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Investigating the Effects of Body Weight Fluctuations on Insulin Resistance in Adults: a NHANES Study

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INVESTIGATING THE EFFECTS OF BODY WEIGHT FLUCTUATIONS ON INSULIN RESISTANCE IN ADULTS: A NHANES STUDY

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ABSTRACT

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The aim of this study was to investigate the effects of a history of weight cycling on insulin resistance (IR) utilizing the 2015-2020 NHANES database. A value greater than 3.2 for homeostatic model assessment of insulin resistance (HOMA-IR) was used to define IR. No study to date has examined the weight cycling question since its application in the NHANES 2015-2016 cycle year. **RESULTS** 53% of the total 4100 participants reported weight cycling at least once and 33% of the total were classified as having IR. Prevalence of IR and obesity were highest amongst those who weight cycled 3 times or more, and diabetics were more likely to weight cycle than non-diabetics. A positive association was found for history of weight cycling and average BMI, maximum historical BMI, waist circumference, HOMA-IR, and fasting insulin levels. Simple logistic regression showed that weight cycling 3 times or more substantially increased the odds of becoming obese (OR 4.42, $P<.001$). After adjusting for obesity, age, sex, and ethnicity, any history of weight cycling revealed no significant effect on a person's odds of developing IR. Rather, obesity was the largest predictor of IR independent of other

confounding variables –an obese person was 8 times more likely to have IR than someone of a normal or overweight BMI ($P<.001$). These results suggest that weight cycling does not increase one's risk of IR but is associated with an increased risk for obesity. Findings of this study have implications for clinicians and specialists as they formulate the most effective and sustainable weight loss or maintenance plan for their patients.

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CHAPTER I

INTRODUCTION

Over the past couple of decades, the number of overweight and obese Americans has increased to unprecedented levels in the United States, with the Centers for Disease Control (CDC) reporting the obesity prevalence at 42.4% in 2017 – 2018.[1] The condition of being overweight is defined as a body mass index (BMI) 25.0-29.9 kg/m^2. Obesity is defined as a body mass index greater than or equal to 30 kg/m^2. Both BMI categories are associated with an increased risk of developing a variety of chronic diseases including hypertension, type 2 diabetes mellitus, coronary heart disease, stroke, gallbladder disease, and some cancers. A higher body mass index is also associated with more severe COVID-19 outcomes and an increased risk for hospitalization, intensive care unit admission, invasive mechanical ventilation, and death according to a CDC report.[2]

Weight loss has often been prescribed to overweight and obese patients as a means to reduce their susceptibility to disease, improve self-image and mobility, and to improve health markers—such as fasting blood glucose, insulin and blood pressure. However, there are many factors in place including biological, environmental, and cultural factors that make it very difficult for an adult to lose weight and maintain a lower weight. In a study which analyzed data from the National Health and Nutrition Examination Survey (NHANES) cycle years 1999-2016, it was found that the average US adult BMI increased by 1.20 over the 18-year period, despite the significant increase in the number of people who attempted to lose weight (34.3% in 1999-2000 to 42.2% in 2015-2016).[3] The most common strategies for weight loss reported by the participants

were reducing their food consumption, exercising, and increasing their water intake.[3] This may indicate that dietary, lifestyle and behavioral change strategies are too difficult to sustain over time and/or that overweight and obese Americans are not receiving the guidance and support they need from healthcare professionals or other resources to sustain weight-loss efforts.

Systematic reviews of weight loss interventions with 2-year follow-ups (minimum) also support the notion that maintaining a lower body weight and battling against the hunger cues is much more challenging than losing the weight itself.[4,5] Furthermore, weight loss program participants tend to regain almost half of their lost weight within the first year and typically return to their original, heavier weight within 2-5 years of the initial weight loss.[4,6]

In a large study which involved data from 122 638 Americans, researchers found that weight cycling was a prevalent behavior—50% of the total population reported intentionally losing weight and regaining at least 10 pounds at least once in their lifetime.[7] Weight cycling was also more prevalent amongst women. Weight cycling, the repeated cycle of intentional weight loss followed by weight regain, has been shown to be linked to adverse cardiovascular health and increased mortality.[8-11] In addition to the detrimental effects on physiological health, weight cycling can also adversely affect an individual's mental, spiritual, and social well-being. Repeatedly trying to change one's body size without success can trigger feelings of low self-worth, shame, depression, and may increase the risk of developing an eating disorder or abnormal eating patterns.[12]

Considering that weight cycling is correlated with increased mortality rate and adverse cardiovascular health, weight stabilization rather than significant weight loss may

be a more reasonable and achievable goal for some overweight and obese patients.[8-11] In a 2020 study by Xie et al. which analyzed data from NHANES III and the continuous cycles 1999-2014, researchers showed that significant weight loss did not result in decreased mortality risk for all BMI categories.[13] The participants who had a change in BMI from obese to overweight had lowered their risk of all-cause mortality by 54% compared with people who had maintained an obese BMI. However, participants who had a change in BMI from overweight to normal had no difference in mortality risk compared with adults who had maintained an overweight BMI.

The National Health and Nutrition Examination Survey (NHANES) uses a serial cross-sectional design and has been collecting information biannually from Americans on their health and nutrition since 1999. About 5000 people each year are recruited to partake in interviews and to complete questionnaires pertaining to health-related behaviors. In addition, participants are administered physical examinations and provide blood, saliva, and urine samples which are used to measure health markers and present diagnostics. Many studies in addition to Xie et al. have used NHANES data to examine the relationship of weight history and health outcomes and/or disease risk. In particular, Knell et al. examined adult participants' long term weight loss percentage (LTWL%) and their metabolic health.[14] LTWL% was calculated using the individual's reported maximum historical weight minus their current weight or weight from 1 year ago (whichever of the 2 was higher), divided by their maximum historical weight. The authors found that maintaining a ≥20% weight loss had the largest protective effect against metabolic syndrome. However, long-term weight loss had no significant effects on the risks for hypertension or hyperglycemia.

Beginning in 2015, the NHANES weight history questionnaire added a new question asking participants how many times they have intentionally lost 10 pounds or more in order to lose weight. No study to date has examined this weight cycling question within the NHANES database. Therefore, the aim of this study was to investigate the effects of a history of weight cycling on one key measure of health: insulin resistance. Insulin resistance has been linked to the onset of cardiovascular disease, dyslipidemia, and type 2 diabetes[15] and can be measured using the HOMA-IR (homeostatic model assessment for insulin resistance). HOMA-IR can be calculated by multiplying the fasting plasma glucose (mg/dL) by the fasting serum insulin (mU/l) and dividing by a factor of 405.[16] HOMA-IR is a convenient and beneficial clinical tool for measuring a patient's insulin resistance and has been shown to be closely correlated to the insulin resistance index measured by the euglycemic-hyperinsulinemic clamp.[17-19]

This study will add to the literature because of its novel utilization of the 2015-2016 and 2017-March 2020 weight cycling question from the NHANES questionnaire data. It also seeks to provide more knowledge on the risks, or the benefits associated with weight cycling, independent of a person's body size. The findings of this study may have implications for physicians, dietitians, and consumers as they make decisions and recommendations for the most effective strategies to improve overall health.

