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# Obesity and cardiovascular disease in the United States: nutritional and lifestyle strategies for prevention

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# OBESITY AND CARDIOVASCULAR DISEASE IN THE UNITED STATES: NUTRITIONAL AND LIFESTYLE STRATEGIES FOR PREVENTION

by

**PATRICK D. HANNAN**

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Approved by

First Reader ______________________________

James Hamilton, Ph.D.
Professor of Physiology and Biophysics

Second Reader ______________________________

Mina Moussavi Ph.D.
Assistant Professor of Physiology and Biophysics

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**OBESITY AND CARDIOVASCULAR DISEASE IN THE UNITED STATES: NUTRITIONAL AND LIFESTYLE STRATEGIES FOR PREVENTION**

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ABSTRACT

Obesity and cardiovascular disease are growing epidemics in the United States, affecting all age groups and ethnicities. With their heavy financial and psychological burden on families and the healthcare system, there is an urgent need for new strategies for prevention and treatment of patients. Herein, I explore the burden that this epidemic has had in the United States, who is affected, and the history of how these diseases have become prevalent. I will focus on some of the potential factors that are associated with disease onset, and consider the best options are available for treatment and prevention. The primary objective of this review is to present underlying issues associated with obesity and cardiovascular disease, an overview on available treatments, and present contemporary evidence-based recommendations for patients.

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# LIST OF ABBREVIATIONS

AE....................Aerobic Exercise

ADP....................Adenosine Diphosphate

AMP....................Adenosine Monophosphate

ATP....................Adenosine Triphosphate

BAT....................Brown Adipose Tissue

BMI....................Body Mass Index

BMR....................Basal Metabolic Rate

BUN....................Blood Urea Nitrogen

CHD....................Coronary Heart Disease

CVD....................Cardiovascular Disease

CVH....................Cardiovascular Health

CR....................Calorie Restriction

CRP....................C-Reactive Protein

DAG....................Diacylglyceride

ER....................Endoplasmic Reticulum

F1P....................Fructose-1-Phosphate

GLUT....................Glucose Transporter Protein

HDL....................High-Density Lipoprotein

HF....................Heart Failure

HFCS....................High-Fructose Corn Syrup

HIIT....................................................................................High Intensity Interval Training

HIIRT............................................................Hight Intensity Interval Resistance Training

IF.........................................................................................................Intermittent Fasting

IMP..............................................................................................Inosine Monophosphate

KHK.................................................................................................................Kenohexokinase

LDL........................................................................................Low-Density Lipoprotein

MAG...........................................................................................................Monoacylglyceride

NHANES............................................National Health and Nutrition Examination Survey

RCT.....................................................................................Randomized Controlled Trial

ROS...............................................................................................Radical Oxygen Species

RT.........................................................................................................Resistance Training

SNP.................................................................................Single-Nucleotide Polymorphism

TAG..............................................................................................................Triacylglyceride

US.......................................................................................................................United States

USDA......................................................................United States Department of Agriculture

WAT..................................................................................................White Adipose Tissue

WC..............................................................................................Waist Circumference

XO.......................................................................................Xanthine Oxidoreductase

# INTRODUCTION

## Introduction and Significance

Obesity and cardiovascular disease (CVD)  are growing and pervasive epidemics in the United States. These two diseases either directly or indirectly impact almost every American, and the annual economic burden of these two exceeds an estimated $500 billion(Virani *et al.,* 2021). Obesity can promote heart disease and many other diseases, such as diabetes and mental health disorders, which increase morbidity and all-cause mortality. CVD is the leading cause of death in the United States accounting for over 600,000 deaths annually (Weir *et al.,* 2016). There is significant need in more effective treatment and prevention, as these two diseases are growing in children and adolescence. Obese adolescents tend to stay obese into adulthood with the occurrence increasing every decade of life. This pattern of behavior is easily passed on to the next generation through feeding and observational learning. There is emerging evidence that feeding behavior from birth impacts the number of Calories that an infant consumes into childhood (Chapparo & Anderson, 2021), which can be an important time for prevention to establish better health outcomes. Finding and establishing a nutritional and lifestyle strategy that can be established from infancy and be able to be perpetuated into childhood and adolescence that is inexpensive and easy to follow is paramount in lowering the impact of obesity and heart disease have on society by lowering the economic burden and reducing the rate of death.

**Literature Review**

Obesity is defined as having a body mass index (BMI) that is in the 95th percentile or greater, or greater than or equal to 30kg/$m^2$ (Bradwisch *et al.,* 2020; Gordon-Larsen *et al.* 2010). BMI is a body measurement that divides the weight of the person by the square of their height in meters. It is used as a convenient tool to categorize people as underweight, normal weight, overweight, or obese while taking into account the amount of body tissue one should have based on height. The prevalence of obesity in the United States has steadily increased over the last three decades, and has reached epidemic proportions, affecting more than 30% of the adult population (Wang and Beydoun, 2007*;* Gordon-Larsen *et al.* 2010*).* This trend is not limited to adults or any one race/ethnicity as it is seen across age groups and race, and is affecting more 18% of children and adolescents (Gordon-Larsen *et al.* 2010, Bradwisch *et al.,* 2020). According to the National Longitudinal Study of Adolescent Health, which tracked a cohort of adolescents and followed their height and weight into their 30s (full range 12-32 years of age) from 1996 to 2008, 90% of obese adolescents remained obese into adulthood, and the prevalence of obesity doubled from their teenage years to early 20s, and doubled again in their second and third decade of life (Gordon-Larsen *et al.* 2010, Figure 1). This highlights that obesity is a growing problem.

CVD, another inflammatory disease that is closely linked to obesity, has a prevalence of 49.2% according to data collected from 2015 to 2018 from the National Health and Nutrition Examination Survey (NHANES)(Virani *et al.,* 2021). The pervasiveness of CVD comprises coronary heart disease (CHD), heart failure (HF), stroke and hypertension, which all together contribute to the deaths of more than 600,000 Americans annually, more than prostate, lung, breast, and colon cancers combined (Weir *et al.,* 2016). CVD had a combined direct and indirect economic impact of over $360 billion per year, while obesity carries an approximate economic burden of $149 billion annually (Rosenthal, 2017). There is a J-shaped association with BMI and risk of stroke, highlighting that these two conditions are linked (Virani *et al.,* 2021). These are both inflammatory diseases that can be treated and prevented with similar or the same therapeutics (Hamilton *et al.,* 2017) simultaneously. Feeding behaviors are impactful on calorie consumption from as early as infancy (Chaparro, 2021). In this review nutritional guidelines for adults from 1980 to 2021 will be examined and distilled towards the aim of developing a nutritional strategy that is easy to follow, inexpensive, and effective in order to decrease the burden of obesity and CVD in the United States.

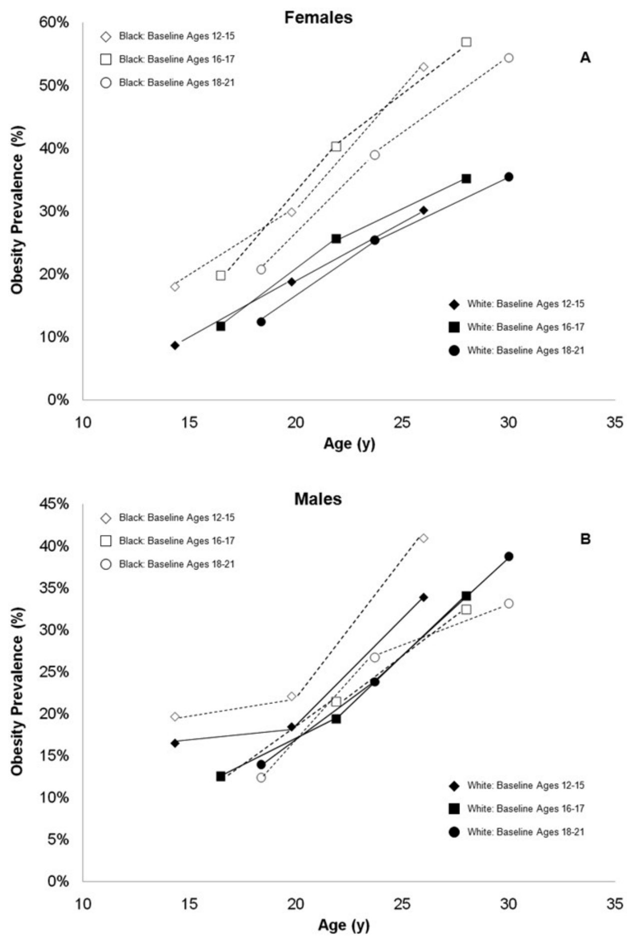


**Figure 1: Obesity Prevalence in Males and Females Across Age (Gordon-Larsen *et al.* 2010). A: Obesity in females subdivided by age and race. B: Obesity in males subdivided by age and race.**

## SPECIFIC AIMS

The goal of this thesis is to explore how nutritional recommendations can shape body composition and health outcomes, with an emphasis on obesity and cardiovascular disease of Americans in the United States from 1980 to 2021. Emphasis needs to placed on, patient compliance to the treatment plan or intervention, and what new discoveries are being made that can reduce the incident rates of obesity and cardiovascular disease, and the overall morbidity of living with these diseases. The focus in this review will be more on lifestyle interventions, but will cover alternatives. The aim is to be able to show the evolution of nutritional knowledge and intervention and assess the future directions of this field that have the strongest evidence to be translated into clinical practice and improve patient health outcomes.

