT, on the other hand, is an energy expenditure organ. BAT consumes energy via non-shivering thermogenesis. High expression of uncoupling protein 1 (UCP1) in mitochondria generates heat through the reduction of the proton gradient created by oxidative phosphorylation in cellular respiration. (Gesta et al., 2007).

BAT is the main source of heat for infants and some small mammals. Until recently, it was uncertain if adult humans had BAT and if BAT had any
physiologic relevance. BAT has been detected in adults with the assistance of radioactively labeled glucose and positron emission tomography (PET) and computed tomography (CT) (Cypess et al., 2009). It is now known that the amount of BAT in adults is inversely correlated to BMI, suggesting a role in preventing obesity (Cypess et al., 2009). The impact of BAT on energy homeostasis has massive implications, especially towards combating obesity. Research is focused on uncovering BAT lineage and differentiation in order to create a therapeutic application.

Adipose is thought to share an embryonic origin with bone and muscle in mesenchymal and mesodermal stem cells. It was thought that WAT and BAT shared a common adipoblast precursor. (Gesta et al., 2007). It is now recognized that BAT shares lineages with both WAT and skeletal muscle precursors. (Seale et al., 2008).

The establishment of separate lineages has led to the classification of a new type of adipose, beige adipose tissue. WAT contains cells that express UCP1 and are called beige or brite cells. These cells have distinct genetic expression patterns from BAT or WAT cells (Wu et al., 2012). During chronic exercise, muscle cells secrete irisin, a hormone that contributes to the “browning” or conversion of WAT to beige adipose tissue (Wu and Spiegelman, 2014).

UCP1 mediated thermogenesis in BAT and beige adipose is mostly activated by cold exposure (Ye et al., 2013). When peripheral neurons sense cold, the hypothalamus increases sympathetic activity. Norepinephrine turns on
β-adrenergic (G-protein coupled) receptors and a cyclic adenosine monophosphate (cAMP) cascade. Transcription of thermogenic genes are controlled by cAMP. It has also been shown that beige adipocytes respond directly to temperature (Ye et al., 2013). Further supporting the importance of these thermogenic adipose tissues, animal models demonstrate that lack of either BAT or beige adipose leads to obesity, insulin resistance, and metabolic dysfunction (Cohen et al., 2014).

To maintain a healthy weight, it is important to have adequate amounts of both WAT and BAT. Not only does WAT store lipids, it also modulates metabolism as an endocrine, paracrine, and autocrine organ. It releases a number of hormones and cytokines, collectively referred to as adipokines (Khandekar et al., 2011).

Leptin is a WAT hormone that regulates appetite and satiety. The leptin melancortin pathway in the hypothalamus suppresses appetite. Congenital leptin deficiency in humans is extremely rare. In the few reported cases, there was hyperphagia and early onset obesity. Limited studies show that leptin is more important for energy intake than energy expenditure in humans. Treatment of leptin deficiency with recombinant leptin leads to sustained weight loss (Farooqi et al., 1999). Obese (ob/ob) and diabetic (db/db) mice are commonly studied with leptin and its receptor knocked out, respectively. Leptin levels correlate well with body fat mass. Obese individuals without suppressed appetites, despite high levels of leptin, have leptin resistance. Leptin’s role outside of satiety continues to
be a research focus. (Coll et al, 2007).

Adiponectin is another WAT hormone that is widely studied. Adiponectin is involved in glucose and fatty acid oxidation. It also has a strong correlation with insulin sensitivity. Adiponectin is found at a relatively higher order of concentration compared to other hormones. Unlike leptin, adiponectin is found at lower levels in obese individuals than in healthy individuals. (Coll et al., 2007).

Other Tissues

The liver plays a central role in systemic metabolism. It is the site of glycogen synthesis and gluconeogenesis. In obesity, high blood sugars reflect excess hepatic glucose production due to insulin resistance. There is a decrease in clearance of lipoprotein, but synthesis of fatty acids and triglycerides still occurs. (Rask-Madsen and Kahn, 2012).