CHAPTER II

LITERATURE REVIEW

NHANES

The National Health and Nutrition Examination Survey (NHANES) is a serial cross-sectional design that has been continuously gathering information on Americans' health and nutrition status since 1999. About 5000 participants from different counties across the US are surveyed each year and report on health-related behaviors via interviews and questionnaires in their own homes. In addition, participants are administered physical examinations by highly trained personnel in the NHANES mobile examination center and provide biological samples from serum, saliva, and urine. By oversampling certain population groups, the survey results provide more reliable estimates of health status in these minority populations. Specifically, from 2015 and onwards, NHANES oversampled Hispanics, Blacks, Asians, people living at or below 185% of the federal poverty level, infants, and children up to 11 years old, and adults aged 80 and older.[20] NHANES survey data is also complex in that it factors in clustering, stratification, and sample weights, which allows for more reliable estimates when combining cycle year data. The data collected by NHANES has been instrumental in reporting the prevalence of chronic diseases and their risk factors, and NHANES findings have been fundamental for making recommendations and setting guidelines for Americans. Information on the sample design and variance estimation can be found elsewhere.[20]

Body Mass Index

Body mass index (BMI) is a convenient and quick tool for health care practitioners to assess a person's weight status and approximate the proportion of body fat. BMI is calculated by taking the patient's weight (in kilograms) and dividing that by their height (in meters) squared. The World Health Organization and the National Institute of Health define an underweight BMI as below 18.5 kg/m^2; a normal BMI as 18.5-24.9 kg/m^2; an overweight BMI as 25-29.9 kg/m^2, and an obese BMI as greater than or equal to 30 kg/m^2.[21] An obese BMI is further stratified into classes: class I obesity is considered as a BMI of 30-34.9 kg/m^2; class II obesity is considered as a BMI of 35-39.9 kg/m^2, and severe or class III obesity is considered as a BMI greater than or equal to 40 kg/m^2.[21] However, it does come with its limitations as it does not account for the weight contributed by lean muscle mass and does not provide a description of the proportion of fat mass. Thus, professional athletes and physically active people with higher amounts of muscle mass have an elevated BMI that does not necessarily correspond to their health status. Nonetheless, BMI is widely used among health professionals as risks for chronic disease increases with increasing BMI.

Body Fat Distribution

The distribution of adipose tissue, rather than body weight and BMI, has often been cited as a better predictor for the risk of developing cardio-metabolic diseases.[22] Visceral fat accumulation in the upper body and especially in the abdominal region has shown to have stronger associations with health risks including insulin resistance than fat accumulation in the lower portion of the body.[22] Visceral fat compared to subcutaneous

fat has a stronger association with insulin resistance because of its location in the human body, the size and vascularity of the adipocytes, and differences in the adipose tissue receptors and synthesis of adipokines.[23] Elevated cortisol levels resulting from chronic stress can also increase visceral fat deposits, which in turn increases the risk of developing insulin resistance.[23] Furthermore, Montague et al. investigated the differences in gene expression in paired omental and subcutaneous adipocytes. While they did not find significant differences between the expression of lipoprotein lipase (LPL), hormone-sensitive lipase (HSL), peroxisome proliferator-activated receptor-y (PPAR-y), tumor necrosis factor-alpha (TNF-α), and adipsin in the 2 types of adipose cells, they did find a significant inverse relationship between adipocyte PPAR-y expression and BMI ($r = -0.7$, $P = 0.0005$).[24] Because PPAR-y is involved in glucose and lipid metabolism and insulin sensitivity, this finding reflects how excess adiposity is related to insulin resistance. However, there is mixed consensus on whether it is visceral truncal fat or instead the subcutaneous truncal fat that influences the development of insulin resistance. Multiple studies have shown a correlation of subcutaneous truncal fat and insulin resistance as well as a positive association with pro-inflammatory biomarkers and macrophage infiltration.[25-29] More research is needed to understand the relationship between types of adipose tissue and disease risks.

Risks Associated with Having a Higher BMI

The prevalence of overweight and obese Americans has increased to unprecedented levels in the past couple of decades. Today, the United States is one of the top 10 countries for percentage of citizens with obesity, and in 2013, Americans

accounted for 13% of obese people worldwide.[30] An obese BMI has been associated with an increased risk of developing hypertension, diabetes, and hypercholesterolemia, regardless of physical activity level,[31,32] as well as cardiovascular disease, stroke, dyslipidemia, gallbladder disease, osteoarthritis, and some cancers.[33,34] A proposed mechanism underlying the relationship between an obese BMI and the increased risk for these chronic diseases is a pro-inflammatory state and oxidative stress.[35] Given the association of obesity and an increased risk of chronic diseases, there has been a great deal of focus in the public health sector on improving the quality and innovation of health interventions for obesity.

Studies have shown that BMI is correlated with mortality risk and displays a U-shaped curve with a BMI 22.5-25 kg/m^2 as having the lowest mortality risk.[36] A BMI below 18.5 kg/m^2 and above 30 kg/m^2 had higher mortality risks than those in the normal to overweight range. In a cross-sectional study using 23 years' worth of NHANES data, those who were obese in early adulthood and lost significant amounts of weight by midlife had lowered their mortality risk by 54% compared to obese subjects who maintained their BMI status (HR 0.46; 95% CI 0.27-0.77).[13] Although it was found that gaining weight from a normal to an overweight BMI did not increase mortality risk, gaining weight from either a normal to obese BMI (HR 1.32; 95% CI 1.15-1.52) or an overweight to obese BMI (HR 1.47; 95% CI 1.28-1.69) were both associated with increased all-cause mortality risk.

However, there have been conflicting results when it comes to weight loss and mortality risks. One study on overweight and obese adults without known comorbidities revealed that those who reported they were trying to lose weight and had lost weight had

an increased mortality rate (HR 1.86; 95% CI 1.22–2.87) at the 6-year follow-up compared to adults who had stable weight and no intentions to lose weight.[37] Other studies have also found that changes in weight, both gains and reductions, are associated with increased mortality risks.[38]

A higher body mass index is also associated with more severe COVID-19 outcomes and an increased risk for hospitalization, intensive care unit admission, invasive mechanical ventilation, and death according to a CDC report that was based on data from March-December 2020.[2] The association between overweight and obese BMIs and adverse COVID-19 outcomes was found even after adjusting for the following: BMI category, age, sex, race/ethnicity, payer type, hospital urbanicity, hospital US Census region, and admission month as control variables. When looking at hospitalizations for people 18 years and older, the underweight and class III obese BMI—which was defined as a BMI 40-44.9 kg/m^2—were at a significantly 20% higher risk than normal and overweight BMI categories. Class IV obesity, defined as a BMI greater than or equal to 45 kg/m^2, was at a 33% increased risk compared to a normal BMI. The risk of ICU admission was only about 6% higher for class III obese individuals ($\geq$40 kg/m^2) and 16% higher for class IV obese individuals, whereas the adjusted relative risk was no different for the lower BMI categories. The risk of death from COVID-19 was significantly higher for all obese BMI categories: an 8% increased risk for class I, a 14% increased risk for class II, a 33% increased risk for class III, and a 61% increased risk for class IV. The risk of requiring invasive mechanical ventilation was higher for overweight and obese BMI categories compared to normal weight BMI. However, when excluding people older than

65, an overweight and a class I obese BMI had a significantly 8% lower risk for ICU admission compared to a normal weight BMI.