## PUBLISHED STUDIES

### How did the US get to this point?

#### Patterns of Growth in the United States

The BMI of the average American was quite stable from the early 1960s through the beginning of the 1980s, ranging from 25.1 to 25.7 for males and 24.8 to 25.2 for females (Wong *et al.,* 2022). Changes in waist circumference (WC) and body mass increased to a similar degree (Figure 2). What is intriguing is that the slope is steeper for women in regards to the correlation of BMI and WC. During the same time period that BMI increased steadily in adults, childhood overweightness increased by 182% from 1971 to 2000 (Jolliffe, 2004). From 1976-1980 to 2009-2010, childhood and adolescent obesity has increased from 6.5%-18% and 5%-18.3%, respectively (Kumar and Kelly, 2016). In 1998 childhood obesity had a prevalence of 11% (Ogden *et al.,* 2002) and in 2016 obesity in the age group of 10-17 has increased to 32% of the national population (Zgodic *et al.,* 2021). Other sources have different percentages, the CDC notes that childhood obesity in 2016 was 18.5% (Hales *et al.,* 2017), and the Mayo Clinic is consistent with 18.3%. In addition, according to the CDC obesity has affected minority populations differently: among men non-Hispanic whites and blacks have similar rates of obesity, while Hispanics and Asians have a rate of obesity significantly greater and lower, respectively than the preceding groups. In women the prevalence is similar across age groups except that non-Hispanic black women have the highest prevalence of all groups (Hales *et al.,* 2017).

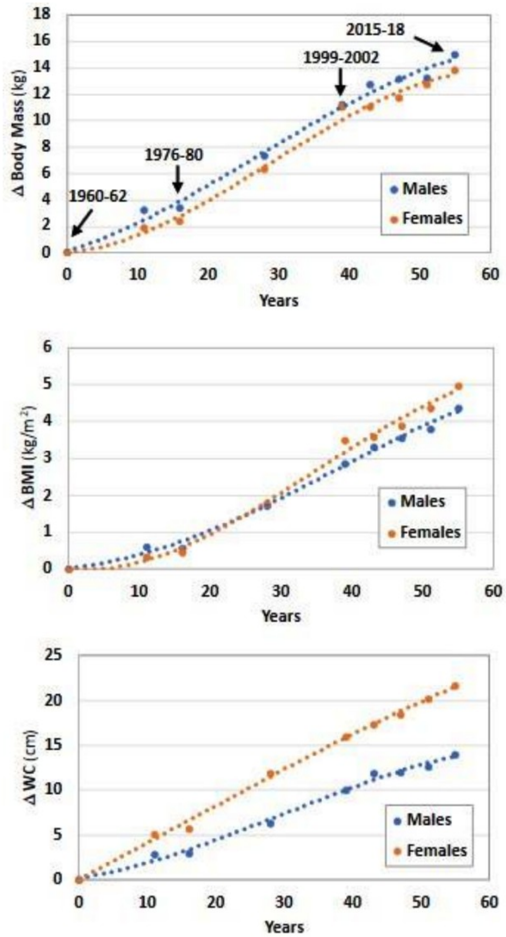


**Figure 2: Trends of BMI, WC, and Body Mass Across Decades. Top: Change in Body Mass Stratified by Sex; Middle: Change in BMI Stratified by Sex; Bottom: Change in WC Stratified by Sex (Wong *et al.,* 2022).**

These trends are also similar in children across racial groups. These data show that this is a universal problem in the United States and not isolated to an age or racial group in the country, and that the problem is worsening. What is alarming is that childhood obesity seemingly does not decrease in adulthood and remains steady in the individual (Kumar and Kelly, 2016).

In contrast, the rate of death caused by CVD has decreased significantly since the 1980s (Van Dyke *etal.,* 2018), showing an inverse relationship between CVD deaths and rates of obesity at the national level. While the rate of obesity has dramatically increased, the prevalence of obese persons to have high cholesterol, high blood pressure, and current smokers have dramatically decreased according to the National Health and Nutrition Examination Survey (NHANES) (Gregg, *et al,.* 2005). These authors correlated this phenomenon to an increase use of anti-hypertensive and lipid lowering medications in obese and overweight individuals when compared to lean individuals. The authors, however, did not discuss the increase in prevalence of high blood pressure and cholesterol from samplings from 1988-1994 to 1999-2000 across all BMI measures despite the largest increase in anti-hypertensive and lipid lowering medications in that same time frame. Another NHANES was performed covering 1999-2010 to follow-up on these trends comparing CVD risk factors with ranging BMIs (Saydah *et al.,* 2014). This survey showed an increased prevalence of CVD risk factors as BMI increased. There was also an increase in individuals with multiple risk factors for CVD risk factors in obese persons while there was a decrease in the normal and overweight groups in the same timeframe. This suggests that even though certain risk factors for CVD are being treated and are under control, other risk factors for CVD such as diabetes, hypertension and dyslipidemia are increasing in individuals who have the highest BMI. With the United States getting heavier year over year,. a review of what changes have occurred during this timeframe and what possible contributing factors to these diseases is necessary in order to find solutions.

**What are the Possible Contributions to this Growth?**

**Fructose**

Fructose is the main sweetener in soft drinks, fruit juices, and many dessert items such as ice cream and popsicles. Fructose (such as high fructose corn syrup (HFCS)) has been replacing table sugar (as sucrose, a disaccharide consisting of one molecule of glucose and fructose) in the American diet since the late 1960s in order to make products cheaper, and the consumption has increased over 100-fold (Russo *et al.,* 2020; Jang *et al.,* 2020). Fructose is similar to glucose in that it is common in a natural diet and are absorbed directly into the blood stream via intestinal epithelium through glucose transport proteins (GLUT) 5 and 2. However, once absorbed into the blood their metabolism can differ greatly. If fructose is consumed in moderate amounts, less than 1g/kg of body weight, it is converted into glucose and does not pose a significant amount of stress on the metabolism (Muriel *et al.,* 2021). However, in high quantities the metabolism is much different and activates numerous pathways. When fructose enters the enterocyte, the cell the lines the intestines, in high amounts it is converted into fructose-1-phosephate (F1P) via the enzyme kenohexokinase (KHK) (Jang *et al.,* 2020). The conversion of fructose to F1P by the removal of a phosphate group from adenosinetriphosphate (ATP) with the byproduct being adenosinediphosphate (ADP), depletes ATP levels in the target organ, primarily the liver. When ATP is depleted, and ADP accumulates the environment is favorable for the reaction of 2ADP to combine to make ATP and producing adenosine monophosphate (AMP). This helps restore ATP concentrations, while also contributing to another pathway that can lead to problems for health. The increase of AMP results in the activation of AMP deaminase which converts AMP into inosine monophosphate (IMP). The phosphate group is subsequently removed by water to form inosine and the ribose group on the inosine is removed by another phosphate group resulting in hypoxanthine. Hypoxanthine is then converted to xanthine via xanthine oxidoreductase (XO), and xanthine is then converted to uric acid again by XO (Muriel *et al,.*2021)(Figure 3). This pathway demonstrates that with a significant increase in the intake of HFCS containing drinks and food, there will also be an increase in circulating uric acid levels. Uric acid itself is not harmful, and has many functions including its antioxidant properties in the central nervous system (Bjornstad *et al.,* 2015). Uric acid also has a protective role in blood plasma where it can prevent lipid oxidation of the cell membranes of erythrocytes, which are red blood cells, by oxygen free radicals in the presence of vitamin C under normal physiological concentrations, ranging from 155–339 μmol/L in premenopausal women and 208–416 μmol/L in men (Sautin & Johnson, 2008; Ndrepepa, 2018). However, high uric acid has pro-oxidant and pro-inflammatory effects particularly on low density lipoproteins (LDLs) and cell membranes (Sautin & Johnson, 2008) by reactive oxygen species (ROS) and peroxides generated during the formation of urate. The main issue with the increasing prevalence of fructose as a sweetener and the resulting conversion to uric acid is that the ROS generated has been linked to obesity and CVS (Ndrepepa, 2018; Sievenpiper *et al.,* 2012). Weight gain associated with high fructose consumption has been linked to excess calories and drinking high fructose beverages, an increasing trend in the US. It has also been shown that gout, a condition brought about by increased uric acid burden, and hyperuricemia has been increasing in older populations of both men and women (Wallace

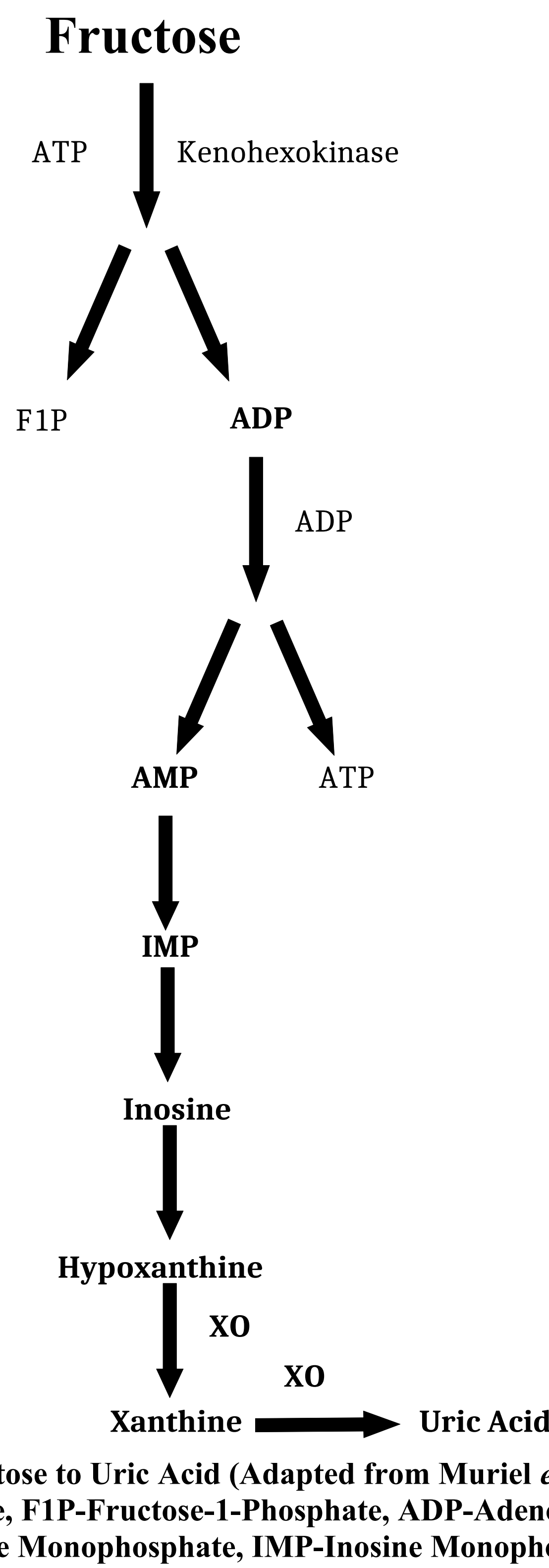


**Figure 3. Pathway from Fructose to Uric Acid (Adapted from Muriel *et al.,* 2021.). ATP-Adenosine Triphosphate, F1P-Fructose-1-Phosphate, ADP-Adenosine Diphosphate, AMP-Adenosine Monophosphate, IMP-Inosine Monophosphate, XO-Xanthine Oxidoreductase**

