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Lourdes A. Valdez

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Ruth Gault, Ph.D., Thesis Advisor

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Erin Edgington, Ph. D., Interim Director, Honors Program

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A Multi-Faceted Review of Obesity and its Application in Treatment Regimens

A thesis submitted in partial fulfillment
of the requirements for the degree of

Bachelor of Science in Community Health Sciences and the Honors Program

by

Lourdes A. Valdez

Dr. Ruth Gault, Thesis Advisor

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Abstract:

Obesity is a major contributor to several health conditions including type 2 diabetes, cardiovascular disease, and hypertension. Over the past three decades, obesity rates have nearly tripled, leading to an obesity epidemic. Current efforts to treat obesity focus solely on nutrition and exercise. While this may help reduce adiposity in many individuals it fails to aid others. This is because many weight loss regimens ignore alternative etiologic factors and fail to provide a robust treatment plan. This paper will focus on the five etiologic factors in obesity that are often overlooked such as gut microbiota, food addiction, adenovirus-36, genetics, and stress, and will evaluate their effects on obesity both independently and in conjunction. This paper will further outline possible treatment plans to aid in the mitigation of these effects in relation to obesity that result from the compilation of several etiologic factors creating an obesogenic cycle.

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Chapter 1: Introduction

Obesity has become an epidemic that continues to worsen every year and claims the lives of over 300,000 American's annually (Flegal, Williamson, Pamuk, & Rosenberg, 2004). Obesity can affect anyone, and its onset can often be silent and stealthy. Individuals who have a Body Mass Index of 30 or more are considered obese, and as of lately 160 million, American's fit this bill (Nuttall, 2015). Obesity comes with an assortment of serious health issues such as hypertension, cholesterol, type 2 diabetes, and cardiovascular disease (Nutall, 2015). Furthermore, children who are born overweight have an increased risk of being overweight throughout their childhood, adolescence, and adulthood (Lifshitz, 2008).

As this epidemic continues to grow the effectiveness of efforts to mitigate the effects and onset of obesity continue to shrink. Doctors and experts alike are frantically trying to find a solution to the epidemic. Many experts are currently treating obesity through a restricted caloric diet and increased activity levels; although this has been proven effective for some individuals for the vast majority this approach simply does not work and could be the reason why efforts to mitigate obesity continue to fail. According to Mann et al. (2007) most individuals who diet do not experience long-term weight loss.

The reason for such failed efforts may stem from a wide range of other factors that may contribute to the onset of obesity. Although there are constantly new areas to explore in the field of obesity treatment there is little research on a multi-faceted approach for long-term sustained weight loss in obese or overweight individuals. Those that have investigated this multi-faceted approach have only done so in the context of nutrition and exercise. Therefore, several areas contributing to the onset of obesity remain to be investigated.

Thus, my thesis will focus on a multi-faceted approach to treating obesity that goes beyond nutrition and exercise through a comprehensive literature review. I hypothesize that several less-well-known factors are contributing to the onset of obesity, making it difficult to achieve long-term sustained weight loss if left unaccounted for. These contributing factors include; stress, gut microbiota, adenovirus 36, genetics, and food addictions. I predict that these factors contribute significantly to the onset of obesity and prevent obese or overweight individuals from achieving long-term weight loss. To test this concept, I will be reviewing several peer-reviewed journal articles on each of the topics. In each journal article, I will be searching for the prevalence and the efficacy of weight loss treatments that address the topic. I will then synthesize the information from each of the topics to create a multi-faceted approach to treating obesity in individuals who are experiencing difficulties in long-term weight loss with nutrition and exercise alone. The research focused on this multi-factorial approach may inform health care and policy, identifying subgroups that have often been overlooked yet remain the most affected by obesity, and can be used in the application of intervention and translation efforts.

Chapter 2: Methodology

The design for this study will consist of a literature review evaluating the existing literature on adenovirus 36, stress, genetics, gut microbiota, and food addictions in relation to their impact on obesity and prevention of sustained long-term weight loss. This will allow for a thorough understanding of each of the topics, as well as identify gaps in the treatment/diagnosis of obesity. A literature review will also allow for a thorough comparison of each of the topics, that can then be synthesized to create a multi-faceted comprehensive approach to the etiology of

obesity for use in the treatment of obesity in individuals who are unable to lose weight following a strict nutrition and activity plan.

An initial literature collection will be conducted on each topic independently to allow for a comprehensive understanding of the topic and the role it plays in obesity. This data will be collected using peer-reviewed journal articles that have been published within the last 19 years in order to exclude outdated information. In order to identify pertinent research conducted in the field of interest keywords will be used for each of the topics. The keywords adenovirus 36, obesity, and prevalence will be used to identify the prevalence of obesity caused by adenovirus 36, the impact that adenovirus 36 has on the onset of obesity, as well as possible treatments used to address the negative effects of adenovirus 36. The same keywords will be used for the remaining factors of interest with the substitution of adenovirus 36 for the title of the factor of interest such as stress, genetics, gut microbiota, and food addiction respectively to identify the same aspects of each topic as previously mentioned above. Only studies that contain all pertinent keywords will be included.

The studies collected will be organized using the software program Zotero. Several folders will be created for each of the topics of interest where the studies related to each topic will be stored. Once the pertinent information on each topic has been gathered, it will then be synthesized. Each topic will be evaluated in conjunction with the other topics to create a multi-faceted diagnostic tool to be used in the treatment of obesity. The prevalence of each topic will be included to discern the probability of the topic as an etiologic factor in obesity. The synthesized articles will then be organized into a table according to their etiologic factor and the main results will be summarized along with any contributing or correlating etiologic factors. This method will allow for the understanding that obesity is caused by a multitude of factors rather

than just a sedentary lifestyle and a high caloric diet. The tables containing the synthesized articles and respective summaries for each etiologic factor of interest have been included below.