Skeletal muscle has one of the largest impacts on energy homeostasis in humans. It is the main insulin sensitive organ in glucose uptake and disposal. Glucose is utilized for glycolysis for energy expenditure and glycogen synthesis. Through skeletal muscles, physical activity is a major component of energy expenditure. Sedentary lifestyles are often cited as a contributing factor to obesity. Insulin resistance leads to impaired glucose uptake and glycogen synthesis. Excess blood sugar leads to increased obesity and adiposity where glucose uptake for triglyceride synthesis is not affected as much. (Rask-Madsen and Kahn, 2012).
The pancreas is an exocrine gland and an endocrine gland. As an exocrine gland, it secretes digestive enzymes and bicarbonate into the digestive tract. As an endocrine gland, the islets of Langerhans are responsible for secreting insulin, glucagon, somatostatin, and pancreatic polypeptide. In obesity, insulin secretion in islet β-cells is progressively impaired, but glucagon levels remain high and glycogenolysis and gluconeogenesis are promoted. (Jin and Patti, 2009).

Contributions to appetite and satiety are mainly mitigated by hormones such as leptin. However, evidence shows that insulin also plays a role. Hypothalamic insulin resistance leads to a decrease in the vagal nerve’s ability to suppress hepatic glucose production. (Rask-Madsen and Kahn, 2012).

The digestive system also contributes to metabolism, affecting insulin secretion, appetite, and motility. Incretins such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP) stimulate β-cell secretion of insulin in response to ingestion of food. Incretin secretion and sensitivity is impaired in obesity and T2DM. Evidence also points to bile acids as signaling molecules that influence metabolism (Watanabe, 2006). In addition, cholecystokinin is a postprandial satiety signal and ghrelin is a hunger hormone produced by the gut (Coll et al., 2007).

Recently, the pathogenesis of MS and T2DM has been linked to inflammation (Shoelson et al., 2006). Adipokines such as tumor necrosis factor α (TNF α) and interleukins such as interleukin 6 (IL6) have been shown to induce
insulin resistance. TNF-α and IL6 are both readily produced by adipocytes and macrophages. Obesity is strongly correlated with acute and systemic inflammation in fat, liver, and the cardiovascular system (Shoelson et al., 2006).
INTERGENERATIONAL PROGRAMMING

Heredity customarily refers to the transmission of traits from parents to children. Due to inheritance, children acquire characteristics that predispose them to certain phenotypes. Mendelian genetics explains inheritance through the transfer of the genome in the form of deoxyribonucleic acid (DNA). Most diseases have multifactorial inheritance patterns; they are rarely caused by a single gene, but rather caused by the culmination of numerous disturbances in gene expression.

Intergenerational or trans-generational programming encompasses all aspects in which the parent or previous generations affect the offspring. Not all differences in phenotype are determined by genetic sequence. Environmental factors play a key role in the development of a child and obesity. People may form adaptations to environmental disruptions. Cumulative adaptations may then lead to a stable disease state. This process, in which events in early life impact long-term health, is called metabolic imprinting (Waterland and Garza, 1999). Crucial stages of development range from prenatal to adolescent. The strongest correlations of intergenerational programming are between parent and offspring.

Parental obesity is strongly associated with adiposity in offspring. This predisposition may be caused by genetics or a number of other influences. The parental state may be “programming” the offspring into a similar metabolic condition. The correlation between offspring and maternal weight is markedly
higher than paternal weight, although still significant for paternal weight (Whitaker et al., 2010). The trend of parent to offspring adiposity holds for an individual parent, but is even stronger if both parents are obese. Figure 5 depicts the association of childhood obesity to each parent’s weight status.

Figure 5. Frequency of child obesity by parental weight status. Normal weight BMI <25, overweight BMI 25-29.9, obese BMI 30-34.9, severe obese BMI ≥35. n= 7078. (Whitaker et al., 2010).


**Parental Behavior**

Parents have an influence over their children’s behavior. At a young age, children may observe and mimic their parents’ poor eating habits and sedentary lifestyles. Childhood weight gain is usually predictive of a person’s body size later in life. Therefore, many studies are testing interventions to reduce the risk of children becoming obese like their parents. The behavior of parents is often a primary target in preventing and combating childhood obesity. Examples of such interventions include feeding infants nutritionally balanced food and reducing the amount of time parents allow children to spend doing sedentary activities such as watching television. (Campbell et al., 2013).

**Socioeconomic Status**

One of the challenges in preventing and combating childhood obesity is that all too often obese children come from families with limited economic resources. Obesity disproportionally affects disenfranchised communities. Food security is a measure of the accessibility of food. The USDA reports on food security in U.S. households (USDA, Economic Research Service, Food Security in the US). Low income populations typically have low food security. According to the USDA, 42% of households in the United States that are below the federal poverty line have food insecurity (Seligman and Schillinger, 2010).