Sustainability of Weight Loss

The initial amount of weight that is lost usually determines how much is gained back within 1-2 years typically.[8,39] Weight loss induces physical and biological changes in the body that act to restore homeostasis and promote weight regain. In a study on obese subjects who participated in a weight loss program and lost weight, ghrelin was shown to increase significantly by 24% on both a daily average and during mealtimes (P=0.006).[40] Ghrelin is a hormone secreted by the stomach that acts to induce hunger and increase food intake. Similarly, the hormone, leptin, which is responsible for signaling satiety, was shown in the same study to be reduced by 37.7% after weight loss (P=.003)[40] and was halved in another diet-induced weight loss study by Ebbeling et al. (P<.001).[41] These findings explain how hunger hormones work to hinder the sustainability of weight loss by upregulating food intake and energy storage and increasing subjective appetite. Another mechanism that favors weight regain is the decrease in energy expenditure that accompanies weight loss, usually due to a decrease in metabolic efficiency and a decrease in involuntary movement, and thus, less calories expended.[41] In a controlled, cross-over study, Ebbeling et al. studied total daily energy expenditure in overweight and obese adults after they had achieved a 10-15% weight loss. The participants were then randomized to a low-fat, a low-glycemic index, and a very low-carbohydrate diet. All 3 groups demonstrated a significant decrease in their resting and total energy expenditure despite no significant change in their physical activity expenditure.[41]

Many studies have proved that weight loss is difficult to maintain in the long term and only a small percentage of people keep the weight off.[8,13,42] In their NHANES study analyzing data from cycle years 1988-1994 and 1999-2014, Xie et al. found that only 2.3% of their sample (N=24 205) had maintained weight loss from age 25 to midlife.[13] With regard to the participants who had a stable weight from age 25 to midlife, only 5.6% were classified as having an obese BMI.[13]

Weight Cycling and its Effects on Health

Weight cycling, which has also been referred to as yo-yo dieting, does not have an universal, agreed-upon definition. Delahanty et al. defined weight cycling as losing at least 5 pounds, gaining at least 5 pounds back and repeating this cycle again.[8] The authors also stated that between 0-6 weight cycles can occur within a 2-year time frame. Stevens et al. made the clear distinction that the weight loss must be intentional and not as a side effect of illness or mental distress.[7] In their large prospective study, they defined a history of weight cycling as intentionally losing 10 pounds or more and then regaining the same amount of weight back. Other studies have calculated percent of weight lost followed by a percent of weight gained back.[43,44]

Weight Cycling, Increased Mortality and CVD Mortality

The Framingham Heart Study is an on-going epidemiological study that originated in 1948, analyzing approximately 5000 participants between the ages of 30-62 in Framingham, MA.[45] Its findings have helped shape recommendations and interventions for cardiovascular health and has even linked weight cycling with

cardiovascular disease. Men and women who had a large range of fluctuations in body weight had increased total mortality and increased morbidity and mortality from coronary heart disease compared to men and women who had a stable weight.[9] The positive association was found even after controlling for obesity, trends in weight status over time, and cardiovascular risk. The results of this study signify the adverse effects on health and longevity from dieting and weight cycling. In another study using The British Regional Heart Study data, it was found that sustained weight loss and weight cycling had significantly higher risk of total and cardiovascular mortality compared to men who had stable weight and sustained weight gain.[43]

Weight Cycling and Hyperinsulinemia

In a study of about 2000 Japanese men of mostly normal BMI status (only 20% were categorized as having an overweight BMI), those who had higher weight fluctuations over a 31-year period had significantly higher fasted insulin levels.[11] Delahanty et al. found in their study on participants in the Diabetes Prevention Program that weight cycling was positively associated with HOMA-IR ($\beta = 0.25$ units per cycle; $P = 0.04$). A history of weight cycling significantly increased a person's risk of diabetes even after adjusting for baseline weight, (HR 1.22, 95% CI 1.02, 1.47; $P = 0.03$) and after adjusting for 2-year weight loss (HR 1.22, 95% CI 1.02, 1.47; $P = 0.03$).[8]

Weight Cycling and the Risk of Developing an Eating Disorder

According to the National Eating Disorders Association, the largest risk factor for developing binge eating disorder is a history of dieting.[46] Many people who try to lose weight may employ strategies such as eliminating entire food groups from their diet, restricting calories, and eating only during a specific window of time. Exercise may also be employed as a means to burn off calories rather than as a pleasurable activity.[47] These exclusive food rules and restrictions are what lead to developing an unhealthy relationship with food. Battling the hunger and fatigue that comes with energy restriction can ultimately drive someone to binge eat and feel a loss of control.[47] The shame and guilt that is brought on from the binge, or from the failed attempt to lose weight, can exacerbate body dissatisfaction, and continue the cycle of dieting and weight fluctuations. Weight stigma and getting teased for one's body size are other risk factors for eating disorders that are also associated with obesity.[46,48] In a study on people who had obese BMIs and struggled with binge eating disorder, it was found that those who frequently dieted had a greater history of weight cycling (3.30 vs 2.67), an earlier onset of binge eating (19 years old vs 28 years old), and an earlier onset of obesity (12 years old vs 18 years old) than participants who infrequently dieted.[49]

Micronutrient Deficiencies in Weight Loss Diets

In a pilot study on adults with obese BMIs, the participants followed a very low-calorie diet (800 kcal/day), which consisted of consuming a vitamin and mineral-fortified formula for 3 months. Despite the formula's claim to contain at least 100% of essential vitamins and minerals, at the end of the 3 months, there was an increased prevalence of

deficiencies in vitamin C, selenium, iron, zinc, and lycopene.[50] Adults looking to lose weight may also try a popular fad diet, such as the Atkins diet or the South Beach diet, which have been shown to increase the likelihood of becoming deficient in a micronutrient from the diet alone.[51] More specifically, the 4 diets that were reviewed were shown to be deprived of the following: vitamin B7, vitamin D, vitamin E, chromium, iodine, and molybdenum. These studies reveal that when an adult restricts their caloric intake and/or alters the macronutrient composition of their diet in order to lose weight, the restriction hinders the ability to consume and absorb the vital micronutrients needed to support a healthy body.

Insulin Resistance

Insulin resistance is defined as when the pancreatic beta cells are releasing enough insulin in response to the postprandial increase in blood glucose levels, but GLUT 4 receptors throughout the body—in the heart, skeletal muscle, liver, and adipose tissue—do not recognize or are less sensitive to the presence of insulin, and therefore do not uptake glucose.[15] Insulin is also responsible for stimulating glycolysis, glycogen synthesis, lipid storage in adipose tissue via lipoprotein lipase, and repressing the hepatic cells from performing gluconeogenesis.[15] Therefore, when insulin goes unnoticed by insulin receptors, the body will stay in a catabolic state despite having plenty of glucose and insulin in the bloodstream.

Insulin resistance often coincides with hypertriglyceridemia, low HDL-cholesterol, and obesity, and all these conditions are risk factors for cardiovascular disease.[15] Insulin resistance is also a characteristic of metabolic syndrome which is

associated with increased mortality from coronary heart disease.[52] In a study on people with type 2 diabetes, it was found that insulin resistance as measured by HOMA-IR independently predicted CVD prevalence at baseline and incidence during a 4-year follow-up.[53] Insulin resistance can be viewed as the precursor to developing type 2 diabetes as it often precedes the disease.[53]

Measuring Insulin Resistance

Hyperinsulinemic Euglycemic clamp

The hyperinsulinemic-euglycemic clamp is an expensive, time-consuming procedure used to directly measure a person's insulin resistance, and therefore should be reserved only for case studies, small clinical trials, and individual treatment care.[52] Patients who are administered the hyperinsulinemic euglycemic clamp are required to fast overnight for 10-12 hours.[54] In the morning, before consuming food or beverage, the patient has an intravenous catheter positioned in the vein of the forearm which supplies a prepared, continuous infusion of insulin that is based on the person's body surface area, generating a state of hyperinsulinemia. The catheter also simultaneously supplies an infusion of glucose to maintain a state of normal glycemia. Another catheter is inserted in a hand vein to measure the blood glucose levels every 5 minutes and then every 10 minutes once the glucose levels stabilize. This measurement essentially depicts how well GLUT 4 receptors recognize insulin and its ability to signal glucose uptake.[54] A low glucose infiltration rate applied in the hyperinsulinemic state means the patient may be diagnosed with insulin resistance.[55] The entire process takes at least 4 hours and is not ideal for measuring insulin resistance in large research studies.