Table 1. Summary of Main Results in Gut Microbiota Studies Relating to Obesity

First Author	Subject Area	Correlating factor	Summary
Bianchi et al. (2018)	Gut Microbiota	Food Addiction	This study examined the relationship between body mass index, weight loss, and bacterial groups. The results revealed that individuals who lost weight over the course of a year through low-calorie diets had an altered microbiome resembling that of a lean individual due to a decreased Firmicutes to Bacteroidetes ratio.
Harakeh et al. (2016)	Gut Microbiota	Food Addiction/ Genetics	Evaluates the role of the gut microbiota as a contributing factor to obesity. Concluded that altered gut microbiome does play a role in the onset of several metabolic diseases including obesity as they disrupt the host immune system and play a role in diet and genomics which are known obesogenic factors.
Sweeney & Morton (2013)	Gut Microbiota	Genetics	Investigates the claim that differences in the gut microbiome can lead to obesity. Examined changes in the gut microbiome of obese and lean phenotypes and determined that obese phenotypes lack a diverse biome with a large proportion of Firmicutes to Bacteroidetes, while lean individuals have the inverse ration. They verified these findings in individuals who had a gastric bypass, and those with Crohn's disease who received a fecal transplant.

Table 2. Summary of Main Results in Food Addiction Studies Relating to Obesity

First Author	Subject Area	Correlating factor	Summary
Avena et al. (2008)	Food Addiction	Genetics/Stress	An experimental animal model revealed that certain reward systems in the brain are activated when consistently exposed to sugar. The deprivation of this substance results in withdrawal symptoms seen in traditional drug users.
Davis et al. (2011)	Food Addiction	Genetics	The legitimacy of food addiction was investigated in humans who possessed the obese phenotype. Using the Yale Food Addiction Scale several participants who were obese were characterized as having a food addiction when compared to their age and weight counterparts. Those who had food addictions tended to self-soothe with food.
Liu et al. (2010)	Food Addiction	Genetics/Stress	Through a literature review, this article explores the legitimacy of food addictions as well as contributing factors such as genetics, dysregulations in the brain, and environmental factors. It was concluded that there are several contributing factors in food addiction and that intervention and prevention encompass genetics, and stress therapy, as well as emerging pharmacological drugs.
Smith & Robbins (2013)	Food Addiction	Genetics	Assesses the underlying processes that contribute to food addictions. Concluded that food addiction is acquired through the same pathway as drug and opioid addictions through the activation of the brain's reward circuits. The removal of these highly palatable foods results in the typical withdrawal symptoms seen in traditional drug addictions.

Table 3. Summary of Main Results in Adenovirus-36 Studies Relating to Obesity

First Author	Subject Area	Correlating factor	Summary
Esposito	AD-36	Genetics/Stress	A review of the available literature on AD-36 revealed inconclusive results as some studies supported the popular findings while others refuted the claims. The conclusion states that additional research needs to be conducted.
Na	AD-36	Genetics	Investigation of a prophylactic vaccine that would protect animal subjects from the increases in adiposity after AD-36 infection. The experimental group demonstrated decreased levels of adiposity, and TG levels when compared to the unvaccinated control group. Established proof-of-concept for AD-36.
Ponterio	AD-36	Food Addictions	Explores a possible link between AD-36 and obesity. Concludes that obesity is multi-factorial and that AD-36 should be considered a possible risk factor given the increased adiposity in mice infected with AD-36. Subsequently, AD-36 should also be considered in glucose uptake pathways and leptin inhibition.
Gabbert	AD-36	Genetics	Assessed a possible relationship between AD-36 and obesity in children aged 8-18. Results showed a positive correlation between AD-36 and childhood obesity are given that 78% of the obese study group was found to be AD-36 positive and that AD-36 was more prevalent in this group than in the non-obese control group.

Table 4. Summary of Main Results in Genetic Studies Relating to Obesity

First Author	Subject Area	Correlating factor	Summary
Barness, Opitz, & Gilbert-Barness (2007)	Genetics	Food Addiction	This article examines the genetic and environmental influences that contribute to obesity. Several genetic loci have been identified in the dysregulation of feeding patterns and behaviors. Alterations in the genes LEP and FTO serve as strong predictors of obesity.
El-Sayed Moustafa & Froguel (2013)	Genetics	Food Addiction	Investigates the genetic factors that make some individuals more susceptible to obesity. Several loci have been identified that are known to contribute to monogenic obesity including those genes such as MCR4, as well as other receptor genes. All identified loci are now known to play a role in the dysregulation of the leptin pathway, thus contributing to obesity.
Herrera & Lindgren (2010)	Genetics	Genetics	Determined that there is a heritability factor to obesity ranging from 40%-70%. Investigates the biological pathways of the genes implicated in the heritability factor to determine their effect and influence over obesity. Concluded that there were several mutations in genes, receptors, and deletions that led to the pathway that increased the risk of obesity.
Silventoinen et al. (2010)	Genetics	Genetics	Twin and family adoption studies on childhood obesity are gathered to determine if a biological component or susceptibility exists in the onset of obesity. The results revealed a strong correlation between the body mass index of the adoptees and the biological parents rather than the adoptees and their adoptive family.
Xia & Grant (2013)	Genetics	Food Addiction	Investigates the etiology of monogenic obesity using genome-wide association studies. These studies revealed a strong correlation between genetics and obesity implicating several emerging factors in its onset including non-coding RNA's, copy number variants, and SNP's.

Table 5. Summary of Main Results in Stress Studies Relating to Obesity

First Author	Subject Area	Correlating factor	Summary
Scott, Melhorn, & Sakai (2012)	Stress	Food Addiction	This literature review explores the effects of chronic social stress on the onset of obesity. Dietary preference, food consumption, and adipose tissue are all observed factors and were heightened in response to chronic social stress.
Sinha & Jastreboff (2013)	Stress	Food Addiction	Stress and its neurobiology are investigated in this review. Stress was determined to be a risk factor for the development and severity of obesity as it dysregulated important neurological functions. Chronic exposure to stress leads to a higher intake of highly palatable foods and reduced energy distribution.
Tomiyama (2019)	Stress	Gut Microbiota/ Genetics	Through a literature review, this article explores the various contributing factors of stress and its effects on obesity ranging from cognitive processes to biochemical pathways, as well as the role that microbiota play. The conclusion stated that further research is warranted but several factors have proven the debilitating effect that stress has on the onset of obesity through several underpinnings.
Wardle et al. (2000)	Stress	Food Addiction	An experimental study was conducted to measure the effects of stress in the workplace and obesity/ weight gain. Results demonstrated a strong correlation between high periods of chronic stress and an overconsumption/ craving of highly palatable foods when compared to their counterparts who were exposed to either no or low periods of stress.