Low income populations are particularly vulnerable to the challenges of obesity due to food insecurity. They often have poor diets because nutritious food
is limited. These populations have fewer resources to allocate towards food and often invest in less expensive energy dense foods. These foods tend to be processed, refined, and high in added sugars, fats, and sodium.

Further exacerbating this problem is the fact that the difference in price between unhealthy food and healthy food is widening. Between 1985 and 2000, the price of fresh fruits and vegetables rose 118% while fats and oils only rose 35%. (Seligman and Schillinger, 2010).

Besides socioeconomic status, food insecurity disproportionately affects certain races and education levels. Households with less education are linked to the consumption of fast foods. This is correlated to improper nutritional intake and excessive caloric intake (Meyer et al., 2014). Some minorities, such as African Americans and Hispanics, have a higher rate of food insecurity than white households (Seligman and Schillinger, 2010). Figure 6 displays the disparities in food security among different races in the United States.
Figure 6. Prevalence of food insecurity in the United States, 1999-2008. (Seligman and Schillinger, 2010).

There is a higher incidence of obesity in children from low-income households of certain races (CDC, Overweight and Obesity, Data and Statistics). In 2008-2011, 11% of children from low-income households were found to be obese. When compared to non-Hispanic Caucasian children, Hispanic children had a 35% higher risk of obesity and American Indian/Alaskan Native children had a 49% higher risk of obesity. (Pan et al., 2013).
Extranuclear Inheritance

The study of genetics places heavy emphasis on nuclear inheritance. Each parent passes half of their nuclear DNA through their gametes to their children. However, there is also extranuclear inheritance. The mother passes genetic information through the mitochondria in her oocytes. Mitochondria have their own DNA (mtDNA) and are important organelles involved in energy production, cell signaling, growth, differentiation, and apoptosis.

The role of mtDNA in lipid and amino acid metabolism makes it a central component in risk for obesity on the cellular level (Sato and Sato, 2013). In humans, the mitochondria in sperm enter the oocyte cytoplasm after fertilization, but the sperm’s mtDNA is eliminated and not transferred to the offspring (Sato and Sato, 2013). The paternal mtDNA is either diluted by a much larger amount of maternal mtDNA or it is selectively degraded. Therefore, this suggests that maternal mitochondrial inheritance has a stronger effect on progeny than paternal inheritance.

Mother’s Weight

While genetic inheritance and socioeconomic factors contribute to adiposity in children, evidence suggests that the relationship between the environment and obesity in offspring is very strong (Gluckman et al., 2008). The intrauterine environment is especially important in nurturing and developing the child. Perturbations in intrauterine metabolism may cause long-term
consequences in a child’s health. Maternal obesity may lead to fetal over-
nutrition, which increases a child’s risk of obesity. Obese mothers are more likely
to have high blood glucose, free fatty acids, and amino acids. These high levels
may alter the neuroendocrine function and energy metabolism in the developing
fetus (Lawlor et al, 2007).

Prospective longitudinal studies have aimed to determine the effects of
weight gain during gestation on the offspring’s risk for obesity. A mother’s high
pre-conception weight is a strong predictor of offspring obesity and
cardiovascular risk (Fraser et al., 2010). Similarly, high maternal gestational
weight gain (GWG) is correlated with offspring who have a higher BMI, waist
circumference, fat mass, leptin and other adipokine levels, systolic blood
pressure, and lower HDL levels (Fraser et al., 2010). The effect is heightened
from early pregnancy to 14 weeks gestation. The United States Institute of
Medicine suggests that healthy GWG is 500 grams per week. Pre-pregnancy
BMI remains a stronger predictor of offspring risk and has a larger relative effect
compared to GWG (Fraser et al., 2010). Nevertheless, both associations suggest
harm from excess maternal adiposity through transmittance of genetics, weight
gain promoting lifestyles, and environment to offspring (Fraser et al., 2010).

Placenta

The placenta plays a critical role in fetal development through nutrient
delivery and waste removal. While the placenta originates from the maturing
blastocyst and shared parental genetic material, it is heavily influenced by the mother’s metabolic state upon implantation into the endometrium and throughout pregnancy. Maternal obesity causes placental lipotoxicity, which features increased oxidative stress and inflammation. It has also been shown to cause alterations in gene expression in angiogenesis, hormone activity, and cytokines. (Saben et al., 2014).