HOMA-IR

Homeostatic model assessment for insulin resistance (HOMA-IR) is a more convenient and beneficial clinical tool for indirectly measuring a patient's insulin resistance and has been shown to be closely correlated to the insulin resistance index assessed by the euglycemic-hyperinsulinemic clamp.[17-19,53] Specifically, Bonora et al. found a highly significant correlation of r= -0.820, P<.001 when comparing HOMA-IR to the hyperinsulinemic-euglycemic clamp.[54] HOMA-IR can simply be calculated from the patient's fasted plasma glucose (mg/dL) multiplied by their fasted serum insulin (μU/L) divided by a factor of 405.[16] Another way to calculate HOMA-IR is to divide the fasted plasma glucose (mmol/L) by a factor of 22.5 and then multiply by the fasting plasma insulin (μU/m).[52] The increasing value of the HOMA-IR translates to an increasing resistance to insulin in the individual. Because it relies on just 2 fasting laboratory measurements, it is very rare to misclassify a person's insulin status, and therefore is a suitable tool for large epidemiological studies.

However, review of the literature shows a lack of a standardized cutoff point for HOMA-IR. Son et al. used a HOMA-IR cutoff of ≥2.5 when assessing patients in Korea who were newly diagnosed with diabetes[56] as did Oliveira et al. in Brazil.[57] A large cohort study by Qu et al. examined insulin resistance in Mexican Americans living in Brownsville, TX using machine learning methods. They found that the best cutoff point was 3.8 as it had the best values for selectivity and specificity.[58] This same cutoff was used in a study on Spaniards without clinical or biochemical insulin resistance parameters or a family history of diabetes or dyslipidemia.[59] However, 3.8 was the value for the 90th percentile, and 3.2 was the value at the 75th percentile. In a later study by Ascaso and

Pardo, they assessed insulin resistance in hospital staff and personnel with normal glucose tolerance.[52] The HOMA-IR value for the 75th percentile was 2.6, and the value for the 90th percentile was 4.1.

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JOURNAL ARTICLE

A HISTORY OF WEIGHT CYCLING DOES NOT AFFECT THE LIKELIHOOD OF DEVELOPING INSULIN RESISTANCE IN AN ADJUSTED MODEL

A history of weight cycling does not affect the likelihood of developing insulin resistance in an adjusted model

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Keywords: weight cycling, insulin resistance, obesity, HOMA-IR, sustainability of weight loss

Word Count: 4378 words; abstract 286 words

RESEARCH SNAPSHOT

Research Question: Is there an association between a history of weight cycling and the development of insulin resistance?

Key Findings: In this cross-sectional study analyzing data from NHANES 2015-2016 and 2017-Mar 2020 cycle years, it was found that a history of weight cycling had a positive relationship with average BMI, HOMA-IR, waist circumference, and fasting insulin. After adjusting for confounding variables, a history of weight cycling had no effect on an individual's susceptibility to insulin resistance. An obese BMI was the largest contributor to developing insulin resistance—almost 9 times a higher odd than a normal or overweight BMI.

ABSTRACT

Background

Weight cycling, or intentional weight loss followed by weight regain has been shown to be linked to adverse cardiovascular health and increased mortality. Beginning in 2015, the National Health and Nutrition Examination Survey (NHANES) weight history questionnaire added a new question asking participants how many times they have intentionally lost 10 pounds or more in order to lose weight. The aim of this study was to investigate the effects of a history of weight cycling on insulin resistance (IR).

Design

Data was obtained from the NHANES survey years 2015- March 2020 on the CDC's website. Statistical analysis was performed using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Fifty-three percent of the total 4100 participants reported weight cycling at least once and 33% of the total were classified as having IR. Prevalence of IR and obesity were highest amongst those who weight cycled 3 times or more, and people with diabetes were more likely to weight cycle than people without diabetes. In a simple model, weight cycling increased a person's odds of developing obesity (OR: 4.42, $P<.001$). After adjusting for obesity, age, sex, and ethnicity, any history of weight cycling revealed no significant effect on a person's odds of developing IR. Rather, obesity was the largest predictor of IR

independent of other confounding variables –an obese person was 8 times more likely to have IR than someone of a normal or overweight BMI (P<.001).

Conclusion

These results suggest that weight cycling does not increase one's risk of IR but is associated with an increased risk for obesity. Findings of this study has implications for clinicians and specialists as they formulate the most effective and sustainable health plan for their patients.

INTRODUCTION

Over the past 30 years, the number of overweight and obese Americans has increased to unprecedented levels in the US, with the Centers for Disease Control (CDC) reporting the obesity prevalence at 42.4% in 2017 – 2018.[1] Weight loss has often been recommended to patients with overweight and obese BMIs as a preventative measure and as a treatment for a variety of chronic diseases such as hypertension, type 2 diabetes mellitus, coronary heart disease, dyslipidemia, and osteoarthritis. Even more, a higher body mass index has been associated with more severe COVID-19 outcomes and an increased risk for hospitalization, intensive care unit admission, invasive mechanical ventilation, and death.[2]

However, there are many factors in place including biological, environmental, and cultural factors that make it very difficult for an adult to lose weight and maintain a lower weight. In one study which analyzed data from the National Health and Nutrition

Examination Survey (NHANES) cycle years 1999-2016, it was found that the average US adult BMI increased by 1.20 over the 18-year period, despite the significant 7.9% increase in the number of people who attempted to lose weight.[3] The most common strategies reported by the participants were reducing their food consumption, exercising, and increasing their water intake. Furthermore, weight loss program participants tend to regain almost half of their lost weight within the first year and typically return to their original, heavier weight within 2-5 years of the initial weight loss.[4,5] Findings such as these indicate the following: traditional weight loss strategies may be too difficult for some people to sustain over time. Moreover, overweight and obese Americans are not receiving optimal guidance and support from healthcare professionals or other resources with regard to weight management and/or dieting for the purpose of losing weight. This can lead to weight cycling and ultimately an increase in BMI.

Weight cycling, or intentional weight loss followed by weight regain of a similar amount has been shown to be linked to adverse cardiovascular health and increased mortality.[6-9] In addition to the detrimental effects on physiological health, weight cycling can also adversely affect an individual's mental, spiritual, and social well-being. Repeatedly trying to change one's body size without success can trigger feelings of low self-worth, shame, depression, and may increase the risk of developing an eating disorder or abnormal eating patterns.[4,5,10]

Considering that weight cycling has been associated with adverse health outcomes, weight stabilization rather than significant weight loss may be a more reasonable, achievable goal for some overweight and obese patients.[6-9] Some studies have shown that significant weight loss from a baseline overweight BMI[11] or an obese BMI[12]

does not reduce mortality risk compared with a stable overweight BMI. Even more, studies that have utilized the Health at Every Size (HAES®) approach have shown improvement in cardiovascular health, psychological measures, eating behaviors[4] and a decrease in hunger and daily energy intake,[13] despite no significant change in weight.

Therefore, the aim of this study was to investigate the effects of weight cycling on one key measure of health: insulin resistance. Insulin resistance has been linked to metabolic syndrome and the development of cardiovascular disease, dyslipidemia, and type 2 diabetes.[14] This study will add to the literature because of its novel utilization of the 2015-2016 and 2017-March 2020 weight cycling question from the NHANES questionnaire data. It also seeks to provide more knowledge on the risks, or the possible benefits associated with weight cycling, independent of a person's body size. The findings of this study may have implications for physicians, dietitians, and consumers as they make decisions and recommendations for the most effective strategies to improve overall health.