Chapter 3: Literature Review

The use of a multi-faceted approach in the treatment of obesity has not been widely used in a larger scope between several different factors. Although some individuals have used a multi-faceted approach in treating obesity, they have only done so within the context of a single contributing factor rather than multiple contributing factors. For example, in a study conducted by Economos & Hammond (2017), the authors proposed using a multi-faceted approach for obesity prevention in children focusing solely on the different facets of health behaviors. Although this study provided a comprehensive review of the multi-faceted approach to behavior modification it failed to provide alternative explanations as to why an increased number of children were becoming obese and failing to lose weight. Therefore, further investigation is needed to develop a multi-faceted approach to treating obesity on a larger scale between the interdisciplinary factors of stress, gut microbiota, adenovirus 36, genetics, and food addictions. Although research has been done on each of these topics independently, there has yet to be a comprehensive analysis of these topics as a cohesive unit in obesity treatments.

Chapter 4: Gut Microbiota and Obesity

The human gastrointestinal (GI) tract is composed of trillions of microorganisms composed from a collection of various entities from the Bacteria, Archaea, and Eukarya domains of life, and are thus termed ‘gut microbiota’ (GM) (Harakeh et al., 2016). These GM have evolved over thousands of years within its host to eventually form a mutually

beneficial relationship. Today it is estimated that more than 100,000,000,000,000 microbiotas reside in the human gut providing its host with various physiological functions including the metabolism of nutrients, regulating host immunity, assistance in the production of vitamins B and K, and strengthening of the host immune system (Sweeney, & Morton, 2013). However, recently the diversity of the GM or the lack thereof, acquired through a combination of environmental factors, diet, and genetic composition is thought to play a role in the development and progression of obesity.

According to Sweeney, & Morton (2013), the GI tract is primarily composed of microorganisms from either the Bacteroidetes or Firmicutes phyla, with an elevated Firmicutes to Bacteroidetes ratio following weight gain, and an inverse relationship following weight loss. In a similar study conducted by Bianchi et al. (2019) an analysis of the GM composition of individuals who lost weight over the course of a year through a low-calorie diet resulted in significant changes to the GM composition with decreases in the Firmicutes phyla and increases in the Bacteroidetes phyla, better resembling the GM composition of a lean individual. Sweeney, & Morton (2013) found similar results among germ-free mice who underwent fecal transplantation from western mice that resulted in their onset of obesity with Firmicutes GM increases. Harakeh et al. (2016), suggests that host interactions with GM, including the altered gut microbial composition, plays a role in the onset of this metabolic disease. The authors hypothesize that bacteria in the Firmicutes and Bacteroidetes phyla exert a role in the development of obesity through pathways such as the host immune system, diet, and genomics, which are known contributing factors in obesity. Harakeh et al. (2016) showed that GM was important for the digestion and metabolism of complex carbohydrates and played an essential role in

harvesting the energy derived from this group. During clinical trials involving human subjects, results showed that in some fecal transplantations involving overweight individuals, the healthy individual experienced obesity due to an altered GM composition that resulted from the fecal transplantation from the overweight individual (Bianchi et al., 2018). The results derived from this study led the researchers to conclude that obesity can be regulated through the modification of GM.

This data provides an important analysis of the role that GM plays within the larger context of obesity including nutrition, and genetics. However, this study explores the influence that nutrition and genetics have on GM rather than the influence that these three factors in conjunction have on obesity. Although the analysis between GM and obesity is thoroughly explored the data raised questions as to whether the influence that GM has on obesity is significant, as data did not provide a quantification of the prevalence of GM related obesity. Therefore, further research is warranted.

Chapter 5: Food Addiction and Obesity

Overeating is a well-known cause of obesity. It has been implicated in the exponential rise of body mass index (BMI) in industrialized countries, as well as several other adverse health consequences such as Type II Diabetes, Cardiovascular Disease, as well as high blood pressure (Liu, Von Deneen, Kobeissy, & Gold, 2010). The etiology behind overeating has given rise to the idea that our body's neural systems, which once motivated our ancestors to forage for food, have now evolved to influence drug-seeking and self-administration behaviors (Avena, Rada, & Hoebel, 2008). This idea has given

rise to the concept of Food Addiction (FA). A relatively nascent idea that has gained acceptance among the general public with the rise of treatment programs modeled after those created to treat substances of abuse such as alcohol, cocaine, or heroin (Davis et al., 2011). FA is described as a tendency to overindulge in highly-palatable foods such as those containing copious amounts of carbohydrates, and sugar (Liu, Von Deneen, Kobeissy, & Gold, 2010). The symptoms associated with FA have come to resemble those associated with drugs of abuse, resulting in the peaked interest of the scientific community, which has only recently given credibility to the idea of FA as a contributing factor to obesity.

FA has become synonymous with drug addictions in that individuals who suffer from overeating become physically and psychologically dependent on highly-palatable foods such as sugar (Smith, & Robbins, 2013). This dependence often takes the form of uncontrollable tendencies that negatively impact other major life activities and increases in severity with repeated exposure (Davis et al., 2011). This dependence or addiction is often characterized by several factors including bingeing (the repeated intake in a high volume of the substance of abuse within an isolated period of time), withdrawal (adverse reactions to abstinence of the drug of abuse), craving (enhanced motivation), and sensitization or hyperactivity in response to the substance after a period of abstinence (Smith, & Robbins, 2013).