*et al.,* 2004; Ndrepepa, 2018). There is controversy as to what the cause of this increase is, with studies suggesting that it may be a result of increased life expectancy and increased use of blood pressure medication (Ndrepepa, 2018), however, with the increased proportion of carbohydrates in the human diet being from fructose and HFCS there is reason to believe that the consumption is one contributing factor to this phenomenon (Caliceti *et al.,* 2017; Cox *et al.,* 2012). This is illustrated in Figure 4A showing that the proportion of sugar that is from HFCS has increased dramatically from 1970 to 2006 from close to 0 g/day to over 50 g/day, making it 50% consumption (Tappy and Lê., 2010). In that same time period calorie consumption has also increased from just over 2,000 Calories to over 2,500 Calories. Mostly from increases in sugar, fats, and cereals. Taken together, the increase in HFCS consumption, which leads to excessive conversion to uric acid, and the increase in Calories consumed by Americans can be demonstrated to be contributing factors to the obesity and CVD epidemics plaguing the US.

Fructose has a potential role in appetite suppressing subsequent caloric intake but this effect is hampered when fructose is mixed with a meal (Tappy & Lê, 2010). Not only does intake of food with fructose containing drinks increase the amount of Calories consumed, fructose has been shown to be less efficient than glucose in stimulating after-meal ghrelin, a hormone partly responsible for appetite suppression, and leptin, a hormone secreted by adipocytes known for suppressing appetite (Tappy & Lê, 2010). This can be explained by the properties of fructose which has a glycemic index that is

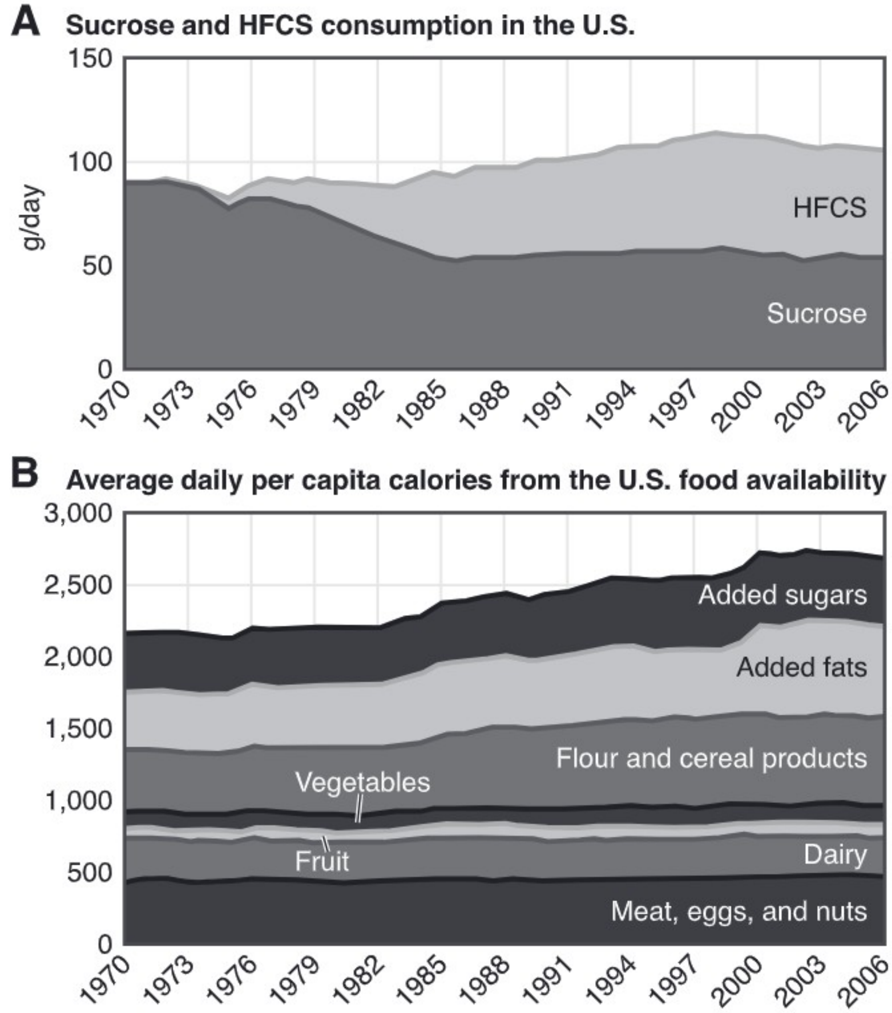


**Figure 4. A. Proportion of sugar consumption that is HFCS increasing over time. B. Calories consumed in US diet increasing over time. Taken from Tappy and Lê, 2010.**

nearly 5 times (4.81 in one study) less than glucose (Wiebe *et al.,* 2011), meaning it takes 5 times the amount of fructose to increase blood sugar than glucose. This was illustrated by Teff *et al.* where they gave women a beverage with every meal containing either high glucose or high fructose at the same mmol concentration and monitored their

blood sugars over a 24-hour period (Figure 5). There was a significant difference in blood glucose levels between the two groups showing lower levels in the fructose group. Circulating blood sugar concentrations monitors energy load and is directly related to insulin secretion. Insulin is a hormone that responds
to circulating blood sugars and is essential in maintaining blood sugars within a normal range, as evident by patients who have Type-I diabetes and are unable to secrete insulin or regulate their blood sugar levels. The same group showed that high fructose beverages with a meal had a dramatic difference in blood insulin levels when compared to the group that was given high glucose beverages (Teff *et al.,* 2004; Fig. 6). Similarly, another group aggregated studies that correlated the subjective experience of satiety with blood glucose levels and they showed that short term insulin levels were significantly correlated with the feeling of satiety in normal weight individuals but not overweight and obese individuals (Flint *et al.,* 2007). Since fructose is not eliciting as much fluctuation in blood sugars when compared to glucose, and the body is responding by releasing less insulin and less insulin can lead to a lesser feeling of satiety, there is reason to support that insulin response to fructose is a contributing factor in overeating when consumed with meals. There seems to be some contribution to the obesity and CVD epidemics in the US by the increasing and overconsumption of fructose, especially as HFCS in beverages and sweetened foods. In the preceding decades fructose has become the dominant form of sugar consumed in the US, and has been shown to increase uric acid levels in the body (Cox *et al.,* 2012). Excessive uric acid contributes to risk factors leading to CVD including inflammation, hypertension, and oxidation of blood vessels

and LDLs through ROS generation. In addition to uric acid production, fructose is associated with weight gain due to excess Calories and the potential for short term inactivation of appetite suppression mechanisms including leptin increases and rises