METHODS

All participants provided informed consent, and all identifying information was removed prior to the survey datasets being made publicly available online.[15] Therefore, this study received exempt status by Central Washington University's Human Subjects Review Council (HSRC). The data was obtained from the CDC's website[16] from 2 consecutive NHANES survey cycles, spanning the years 2015- March 2020. The 2019-2020 collection of data was interrupted in March 2020 due to the COVID-19 pandemic and thus, was not completed. As a result, the 1.2 data obtained from January 2019

through March 2020 was combined with the 2017–2018-year cycle to form a nationally representative sample. All data was downloaded in statistical analysis system (SAS) transport file format and then opened using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina, USA). A 5.2-year sample weight was calculated and applied according to the specific coding instructions listed on the CDC website regarding combining the pre-pandemic files with prior 2-year cycles. Data analysis was conducted for approximately 4 months.

A total of 25 531 people participated in the NHANES survey from 2015-March 2020. The weight history questionnaire was administered during household interviews to participants 16 years and older. A total of 16 522 participants answered the question (WHQ225) as to how many times they have intentionally lost 10 pounds or more to lose weight. WHQ225 responses were categorized as "Never," "1-2 times," "3-5 times," "6-10 times," "11 times or more," "Refused," and "Don't Know."

Subject inclusion criteria for the analysis were adults 30 years or older at the time of the survey as lean body mass progressively decreases after 20–30 years of age,[17] and it has been found that adults younger than 45 exhibit higher rates of weight cycling than older adults.[6] Subject exclusion criteria for the analysis consisted of participants who were not fasted and did not provide the morning blood sample at the mobile examination center (n=18 312); participants younger than 30 (n=2063); were pregnant or lactating at the time of testing (n=51), and those who were taking hypoglycemic agents or insulin (n=899). The study analysis also excluded people who answered "don't know" or "refused" to WHQ225 (n=15) and who had an underweight BMI (<18.5 kg/m^2) (n=91).

Applying the subject inclusion and exclusion criteria narrowed down the number of subjects to 4100.

The primary dependent variable, HOMA-IR, was calculated by multiplying the participant's fasting blood glucose (mg/dL) by fasting insulin (μU/mL) and then divided by a factor of 405. A categorical variable was then created for IR: a HOMA-IR value greater than 3.2 was classified as having IR and anything less than 3.2 was classified as not having IR. Review of literature shows a lack of a standardized cutoff point for HOMA-IR. A study by Qu et al. examined IR in Hispanic Americans using machine learning methods and found that the best cutoff point was 3.8.[18] This same cutoff was used in a study on Spaniards without clinical IR parameters or family history of diabetes or dyslipidemia.[19] However, 3.8 was the value for the 90th percentile, and 3.2 was the value at the 75th percentile. Son et al. used a HOMA-IR cutoff of ≥2.5 when assessing newly diagnosed diabetes patients in Korea[20] as did Oliveira et al. in Brazil.[21] Ascaso found in another study with Pardo that 2.6 was the HOMA-IR value at the 75th percentile and 4.1 for the 90th percentile.[22] It was decided for the present study that a HOMA-IR value of 3.2 would be an appropriate value for the diverse population because it is close to the median of the studied cut-off values.

STATISTICAL ANALYSIS

Subjects were stratified into 3 groups based on their response to WHQ225— if they have never weight cycled, if they have weight cycled 1-2 times, or if they have weight cycled 3 times or more. The SAS command proc surveyfreq was then used to

calculate the percentages of sex, age group (30-44, 45-59, and 60 years and older), insulin resistance (HOMA-IR > 3.2), ethnicity [Non-Hispanic (NH) white, NH black, Asian American, Mexican Americans, and Other Ethnic Group], and BMI category for each weight cycling group. Normal BMI was defined as ≥18.5 kg/m^2 and <25 kg/m^2; an overweight BMI was defined as ≥25 kg/m^2 and <30 kg/m^2, and an obese BMI was defined as ≥30 kg/m^2. The percentage of participants who were classified as prediabetic based on a fasting blood glucose between 100-125 mg/dL was calculated for each weight cycling group. Next, proc surveyfreq was also used to calculate the percentage of people with diabetes in the fasted adult population including those who took insulin or hypoglycemic agents and who answered the weight history questionnaire. Rao-Scott chi-square tests were analyzed for differences between categorical variables, and *P* values were considered significant if <.05.

Proc surveymeans was used to calculate the average values and corresponding standard deviations for BMI (kg/m^2), maximum historical BMI (kg/m^2), difference in BMI from maximum historical to current (kg/m^2), waist circumference (cm) for men and women separately, HOMA-IR, and % glycosylated hemoglobin. Multiple *t* tests were performed for mean differences between no weight cycling and weight cycling 1-2 times, and then for weight cycling 1-2 times versus weight cycling 3 times or more. To control for type 1 error, a Bonferroni adjustment was made, resulting in a *P* value <.017 being considered significant.

Simple logistic regression (proc surveylogistic) was performed to examine the odds of developing obesity from weight cycling at least once compared to people who have never weight cycled as the reference. Another simple model was set up to examine the

odds of developing IR based on a history of weight cycling as well as other predictor variables: obesity, sex, ethnicity, and age group. The lowest risk factors for developing IR were used as the parameter references for each—never weight cycled, not obese, female, non-Hispanic white, and ages 30-44. Finally, a multivariate logistic regression was performed to determine the odds of developing IR after adjusting for a history of weight cycling, obesity, sex, ethnicity, and age.

RESULTS

In this study's sample population, 53% of the 4100 participants reported weight cycling at least once in their lifetime. Participants' characteristics and cardiometabolic prevalence are presented in Table 1. Prevalence of weight cycling between sexes were significantly different; more females weight cycled than males with 2/3 of the female population having reported weight cycling at least once. Almost half of the male population reported no history of weight cycling. The percentage of each age group—30-44, 45-59, and 60 and older—across the 3 weight cycling categories was significantly different. Adults ages 60 and older were the least likely to have a history of weight cycling, and adults ages 45-59 had the highest prevalence of weight cycling. However, adults ages 30-44 had a prevalence of weight cycling that was only about 2% less than adults ages 45-59. The percentage of each ethnic group was representative of the national population and differences in weight cycling were significant between race/ethnicities. Non-Hispanic Whites weight cycled the most out of all the ethnic groups, and Non-Hispanic Blacks were second. Asian Americans displayed the lowest prevalence of weight cycling.