In a study conducted by Avena, Rada, & Hoebel (2008) they developed an animal model in which they demonstrated the addictive characteristics of sugar in rats, which resembled those seen in individuals who abuse opiate drugs. In this model, rats were

given intermittent access (12 hours) to a sucrose solution and food pellets, after previous 12-hour food deprivation. This intermittent access resulted in the consumption of substantive amounts of sugar solution and food pellets. After one month of this operant conditioning, the rats began to exhibit addictive symptoms such as bingeing, withdrawal, craving, and cross-sensitization.

Rats who were fed intermittently not only increased their sugar intake during the first hour of availability but consumed the same amount of sugar in 12 hours as their counterparts did in 24 hours (Avena, Rada, & Hoebel, 2008). Furthermore, this intermittent feeding pattern resulted in the rats consuming larger meals of sugar, in smaller instances throughout the day when compared to their counterparts (Avena, Rada, & Hoebel, 2008). These results demonstrate a strong association between sugar and binge eating, or bingeing behavior often seen in opiate addictions.

Animals have also been known to exhibit signs of withdrawal in studies involving the self-administration of opiates, when the drug is removed or blocked synergistically (Davis et al., 2011). When this occurs instances of anxiety, aggression, depression, and a decrease in body temperature have been observed in animals suffering from opiate withdrawal (Liu, Von Deneen, Kobeissy, & Gold, 2010). In the study conducted by Avena and colleagues, these somatic symptoms were observed in rats who were intermittently fed a sugar solution. When withdrawal was induced using an opioid antagonist the rats began to exhibit signs of tremors, head shaking, and teeth chattering; behavior consistent with opiate addiction withdrawal. The rats also demonstrated behavioral depression when sugar was removed for 24 hours. According to Galic &

Persinger (2002), Aggressive behavior can be observed following the removal of intermittent sugar access, which remains consistent with the behavior demonstrated in human individuals suffering from withdrawal.

The rats used in this addiction model were also seen to suffer from cravings and cross-sensitization. This was demonstrated through the rats' tendency to seek out sugar during periods of abstinence, as well as a greater tendency to self-administer drugs of abuse such as cocaine, and amphetamines when on an intermittent sugar feeding pattern. Conversely, rats who were subjected to periods of sugar abstinence exhibited a higher tendency to self-administer alcohol (Avena, Rada, & Hoebel, 2008). These results demonstrate a linear relationship between sugar and other gateway drugs, which was previously observed with drugs of abuse.

Chapter 6: Adenovirus- 36 (ADV-36) and Obesity

Adenoids were first discovered in tissue patches located at the back of the throat. As part of the immune system, adenoids are responsible for helping our body fight off infectious diseases (Ponterio, & Gnessi, 2015). However, these adenoids can be infected with viral infectious agents called Adenovirus' which can typically cause upper respiratory and intestinal tract infections by invading the adenoid tissue (Esposito, Preti, Consolo, Nazzari, & Principi, (2012). Recently, Adenovirus' has been implicated as a possible factor in the onset of obesity, and emerging research is currently investigating a possible causal relationship. As, the immune response is greatly influenced by nutritional intake it is thought that this dysregulation, often seen in obesity, can increase the risk of

Adenovirus infection and vice versa, thus perpetuating the cycle of obesity (Ponterio, & Gnessi, 2015). ADV-36's influence on obesity is hypothesized to be due to ADV-36's ability to dysregulate the leptin pathway thereby disrupting the body's natural satiety and appetite signals (Esposito, Preti, Consolo, Nazzari, & Principi, 2012). ADV-36 may also play a role in activating cytokines in adipose tissue leading to inflammation making it difficult for obese individuals to lose weight (Esposito et al., 2012). The potential role that ADV-36 may have on obesity has led to its popularization in obesity research.

Adenovirus infection is commonly transmitted through direct contact, fecal-oral transmission, or through infected water sources (Ponterio, & Gnessi, 2015). In several animal model studies, these transmission methods were used to test the effect of ADV-36 on animal adiposity. For example, in a study conducted by Ponterio & Gnessi (2015) chickens infected with the Adenovirus demonstrated an increase in adiposity, and a decrease in cholesterol and triglyceride concentrations; while their counterparts infected with an avian virus did not result in significant increases in weight. Similarly, when monkeys were infected with the Adenovirus-36 their average adiposity increased between 15%-30% and a protective factor for cholesterol and triglyceride concentrations was observed (Gabbert, Donahue, Arnold, & Schwimmer, 2010).

Pasarica et al. (2008) also demonstrated that animals infected with ADV-36 can result in sharp increases in body mass. In this study, Pasarica and colleagues infected rats with the ADV-36 and observed sharp increases in weight gain, and low levels of cholesterol and triglycerides. However, unlike the other studies conducted in this field, they discovered that ADV-36 infection also increased insulin sensitivity and glucose

uptake. Perhaps the most convincing results were yielded when three male marmosets were infected with ADV-36 and after 28 weeks tripled in body weight, with increases in fat accumulation and decreases in cholesterol and triglyceride levels when compared to their uninfected counterparts (Gabbert, Donahue, Arnold, & Schwimmer, 2010).

Furthermore, a proof-of-concept study was conducted by Na & Nam (2014) to test whether animals who were vaccinated against ADV-36 would be protected against the deleterious effects of the virus when compared to their unvaccinated controls. Using UV-irradiation ADV-36 was inactivated and purified, and then injected in mice twice every two weeks. Their unvaccinated counterparts were given injections consisting of phosphate-buffered saline. When the mice were probed with live ADV-36 the vaccinated group showed decreases in both body weight, and fat depots compared to the unvaccinated control group. There were no significant differences in food and water intake indicating that the ADV-36 vaccine exhibited a protective factor against increases in weight and fat accumulation during exposure to the live virus (Na, & Nam, 2014).

These animal models demonstrate a clear relationship between ADV-36 infection and increases in adiposity. The positive correlations between this infection and fat accumulation led researchers to test this theory in human models, to identify a possible relationship. One such study conducted by Gabbert et al., (2010) sought to test the frequency of ADV-36 antibody positivity in obese and nonobese children between the ages of 8-18. The results demonstrated that approximately 15% of the children enrolled in the study tested positive for ADV-36, and among this 15% the majority who tested positive belonged to the obese group while only 3.2% belonged to the non-obese group.