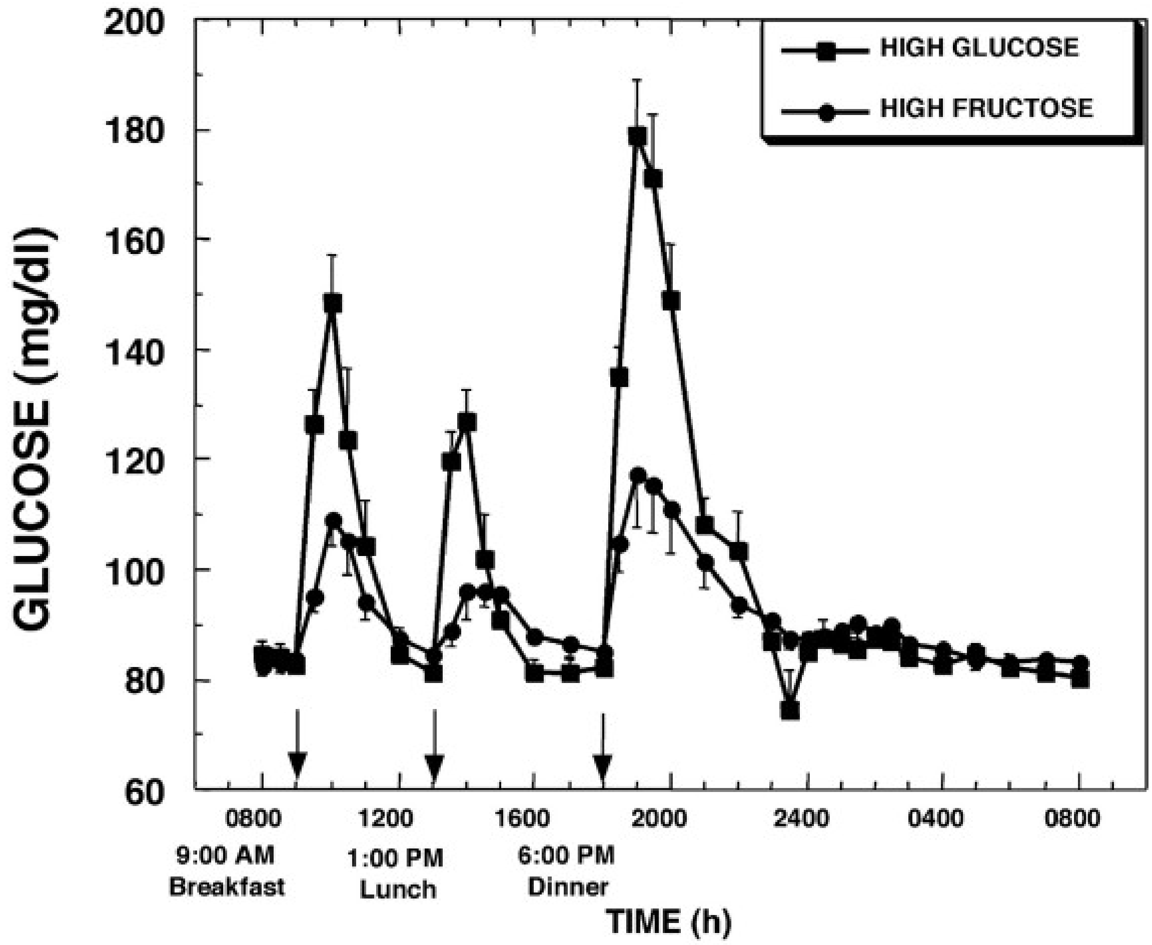


**Figure 5. Effects of high glucose or high fructose beverages taken with a meal on post-prandial blood glucose levels. Taken from Teff *et al.,* 2004.**

of insulin in response to blood sugar changes. However when fructose is consumed as sucrose, or table sugar, in small amounts or is consumed as fruit where there is plenty of fiber to slow the absorption of it thereby allowing the liver to be able to metabolize the relatively low amount in fruits, there seems to be no meaningful changes in health, so

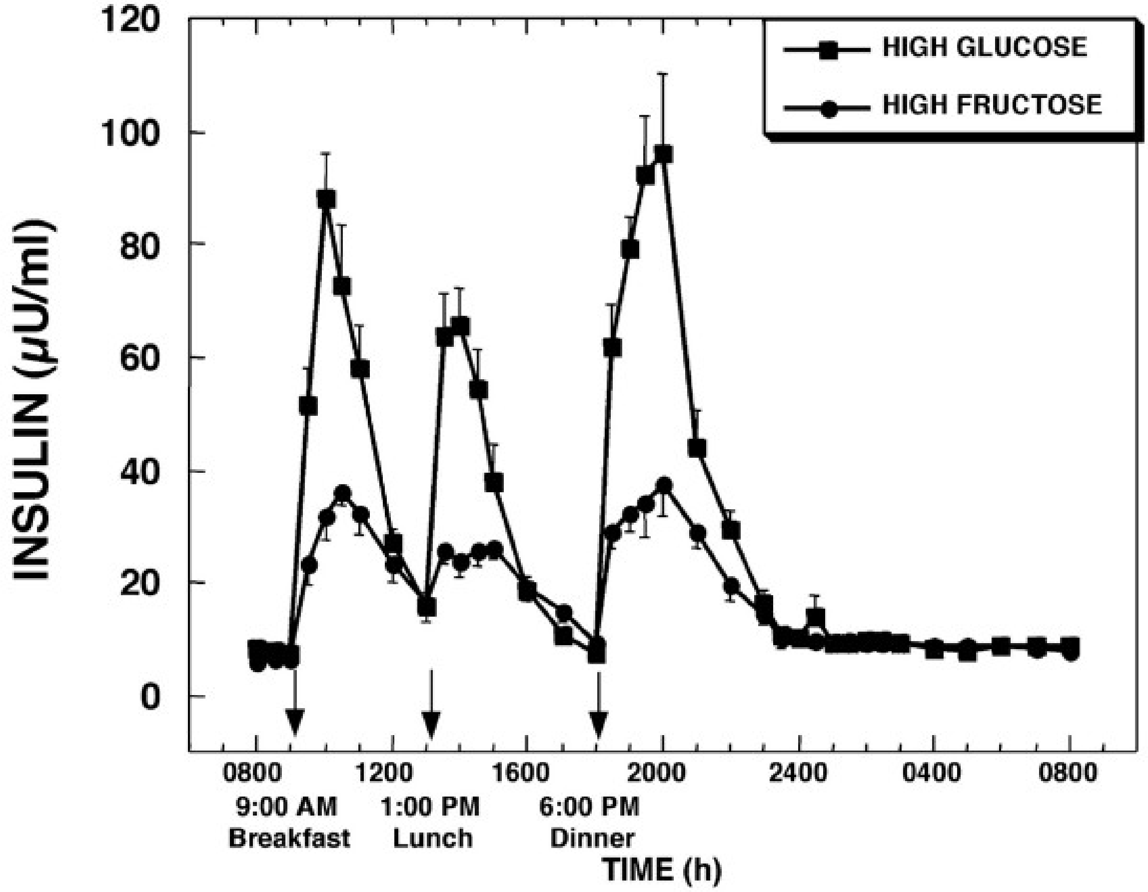


**Figure 6. The effects of high glucose or high fructose beverages taken with a meal on post-prandial blood insulin levels. Taken from Teff *et al.,* 2004.**

fructose in itself is not the cause of the health epidemics in the US, but is a contributing factor that needs more attention from the scientific community and medical doctors who need to be able to inform their patients of the potential problems that a high fructose diet can lead to. Fructose is not nutritional leading to major contributions to obesity and CVD. Another potential contribution may be the increase in fad diets and marketable diets such as the low-fat diet that has swept across the US.

**Low-Fat Diets**

Before Americans became increasingly overweight nutritionists started suggesting that fat the underlying cause of individuals becoming overweight and obese. As this became popular many different companies started to advertise and change their products into low-fat alternatives, with margarine and food labels on display telling consumers that their products are low-fat or fat-free. However, Americans began to gain weight and fat on their bodies (Berg, 2008). Here I will explore how these diets have been contributing to the epidemic of obesity and CVD in the US.

The beginning of the low-fat diet being used as a way to promote weight loss and to reduce the incident of CVD started with observations made in the 1940s and 1950s by scientists who associated diets that contain high saturated fats, fats that do not contain double bonds between their carbon tails, and cholesterol as the major cause of CVD in the US. These studies came into being because at the time CVD was the leading cause of death and there was an urgent need to find preventative strategies in order to curtail the incidence of death (Berg, 2008) and this became known as the diet-heart hypothesis- high fat diets lead to an unhealthy, diseased heart. In 1983 an association study correlated that obesity itself was a risk factor for CVD (Hubert *et al.,* 1983) and one of the conclusions made from this is that a low-fat diet could not only prevent CVD but also be used as a weight loss treatment to reduce obesity levels, thereby treating two risk factors at once in the hope of reducing CVD related mortality. Through the 2000s the US had been increasingly convinced that the diseases of obesity and CVD was caused by dietary fat intake (Berg, 2008). This created opportunity for the food industry corporations to profit from the new consensus and the development of low-fat and fat-free products had exploded and were marketed as heart healthy and weight reducing foods. One way the food industries reduced fat in their products while keeping them satisfying for their customers was to replace the fats with sugars (Berg, 2008). As what has been explored above, increasing sugars is not associated with reducing weight or heart disease and can actually exacerbate the problem. Nonetheless, federal government entities like the United States Department of Agriculture (USDA) and corporations inundated Americans into eating primarily low-fat and higher carbohydrate meals in the 1980s and 1990s, the same time seen above when Americans had gained the most weight in decades, for the purpose of reducing weight and CVD in the US. The recommendations included heavily processed foods that have been stripped of its fat and then enhanced with sugars to add taste and calories. In 1992 the USDA released a food pyramid (Fig. 7) showing their recommendations for what Americans should eat.

This pyramid shows a diet that is very heavy in carbohydrates and refined foods such as breads, pastas and cereals. The concern about this other than raising the consumption of carbohydrates is the promotion of processed foods in contrast to natural foods. The food pyramid of 1992 would have Americans eating more breads, pasta, and cereals than vegetables, fruits and meats combined. Over 40% of the dietary recommendations of the pyramid are from processed foods for the sake of reducing fat intake as much as possible in the hope of reducing obesity and CVD. A review in 2014 studied adherence to the recommended food pyramids and demonstrated that there is low adherence to fruit, vegetable, and dairy servings while meat and grain recommendations were the most likely to be met (Haack & Byker, 2014). As mentioned above this is the period of time where the greatest rise in obesity and CVD occurred, so the question that is being explored further here is does dietary fat intake actually cause an increase in obesity? Enough time has passed since the introduction of the low-fat diet for the evidence to accumulate.

