2014

The Associations Between HOMA-IR and Muscular Strengthening Activity in Euglycemic U.S. Adults

William Robert Boyer II
University of North Florida

The Associations between HOMA-IR and Muscular Strengthening Activity in euglycemic U.S. Adults

by

William Robert Boyer II

A thesis submitted to the Department of Clinical and Applied Movement Science

in partial fulfillment of the requirements for the degree of

Master of Science in Exercise Science and Chronic Disease

UNIVERSITY OF NORTH FLORIDA

BROOKS COLLEGE OF HEALTH

July, 2014

Dedication & Acknowledgements

The completion of a Master's program requires a strong will, work ethic and desire to learn. It also cannot be obtained without full support from the ones closest to you. My academic goals have become a reality because of the patience and support of my wife and family. This thesis project is dedicated to my wife and family.

Thank you to my wife Hannah Rose Boyer for her support, understanding, love and sacrifice. Without you I never would have completed this project. Thank you to my mother and father for being an incredible source of strength and encouragement and for setting the example for hard work and dedication in my life. Thank you to my little brother Matt for your friendship, encouragement, and love over the past 19 years. I love you all.

I would also like to thank my committee members Dr. Tammie M. Johnson, DrPH, M.P.H., and Dr. Eugene C. Fitzhugh, Ph.D. for their guidance and leadership. To Dr. Johnson, I cannot thank you enough for your patience, guidance, and wisdom in helping me achieve my goal. I will always remember to just "slow down" in my future work. To Dr. Fitzhugh, I cannot thank you enough for your contribution to this project and for the opportunity to continue my education and passion at the University of Tennessee. You both exemplify what it truly means to be an expert. Thank you also goes to my fellow graduate research assistant Michael Ryan Richardson. Without your knowledge, wisdom and friendship this project would not have been finished. It is an honor to call you a friend.

Finally, I would like to thank my committee chairperson and mentor, Dr. James R. Churilla, Ph.D., MPH, M.S., RCEP, FACSM, for believing in me as a person and as a student. Your mentorship, friendship, and wisdom have been priceless and I cannot thank you enough. Without you none of this would have happened. Thank you.

The thesis of William Robert Boyer II is approved: (Date)

_____ _____

Dr. James R. Churilla, Ph.D., M.P.H., M.S., RCEP, FACSM
Committee Chairperson

_____ _____

Dr. Tammie M. Johnson, Dr.P.H., M.P.H.
Committee Member

_____ _____

Dr. Eugene C. Fitzhugh, Ph.D.
Committee Member

Accepted for the Department:

_____ _____

Dr. Joel W. Beam, Ed.D, ATC, LAT
Chair, Department of Clinical & Applied Movement Sciences

Accepted for the College:

_____ _____

Dr. Pamela S. Chally, PhD, RN
Dean, Brooks College of Health

Accepted for the University:

_____ _____

Dr. Len Roberson, Ph.D.
Dean of the Graduate School

Table of Contents

Appendices

List of Tables

Table **Page**

Nomenclature

cm	centimeter
drinks/day	drinks per day
kg/m^2	kilograms per meter squared
mg/L	milligrams per liter
min/wk	minutes per week
mmHg	millimeters of mercury
mmol/L	millimols per liter
mU/ml	milli units per deciliter
Q	quartile
R_s	Spearman correlation coefficient
yr	year

List of Abbreviations

AT	aerobic training
ATP	Adult Treatment Panel
β-cell	Beta cell
BMI	body mass index
BRFSS	Behavioral Risk Factor Surveillance System
CDC	Centers for Disease Control and Prevention
CHD	coronary heart disease
CI	confidence interval
CIGMA	continuous infusion of glucose with model assessment
CRP	C - reactive protein
CVD	cardiovascular disease
DBP	diastolic blood pressure
DHHS	Department of Health and Human Services
DIQ	Diabetes Interview Questionnaire
Glut4	Glucose transporter 4
HDL-C	high-density lipoprotein cholesterol
HOMA-IR	homeostatic model assessment of insulin resistance
IFG	impaired fasting glucose
IGT	impaired glucose tolerance
IR	Insulin Resistance
LBM	lean body mass
LDL-C	low-density lipoprotein cholesterol