Animal studies also show that a mother’s obesity or diet may change placenta and nutrient delivery. High sugar and high fat diets (HFD) during pregnancy increases maternal adiposity and reduces fetal placental growth. Affected placentas showed increased glucose and amino acid transport as well as up-regulation of fatty acid transport, PI3K, MAPK, and growth pathways (Sferruzzi-Perri et al., 2013). These changes have significant ramifications on offspring growth and health and are likely components in an offspring’s future metabolic dysfunction and cardiovascular dysfunction.

*Maternal Stress and Diet*

A mother’s diet can also affect the metabolism of offspring. Maternal HFD during gestation leads to poor glycemic control in offspring and increased risk of T2DM (Ainge et al., 2011). Researchers found that either stress or maternal HFD during gestation may promote predisposition to adiposity. In an animal model, pregnant Sprague-Dawley rats were given either control chow or a HFD. Variable stress was administered during gestation through a combination of restraint,
swimming, and cold exposure. Pups from dams that were on a HFD, administered stress, or both were heavier. They were also more likely to have increased adiposity and impaired glucose tolerance when weaned onto high fat diets (Tamashiro et al., 2009).

In a subsequent study, it was shown that the early postnatal period might be more crucial in determining the metabolic phenotype of offspring than the prenatal period (Sun et al., 2012). Dams were fed either control chow or a HFD during both gestation and nursing. A cross fostering model, generating four groups, was used to compare the relative effects of the postnatal nursing period to gestation. Pups cross fostered to the HFD dams gained more body weight and adiposity, had higher leptin levels, had higher impaired glucose tolerance, and were hyperphagic after weaning when compared to pups fostered to control chow dams (Sun et al., 2012).

Maternal Insulin Resistance

In addition, other metabolic phenotypes have been characterized to have similar effects on offspring. Both maternal T2DM and GDM have been associated with greater offspring adiposity independent of maternal BMI in early pregnancy. These correlations held when comparing siblings that experienced maternal diabetes and those that did not, suggesting intrauterine mechanisms play a bigger role than shared familial characteristics like genetics and lifestyle (Lawlor et al., 2011).
Many experimental models share maternal characteristics of metabolic dysregulation. It is difficult to discern whether individual aspects or a combination of factors are responsible for amplifying offspring risk. In a mouse model of maternal insulin resistance, offspring were hyperinsulinemic, glucose intolerant, and had dysregulated lipid metabolism. The offspring became insulin resistant when fed a HFD. These changes occurred despite normal maternal blood glucose and body weight, demonstrating that maternal insulin resistance alone may program obesity risk in offspring. (Isganaitis et al., 2014).

Intrauterine Growth Restriction

Perhaps more striking than prenatal overnutrition may be prenatal undernutrition in terms of developmental programming of obesity risk. Intrauterine growth restriction (IUGR) may occur from placental insufficiency, suboptimal perfusion, or maternal malnourishment.

IUGR often leads to low birth weight (LBW) in children. Both human and animal studies have shown that LBW is associated with increased risk of obesity, MS, T2DM, and CVD (Gluckman et al., 2008). A widely accepted theory is that nutritional disruptions and other challenges during growth are met with developmental plasticity. Adaptation permits survival in an environment that is predicted by this challenge. In IUGR, the predicted environment is scarce and deficient of resources. For example, increase adiposity as storage when there are not enough energy supplies or decrease efficiency in expenditure in order to
conserve energy. Alterations such as these may persist into adulthood and manifest into higher risk of diseases, including obesity and T2DM. (Gluckman et al., 2008). IUGR caused by decreased fetal placental perfusion has been found to lead to cardiovascular adaptations in offspring, increasing risk for CVD (Gaillard et al., 2013).

Maternal Undernutrition

Undernutrition negatively affects offspring. Animal studies have shown that metabolic programming begins very early. A common model of IUGR or undernutrition is food restriction during gestation to simulate maternal malnourishment. Additionally, some models use synthetic glucocorticoid administration. Glucocorticoids have anti-inflammatory and immunosuppressant effects and are released in response to stress. High levels of maternal glucocorticoids are linked to abnormal pancreatic islet development in offspring. Beta cell growth is retarded and insufficiency of the resultant endocrine pancreas causes disruption of glucose homeostasis. (Somm et al., 2012).