Table 1. Categorical descriptive statistics stratified by weight cycling history[a]

	Never weight cycled	Weight cycled 1-2 times	Weight cycled 3 times or more	Total	*P* value[b]
N	1922	1146	1032	4100	
Sex (%)					<.001
Females	33.3	31.3	35.5	52.8%	
Males	47.0	27.1	25.8	47.2%	
Age (%)					.007
30-44	37.7	31.8	30.5	33.7%	
45-59	36.0	30.3	33.7	34.2%	
≥60	45.9	25.7	28.4	32.1%	
Race/Ethnicity (%)					<.001
Non-Hispanic Whites	35.8	29.5	34.7	65.6%	
Non-Hispanic Blacks	42.0	28.7	29.3	10.1%	
Mexican Americans	47.0	33.1	19.9	7.5%	
Asian Americans	61.5	27.2	11.3	5.8%	
Other	44.7	27.4	27.9	11.0%	
Body Mass Index Category[c]					<.001
Normal (%)	63.5	23.0	13.5	25.1%	
Overweight (%)	40.5	32.6	26.9	35.1%	
Obese (%)	24.1	30.4	45.4	39.7%	
Insulin Resistance[d] (%)					<.001
Insulin Resistant	33.8	27.7	38.5	33.1%	
Not Insulin Resistant	42.7	30.1	27.2	66.9%	
Prevalence of Prediabetes[e] (%)					.52
Pre-diabetic	40.5	30.0	30.0	56.4%	
Not Pre-diabetic	38.8	29.0	32.3	43.6%	
Prevalence of Diabetes[f] (%)					<.001
Diabetic	29.4	29.6	41.0	18.3%	
Not Diabetic	40.6	29.1	30.3	81.7%	

[a] Data was obtained from participants of the 2015-2016 and 2017-Mar 2020 National Health and Examination Survey (NHANES) who were age 30 and older, not pregnant or lactating, fasted overnight, and who were not taking insulin or hypoglycemic agents. [b] *P* values are given for Rao-Scott chi-square tests and are considered significant if <.05. [c] People with a BMI of less than 18.5 kg/m^2 were excluded (n=91). Normal BMI was defined as 18.5-24.9 kg/m^2; overweight BMI was defined as 25-29.9 kg/m^2, and obese BMI was defined as ≥30 kg/m^2. [d] Insulin resistance was defined as a HOMA-IR >3.2. HOMA-IR was calculated by multiplying the fasting glucose (mg/dL) by the fasting insulin (μU/mL) and then dividing by 405. [e] Prediabetes was defined in individuals who had a fasting blood glucose ≥100 mg/dL and <126 mg/dL. [f] Prevalence of diabetes was analyzed after including individuals who had a fasting blood glucose of ≥126 mg/dL or who were taking insulin or hypoglycemic agents (N=4999).

Approximately 40% of the study's participants had an obese BMI, 35% had an overweight BMI, and 25% had a normal BMI. The average BMI value significantly increased from 27.0 (overweight) to 33.0 (obese) as the history of weight cycling increased from 0 to 3 times or more (Table 2). Furthermore, there was a significantly higher percentage of normal weight and overweight people who did not weight cycle as compared to normal weight and overweight people that had at least some history of weight cycling. In contrast, a significantly higher percentage of people who were obese weight cycled 1-2 times or 3 times or more than those who had never weight cycled. The self-reported highest historical BMI significantly increased as weight cycling history increased. The average difference between the average highest historical BMI and the average current BMI also significantly increased as weight cycling history increased. In other words, participants who never weight cycled had an average overweight BMI and reported their average highest historical BMI to be of overweight status at an average of 1.6 units higher. Participants who weight cycled 1-2 times had an average overweight BMI and reported their average highest historical BMI to be of obese status at an average of 2.0 units higher. Participants who weight cycled 3 times or more had an average obese BMI and reported their average highest historical BMI to be of obese status at an average of 3.0 units higher.

Females' average waist circumference increased as the history of weight cycling increased, and all 3 groups' average value exceeded the 88 cm cutoff that is used as a risk factor for metabolic syndrome. For males, only the "never weight cycled" group had an average waist circumference that was classified as metabolically healthy (<102 cm);

Table 2. Body composition and metabolic variables stratified by weight cycling history[a]

	Never weight cycled	*P* value[b]	Weight cycled 1-2 times	*P* value[c]	Weight cycled 3 times or more
Body Mass Index (kg/m^2)	27.0 ± 0.2	<.001	29.9 ± 0.2	<.001	33.0 ± 0.4
Max historical BMI[d] (kg/m^2)	28.5 ± 0.2	<.001	31.8 ± 0.2	<.001	36.0 ± 0.4
Change in BMI[e]	1.6 ± 0.1	.011	2.0 ± 0.1	<.001	3.0 ± 0.2
Waist Circumference (cm)					
Females	93.3 ± 0.7	<.001	98.4 ± 0.9	<.001	105.4 ± 0.8
Males	97.4 ± 0.6	<.001	104.9 ± 0.8	<.001	112.1 ± 1.3
HOMA-IR[f]	2.8 ± 0.1	.013	3.1 ± 0.1	<.001	3.7 ± 0.2
Fasting Insulin (µU/mL)	10.2 ± 0.4	.002	11.5 ± 0.5	.002	13.4 ± 0.7
% Glycosylated hemoglobin	5.5 ± 0.02	.36	5.6 ± 0.02	.36	5.5 ± 0.02

[a] Data is presented as means ± standard deviations and was obtained from 4100 participants of the 2015-2016 and 2017-Mar 2020 National Health and Examination Survey (NHANES) who were age 30 and older, not pregnant or lactating, fasted overnight, and who were not taking insulin or hypoglycemic agents. Multiple *t* tests were performed for mean differences and a Bonferroni adjustment was made. A *P* value <.017 was considered significant. [b] *P* values for *t* tests ran for significant difference between never weight cycled and weight cycled 1-2 times. [c] *P* values for *t* tests ran for significant difference between weight cycled 1-2 times and weight cycled 3 times or more. [d] Maximum historical BMI was calculated from participants' self-reported highest historical weight (lbs.) and self-reported height (inches). [e] Change in BMI is the Max historical BMI – current measured BMI. [f] HOMA-IR was calculated by multiplying the fasting glucose (mg/dL) by the fasting insulin (µU/mL) and then dividing by 405. HOMA-IR is a dimensionless variable.

males who weight cycled 1-2 times and males who weight cycled 3 times or more had higher waist circumferences that could be used to classify metabolic syndrome.

Average HOMA-IR values significantly increased as history of weight cycling increased (*P*<.017). In total, 33.1% of the study population were classified as having insulin resistance (IR), or a HOMA-IR greater than 3.2. However, only the "never weight cycled" group had an average HOMA-IR that was not IR (2.78 ± 0.1). Even though the "weight cycled 1-2 times" group had the lowest percentage of participants who were insulin resistant at 27.7%, their average HOMA-IR was on the verge of being classified as IR (3.1 ± 0.1). The "weight cycled 3 times or more" group had the highest percentage

of participants who were insulin resistant at 38.5% and an average HOMA-IR that was classified as being IR (3.71 ± 0.2). Average fasting insulin levels significantly increased as history of weight cycling increased ($P<.017$). Average fasting glucose levels between the weight cycling groups showed no significant difference, although all 3 were classified as pre-diabetic. The average values for percent of glycosylated hemoglobin were similar for all 3 groups and showed no significant difference.

Based on having a fasted blood glucose measurement between 100-125 mg/dL, more than half of the study population (56.4%) were categorized as pre-diabetic. However, there was no significant difference in the percentage of people with prediabetes between the 3 weight cycling groups. When including people who took insulin or hypoglycemic agents in the study sample, 18.3% of the population (fasted adults older than 30 who were not breastfeeding nor pregnant) had diabetes. There was a significant difference between the prevalence of diabetes in the 3 groups: more people with diabetes weight cycled 3 times or more. People with diabetes were also more likely to weight cycle than people without diabetes.