These results led to the conclusion that the presence of ADV-36 may, in fact, play a role in increases in weight, and waist circumference in children. Given this positive correlation between ADV-36 and obesity in children, many researchers begged the question as to whether these results could be replicated in adult participants.

One study that demonstrated this relationship was that of Ponterio, & Gnessi (2015). In this study 502 adult participants were recruited, including 360 obese individuals and 142 non-obese controls, and tested for the presence of ADV-36. The results indicated that approximately 30% of the obese individuals possessed ADV-36 and only 11% of the non-obese controls possessed ADV-36. This result demonstrated a significant correlation between ADV-36 infection and obesity as seen in the studies involving children. Additionally, those who tested positive for ADV-36 in this study also demonstrated low cholesterol and triglyceride levels as previously established through animal models (Ponterio, & Gnessi, 2015). Similar results were reported in various studies including that of Trovato et al. (2012) in which they examined 203 adults for the presence of ADV-36, and found that 64% of the obese individuals in this group tested positive which was significantly greater than the 32% that tested positive in the non-obese control group.

However, given that some of the individuals belonging to the control groups in various studies did test positive for ADV-36 several studies reported contrasting results that did not yield a statistical significance between ADV-36 and obesity. For example, Esposito and colleagues (2012), examined the ADV-36 presence in obese and non-obese individuals in Denmark and determined that the presence of ADV-36 is not a predictor or

indicator of obesity as previously hypothesized. Similarly, a study conducted by Goossens et al. (2012), found that among 509 Dutch and Belgian adults the prevalence of ADV-36 was too low to be considered statistically significant in both obese and non-obese groups. Furthermore, this study also reviewed the literature among ADV-36 and obesity in children and determined that their findings among a younger population were in accordance with the results found in the animal experimental models, indicating that ADV-36 infection may have a greater influence over childhood obesity than later on in the life course (Goossens et al., 2012).

Although, there are several conflicting data among human ADV-36 infection and obesity there remains a significant amount of evidence among animal experimental models and some human models that indicate the possibility of this infection as an etiologic factor in obesity. Several experimental studies have demonstrated that ADV-36 can result in sharp increases in fat accumulation, and weight gain. These results may be due to ADV-36's role in the disruption of the leptin pathway, which regulates appetite and satiety, or its role in the inflammatory response both of which can make it difficult for obese individuals to lose weight or decrease their overall adiposity. Furthermore, these studies revealed that ADV-36 infection may have a greater influence over a certain number of individuals, particularly adolescents, and it's the effect on obesity cannot be generalized to the obese population in its entirety. However, it does remain evident that further research is necessary for this field of study before a definitive relationship between ADV-36 infection and obesity can be established. To ignore the role of ADV-36 would be a gross oversight in the treatment of obesity, as a possible relationship may be important in aiding the prevention and progression of obesity.

Chapter 7: Genetics and Obesity

It is widely accepted among the academic community that genetics and heritability play a role in the onset of obesity. However, the influence of this factor is often underscored and misunderstood by the general public thus rendering traditional weight loss therapies futile. It has been estimated that there is approximately a 40%-70% chance of obesity heritability (Herrera, & Lindgren, 2010). This poses a serious public health issue as obesity statistics continue to climb with experts predicting that approximately 70% of overweight/obese children will continue to be obese well into adulthood (Xia, & Grant, 2013). This data indicates a dire need for personalized early intervention strategies. With emerging sequencing technology such as 23 and Me personalized medicine has never been easier, or more readily available. Therefore, it is important to understand the genetic underpinnings of obesity so that emerging sequencing technologies may be applied to enhance weight loss regimes in individuals who struggle to maintain a healthy weight.

Obesity can be separated into three different subtypes including monogenic, syndromic, and polygenic obesity (otherwise known as common obesity) (Herrera & Lindgren, 2010). Using genome-wide association studies (GWAS), the genetic etiologies of both monogenic and polygenic obesity have been largely mapped to determine the biological underpinnings of approximately 20 genetic loci that currently influence the onset of obesity (Xia, & Grant, 2013). In GWAS the genetic variants of several individuals are observed for links relating to the obesogenic phenotype. Through this technology, the gene LEP which codes for leptin was discovered in mouse models.

Leptin is a hormone secreted by adipose tissue that regulates appetite and fat storage through neuronal signaling to the hypothalamic region (Silventoinen, Rokholm, Kaprio, & Sorensen, 2010). According to a study conducted by El-Sayed Moustafa, & Froguel, (2013) mutations in the leptin receptors that can detect and respond to the hormone lead to dyslipidemia, obesity, and type 2 diabetes in experimental mice. While in humans the homozygous mutation of the leptin receptor can result in severe early-onset obesity (El-Sayed Moustafa, & Froguel, 2013). Furthermore, human individuals who lack sufficient leptin levels can be subject to obesity, as well as hyperphagia, and hyperthyroidism (El-Sayed Moustafa, & Froguel, 2013). Leptin is thought to have such an inducing effect on obesity due to its influences on the central nervous system. Leptin helps regulate satiety, and energy balance, however, when this gene or its associated variants are mutated it miscommunicates with the hypothalamus, which regulates many of our homeostatic processes, resulting in altered satiety levels that can lead to altered eating behaviors (Xia, & Grant, 2013).

Other genetic variants known to alter the central nervous system in relation to obesity is that of the proopiomelanocortin (POMC) hormone which is cleaved to produce melanocortin 4 receptor (MCR4) (Xia, & Grant, 2013). POMC is thought to be regulated by leptin and therefore plays a hand in feeding behaviors, while MCR4 is thought to regulate the effects of leptin on body weight and food consumption (Xia & Grant, 2013). According to a study conducted by Herrera, & Lindgren (2010), mutations of the MCR4 receptor can account for 6% of severe or early-onset obesity. Give that current obesity trends report that approximately 2.1 billion people in the world are obese, approximately 126,000,000 of these cases could be attributed to PMOC or MCR4 mutations

(Silventoinen, Rokholm, Kaprio, & Sorensen, 2010). Furthermore, mutations in the MCR4 region in mice have resulted in obesogenic comorbidities such as hyperglycemia, and hyperinsulinemia (Herrera, & Lindgren, 2010). While mutations in the POMC region have been proven to be positively correlated with severe obesity and red hair pigmentation in humans (El-Sayed Moustafa, & Froguel, 2013). Other genetic variants that dysregulate the correct expression of either PMOC or MCR4 can result in similar phenotypes.