To answer these questions one must know what happens when dietary fat is consumed. The dietary fats of interest here are triacylglycerols (TAGs) or more commonly triglycerides, which consist of a glycerol backbone, a three carbon sugar alcohol, connecting three fatty acids via ester bonds (Fig. 8) and are the dominant form of fat consumed in the human diet. When fat enters is chewed the surface area of the fat exposed to digestive enzymes is increased to enable faster and more efficient digestion. Digestive enzymes called lipases are excreted from the mouth and stomach and work on the ingested TAG to break it down into diacyleglycerols (DAGs) and free fatty acids within the stomach, digesting around 10-30% of the ingestedTAGs being consumed (Mu & Høy, 2004). This partial digestion in the stomach allows the normally water insoluble TAG to become more soluble in the DAG and free fatty acid form, which enables further lipases downstream from the stomach to work on theremaining fat more effectively. Once the food bolus exits the stomach and enters the duodenum another mechanism is used to further enable TAGs become more soluble. The gall bladder is triggered to release its bile acids where it mixes with the bolus and further emulsifies the fat present. With even more surface area exposed, the pancreas expels lipase into the duodenum to hydrolyze the remaining of the TAGs, DAGs and free fatty acids (Mu & Høy, 2004). Furthermore, the bile acids enable the micellization, a process of aggregating fatty acids, TAGs, DAGs

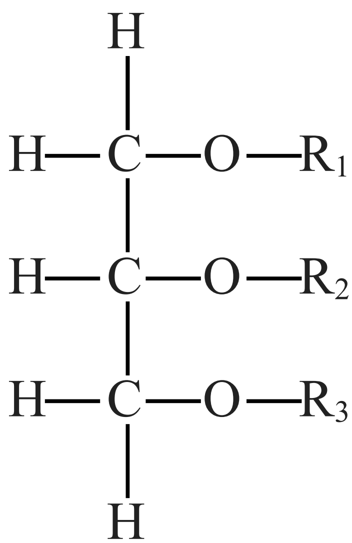

**Figure 7. The General Structure of a TAG. R representing fatty acid tails attached to the three-carbon glycerol**

and fat soluble vitamins together, of the fat soluble components in the duodenum to prepare for absorption across the intestinal wall (Iqbal & Hussain, 2009). Thereafter, TAGs that remain are mostly absorbed in the upper jejunum where pancreatic lipases hydrolyze them into predominantly 2-monoacylglycerols (2-MAGs) and free fatty acids, and the 2-MAG can be further processed into free glycerol and free fatty acids (Iqbal & Hussain, 2009). These MAGs and free fatty acids are taken in by the enterocyte that makes up the luminal wall via diffusion and protein dependent transporters. Once inside of the enterocyte the TAGs are re-synthesized in a stepwise manner that that forms DAG from MAG and subsequently to TAGs within the cytosol and the endoplasmic reticulum (ER)(Iqbal & Hussain, 2009). TAGs made within the enterocyte are then used to form chylomicrons, lipoproteins that carry TAGs from the intestine to the blood stream in order to deliver TAGs, phospholipids, fat-soluble vitamins, cholesterol and proteins (Iqbal & Hussain, 2009). The chylomicrons enter the blood stream via intestinal lacteals that connect with the lymphatic system and enter the blood stream through the thoracic duct in the subclavian vein where they can then enter the liver to be metabolized (Zhang *et al.,* 2018).

In the early 2000s a group (Yancy *et al.,* 2004) performed a randomized controlled trial (RCT) that compared the effects of a low-fat vs. a low carbohydrate diet for overweight individuals over a 24 week period. To be included in the study, participants needed to have higher than normal levels of, LDLs, or triglycerides with no serious medical conditions and on no therapeutic intervention. Both groups were given exercise recommendations, group meetings and diet instruction. The primary outcome measurements were body weight and BMI, and secondary outcome measurements were adherence, diet composition, ketonuria, body composition, vital signs, serum lipids and lipoproteins, metabolic health, and adverse effects. Overall, the adherence to the low-carbohydrate diet compared to the low-fat diet was significantly different with 76% completing the low-carbohydrate diet while 57% completed the low-fat diet. Both groups were able to lose weight, however, the low-carbohydrate group lost on average of 12 kg while the low-fat group lost 6.5 kg. The composition of food was 8% of the diet of the low-carbohydrate group was carbohydrate while 52% of the low-fat group's diet was carbohydrate, and the percentage of fat in the diets were 68% vs 29% in the low-carbohydrate and low-fat, respectively. Within the first two weeks of the study, 86% of the participants in the low-carbohydrate had a urinary ketone level described as trace or greater, suggesting that the group adhered to the diet, and decreased to 42% at the study's end. Both groups lost a similar amount of fat mass, and both groups had a similar improvement in blood pressure and pulse rates. For serum lipids and lipoproteins the low-carbohydrate group had significant changes compared to the low-fat group in that triglycerides were lower, high-density lipoprotein (HDL) cholesterol was greater, ratio of cholesterol to HDL cholesterol was improved, and ratio of triglycerides to HDL cholesterol was improved. Total cholesterol in the low-fat group was lower but not significantly different compared to the low-carbohydrate group. For adverse effects there were significantly more effects in the low-carbohydrate group. This result is curious because the adherence to the low-carbohydrate diet was much higher than the low-fat diet. Overall, when these methods are compared both result in weight loss, with carbohydrate restriction yielding a greater amount of weight loss, a greater improvement of blood lipid levels, while having greater adherence even with greater side effects. A key difference between the group was how Calories were being restricted, the low-fat group had a set amount of Calories which was 500 to 1000 Calories less than what they needed for weight maintenance while the low-carbohydrate group was able to self-restrict, meaning they did not have a Calorie restriction, only a carbohydrate restriction. The average amount of Calories consumed in the low-carbohydrate group was 1461, while the low-fat group was 1502. This suggests that a diet consisting predominantly of fat is more satiating than a carbohydrate dominant diet. The authors suggested that this could be the result of the increased thermogenic effects of a higher protein diet, however the amount of protein consumed was 19% and 26% by the low-fat and low-carbohydrate groups respectively. This study was limited by the amount of time for follow-up as 24 weeks is not adequate time to fully parse out what can be a lasting lifestyle change.

Another RCT was conducted comparing low-fat and low-carbohydrate diets (Gardner *et al.,* 2018) using 600 participants with a follow-up period of 12 months. The study aimed to explore the effects of genotype patterns and insulin secretion on weight loss and as to what diet is appropriate for the individuals based on their genotype. The composition of the foods for the low-carbohydrate and low-fat diets were as follows: 30% vs 48% carbohydrate, 45% vs 29% for fats, and 23% vs 21% for protein, respectively. The participants were aged 18 to 50 years old, men or premenopausal women, and were without uncontrolled hypertension, metabolic disease, diabetes, cancer, heart, renal, or liver disease, and not pregnant or lactating. Medications excluded were hypoglycemic, lipid-lowering, antihypertensive, or antipsychotic drugs. Other drugs were allowed if the participants were stable and on them for over 3 months prior to baseline. For genotype patterns the group was focused on three genes with single-nucleotide polymorphisms (SNPs) (*PPARG, ADRB2,* and *FABP*) to determine if they play a role in weight loss success when assigned to either a low-carbohydrate or low-fat diet, based on previous studies that showed a significant interaction. The participants were subjected to glucose tolerance tests at baseline, 6 months, and 12 months to assess insulin sensitivity 30 minutes after 75 grams of oral glucose consumption in order to assess if insulin sensitivity has a predictive factor in weight loss. After 12 months both groups lost a similar amount of weight with the low-fat group losing on average 5.3 kg and the low-carbohydrate group losing 6 kg. In this study the amount of Calories consumed was more controlled than in the prior study, with both groups on average reducing the amount of Calories consumed by 500 to 600, which could explain why weight loss was not statistically different. For genotype interaction, there was no association between the SNPs and weight loss across both groups suggesting that the weight loss was mostly the effect from the diets than on the genotype of the individuals within the groups. Similarly, the authors found no association between insulin resistance, the type of diet and weight loss suggesting that the weight loss was due to diet and not changes in participant insulin sensitivity. The authors also examined the effects these diets had on blood lipid levels and lipoproteins similar to the previous study above and showed that HDL cholesterol was significantly higher for the low-carbohydrate group when compared to the low-fat group, triglycerides were significantly lower for the low-carbohydrate group compared to the low-fat group, and LDL cholesterol was significantly lower in the low-fat group compared to the low-carbohydrate group. Similar results across both groups were shown in regard to blood pressure, insulin, glucose levels, BMI, body fat percentage, and waist circumference. Adverse effects were similar across both groups as well. Taken together these results show that a longer term study comparing low-carbohydrate vs low-fat diets yield similar weight loss results and a more dramatic improvement in blood lipid profiles with a low-carbohydrate with the exception of LDL cholesterol. This study had a less dramatic difference in the macronutrient profiles between the two groups when compared to Yancy *et al.,* but yielded similar results suggesting that there may be an ideal amount of fat composition being consumed for body weight reduction to increase with low-carbohydrate diets. A one year followup study like Gardner *et al* has done is a good starting point to explore how diets affect people in terms of weight reduction and blood profiles but there needs to be longer studies done in order to see the longer term effects these changes have.

In 2008 an RCT was published by Shai *et al,* that compared three different diets: low-fat with restricted Calories, Mediterranean with restricted Calorie, and low-carbohydrate with no Calorie restriction. This study followed 322 participants for a total time of 24 months. Participants were between the ages of 40 and 65 and either had a BMI of 27 or greater, or had type II diabetes or CVD regardless of BMI or age. The participants could not be pregnant or lactating, or have a serum creatinine level 2 mg/dL or greater, liver function tests must be normal and have good gastrointestinal health in order to eat the diets. The participants could also not have cancer or participate in other diet trials. Each group was divided into subgroups and were assigned a dietician to help them through the trials and met with them a total of 18 times during the 24 month study. The low-fat diet was based on the American Heart Association guidelines and the goal was for women to consume 1500 Cal./day while men consumed 1800 Cal./day with 30% of Calories coming from fat, 10% from saturated fat, and a max of 300 mg cholesterol per day. The Mediterranean diet had the same Calorie restrictions as the low-fat group but were allowed 35% of Calories from fat with its main source coming from olive oil and nuts. The low-carbohydrate had no Calorie restriction but only a carbohydrate restriction of 20 grams a day for the first 2 months and then a gradual increase to 120 grams to maintain weight loss. All groups were instructed to eat primarily whole foods and avoided processed foods. Weight was measured for every group once a month, blood pressure was measured every 3 months, and blood samples were taken at 6, 12, and 24 months after baseline. After the first 12 months overall adherence to the study was 95.4%, but then dropped to 84.6% at the 24 month mark. For each group the adherence was 90.4% in the low-fat group, 85.3% in the Mediterranean group, and 78% in the low-carbohydrate group, showing a difference from the 24 week study by Yancy *et al.* where the adherence to the low-carbohydrate group was higher than low-fat. The authors report many levels of results for weight loss which is the primary outcome measurement. For all 322 participants, regardless if they completed the full 24 months of the study, weight loss was experienced in all groups with 2.9 kg loss in the low-fat group, 4.4 kg loss in the Mediterranean group, and 4.7 kg loss in the low-carbohydrate group. This study looked at the difference between males and females as 86% of these participants were male. For the males weight loss was achieved in all groups at 3.4, 4, and 4.9 kg for low-fat, Mediterranean and low-carbohydrate, respectively. For females the weight loss was 0.1, 6.2, and 2.4 kg for the respective groups. This shows a differential effect of sex on weight loss and had a significant interaction between diet type and sex, suggesting that depending on the sex of the individual there may be value in tailoring a weight loss diet strategy that meets their needs. Of the 272 individuals who completed the full 24 month study weight loss in the respective groups were 3.3, 4.6, and 5.5 kg, with a significant difference between the low-fat and low-carbohydrate groups at 24 months. This result is interesting because the low-carbohydrate group was not Calorie restricted and was able to self modulate the amount of food they were eating, which is similar to the 24 week study by Yancy *et al* suggesting again that a low-carbohydrate diet may be more satiating, but more work needs to be done to explore that. It may also suggest that food choices were scarce. Conversely the low-carbohydrate group had the lowest adherence so other factors may need to be investigated.