In a simple model with obesity listed as the outcome, weight cycling 1-2 times increased the odds of developing obesity by 2 times compared to those who had never weight cycled, and weight cycling 3 times or more increased the odds of developing obesity by 4 times (Table 3). As shown in Table 4 for the results of the simple logistic regression, weight cycling 1-2 times had no significant effect on the odds of developing IR, but those who weight cycled 3 times or more had a 79% higher chance of developing IR ($P<.001$). People with an obese BMI were 8 times more likely to develop IR than

Table 3. Odds of developing obesity from a history of weight cycling[a]

Factors[b]	**Odds Ratio**	**95% CI**	***P* value**[c]
Never Weight Cycled	**reference**		
Weight Cycled 1-2 times	2.21	1.82 – 2.67	<.001
Weight Cycled 3 times or more	4.42	3.49 – 5.59	<.001

[a] Based on a simple logistic regression model with 95% Wald confidence intervals. Obesity was defined as a BMI ≥ 30 kg/m^2. [b] Weight cycling was defined as how many times participants reported intentionally losing 10 pounds or more for the purpose of losing weight. [c] A *P* value <.05 was considered significant.

people with a normal or overweight BMI (*P*<.001), and men were 29% more likely to develop IR than women (*P*=.009). With ethnicity listed as an exposure, the simple model showed that Mexican Americans were 83% more likely to develop IR than NH whites (*P*<.001), and people who identified as other ethnicity were 43% more likely to develop IR than NH whites (*P*=.002). Asian Americans and NH blacks did not differ significantly

Table 4. Odds of developing insulin resistance from independent risk factors[a]

Factors[b]	**Odds Ratio**	**95% CI**	***P* value**[c]
Never Weight Cycled	**reference**		
Weight Cycled 1-2 times	1.16	0.90 – 1.50	.24
Weight Cycled 3 times or more	1.79	1.43 – 2.24	<.001
Not Obese	**reference**		
Obese	8.01	6.43 – 9.98	<.001
Female	**reference**		
Male	1.29	1.07 – 1.55	.009
NH white	**reference**		
Asian American	0.94	0.67 – 1.31	.69
Mexican American	1.83	1.36 – 2.46	<.001
NH black	1.19	0.98 – 1.43	.07
Other ethnic	1.43	1.15 – 1.77	.002
Age 30-44	**reference**		
Age 45-59	1.04	0.79 – 1.36	.78
Age 60+	1.10	0.88 – 1.38	.38

[a] Based on a simple logistic regression model with 95% Wald confidence intervals. Insulin resistance was defined as a HOMA-IR > 3.2. HOMA-IR was calculated as follows: fasted plasma glucose (mg/dL) x fasted serum insulin (μU/L) /405. [b] Weight cycling was defined as how many times participants reported intentionally losing 10 pounds or more for the purpose of losing weight. [c] A *P* value <.05 was considered significant.

from NH whites for the odds of developing IR in the simple model. Age groups also did not differ significantly for the odds of developing IR.

However, when adjusting for obesity, sex, ethnicity, and age, the multivariate logistic regression revealed that any history of weight cycling had no effects on the development of IR (see Figure 1). On the other hand, an obese BMI increased the likelihood of developing IR by almost 9 times compared to a normal or overweight BMI ($P<.001$). In this adjusted model, men's odds of developing IR increased to 50% higher than women's odds ($P<.001$). Adjusting for a history of weight cycling, obesity, sex, and age, the odds of IR increased between race/ethnicities. Asian Americans were 2 times more likely to develop IR than whites ($P<.001$); Mexican Americans were 92% more likely to develop IR than whites ($P<.001$), and other ethnic groups were 45% more likely to develop IR than whites ($P=.002$). Blacks were neither at a higher or lower odds of developing IR than whites. The multivariate model also showed that adjusting for the other factors, people ages 60 and older were 51% more likely to have IR than those in younger age groups ($P<.001$).

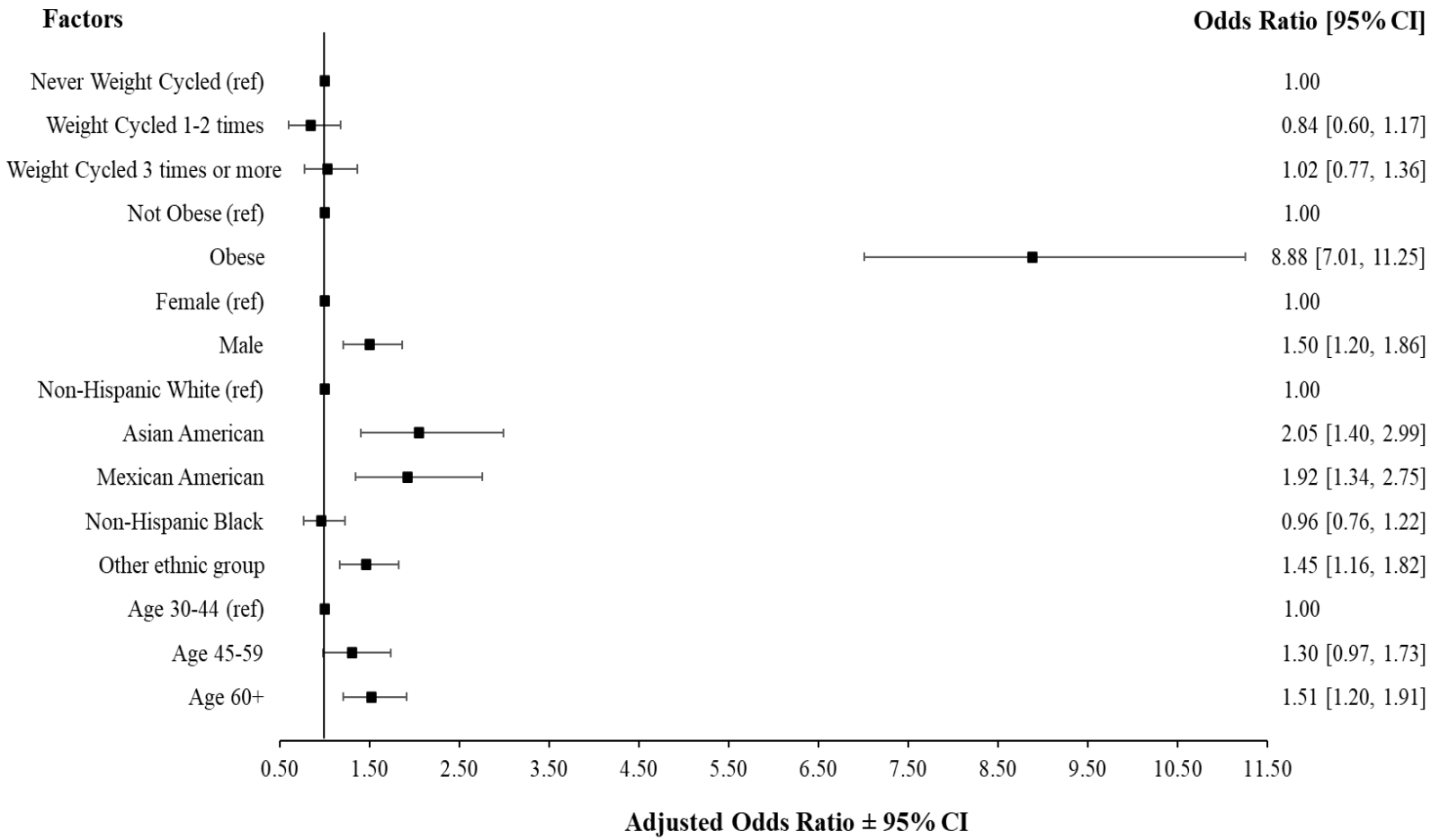

Figure 1. Risk factors for insulin resistance in a multivariate logistic regression for fasted adults without diabetes from the 2015-Mar 2020 NHANES sample (N=4100).