In a model used by Somm et al., Sprague Dawley rats were restricted to 30% of normal food intake throughout gestation. A parallel synthetic glucocorticoid model was also run. Dexamethasone was infused via pump during the last week of gestation. Postnatally, all groups were treated the same and dams were allowed to eat ad libitum. Both groups of LBW pups were hyperglycemic, had decreased glucose tolerance, and had reduced islet size and
numbers. Additionally there was upregulation and expression of hepatic gluconeogenesis, decreased insulin sensitivity, and changes in pancreatic and adipose gene expression. These results were found before weaning and while the LBW pups still weighed less than control. The findings are consistent with early metabolic dysregulation and could provide the basis of fetal programming leading to obesity and other complications in later life. (Somm et al., 2012).

Accelerated growth typically occurs postnatally in early stages of life. This phenomenon is referred to as “catch-up growth.” When coupled with IUGR, high growth rates tend to overcompensate and LBW offspring become heavier than their normal weight counterparts. Extra acquired weight is often in the form of adiposity.

In a mouse model of prenatal undernutrition, ICR mice exposed to 50% food restriction during the third week of gestation were born with LBW (Jiménez-Chillarón et al., 2006). Similar to human populations, mice exposed to prenatal undernutrition developed increased adiposity. In ICR mice, increased adiposity is found in visceral gonadal fat tissue. Interestingly, this has been found to be caused by lipogenesis and not by adipogenesis. Although adipocyte number does not increase, adipocyte diameter and lipogenic gene expression does increase (Jiménez-Chillarón et al., 2006). mtDNA copy number is also reduced (Isganaitis et al., 2009). Consequently, obesity may occur as early as 2 months both in humans and mice. This altered trajectory in growth parallels higher rates of MS, T2DM, and CVD. Intervention to mitigate catch-up growth may be
achieved by early postnatal caloric reduction. This restriction also prevents glucose intolerance and obesity (Jiménez-Chillarón et al., 2006).

A possible explanation as to why undernutrition causes increased offspring adiposity is disruption in leptin signaling. An unexpected rise in leptin is observed in the neonatal period of mice exposed to undernutrition. Researchers found that offspring that had normal intrauterine nutrition but administered leptin in early age had an accelerated weight gain with HFD. This group on normal chow also had impaired leptin resistance, similar to undernutrition mice. Also, leptin transport in the brain was diminished. These finding suggest that premature leptin surge leads to leptin resistance and is a contributing factor towards obesity. (Yura et al., 2005).

A new direction in the field of developmental programming is studying how effects may be passed on to subsequent generations beyond just immediate offspring. LBW offspring have been documented to have LBW children, even without further environmental stress, both in humans and mice (Patti, 2013a). At the Joslin Diabetes Center, researchers have developed an intergenerational IUGR LBW model using caloric restriction in ICR mice. In order to determine if programmed risk has an effect on multiple generations, LBW offspring were intercrossed with control offspring. Undernutrition was implemented with 50% caloric restriction in the final week of gestation. Second generation crossings were done with no dietary or stress manipulations. Experimental groups in these crossings did not differ in blood glucose, triglycerides, free fatty acids, insulin or
leptin levels. Nevertheless, second generation offspring through LBW males were found to have statistically significant reductions in birth weight. Second generation offspring through LBW females had increased adiposity in the form of visceral fat. Impaired glucose tolerance and pancreatic islet function was transmitted through both lineages. (Jiménez-Chillarón et al., 2009).

It is unknown which intergenerational transmission of risk mechanisms has the strongest influence on offspring. As summarized in Table 2, maternal and paternal contributions share equal parts in some but not all processes; some processes have gender specific impact from parent to offspring. Additional studies are required to further characterize each effect.
Table 2. Potential mediators of maternal and paternal intergenerational phenotypic transmission. (Adapted from Patti, 2013a).

<table>
<thead>
<tr>
<th>INTERGENERATIONAL EFFECTS</th>
<th>Maternally Mediated</th>
<th>Paternally Mediated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal environment (diet, stress, socioeconomic factors)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Genetics (nuclear DNA sequence)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Mitochondrial DNA</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Placental structure/function</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Intrauterine and early postnatal environment (dysregulation of maternal nutrition or metabolism, altered uterine structure/function, maternal behavior, alterations in maternal nursing behavior or milk composition)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Germ cell epigenetic effects (nuclear and cytosolic)</td>
<td>✓</td>
<td>✓</td>
</tr>
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</table>
EPIGENETICS

An emerging concept is the science of epigenetics. This relatively new field has grown dramatically in recent years. Epigenetics is loosely defined as the study of the heritable changes of gene regulation and expression not caused by mutations or changes in DNA sequences.