LTPA	leisure-time physical activity
MEC	mobile examination center
MetS	metabolic syndrome
MyHC	myosin heavy chain
MSA	muscle strengthening activity
NCEP	National Cholesterol Education Program
NCHS	National Center for Health Statistics
NGT	normal glucose tolerance
nH	non-Hispanic
NHIS	National Health Interview Survey
NHANES	National Health and Nutritional Examination Survey
OGTT	oral glucose tolerance test
OR	odds ratio
PA	physical activity
PAD	physical activity data
PPS	probability proportional to a measure of size
PSU	primary sampling unit
QUICKI	quantitative insulin sensitivity check index
RM	repetition maximum
RT	resistance training
SAS	statistical analysis software
SBP	systolic blood pressure
SE	standard error

SMI	skeletal muscle index
SUDAAN	software for survey data analysis
WC	waist circumference
U.S.	United States

Abstract

Background: Muscular strengthening activity (MSA) has been shown to be inversely associated with insulin resistance (IR). The associations between quartiles of the homeostatic model assessment of insulin resistance (HOMA-IR) and self-reported MSA in a nationally representative sample of euglycemic U.S. adults were examined.

Methods: Sample included adult participants (≥20 years of age [n=2,543]) from the 1999-2004 National Health and Nutrition Examination Survey (NHANES). HOMA-IR was categorized into quartiles based on every 25th percentile. No MSA was the dependent variable.

Results: Following adjustment for covariates, those with HOMA-IR values in third ($p<0.01$) and fourth ($p<0.001$) quartiles were found to have significantly greater odds of reporting no MSA. Following further adjustment for non-MSA specific leisure time physical activity, results remained significant ($p<0.05$ third, $p<0.001$ fourth). A significant positive trend was seen across quartiles of HOMA-IR ($p=0.01$) for odds of reporting no MSA.

Conclusions: Having a higher HOMA-IR value is associated with greater odds of reporting no MSA in euglycemic U.S. adults.

Chapter One: Introduction

Background

Insulin resistance (IR) is characterized by the inability of the body to properly utilize endogenous insulin in order to maintain glucose homeostasis. Insulin resistance has been shown to be highly associated with type 2 diabetes(1,2). Moreover, studies have also shown that IR is highly prevalent in subjects who are apparently healthy(3,4), approximately 1/3 of euglycemic adults. Bonora et al.(1) investigated the association between risk factors for type 2 diabetes and incidence of type 2 diabetes in white subjects without diabetes. Results revealed that subjects in the highest quartile of IR as well as subjects with lowered β-cell secretion rates had higher rates of incidence for type 2 diabetes ($p<0.001$). Currently diabetes is estimated to affect approximately 8.3% of the population, both diagnosed and undiagnosed(5). According to a study conducted by Boyle et al.(6), diabetes prevalence is projected to reach between 21-33% by the year 2050, depending upon incidence and mortality rates. The economic burden of diabetes in 2012 was approximately $245 billion(7), a significant increase compared to the $174 billion in 2007(8).

Many studies have shown a significant association between higher levels of IR and cardiovascular disease (CVD)(1,9,10); all-cause mortality(11) as well as several cardio metabolic risk factors such as obesity(12-14), inflammation(15,16), hypertension(18), dyslipidemia(13,17,19) and hyperglycemia(13,17) in subjects without diabetes. Hanley et al.(9) investigated the associations between higher levels of IR (categorized into quintiles) and CVD risk in Mexican Americans and Non-Hispanic Whites without diabetes. Results revealed a significant trend ($p<0.0001$) in risk for CVD across quintiles of IR. Furthermore, a significantly increased relative risk for CVD was

seen in those in the highest quintile of IR compared to the lowest (2.52, 95% CI 1.46–4.36). Results also revealed a significant positive trend across quintiles for IR for several cardio metabolic risk factors including blood pressure, high-density lipoprotein cholesterol (negative trend [HDL-C]), low-density lipoprotein cholesterol (LDL-C), adiposity measurements, fasting insulin and glucose and triglycerides.

Traditional Approach-Muscular Strengthening Activity and Insulin Resistance

In order to properly treat or prevent the progression of IR, physical activity (PA), specifically muscular strengthening activity (MSA), has been investigated as a potential modality. Traditionally, MSA (or characteristics of MSA such as lean body mass or strength) has been investigated as the independent variable and IR as the dependent variable(20-28). Miller et al.(24) reported a significant reduction (37.5%, $p<0.05$) in basal insulin levels in response to an oral glucose tolerance test (OGTT) in eight young healthy male subjects following a 10-week progressive MSA protocol, illustrating decreases in peripheral IR. Furthermore, Cheng et al.(21) investigated the associations between volumes of MSA and IR, measured via the quantitative insulin sensitivity check index (QUICKI), in subjects without diabetes utilizing data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES). Results revealed a significant difference in QUCIKI levels for subjects reporting ≥1 day/week of MSA ($p<0.05$). Following adjustment for covariates, results remained significant in females but not males. Significance was only seen in volumes of MSA ≥3 days/week ($p<0.05$) in males. These data suggest that MSA is inversely associated with IR in apparently healthy subjects.