Although LEP, POMC, and MCR4 can have deleterious effects on body mass they pale in comparison to the gene called the fat mass and obesity-associated (FTO) gene. This gene was first discovered in 2007 by mistake, researchers were actually trying to find the genetic loci related to type 2 diabetes and stumbled upon the FTO gene instead (Xia, & Grant, 2013). Shortly after its discovery researchers soon realized that FTO was responsible for the obesogenic phenotype through animal experimental models. Researchers created a mouse that was deficient in both the maternal and paternal copies of the FTO gene to determine its function by observing the biological changes that took place in its absence (Silventoinen, Rokholm, Kaprio, & Sorensen, 2010). Mice that possessed this genotype were found to have significant reductions in body mass, and adipose tissue with significant increases in muscle mass, compared to mice who possessed at least one functional copy of the gene (Xia, & Grant, 2013). After similar studies were conducted, and the results were duplicated FTO was established as having one of the greatest associations with obesity due to its role in the regulation of appetite, and energy expenditure (El-Sayed Moustafa, & Froguel, 2013).

Another type of genetic mutation that can have lasting effects on obesity is that of deletions. According to El-Sayed Moustafa, & Froguel (2013), large deletions occurring on the 16p11.2 chromosome has led to an increased risk of severe obesity. In a retrospective analysis, it was discovered that individuals who possessed this deletion had an increased risk of morbid obesity approximately 43 times that of an individual who possessed a normal copy of the gene and that approximately 7 % of individuals who were clinically diagnosed as morbidly obese possessed these deletions. This influence was further confirmed when it was discovered that duplications at this chromosome led to increased risk of being clinically underweight (El-Sayed Moustafa, & Froguel, 2013).

Confirmation for the genetic component in obesity has also been established using family studies. Twin, and adoption studies have demonstrated that genetic influence on obesity is present among individuals who share the same or similar DNA (Herrera, & Lindgren, 2010). In monozygotic or identical twins, the individuals share 100% of their DNA, while dizygotic or fraternal twins only share 50% of their DNA (Xia & Grant, 2013). Therefore, it was unsurprising when it was discovered that fat mass among identical twins had a concordance rate of approximately 70%-90%, while only 35%-45% in fraternal twins (Herrera, & Lindgren, 2010). In adoption studies, it was reported that there was a significant association between the BMI of children who were adopted and their biological parents, then between adopted children and their adoptive family (Xia, & Grant, 2013).

Overall, the link between genetics and obesity has been well established in the scientific community, with the emergence of empirical and unequivocal data. Mutations

in several genes including that of LEP, POMC, MCR4, and FTO have now been established as contributing factors in the onset and severity of obesity. While mutations in the form of deletions in certain areas of our chromosome can lead to increased adiposity, and fat storage (Xia, & Grant, 2013). Furthermore, the use of twin and adoptive studies has provided us with additional evidence stressing the effect of genetics on obesity. Although the evidence surrounding genetics and obesity is largely robust there remain several questions regarding the heritability of obesity. The onset and severity of obesity cannot be solely attributed to genetics as environmental influence can exacerbate or challenge existing mutations. Additionally, the existence of these genes/ mutations within an individual does not always lead to the phenotypic expression of obesity, as this genotype can largely be suppressed in physically active individuals. Nevertheless, future research is warranted as there may be several genetic variants and genetic influences that remain largely undiscovered.

Chapter 8: Stress and Obesity

Stress is a state of tension whether it be emotional, physical, or psychological. It is our body's natural response to environmental challenges and demands. In ancestral times stress was the body's defense mechanism as we prepared for the fight- or flight- a response that occurred when we encountered predators (Tomiyama, 2019). However, in today's modern world we encounter minor stressors every day whether it's an upcoming deadline or sitting in traffic. Regardless of the stressor our body still reacts to this event as if it were encountering a predator activating our flight or fight response. The chronic activation of this fight or flight response can have detrimental effects on health, and

obesity. Stress can have serious health effects throughout the life course such as the increased risk of heart disease, and increased blood pressure, however when stress begins to influence obesity a multitude of comorbidities arise leading to a decreased quality of life (Wardle, Steptoe, Oliver, & Lipsey, 2000). Therefore, an understanding of the effects of stress and its impact on obesity is essential to developing treatment regimens aimed at decreasing the incidence and prevalence of stress-related obesity, and its associated weight-related ailments.

Stress can come in two forms either acute or chronic stress. Acute stress occurs in response to future or past events or demands and is quickly counterbalanced by our body's rest and digest response following the stressor and thus reversing its negative effects (Sinha, & Jastreboff, 2013). However, chronic stress is a prolonged and recurrent response to the stressor. Stressors can be of any nature and the most common ones are related to interpersonal relationships, low socioeconomic status, stressful employment, or a general lack of control in one's life (Scott, Melhorn, & Sakai, 2012). It these types of stressors that cause chronic stress resulting in the deleterious effects on our health that can influence or precede obesity through a multitude of pathways that influence energy expenditure, and food intake (Tomiyama, 2019).

One of the pathways that allow stress to influence obesity is the activation of the sympathetic nervous system (SNS) in response to chronic stress (Scott, Melhorn, & Sakai, 2012). The sympathetic nervous system regulates our survival responses such as the fight-or-flight response. Therefore, when this system is chronically activated our body composition is altered through the release of several hormones (Scott, Melhorn, & Sakai,

2012). One of the hormones that are released is cortisol which belongs to the glucocorticoid family. The chronic release of cortisol promotes fat storage in the abdomen, feeding behavior, body weight, and leptin levels (Sinha, & Jastreboff, 2013). In a study conducted by Epel et al. (2001) participants were exposed to a laboratory stressor, and their food intake was then measured. They found that participants who had higher cortisol levels when exposed to the stressor subsequently consumed more food, than the control group who were not exposed to a stressor. Furthermore, exposure to cortisol increases fat storage in the abdomen as observed through the metabolic disorder known as Cushing's disease. This disease is characterized by high levels of cortisol resulting in the phenotype of abdominal obesity (Tomiyama, 2019).