This study showed that low-carbohydrate diets increase HDL cholesterol significantly more than low-fat diets, and similarly decrease triglycerides. The Mediterranean diet performed similarly to the low-fat diet in terms of HDL cholesterol and triglycerides and were not statistically different from one another. Conversely, while the other studies explored show low-carbohydrate groups increase LDL cholesterol, this study showed no significant difference between any of the groups. All groups showed an improvement in the ratio of total cholesterol to HDL cholesterol, with the most significant change coming for the low-carbohydrate group while having significant difference between the low-fat group. This study looked further at other biomarkers for health in addition to what has already been explored. One of the markers is C-reactive protein (CRP) which is a measure of systemic inflammation. Both the low-carbohydrate and Mediterranean group had a significant decrease in CRP while the low-fat group had a slight decrease, however there was no statistical significance between the three groups. Other markers adiponectin and leptin decreased significantly in all groups and were not different from each other. There was a significant interaction with a decrease of leptin low-carbohydrate diet and sex when compared to the low-fat group, showing the difference between sexes. For participants with type II diabetes, their fasting glucose was significantly reduced only with the Mediterranean diet. Insulin levels were also decreased across groups with or without type II diabetes. For HbA1c, a proxy used to represent the 3 month average of blood glucose levels, only the diabetics on the low-carbohydrate diet had a significant reduction. Liver function tests were significantly lower than at base line only in the Mediterranean and low-carbohydrate groups. Taken together this study undertook a tremendous challenge by recruiting so many participants and following them for 2 years. These large RCTs provide the level of evidence that enable medical professionals to see the benefits and adverse effects of a dietary intervention. This study provided considerable amounts of data and supported findings in prior studies.

Firstly, a low-carbohydrate diet is comparable to a low-fat diet in terms of weight loss, and may even be superior in some circumstances for men. Secondly, a low-carbohydrate diet with higher fat consumption has been shown to be heart healthy evidenced by lipid profiles and by the reduction in blood pressure and pulse rates. Thirdly, in two of these studies the low-carbohydrate group was not calorie restricted but elicited greater weight loss than a Calorie restricted low-fat diet. More studies are needed to find what the possible mechanism for this result is. Table 1 shows a summary of the key data from the three studies that have been explored comparing the results that were given from low-fat and low-carbohydrate diets.

According to the results of these three studies, there is little reason for concern that dietary fat consumption will lead to obesity and CVD. These data show that both of these can potentially be treated by diets that are low in carbohydrate and higher in fat compared with low-fat diets, with the draw back of potential complications that can arise from an increase in LDL cholesterol. These studies were RCTs of varying lengths of time with slightly different proportions of macronutrients in the low-carbohydrate groups, and with these in mind what do more recent meta-analyses show when comparing low-fat and low-carbohydrate diets?

| **Author** | Yancy *et al.,* 2004 | Gardner *et al.,* 2018 | Shai *et al.,* 2008 |
|---|---|---|---|
| **Low-Carbohydrate Macronutrients** | F: 68%; P: 26%; C:8% | F: 45%; P: 23%; C: 30% | F: 39%; P: 22%; C: 40% |
| **Low-Fat Macronutrients** | F: 29%; P: 19%; C: 52% | F: 29%; P: 21%; C: 48% | F: 30%; P: 19%; C: 51% |
| **Low-Carbohydrate Weight Loss** | -12 kg | -6.0 kg | -5.5 kg |
| **Low-Fat Weight Loss** | -6.5 kg | -5.3 kg | -3.3 kg |
| **Low-Carbohydrate HDL Cholesterol (mg/dl)** | +5.5 | +2.64 | +8.4 |
| **Low-Fat Lipid HDL Cholesterol (mg/dl)** | -1.6 | +0.40 | +6.4 |
| **Low-Carbohydrate LDL Cholesterol (mg/dl)** | +1.6 | +3.62 | -3.0 |
| **Low-Fat Lipid LDL Cholesterol (mg/dl)** | -7.4 | -2.12 | -0.05 |
| **Low-Carbohydrate Triglycerides (mg/dl)** | -74.2 | -28.20 | -23.7 |
| **Low-Fat Triglycerides (mg/dl)** | -27.9 | -9.95 | -2.8 |

**Table 1. Results comparing low-carbohydrate vs low-fat diets.**

In a recent meta-analysis performed in 2020 (Chawla *et al.,* 2020) the group compiled a total of 38 studies with 6499 total participants across them and compared the results of low-fat vs low-carbohydrate diets with regards to weight loss and blood lipid profiles. The group found that weight loss favored the low-carbohydrate diets overall by a weight reduction of 1 kg. While looking at the lipid profiles of participants across the studies they found what has been reported here that the low-carbohydrate diets resulted in significant improvements in HDL cholesterol and TAGs, while low-fat diets had greater improvements in LDL and total cholesterol. The authors comment that the weight loss was greater in the short term as studies that were analyzed that were greater than 12 months showed a reduction in weight loss on low-carbohydrate diets, probably due to lower adherence in this time frame, however the authors only had two studies of greater than 12 months to analyze so the results for their analysis could be different with more quality long term studies. Nevertheless, this meta-analysis gives support to the idea that higher fat, low-carbohydrate diets are not causing obesity and heart disease, as suggested by the studies detailed here.

In another more recent meta-analysis in 2021 (Yang *et al.,* 2021) the group analyzed literature that compared results from low-carbohydrate vs low-fat diets in terms of weight loss, lipid profiles, blood pressure, glucose and fat mass. They combined data from eleven studies utilizing 739 participants and further found support to the above meta-analysis and the three studies previously explored. Low-carbohydrate, high-fat diets resulted in significantly more weight loss than low-fat, high-carbohydrate diets with an average of 1.1 kg more weight loss for the low-carbohydrate groups. When comparing the lipid profiles, the low-carbohydrate diet raised HDL more than low-fat, while low-fat had a greater decrease in total and LDL cholesterol. Interestingly, there were no significant differences in TAG levels between the two diets, and differences in blood pressure, glucose levels, and fat mass were non-significant. Overall, the data supports that low-carbohydrate diets with higher fat contents are either just as or more successful as low-fat diets at lowering obesity and CVD parameters.

There have been numerous studies that have examined the relationships between diets with different macronutrient profiles. Our discussion with fats started with how dietary fat was a nutrient that is a major cause of obesity and CVD and how After examining RCTs and meta-analyses that have looked at the relationship between low-carbohydrate, high fat diets and weight loss and CVD risk factors there is reason to believe that these previous beliefs are unfounded. From the 1980s to the early 2000s, obesity and CVD had risen more than any other time in American history, when the low-fat diet was recommended the most and food companies were taking out fat of their products and labeling them fat-free or low-fat to show they were healthy. A growing concern that additional processing of foods and the adding of simple sugars such as HFCS to drinks and other packaged foods that may have had more of an impact on overall health. More research needs to be done to investigate if there is a causal link between HFCS and obesity and CVD. The low-fat food shift could have caused more harm than good, however according to the data presented if a low-fat diet is comprised of whole, healthy foods as they were in these studies then it too is can help people lose weight and have enormous benefit to human health. The same goes for low-carbohydrate, high-fat diets, if they are comprised of ultra-processed foods and foods fried in oils that contain *trans* fats then the benefits that have been outlined will not manifest.

**What are Possible Solutions?**

Since it has been shown that the increase in processed, sugary foods being consumed by Americans is at least somewhat responsible for the epidemics of obesity and CVD, what are some solutions? What can Americans do to treat or prevent these problems? The goal is look at the literature and see what populations may benefit from certain interventions such as exercise type, certain drugs, and lifestyle changes.

**Exercise Programs**

It has long been known that exercise is essential for optimal human health (JAMA, 1964), however exercise is a very general term. Exercise encompasses many different types of activities whether it be resistance training with weights and bands, or cardiovascular training such as running, biking and rowing. Even within these distinct types of exercise there are variations such as light or heavy weights for resistance training, or low vs high intensity for cardiovascular training. Each have their own benefits and drawbacks. Here the goal is explore what the literature says about these different kinds of training routines with regards to losing weight and improving cardiovascular health (CVH) in the long term as a form of treatment that may help inform physicians and health professionals what may be best for their patients.