Non-traditional-Clinical Approach

A novel approach to surveillance data utilizes a model with the adverse metabolic condition as the independent variable and the health behavior as the dependent variable. This method provides insight into PA and MSA patterns among groups who are at greater metabolic risk. Few studies have used this model(29-33). Zhao et al.(32) reported that subjects with diabetes reported lower levels of total, moderate and vigorous PA compared to those without diabetes. Furthermore, subjects with diabetes had lower odds of reporting meeting the 2008 DHHS and 2007 American Diabetes Association PA recommendations compared to those without. Another cross-sectional analysis conducted by Zhao et al.(33) found similar associations between diabetes status and reported PA patterns among adults ≥65 years of age. Churilla et al.(29) reported the prevalence of meeting the 2008 DHHS PA recommendations to be 59.1% among participants reporting high-cholesterol (HC) and 68.3% among participants not reporting HC ($p<0.05$). Another study by Churilla et al.(30) reported significantly lowered odds (OR 0.85, 95% CI 0.82-0.88) for meeting the DHHS PA recommendations in subjects with hypertension compared to those without hypertension. These studies, utilizing what could be viewed as a clinical approach to surveillance research all illustrate that at a population level, those with chronic conditions may be engaging in significantly lower volumes of PA, thus not receiving the proven health benefits of leading an active lifestyle. This approach to analyzing surveillance data may assist clinicians (e.g., physicians) in identifying those who need lifestyle counseling and PA recommendations.

Physician Recommended Physical Activity

Barnes et al.(34) reported that the prevalence of doctors recommending exercise

or physical activity to adult patients is approximately 32.4% and is significantly higher in subjects with diabetes, CVD, or hypertension compared to those without. Despite these recommendations, Zhao et al.(32) showed that subjects with diabetes report being less active than those without diabetes. Interestingly, there have been no studies investigating specifically the prevalence of doctor recommended PA among subjects with IR, a highly prevalent, deleterious metabolic condition among euglycemic adults.

Prevalence of Muscular Strengthening Activity

Currently, approximately 30% of the U.S. adult population meets the 2008 DHHS MSA recommendations of ≥2 days/week(35-38). From these prevalence estimates it can be deduced that 70% of U.S. adults are not participating in adequate amounts of MSA, which has been shown to reduce the risk of diabetes(39) and CVD(40) as well as reduce levels of IR. However, no studies have investigated the MSA among euglycemic subjects with IR.

Purpose and Research Questions

There is a paucity of literature investigating the relationship between IR and MSA in euglycemic adults. The proposed study will investigate the potential associations between quartiles of IR (via HOMA-IR) and self-reported MSA in euglycemic U.S. adults. The specific research questions addressed by this study are as follows:

1. Is there a significant association between quartiles of HOMA-IR and self-reported MSA in euglycemic U.S. adults?

2. Is there is a significant association between quartiles of HOMA-IR and self-reported MSA in euglycemic U.S. adults adjusting for non-MSa specific leisure time physical activity (LTPA)?

To the best of our knowledge, this is the first study to investigate these associations utilizing HOMA-IR as the primary independent variable and MSA as the dependent variable. This is a novel approach to the study design characterized by using IR as an explanatory variable rather than the outcome variable. Ultimately, this study will add to the existing literature that investigates the relationship between IR and MSA as well as the literature utilizing metabolic health as the independent variable and health behavior as the dependent variable.

Project Description

In this study the sample will be limited to adults ≥ 20 years of age that participated in the 1999-2004 NHANES. Non-fasted participants, participants with pre-diabetes or diabetes, participants with missing data on any covariates, and pregnant women will be excluded from this study. There are several limitations inherent to the cross-sectional design:

1. Inability to establish causality.
2. Potential for recall bias due to the use of questionnaires to assess certain variables.
3. The self-reported variables are subject to the social-desirability effect.
4. Residual confounding.