However, stress's effects on obesity are not simply limited to the activation of the SNS, as chronic exposure to stress is also known to alter feeding behaviors (Sinha, & Jastreboff, 2013). According to the American Psychological Association individuals who undergo stressful events are more likely to consume and crave high-calorie and fat foods during periods of stress (2013). It is hypothesized that this is due to the reward circuit activated in response to the highly palatable food which according to 37% of adults who overeat or binge eat helps distract them from the stress (Am. Psychol. Assoc, 2013). This is exemplified in the study conducted by Wardle et al. (2000) in which they sought to evaluate the associations between food intake and work stress. In this study, employees reported increased consumption of palatable foods high in sugar and fat when exposed to high levels of stress in the workplace, compared to that during low periods of stress. Further validation for these results was provided by Zellner et al. (2006) during their study in which they randomly assigned participants to either an unsolvable anagram

group (high stress) or a solvable anagram group (low stress/control). The results showed that those who participated in the unsolvable anagram group reported increased consumption of fat and sugar when compared to their solvable anagram counterparts. In similar studies, such as that conducted by Scott, Melhorn, & Sakai (2010) they found that this effect was exacerbated in individuals who were already obese or at risk of becoming obese as stress promotes altered eating and food preference behaviors during its disruption of the homeostatic control centers.

The effects of stress and altered eating behaviors are hypothesized to be due to the activation of the brain's reward system when exposed to highly palatable foods. The consumption of highly palatable foods is thought to activate these symptoms thus mitigating the effects of stress (Scott, Melhorn, & Sakai, 2012). Furthermore, repeated acute stress is thought to increase compulsive food seeking behaviors as it alters the responses of the limbic and prefrontal brain regions that are associated with motivation, emotion, learning, and memory (Sinha & Jastreboff, 2013). In fact, according to Tomiyama (2019), many of these foods possess addictive qualities marked by wanting, and bingeing during withdrawal periods that are triggered or exacerbated during stress.

Not only is stress associated with the alteration of food behaviors but it also is known to alter physical activity and sleeping patterns which can contribute to the onset of obesity. Tomiyama (2019), found that chronic stress can decrease the motivation for physical activity or increase the motivation for sedentary behavior. This can be exemplified through a survey conducted by Ng & JeffePrey (2003) in which participants reported a decreased motivation for physical activity when exposed to high periods of

stress, then when experiencing relatively low periods of stress. Furthermore, stress can also affect sleep duration which according to Sinha, & Jastreboff, (2013) , diminished sleep duration can increase the risk of obesity. In a study conducted by Cappucccio et al. (2008) diminished sleep increased body mass by approximately 1.55% while every additional hour of sleep decreased body mass by about 0.35%.

Stress can influence obesity through a multitude of pathways. Its primary effects are observed through the activation of our body's sympathetic nervous system which creates a cascade of detrimental effects leading to obesity. The SNS not only can release hormones such as cortisol in excess, but it can also alter our feeding behaviors, food preferences, physical activity and sleep patterns that can lead to weight gain. Although, these effects are not always applicable to everyone as some individuals may experience decreased appetite and increased physical activity during periods of stress it most certainly applies to individuals who are obese or at risk of becoming obese. This is a problem in and of itself as these individuals represent our most vulnerable population due to their increased risk of type 2 diabetes, cardiovascular disease, and mortality. Therefore, it is important to understand the underlying associations between stress and obesity so targeted and specific intervention strategies may be employed in the near future.

Chapter 9: Conclusion

Obesity has risen dramatically over the years with more and more people being categorized with a BM of over 30 $kg/m^{2.}$ (Barness, Opitz, & Gilbert-Barness, 2007). With this categorization comes several obesity-related comorbidities such as hypertension, type

2 diabetes, cardiovascular disease, dyslipidemia, and many others (Scott, Melhorn, & Sakai, 2012). As of late the financial strain of these metabolic disorders is estimated to be as high as $6.38 billion (Barness, Opitz, & Gilbert-Barness, 2007). Thus, efforts to tackle and mitigate the severity of obesity is of the utmost importance. Therefore, obesity intervention must come from a combined effort at the individual, local, and national levels. However, given that these combined efforts have resulted in disappointing outcomes there is a need to evaluate the current treatment regimens and its efficacy.

A possible explanation for the failure of these programs is that they are not expansive and currently only focus on dietary, and physical activity behaviors. While these behaviors may account for most obesity cases, there remains a large population who are unaffected by these factors and are unable to maintain a healthy weight due to unknown underlying causes. Therefore, there is a need for more robust treatment regimens that incorporate emerging and existing etiologic factors as outlined in this paper. Through this multi-faceted approach, several etiologic factors can be examined in conjunction or individually to create more inclusive treatment regimens aimed at reducing overall adiposity and body mass index measures.