A study was performed in 2017 (Villareal *et al.,* 2017) that took a total of 160 participants (141 completed the program) that were split into three groups, an aerobic exercise (AE) only, resistance training (RT) only, and a combination of both for 26 weeks. The participants were 65 years or older and obese (BMI of ≥30), and were excluded if they had severe cardiopulmonary disease, muscle or neuromuscular impairments, cognitive impairments, or on medication for bone mineralization. Across the groups the diet composition was the same and participants were instructed to have a Calorie deficit of 500-750 per day while consuming 1 gram of protein per kg of body weight. This way the effects of the exercise modalities were isolated. For the AE group, they exercised 3 times per week on either a treadmill, stationary bike, or stair climber. The exercise consisted of 10 minutes of flexibility, followed by 40 minutes of AE, and finally 10 minutes of balance exercises. The AE was at 65% of maximum heart rate, and gradually raise to 70-85% so the range of intensity was from low to moderate. The RT group had a similar workout routine, but the AE component was replaced by RT. Participants used weight machines and were lifting 65% of their 1 rep maximum for 1-2 sets at 8-12 reps, and was increased to 2-3 sets at 85% of their maximum. The combination group sessions were longer than the other groups because they combined the AE and RT so the total duration was 75 to 90 minutes. All other parameters were the same. The control group did not participate in exercise and attended monthly educational sessions about health. Remarkably the three groups lost the same amount of weight on average with a 9% reduction. The AE group lost more lean mass than the other groups and also lost more bone density, with only the RT group not having a significant decrease from the control group. The greatest increase in fitness and quality of life was observed in the combination group. This is an interesting study because it involved older people who were already obese and compared different exercise modalities. Based on the data, and considering the demographics it seems that at this age RT may be the most suitable option. Weight loss was similar and more importantly RT preserved bone density, which at this stage in life is critical to mortality and morbidity. In addition, it takes less time than combining AE and RT and is therefore more efficient if one is trying to lose weight and gain quality of life. RT also increases resting energy expenditure (Moro *et al.,* 2020) so this may help with long term weight management. The study was only 24 weeks so longer term studies are needed to fully assess what training method is optimal but this is a step in the right direction.

Another group (Moro *et al.,* 2020) performed a short term study of 8 weeks investigating the impact of high intensity interval resistance training (HIIRT) which combines high intensity interval training (HIIT) and RT. The idea behind this is to reduce total exercise time and maximize results, as time is one of the most common complaints to exercise which is why HIIT had become popular. There were only 20 participants who were a healthy weight with an average ago of 22 years and BMI of 23.57. The group was comparing the results of RT and HIIRT with lean body mass and strength. The RT group performed 3 sets of 15 reps at 60% of their 1 rep maximum with 1 minute and 15 seconds break between sets 3 times per week, while the HIIRT group performed 6 reps at 80% of their 1 rep maximum with a 20 second rest and then lifted the same weight until failure, followed by another 20 second rest and reps until failure which all consisted of 1 set and then had 2 minutes and 30 seconds of rest before the next set. In this short study they found that HIIRT resulted in gaining weight compared to the RT group, however that weight consisted of lean muscle mass, with no gain in fat mass across both groups. Both groups experienced significant increase in lower body strength and only the HIIRT group gained upper body strength endurance. This study was too short and had too few participants but did show that shorter exercise time with an increase in pace and intensity is at least on par with traditional RT. This may be an intriguing option for younger people who have many time commitments that get in the way of traditional RT or AE. The authors did comment that adherence to the HIIRT protocol is higher in the long term than traditional exercise programs due to the shorter time commitment. These results were also obtained without controlling for diet, so further study controls are needed to assess whether these results would change. Overall, these results are optimistic to those who are searching for ways to be in shape with little time to spare.

The previous study did not have a control for diet, therefore we would like to parse out the effects of RT with a Calorie restriction (CR) component and compare this with RT alone. A group in 2015 (Nicklas *et al.,* 2015) was able to do this with 126 participants (111 completed the program; 88% retention) between the ages of 65 and 79 who were overweight or obese (BMI: 27-35) and otherwise healthy and nonsmoking and were followed for 5 months. Both groups were prescribed RT 3 times per week, and the RT+CR group were instructed to be in a Calorie deficit of 600 Calories per day. The training protocol was for 3 sets of 10 reps at 70% of their 1 rep maximum for a particular exercise with about 1 minute rest between sets. If a participant was able to perform 10 reps on the 3$^{rd}$ set for two consecutive sessions, the weight was increased to maintain intensity at 70% of 1 rep maximum. The results showed that only the RT+CR significantly reduced body mass (RT: -0.1 kg; RT+CR: -4.9 kg). Fat mass was reduced in both groups but significantly greater in the RT+CR group (RT: 0.6 kg; RT+CR: -3.6 kg). However, lean body mass was only reduced in the RT+CR group (RT: +0.3 kg; RT+CR:

-1.1 kg) indicating that muscle mass was also lost when CR is added. Total thigh volume decreased significantly in the RT+CR (RT: +5.2 $cm^3$; RT+CR: -94.2 $cm^3$) but that was consisting mostly of fat volume, while in the RT group there was a significant increase in thigh muscle volume compared with RT+CR (+20.2 $cm^3$ vs -0.9 $cm^3$, respectively). Both groups experienced a similar increase in lower body strength and power. Interestingly, only the RT+CR group exhibited an increase in grip strength, though not significant from RT alone, but when adjusted for body weight grip quality was better in the RT+CR group compared to RT alone (+0.06 kg/kg body weight vs + 0.01kg/kg body weight, respectively). From these data it seems that adding a CR component to RT leads to significantly different outcomes than just RT alone, with the drawback being that lean body mass may suffer. Since these are older individuals, the increase in grip strength quality can be seen as critical since one cause of mortality and morbidity in this population is from being unable to stop a fall.

What we explored are three different studies showing different exercise modalities that can improve health: AE, RT, combination AE and RT, RT+CR and HIIRT, summarized in table 2. All of these modalities improved a wide range of physical parameters and on average resulted in better health for the participants. The question is what could be the most efficient outlet that improves overall health, results in the least injury and can be used as treatment for obesity? After looking at these approaches and the resulting data, it seems that RT may have the best all-around results because not only was there significant weight loss in the studies that involved overweight and obese subjects, but there was also significant  strength gains, quality of life improvement, and lowest risk

| **Author** | Villareal *et al.,* 2017 | Moro *et al.,* 2020 | Nicklas *et al.,* 2015 |
|---|---|---|---|
| **Exercise Modalities Compared** | AE, RT, and AE+RT | HIIRT, and RT | RT, and RT+CR |
| **Weight Change** | All Groups: -9% Body Weight | HIIRT: +2.27%; RT: +0.36% | RT: -0.15%; RT+CR: -5.67% |
| **Time Commitment** | AE: 1 hour; RT: 1hour; AE+RT: 75-90 minutes All Groups 3x/week | HIIRT: 43 minutes; RT: 62 minutes Both Groups 3x/week | Both Groups: 5 minute war-up, 5 min cool-down, 1 minute rest between sets, 3x/week |

**Table 2. Summary of exercise data. AE-Aerobic exercise; RT-Resistance Training; HIIRT: High Intensity Interval Resistance Training; CR-Calorie Restriction**

of possible injury while only taking a modest amount of time to see improvements. It would be interesting to see more data on the HIIRT protocol because the subjects in this study were young and healthy and the number of subjects limited the findings. HIIRT could be a potential treatment for the prevention of obesity and CVD due to its short amount of time needed and the increase in lean body mass associated with it. Due to its higher intensity requirements to make this effective, caution should be taken before embarking on this protocol, which could be why the authors used younger, healthy subjects instead of obese ones. Risk of injury could outweigh the benefits in an obese group. AE alone resulted in significant weight loss, but the decrease in lean mass and bone density is not a favorable result for treatment in older populations and could increase risk of injury. Combination of RT and AE had very robust results in terms of weight loss, strength gains, and aerobic capacity, however because it takes much more time than the other modalities it may not be the best protocol for beginners, and indeed it had the lowest adherence of the three groups in the study. Adding CR amplifies the results of RT and should be used in conjunction with each other if the goal is losing weight and improving strength. The best routine is the one that the individual can adhere to long term without major injury. However, some individuals are too out of shape to start a consistent exercise program and may need additional options to get their weight down before focusing on an exercise program.

**Weight Loss Drugs**

Since obesity has reached epidemic proportions in the US and across the world, pharmaceutical companies have been attempting to bring anti-obesity drugs to market. Since 2012 there have been a number of long-term anti-obesity drugs that have been approved for human use. These drugs may be a good option for those that need a boost in initial weight loss before wanting to start an exercise program. A review of several therapeutics was performed in 2020 (Dragano *et al.,* 2020), ranging from short to long term use and effectiveness. The review introduced first the short-term anti-obesity drugs, however these drugs all had a host of associated negative reactions and were approved in the 1950s and 1960s. Side effects included insomnia, constipation, dry-mouth, chest pain, heart palpitations, and mood changes. Of the short-term drugs introduced it seemed that phentermine, an appetite suppressant, is still widely used today. Phentermine is similar to an amphetamine and reduces appetite and increases basal metabolic rate (BMR) and in a clinical trial showed robust weight loss compared to a placebo group (8.1 kg vs 1.7 kg, respectively). The drawback is that this is used for short-term weight loss due to lack of safety data, and after discontinuation there seems to be a rebound effect where patients regain the weight. That being said, some physicians do use this long-term with good results (Dragano *et al.,* 2020). This drug should be used for someone that is motivated to lose weight and is ready to change their lifestyle by adding exercise and CR after discontinuing from the drug.