REFERENCES

1. Bonora E, Kiechl S, Willeit J et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes 2004;53:1782-9.
2. Zavaroni I, Bonora E, Pagliara M et al. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 1989;320:702-6.
3. Li C, Ford ES, McGuire LC, Mokdad AH, Little RR, Reaven GM. Trends in hyperinsulinemia among nondiabetic adults in the U.S. Diabetes Care 2006;29:2396-402.
4. Ioannou GN, Bryson CL, Boyko EJ. Prevalence and trends of insulin resistance, impaired fasting glucose, and diabetes. J Diabetes Complications 2007;21:363-70.
5. Centers for Disease Control and Prevention. 2011 National Diabetes Fact Sheet. http://www.cdc.gov/diabetes/pubs/estimates11.htm, 2011.
6. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. Popul Health Metr 2010;8:29.
7. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. Diabetes Care 2013;36:1033-46.
8. American Diabetes Association. Economic costs of diabetes in the U.S. In 2007. Diabetes Care 2008;31:596-615.

9. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177-84.

10. Hedblad B, Nilsson P, Engström G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002;19:470-5.

11. Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the U.S. Diabetes Care 2010;33:1179-85.

12. Farin HM, Abbasi F, Reaven GM. Body mass index and waist circumference both contribute to differences in insulin-mediated glucose disposal in nondiabetic adults. Am J Clin Nutr 2006;83:47-51.

13. McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G. Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. Metabolism 2004;53:495-9.

14. Reaven G, Abbasi F, McLaughlin T. Obesity, insulin resistance, and cardiovascular disease. Recent Prog Horm Res 2004;59:207-23.

15. Chen J, Wildman RP, Hamm LL et al. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2960-5.

16. McLaughlin T, Abbasi F, Lamendola C et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002;106:2908-12.

17. Resnick HE, Jones K, Ruotolo G et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic american indians: the Strong Heart Study. Diabetes Care 2003;26:861-7.

18. Ferrannini E, Buzzigoli G, Bonadonna R et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350-7.

19. Kim JS, Kang HT, Shim JY, Lee HR. The association between the triglyceride to high-density lipoprotein cholesterol ratio with insulin resistance (HOMA-IR) in the general Korean population: based on the National Health and Nutrition Examination Survey in 2007-2009. Diabetes Res Clin Pract 2012;97:132-8.

20. Ahmadizad S, Haghighi AH, Hamedinia MR. Effects of resistance versus endurance training on serum adiponectin and insulin resistance index. Eur J Endocrinol 2007;157:625-31.

21. Cheng YJ, Gregg EW, De Rekeneire N et al. Muscle-strengthening activity and its association with insulin sensitivity. Diabetes Care 2007;30:2264-70.

22. Craig BW, Everhart J, Brown R. The influence of high-resistance training on glucose tolerance in young and elderly subjects. Mech Ageing Dev 1989;49:147-57.

23. Kodama S, Shu M, Saito K et al. Even low-intensity and low-volume exercise training may improve insulin resistance in the elderly. Intern Med 2007;46:1071-7.

24. Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. Med Sci Sports Exerc 1984;16:539-43.

25. Miller JP, Pratley RE, Goldberg AP et al. Strength training increases insulin action in healthy 50- to 65-yr-old men. J Appl Physiol (1985) 1994;77:1122-7.

26. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab 2011;96:2898-903.

27. Barzilay JI, Cotsonis GA, Walston J et al. Insulin resistance is associated with decreased quadriceps muscle strength in nondiabetic adults aged >or=70 years. Diabetes Care 2009;32:736-8.

28. Karelis AD, Tousignant B, Nantel J et al. Association of insulin sensitivity and muscle strength in overweight and obese sedentary postmenopausal women. Appl Physiol Nutr Metab 2007;32:297-301.

29. Churilla JR, Johnson TM, Zippel EA. Association of physical activity volume and hypercholesterolemia in US adults. QJM 2013;106:333-40.

30. Churilla JR, Ford ES. Comparing physical activity patterns of hypertensive and nonhypertensive US adults. Am J Hypertens 2010;23:987-93.

31. Zhao G, Ford ES, Li C, Mokdad AH. Are United States adults with coronary heart disease meeting physical activity recommendations? Am J Cardiol 2008;101:557-61.

32. Zhao G, Ford ES, Li C, Mokdad AH. Compliance with physical activity recommendations in US adults with diabetes. Diabet Med 2008;25:221-7.