Until recently, it was unknown how intergenerational metabolic risk was transmitted. In female offspring, oogenesis begins in the fetus and oocytes are completely developed at birth; thus the second-generation offspring is affected during the first generation’s pregnancy. Studies have shown that the health of a parent can negatively affect the metabolic outcomes of offspring beyond the second generation. Additional studies have shown that male lineages are also affected (Patti, 2013a).

These trends, coupled with twin and adoption studies, suggest that there is an influence on metabolic fates beyond genetics and the immediate environment. Epigenetics provides a viable avenue for mechanistic explanations of intergenerational programming. An adaptive epigenetic model provides support to a stable and reversible theory of metabolic plasticity (Gluckman et al., 2008).

Two classic examples of epigenetics are DNA methylation and chromatin-related proteins that activate and suppress transcription. Polycomb and trithorax protein systems work to maintain gene transcription and expression in both
silenced and active states (Bird, 2007). These protein systems often function through modulating chromatin remodeling as well as binding directly to DNA. Chromatin remodeling such as histone modifications is also now included in epigenetics. Even though certain chromatin marks (i.e. phosphorylation) may be transitory and therefore may or may not be heritable, they do indirectly affect acetylation, methylation, and repressor proteins (Bird, 2007).

Lately, epigenetics has further expanded to also include noncoding RNAs such as microRNAs (miRNA). Even though the majority of the genome is transcribed, only a small proportion is translated into protein. Noncoding RNAs are the short strands of RNA that are not translated. They can act with repressor protein complexes to suppress gene expression. miRNAs can also bind to messenger RNA (mRNA) and inhibit translation of target genes. They also play a role in RNA-induced silencing complexes. (Tammen et al., 2013).

Epigenetic Mechanisms

There are several distinctive mechanisms of epigenetics. The most studied epigenetic mark and process is DNA methylation. Methylation occurs most frequently on cytosines at the 5’ position. Cytosines followed by guanine (connected by a phosphodiester bond) in the genomic sequence are preferentially methylated. Regions are commonly referred to as CpG islands when there is a high frequency of these repeats. Recent reports have found
methylation outside of these areas, but most epigenetic studies focus on the nearly 30 million CpG sequences in our genome. (Tammen et al., 2013).

DNA methyltransferases methylate cytosines with donated methyl groups from adenosylmethionine. Methylation found in gene promoters is usually associated with repression and down regulation. While the mechanism of action is not completely understood, recruitment of inhibitory proteins can prevent transcription and consequently adjust expression patterns. Hydroxymethylation is usually associated with the up regulation of genes. Hydroxymethylated cytosines
are sometimes considered as intermediates in de-methylation or as mediators that release the methyl-binding proteins. Maintenance and the removal or generation of marks is associated with age and disease (Tammen et al., 2013).

One of the most characterized models of reversible methylation is the agouti mouse (Jirtle and Skinner, 2007). The agouti gene encodes for a signaling molecule that promotes yellow pigment production in melanocytes. Expression of agouti in other tissues besides the skin leads to obesity, T2DM, and tumorigenesis. Methylation of a locus upstream of the transcriptional start site inhibits expression. This was the first model to show how the maternal diet can affect offspring adult phenotype through methylation. Dietary supplementation of methyl-donors to mothers during pregnancy decreased agouti expression in offspring. Figure 8 shows the progressive distribution of phenotype. Offspring are raised in the same environment with no difference in diet or environment except maternal exposure during gestation. Low methylation leads to an obese mouse with yellow fur and high methylation leads to a leaner mouse with brown fur. (Jirtle and Skinner, 2007).
The other main class of epigenetics is histone modifications and chromatin remodeling. Histones participate in structuring chromatin by packaging DNA. They can be modified post-translationally via acetylation, phosphorylation, methylation, ubiquitination, biotinylation, ADP-ribosylation, and sumoylation. Many of these modifications occur on the histone tails. Some of the modifications will recruit repressor proteins similar to DNA methylation mechanisms, while some will influence ionic charge. In turn, the interaction between the histones and the bound DNA is altered. The state of DNA packaging determines the state of heterochromatin and euchromatin. Gene expression is increased or decreased based on spatial constraints for transcription factors and ribonucleic acid (RNA) polymerases. (Tammen et al., 2013).
Observations in Intergenerational Programming

Epigenetics as a process that is involved in intergenerational programming is gaining more support. Many investigators in the field of developmental programming are testing the hypothesis that alterations in epigenetic marks, such as DNA methylation, may contribute to the intergenerational transmission of metabolic traits (Patti, 2013b). Strong associations with changes in the epigenome or total epigenetic state could help elucidate the underlying etiology of disease. At the very least, significant associations would provide biomarkers and predictors of susceptibility to disease.