Long-term use drugs for obesity must be monitored and carefully assessed The first one described by Dragano is orlistat, which inhibits pancreatic and stomach lipases which would digest fat, thereby allowing the fat to move through the intestines unabsorbed and making a Calorie deficit. However, this drug leads to many unwanted side-effects (diarrhea, abdominal pains) and is not very effective, averaging only 1.8 kg of weight loss after 12 months. Another drug mentioned for long-term use is lorcaserin, which was FDA approved in 2012. Lorcaserin is a serotonin receptor agonist and works downstream to suppress appetite via the hypothalamus. Lorcaserin showed robust improvement in weight after a 12 month follow-up study, 47.5% of participants lost at least 5% of their body weight while 22.6% lost at least 10%. There were a host of side-effects as well such as headache, nausea, dry mouth, cognitive impairment, priapism and bradycardia. There were also heart valve diseases associated with this drug. Another drug that was FDA approved in 2012 is combination of phentermine, previously discussed, and topiramate. A long 108 week followup study was performed and showed the combination to result in 9.6 kg of weight loss with a dosage of 7.5 mg phentermine and 46 mg topiramate (7.5/46) and 10.9 kg of weight loss with a dose of 15/92. There was also improvement in blood lipid levels namely triglycerides and HDL/LDL cholesterol levels. Side-effects associated with this combination are insomnia, constipation, dizziness, parsethesia, dysgeuia and dry mouth. Cardiovascular issues and kidney stones were also reported. Another drug combination was naltrexone-bupropion and after a 56 week followup showed 6.5 and 8.0 kg weight loss for 16 mg and 23 mg naltrexone plus bupropion, respectively. It had similar side-effects to the phentermine-topiramate combination and is contraindicated for hypertension, seizures, and alimentary disorders.

Finally, the review introduced liraglutide a GLP-1 receptor agonist which mimics the hormonal changes brought upon by bariatric surgery. It works by suppressing appetite and food consumption along with delaying stomach emptying, giving a perception of being full. In trials liraglutide produced weight loss of 8.4 kg over 3 years along with improvements in CVD risk factors, glycemic control and metabolic improvements. There are gastrointestinal side-effects associated with liraglutide including nausea, diarrhea, constipation, and vomiting. There were no cardiac side-effects according to this review, which is something we have not seen in the other medications listed above which may make this drug a valuable tool for those who have obesity and CVD. Another drug, semaglutide, which is also a GLP-1 agonist has recently undergone a phase III clinical trial (Davies *et al.,* 2021)and has been FDA approved showed promise in reducing weight. After a 68 week trial, those on semaglutide exhibited a weight loss of 9.6% of their body weight compared to 3.4% in the placebo group, with about 69% achieving at least 5% weight loss. Side effects were similar as with liraglutide. However, unlike liraglutide, semaglutide is a once a week subcutaneous injection so less drug is required for the desired effect and less chance to miss a dose. There is an oral option for those who are not comfortable injecting themselves.

Overall, these drugs should be used by overweight and obese patients who are looking for a head-start to their exercise and lifestyle change journey. Since most of these drugs have adverse reactions to both gastrointestinal and cardiac systems, a person with history of CVD should probably avoid these. The recommendation would only to use these if weight loss has not started by adherence to a diet and exercise plan, and the patient is heart healthy, especially with the short-term and combination drugs. However, it seems that the GLP-1 agonists may be the most attractive option out of these drugs. There are side effects but not assevere, and has the added benefit of helping with blood lipids, blood glucose, type II diabetes, and hypertension. For the obesity and CVD epidemics in the US more drugs like these should be researched and developed in order to help treat people in the beginnings of their weight loss. Now that we looked at different exercise modalities, and various drugs that may help patients in the beginning for their weight loss goals, let's explore a way of eating that has gained a lot of attention recently.

**Intermittent Fasting**

Intermittent fasting (IF) is a type of eating that has become increasing popular over the past decade. Simply, it is a way of eating that restricts that time in which one eats their foods. A common protocol is 16:8, which means fasting for 16 hours and eating for 8 hours. During the feeding time windows, people can eat as much or little as they want in most protocols. Another protocol could be alternative day fasting where a patient fasts one day or extremely reduces Calories and then the next day eat ad libitum. This way of eating is an alternative to CR which can be very difficult to follow long-term. A recent meta-analysis in 2020 (Welton *et al.,* 2020) compiled data from the year 2000 to 2019 and found 27 trials that involved IF and weight loss in overweight and obese patients. The data compiled showed that IF reduced body weight with a range of 0.8-13% down from baseline. Interestingly weight loss was shown even in the absence of Calorie restriction. The authors also report that most of the weight that was lost was fat.

Another study (Li *et al.,* 2017) looked at what effects IF has on the body, and what they showed was that IF promotes the white adipose tissue (WAT) to become beige, having characteristics of brown adipose tissue (BAT) which is thermogenic. What this means is that WAT is becoming thermogenic, creating heat and burning more Calories at rest, which is another possible mechanism as to why IF is effective for weight loss. In another meta-analysis (Patikorn *et al.,* 2021) the group reviewed 11 meta-analyses of IF on weight loss and found that alternative day fasting had the strongest evidence as being helpful for overweight and obese individuals lose weight and improve health parameters.

A recent review (Vasim *et al.,* 2022) interrogated the relationship between IF and metabolic health, including CVD. What they discovered was that IF (most data comes from Ramadan fasting) lowers blood levels of TAGs and LDL cholesterol, while raising HDL cholesterol even in the absence of overall weight-loss (Santos & Macedo, 2018). This suggests there may an added benefit of IF for patients with CVD. Others have reviewed evidence of IF on health and have determined that IF can be beneficial long term in regards to longevity, cancer, and obesity prevention (de Cabo & Mattson, 2019). Taken together, IF can be seen as an invaluable tool to help patients lose weight. The advantage is that there are no restrictions as to what the participants are eating, or need to measure or keep track of macronutrients, just the time window of when they are eating. More studies are needed to elucidate exactly what time of the day is best for eating or the duration of fast that would be most beneficial for health. In addition more needs to be done on what are the best foods to eat during the feeding window. An interesting study would be how old one can start IF, and if IF has any harmful repercussions on overall growth or health. With the ability of IF to decrease weight, and the potential benefit of reducing CVD risk factors, more research needs to be performed in order to evaluate who could benefit the most from IF. .

## CONCLUSION

In this review we examined the obesity and CVD epidemics in the US, which started to become a public health concern in the later part of the twentieth century. The potential contributing factors explored were the significant increase in the use of HFCS in beverages and sweetened foods, and the transition to low-fat diets which are consisted of more processed foods . We have shown that added HFCS not only leads to easy excess Calories but also favors a metabolic pathway that produces excesses in uric acid, which has been shown to lead to an increase in ROS, inflammation, hypertension, and oxidation of lipid membranes, particularly those in lipoproteins and lining blood vessels (Muriel *et al.,* 2021). The addition of HFCS when taken in liquid form with meals also suppresses the feeling of satiety, leading to overconsumption during and between meals. We have also shown that the caution against fat-containing foods has been unwarranted, several studies have been performed comparing low-fat diets against low-carbohydrate, high-fat diets with results that either favor low-carbohydrate diets or at least are comparable in terms of weight loss. In addition, low-carbohydrate, high-fat diets comprised of whole foods were shown to significantly improve blood triglycerides, HDL cholesterol, the ratio of HDL to total cholesterol, and patients with type II diabetes saw a decrease in their HBA1c values, meaning their average blood sugar over 3 months was reduced. The primary result that would caution against these diets is the modest increase in LDL cholesterol that was shown across multiple studies. Low-carbohydrate diets were also shown to have comparable reduction in heart health measures such as blood pressure and pulse rate with low-fat diets, displaying that a heart healthy diet can be achieved with either method.

Along with the potential causes of the obesity and CVD epidemics we explored solutions available for patients wanting to treat or prevent these with a focus on exercise, weight loss drugs, and IF. All exercise methods (AE, RT, combination, RT+CR) resulted in a significant decrease in weight in overweight and obese patients. Only one method resulted in a gain of weight (HIIRT) however that was comprised almost entirely of lean muscle mass, with no loss or gain of fat mass, and these results were from a young, healthy group as opposed to overweight or obese. When looking at the data complied, the most compelling exercise method seemed to be RT because of the significant weight loss, gain of strength, and limited loss of bone mass compared with AE and combination AE and RT. This method also does not require significant time commitments, with results being shown from 1 hour 3 times per week. In regard to amount of time it takes to see results, HIIRT was the most efficient however because of the high intensity involved there should be caution with recommending this to patients with significant weight to lose as the risk of injury may out-weight the benefits. As for weight loss drugs, many of them resulted in significant weight loss, however there were a variety of side-effects associated with these drugs ranging from gastrointestinal to cardiac effects. In populations that are overweight or obese and have heart conditions there should be caution before prescribing. These should be reserved for patients who either need to see some results before starting an exercise program or someone who is heart healthy and wants an added boost to their results in the short term before being able to maintain their weight loss on their own. The most promising drug class with minimal side effects on the heart are the GLP-1 agonists. More research is needed to develop a drug that is safe and effective for the at risk population. Finally, we explored results from IF studies. IF trials showed weight reduction in most studies even in the absence of CR, with alternate day fasting showing the most promise. Others have shown that IF induces the beiging of WAT to become more thermogenic, and other studies have shown there could be major implications to longevity and prevention of many chronic diseases such as cancer and obesity.

Obesity and CVD in the US is an increasing problem not only here but worldwide. Many health care providers discuss diet and exercise but the goal needs to go beyond that and start emphasizing that in order to have long lasting weight loss and improvements in health, the changes that one undergoes in a diet and exercise routine has to become a permanent part of the person's life. The language of diet has to be changed to lifestyle management. Many diets result in short term weight loss and then regaining of the weight because of this.  Multiple small improvements to a lifestyle can cumulatively lead to significant advances in health. Health care providers will be able to improve patients' health and wellbeing the most by having a holistic method of practicing medicine. Understanding why a person eats can be just as important as what and how much they eat. There is even evidence that reducing stress in a person's life affects the degree with which they lose weight (Radin *et al.,* 2020). There is a lot of work to be done on this subject, and hopefully the healthcare field is ready to work on this and give patients the time and tools to discuss long lasting change to their health.

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