DISCUSSION

This nationally representative study revealed that weight cycling is common amongst American adults, especially amongst women, people ages 30-59, non-Hispanic whites, and people currently with obese BMIs. Women tend to lose weight at a slower rate than men do due to differences in hormone levels and body composition.[23] There is also more pressure for women in westernized countries to comply with the cultural beauty standards that are placed upon them, including the thin ideal. It was for these reasons that it was expected that women would have a greater history of weight cycling than men. Our results in that aspect were similar to what Stevens et al. found[24] but differed from Delahanty et al., who found in their study that males weight cycled more than females.[6] As for the age groups, as expected, the adults aged 60 and older weight cycled the least. A theory for this tendency is that adults who were born in the mid-1950s and earlier were less influenced by diet culture and had different eating patterns than the generations to follow. The prevalence of substantial weight cycling differed between race/ethnicities. Non-Hispanic whites weight cycled the most, followed by non-Hispanic blacks which may indicate that culture plays a role in body acceptance and the relationship with food and exercise. Our results also differed again from Delahanty et al. who found in their study that non-Hispanic blacks weight cycled more than the other ethnic groups.[6] However, in their study, they utilized the Diabetes Prevention Program which studied Americans at high-risk for diabetes and defined a weight cycle as a 5-pound weight loss/regain.

In addition, the data supports the body of literature showing that obesity and related metabolic disorders are prevalent in the US. The average BMIs for the 3 groups

were classified as overweight and obese, and 5 out of 6 of the average waist circumferences exceeded the cutoff used to define metabolic syndrome. The average BMI and waist circumference for both men and women increased with the history of weight cycling, which suggests that a history of weight cycling may be associated with a weight gain and central obesity. However, BMI has its limitations and does not describe lean or fat mass percent and cannot be the sole basis for determining a patient's health status.

What was even more interesting was that weight cycling was the most prevalent amongst participants with obese BMIs. This finding agrees with the evidence that long-term successful weight loss is very difficult to sustain, especially without professional guidance and support during both the weight loss and the weight maintenance phase. As shown in Table 3, repeated attempts to lose weight with the result of gaining it back also led to higher odds of developing obesity (Weight Cycled 1-2 times: OR 2.21, $P<.001$; Weight Cycled 3 times or more: OR 4.42, $P<.001$). This key finding correlates to what Yoo et al. found in their study on obese Korean women—those with a history of weight cycling lost more fat-free mass and less fat mass than women without a history of weight cycling.[25] Furthermore, attempting to manipulate body size through creating an energy deficit can result in negative consequences such as lowering a person's metabolic rate and predisposing them to gaining weight back;[10,24,27] damaging a person's self-efficacy and self-esteem, and can also lead to disordered eating such as binge eating.[10,25] In fact, binge eating has shown to have a bidirectional relationship with obesity.[26] At the same time, it also calls for health professionals to recognize that weight stabilization may be more realistic and healthful for some patients than the goal of reducing body weight via caloric restriction.

Insulin resistance, as established with an elevated HOMA-IR value, affected 33.1% of the total sample population, and prediabetes affected 56.4% of the total sample population. It was interesting that the prevalence of IR was less than the prevalence of prediabetes, because IR usually precedes type 2 diabetes. This may have been due to the limitation of using HOMA-IR to estimate IR in the study population. A person with prediabetes could still display a normal HOMA-IR if they had a fasted glucose in the lower range of the values (<110 mg/dL) and a fasted insulin value that was in the optimal range (<10 μU/mL). Another interesting finding was that the 3 weight cycling groups had either identical or very similar average hemoglobin A1C values. The average values, 5.5 and 5.6, were classified as normal glycosylated hemoglobin values, whereas the average fasting blood glucose values were classified as prediabetic for all 3 weight cycling groups (>100 mg/dL). It is not uncommon for people in the early stages of disease such as prediabetes to have differing diagnostic test results.[28] However, fasting insulin levels significantly increased with the increasing history of weight cycling, which was similar to what Yatsuya et al. found in their study on Japanese men.[9]

When including participants who took hypoglycemic agents or insulin in the study sample, it was found that people with diabetes—those whose fasted glucose level was >125 mg/dL or who used diabetes medication—weight cycled more than people without diabetes. Only about 30% of people with diabetes had reported no history of weight cycling. Furthermore, the adjusted logistic regression found that compared to people with no history of weight cycling, people with a history of weight cycling had no greater likelihood of becoming insulin resistant. This result signified that it was not the higher prevalence of weight cycling that predisposed the people with diabetes to develop

abnormal glucose metabolism but other factors such as genetics, nutrition, and lifestyle. Therefore, we rejected our experimental hypothesis, which was that after adjusting for the confounding variables of BMI category, sex, age category, and race/ethnicity, weight cycling 3 times or more would increase the odds of developing insulin resistance.

The multivariate logistic regression showed that having a BMI $\geq$30 kg/m^2 was by far the leading predictor of developing IR. It was not the weight cycling that increased the risk of insulin resistance per se, but the effects of weight cycling—the increased likelihood of developing obesity—which were highly associated with developing insulin resistance. The multivariate logistic regression presented another interesting result—Asian Americans and Mexican Americans were at an increased risk for insulin resistance after adjusting for weight cycling, obesity, sex, and age. However, this finding may have been due in part to defining IR based on an universal HOMA-IR cutoff value, which could have underestimated IR in the different race/ethnicity populations. On the other hand, Qu et al. had established in their study that the most specific and sensitive HOMA-IR cutoff for Hispanic Americans was 3.8,[18] which implies that our cutoff value of 3.2 may have overestimated IR in Mexican Americans.

Strengths of this study include its large sample size (N=4100) and diverse population. Another strength was that the NHANES weight history questionnaire asked how many times participants had lost 10 pounds or more in order to lose weight. Ten pounds is viewed as a good cutoff point for defining a significant amount of weight for all BMI categories. A fluctuation of 5 pounds which was used by Delahanty et al.[6] seemed insignificant and could be associated with normal bodily responses to diet, fluid intake, and exercise.

Limitations to this study include for one that HOMA-IR has no standard cutoff value for measuring IR, and so a median value of 3.2 from multiple previous studies was chosen. This value may have underestimated IR overall in our study, but also could have overestimated IR in certain race/ethnicities. Thus, using a lower value for HOMA-IR could have shown different effect sizes for weight cycling and insulin resistance. Another limitation to this study was the observational design. Participants self-reported how many times they intentionally lost 10 pounds or more in order to lose weight based off their memory, which gave rise to the possibility of reporting error. Even more, there was no way of quantifying exactly how much weight was lost and in what timeframe, nor how much weight was regained during each weight cycle. It was also assumed that if a participant lost for example, 10 pounds, maintained that weight and then lost another 10 pounds, then that participant would report this as 1 weight loss attempt. In addition, the weight cycling question presumed that the participants measured their weight frequently with an accurate scale during each weight cycle. Another limitation to this study was that the oral glucose tolerance test (OGTT) was not administered in the NHANES mobile examination center during each cycle year. Thus, estimating insulin resistance was limited to using fasting insulin and fasting glucose. Lastly, physical activity status, smoking status, and current weight were not controlled for when predicting insulin resistance in the regression model.

CONCLUSIONS

Findings of this study generally coincide with the review of the literature that weight cycling is associated with an increase in baseline weight and fasting insulin levels.[9] However, even though weight cycling was found to be positively associated with HOMA-IR, it was not the weight cycling that increased the risk of insulin resistance per se, but the effects of weight cycling—the increased likelihood of developing obesity—which were highly associated with developing insulin resistance. A key finding in this study was that Asian Americans and Mexican Americans were at an increased risk for insulin resistance after adjusting for weight cycling, obesity, sex, and age. Future research needs to aim at deciphering optimal ranges for HOMA-IR in different race/ethnicities and for people with normal glucose metabolism. Prospective students and researchers may also desire to use the NHANES 2015-2020 data to determine if an association between a history of weight cycling and cardiovascular risks mirrors the findings in the current literature.

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