The most common approach of initial epigenetic research into intergenerational programming has been manipulations of diet. Nutrition is one of the easier controlled environmental factors. Experimental design has included HFD, overfeeding, low protein diets, and caloric restriction both during IUGR and during critical periods of development postnatally (Jiménez-Chillarón et al., 2012). Another focal point of diet modification is supplementation of methyl-donors. Folic acid has been the most popular chosen micronutrient. Others include choline, betaine, B vitamins, and methionine. (Anderson et al., 2012).

Other models of intergenerational and epigenetic study include paternal stresses. Male mice fed a HFD have offspring with dysregulation of hepatic cholesterol and lipid metabolism and reproducible changes in epigenetic profiles (Carone et al., 2010). In a similar study, males with prediabetes had offspring with glucose intolerance and insulin resistance. Methylation of paternal sperm
corresponded to altered pancreatic gene expression in offspring. (Wei et al., 2014).

Similar to maternal models, paternal epigenetic transmission can persist through multiple generations. One study found that diet induced obesity in males caused two subsequent generations to have increased adiposity and insulin resistance (Fullston et al., 2013). These phenotypes developed in subsequent generations under normal diet and environment. Changes in the gene expression and miRNA profiles of the original males were found in testis and sperm (Fullston et al., 2013). Collectively, these studies implicate paternal contributions in intergenerational programming via epigenetics.

One of the challenges that come with epigenetic studies is that these alterations occur in all systems of the body. Given that our complex metabolism incorporates so many tissue types, it is important to examine changes in each. In order to determine cell specific roles, it is essential to compare methylation patterns between them to find differences. Epigenetic signatures of differentially methylated sites as a whole can be used as predictors for disease. Under multiple models of maternal IUGR and paternal stress, reproducible epigenetic signatures have been found to be associated with nutritional history. (Colaneri et al., 2013).

Far less data has been published on humans than animals. Ethical constraints prevent easy tissue sampling for epigenetic mark testing. However, early returns are encouraging and imply that results do translate over.
Associations have been established between gene promoter methylation in umbilical cord tissue with childhood adiposity (Godfrey et al., 2011). Differential methylation of cord blood and placental tissue has also been found between mothers with insulin-dependent GDM compared to those without (El Hajj et al., 2013).

Initial studies on weight loss have also suggested epigenetic processes as a possible mechanism of metabolic programming. Differences in adipose methylation comparing before and after a 6 month exercise intervention highlighted genes involved in oxidative phosphorylation. Expression is typically lower in obese or elderly individuals (Rönn et al., 2014). Differential methylation has also been found in offspring born before and after maternal bariatric surgery and weight loss. Reduced maternal weights lead to offspring who are less obese and have lower metabolic risk. Patterns in methylation correlated with expression of genes associated with glucose regulation, inflammation, and vascular disease. (Guénard et al., 2013).
DISCUSSION

Obesity, along with its associated comorbidities, is becoming one of the most significant health problems of our generation. Despite the wealth of information that is known about risk, prevention, and treatment, obesity continues to become more and more prevalent. Preventing obesity has been shown to be more cost-effective than treating its complications (Fradkin et al., 2012). The approach to fighting obesity may need to be revitalized with new initiatives to bring more awareness to the general public. Organizations, like the AMA, have been reluctant to take strong public stances on obesity until now. Hopefully, the added attention to obesity awareness and prevention will reach policy makers, insurance companies, and the general public to reduce this public health epidemic.

Long term goals should focus on further characterizing obesity’s various risks and causes. Although there is overall optimism in obesity prevention in children since the overall rates have recently leveled off, the incidence has also been occurring at earlier ages (Cunningham et al., 2014). This emphasizes the impact of metabolic programming and environmental stresses during early development. Perhaps obesity may not be prevented with only diet and exercise; there may be additional factors that are outside of one’s control.
Genetics has long been recognized as a contributor to human metabolism. Parental and earlier generational phenotypes have also been shown to affect genetic expression patterns of offspring.