As demonstrated in this paper there are several obesogenic factors that have yet to be considered in the treatment of obesity. These factors include gut microbiota, food addiction, adenovirus-36, genetics, and stress. Not only do these factors act at the individual level to influence the onset and severity of obesity, but they also at the communal level interacting with one another to create an incessant cycle of perpetual adiposity. For instance, food addiction as characterized by the overindulgence of highly

palatable foods such as sugar, and fat can influence the gut microbiota (Avena, Rada, & Hoebel, 2008). Through the digestion of these palatable foods, the gut microbiota composition is altered towards that of a high Firmicutes to Bacteroidetes ratio (Sweeney, & Morton, 2013). As previously discussed in this paper individuals who lack a diverse microbiome in the gastrointestinal tract due to a higher proportion of the Firmicutes phyla have an increased risk of obesity (Harakeh et al., 2016). Furthermore, the overindulgence in highly palatable foods can cause weight gain leading to social stigma creating a high-stress environment for the individual which can perpetuate the tendency to overeat, as well as alter homeostatic regulations of SNS, physical activity, and sleep; all of which in increase the onset as well as the severity of obesity (Tomiyama, 2019)

Conversely, the altered gut microbiome can affect our psychological and emotional processes causing affected individuals to experience higher levels of stress, and anxiety. According to Tomiyama (2019), the diversity of the gut microbiome can affect how an organism responds to stress, and the lack of diversity in the microbiome can lead to increased levels of stress. This is exemplified through fecal transplants in mice. The microbiome in mice prone to stress is replaced through a fecal transplant with the microbiome of mice who rarely experience stress, resulting in decreased anxiety in the previously stress-prone mice, with an inverse relationship in the previously stress-free mice (Tomiyama, 2019). These results exemplify the association between gut microbiota and stress whose common factors can influence obesity.

Other correlated factors include that of stress and Adenovirus-36. Stress is known to suppress our immune system, thereby dysregulating immunologic defenses and

creating a pathway to illness (Esposito, Preti, Consolo, Nazzari, & Principi, 2012). Therefore, when individuals experience chronic stress their immune system is inhibited making these individuals more susceptible to illnesses and infection such as Adenovirus-36. Furthermore, genetics can influence the risk of contracting ADV-36 as some individuals are immunodeficient due to various genetic disorders and this increases the likelihood of the contraction of various infectious diseases and viruses such as that of ADV-36. However, genetics does not only exert an influence on ADV-36 but on food addictions as well. It is widely accepted that a genetic component plays a role in traditional addiction disorders such as that of alcohol and opiate addictions. Given the similarity in the symptomatic effects between opiate and food addictions, it is unsurprising that a genetic predisposition exists among food addictions. According to Smith & Robbins (2013), a gene referred to as Taq1A is often overexpressed in drug users and has also been linked to compulsive eating behaviors. Furthermore, the gene OPRM1 has also been linked to an overexpression of the reward circuit in both drug users and compulsive overeaters (Smith & Robbins, 2013).

Given the vast coupled influences of gut microbiota, stress, food addiction, ADV-36, and genetics it is important to identify possible areas of treatment for these influences both individually and in combination. A possible treatment for the alteration of gut microbiota would be through the widespread use of probiotics. Probiotics are often referred to as helpful bacteria as they aid your digestive system and alter the ratio of your microbiota with higher proportions of the Bacteroidetes phyla. Although there are other methods of altering your microbiome such as fecal transplants, these methods are extreme and may not be beneficial for certain individuals. Therefore, the use of probiotic

supplements or increased consumption of foods that contain probiotics such as yogurt the microbiome can be altered thus reducing the risk of both obesity, and possible modifications to our neural system causing high anxiety and stress. Possible treatments for ADV-36 include a vaccine containing inactivated fragments of ADV-36. As previously mentioned in this paper a proof-of-concept vaccine was developed and injected in mice yielding successful results (Na, & Nam, 2014). Although, further research in this area is warranted a human vaccine for ADV-36 could potentially reduce the risk of infection. Furthermore, as with any bacterial or viral infection, it is important to practice proper hygiene techniques such as hand-washing to avoid the contraction or the spreading of ADV-36.

Additional treatments for the remaining factors include mindfulness techniques to reduce stress and its associated effects, possible genetic sequencing, as well as the use of therapy and pharmacological drugs prescribed for traditional opiate addictions. With the technological advances regarding the human genome, sequencing our DNA has never been easier. Through programs such as 23 and me, an individual can not only sequence their DNA, but they can use the results to determine what types of food they should be eating for their body, and what type of physical activities are the most efficient for their DNA (Silventoinen, Rokholm, Kaprio, & Sorensen, 2010). As far as treating food addiction several drugs exist such as Naltrexone and Buprenophrine that are used to treat opioid addictions (Smith, & Robbins, 2013). Given the similarity between opioid and

food addictions, they can be used to treat the symptoms of food addictions. A visual representation of the correlating etiologic factors can be seen in figure 1.

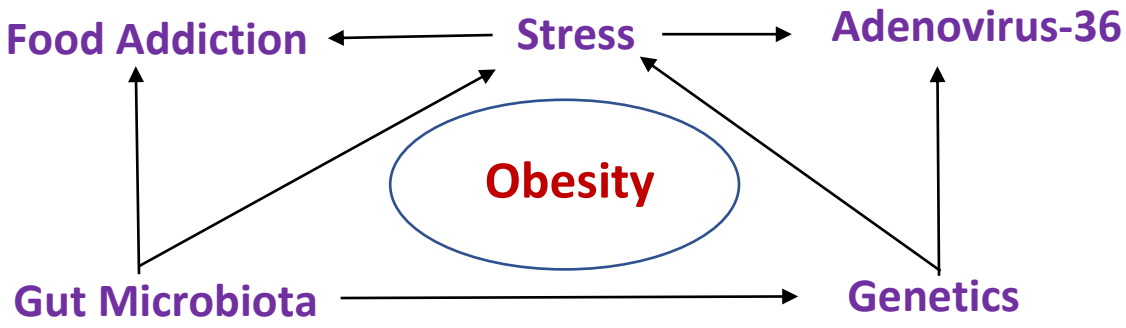

Figure 1. Conceptualization of interrelated obesogenic factors

Intervening in obesity seems like a daunting task and may be more complicated than originally thought. Current efforts to treat and prevent the onset of obesity focus solely on the nutritional and energy expenditure facets. Given the discussion provided in this article, obesity is a multi-faceted disease that must be treated beyond these means. Although, the ideas and etiologic factors put forth in this review may not be comprehensive, or applicable to everyone they certainly provide alternative explanations and solutions for individuals struggling to maintain a healthy weight that serves as a starting point in shifting the conversation in obesity prevention from nutrition and exercise to more robust and inclusive etiologic factors. This shift in conversation may serve to aid in the obesity epidemic that is currently affecting several parts of the world, with the United States at the forefront.

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