Understanding the contribution of intergenerational programming and epigenetics will provide a strong basis for obesity prevention and treatment. Evidence already suggests that epigenetics has a strong impact on health. Questions remain about whether epigenetic signatures are a possible mechanism of causation or merely a correlation. Epigenetic profiles still can serve as early predictors of the developmental origins of disease and assist in discerning predisposition in future generations.

There are a number of challenges that make progress in these fields difficult. Changes in epigenetic marks are on a miniscule scale. The impact of environmental stresses and their consequent epigenetic changes are understood to be small and cumulative. The pathogenesis of obesity also seems to be caused by small cumulative changes. The multi-dimensional interactions of molecular signals create an incredibly complex network. Evaluating each change and its relative contribution is a daunting task.

Furthermore, methods of detection of epigenetic change are numerous. The field of epigenetics has expanded to include many different alterations from DNA methylation to histone modification to RNA expression. Early research in epigenetics has featured many different methods of measurement. There is no universal standard of assessing the overall epigenome.
Many researchers choose to focus on CpG islands, where methylation is most prevalent. However, sometimes this fails to incorporate areas that are outside of these genomic regions where methylation still occurs. Others choose to do genome wide epigenetic studies. These are more general and search for consistent differences between experimental groups. Differential studies in tissue specific methylation attempt to define the individual contributions of different cells. The caveat here is that individuals are very different, even within the same category or experimental group. For example, not all patients with the same BMI have the same health outcome. Obesity and metabolic disease are continuums; it is impossible to categorize severity with arbitrary benchmarks. Small changes in epigenetic marks may be easily overlooked. Furthermore, histone modifications are so diverse and seldom studied, that it is a challenge to compile and compare studies. It is still unknown which marks are more influential on phenotype.

It is important to study epigenetic marks and their modulation of gene expression to determine their effect on molecular, cellular, and systemic development. This field continues to progress and more accurate methods of measurement will be developed.

Alterations in epigenetic patterns have been strongly linked to both obesity and weight loss. Discovering how to influence epigenetic changes could unveil potential therapeutic targets. It will also aid researchers in the development of better prevention and treatment strategies. Epigenetic patterns can be applied to
the analysis of existing treatments. Comparison of epigenetic profiles in healthy versus unhealthy individuals, as well as successfully and unsuccessfully treated patients, could provide a measure of efficacy. Results may help us better assess the risks and benefits of different strategies.

One of the most debated weight management approaches is bariatric surgery. Given the recent emphasis on metabolic programming, there is interest on the effect of maternal bariatric surgery on offspring. Some studies have found that these operations significantly increase the chances of a preterm delivery. Infants of these mothers were also more likely to be small for their gestational age. This may be caused by poor nutrient absorption after bariatric surgery (Roos et al., 2013).

However, others have shown that maternal bariatric surgery actually improves offspring metabolism and it changes methylation patterns (Guénard et al., 2013). It is difficult to compare among recent studies because there are not very many and the populations vary so widely in age, genetics, environment, lifestyle, and weight loss. There may also be a metabolically unstable period after surgery that is suboptimal for pregnancy. It is important to determine which changes affect which outcomes. Nevertheless, optimism remains that these research studies will eventually pave the way in reducing maternal obesity and preventing offspring risk (Patti, 2013b).

Overall, future directions should include large-scale prospective studies. Longitudinal research will allow us to study epigenetics, disease, age, and
intergenerational transmission of risk and how they are affected by each other. It will be interesting to see how far intergenerational programming can go and if risk can be mitigated.

Both animal and human studies are needed. Animal studies are less expensive, can be done on a larger scale, are easier to control for variation, and provide more opportunities ethically. At the same time, findings in animal studies face limitations in translation and application to human disease.

In conclusion, although obesity is so prevalent in modern society, much remains unknown about its causes. It is hoped that by further studying the epigenetics and intergenerational transmission of risk of obesity, a cure and infallible method of prevention will be discovered.
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• Volunteer (25 hours) 2013 –
  BUMC Outreach Van Project – Boston, MA Present
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  − Molecular Biology – Oxidative stress in *Saccharomyces cerevisiae* with methionine sulfoxide reductases

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