33. Zhao G, Ford ES, Li C, Balluz LS. Physical activity in U.S. older adults with diabetes mellitus: prevalence and correlates of meeting physical activity recommendations. J Am Geriatr Soc 2011;59:132-7.

34. Barnes PM, Schoenborn CA. Trends in adults receiving a recommendation for exercise or other physical activity from a physician or other health professional. NCHS Data Brief 2012:1-8.

35. Carlson SA, Fulton JE, Schoenborn CA, Loustalot F. Trend and prevalence estimates based on the 2008 Physical Activity Guidelines for Americans. Am J Prev Med 2010;39:305-13.

36. Loustalot F, Carlson SA, Kruger J, Buchner DM, Fulton JE. Muscle-strengthening activities and participation among adults in the United States. Res Q Exerc Sport 2013;84:30-8.

37. Centers for Disease Control and Prevention. Adult Participation in Aerobic and Muscle-Strengthening Physical Activities-United States, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6217a2.htm, 2013.

38. Centers for Disease Control and Prevention.Trends in strength training--United States, 1998-2004. MMWR Morb Mortal Wkly Rep 2006;55:769-72.

39. Grøntved A, Rimm EB, Willett WC, Andersen LB, Hu FB. A prospective study of weight training and risk of type 2 diabetes mellitus in men. Arch Intern Med 2012;172:1306-12.

40. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. JAMA 2002;288:1994-2000.

Chapter Two: Review of Literature

Insulin Resistance: Definition, History, and Prevalence

Insulin resistance (IR) is characterized by the inability of the body's tissues to proper utilize and respond to endogenous insulin(1). Insulin resistance manifests itself in the body though multiple mechanisms and at different sites. Two examples are: hepatic IR manifesting itself as impaired fasting glucose (IFG); and peripheral IR manifesting itself as impaired glucose tolerance (IGT)(2). Both of these states of glucose imbalance lead to metabolic issues attributable to hyperinsulinemia; which is considered a state of IR(1).

The idea of insulin insensitivity or "resistance" was first demonstrated in 1936 by Himsworth(3). It was in this study that the differentiation of insulin-sensitive diabetes (type 1) and insulin insensitive diabetes (type 2) was determined through specific tests investigating insulin response to carbohydrates. Furthermore, this study proposed several possibilities that could contribute to the insulin resistive state: 1) the liver may be pouring so much sugar into the blood that the effect of the injected insulin is overwhelmed; 2) the liver may be incapable of storing the ingested sugar; or 3) the characteristic action of insulin in promoting storage of blood-sugar in the peripheral tissues may be unable to manifest itself(3). In 1960, Yalow and Berson(4) suggested that insulin sensitivity, and not deficiency in insulin secretion, could play an important role in the hyperglycemia of diabetes.

Current prevalence estimates of IR vary depending on definition, site and measurement of IR(2). In the 1988 Banting lecture, Reaven(5) stated that IR is present in the majority of patients with IGT or type 2 diabetes and in approximately 25% of non-obese individuals with normal oral glucose tolerance. In a cross-sectional analysis

conducted by Ioannou et al.(6) prevalence of IR was determined using a representative sample from the Third National Health and Nutrition Examination Survey (NAHNES III, 1988-1992) and from the 1999-2002 NAHNES with and without diabetes. Insulin resistance was defined using the homeostatic model assessment of IR (HOMA-IR). Subjects in the upper quartile of HOMA-IR were characterized as being insulin resistant. Following adjustment for covariates, the prevalence of IR in subjects from NHANES III without diabetes or IFG was 26.2% (95% CI 23.6–28.9). Prevalence of IR was significantly higher in subjects from the 1999-2002 NHANES; 32.2% (95% CI 29.5–35.0) indicating a significant positive trend in IR among subjects with normoglycemia. In another cross-sectional analysis conducted by Li et al.(7), investigators sought to determine specific trends in hyperinsulinemia among U.S. adults without diabetes utilizing data from NHANES III and the 1999-2002 NHANES. Hyperinsulinemia was defined as residing in the upper 75^{th} percentile of log-transformed fasting insulin. Across the entire sample, the mean fasting insulin level was significantly higher ($p=0.025$) in subjects from the 1999-2002 NHANES (2.16 ± 0.01) compared to those from NHANES III (2.12 ± 0.01). Moreover, the age-adjusted prevalence of hyperinsulinemia increased by 35.1% (25.8% in NHANES III to 34.8% in the 1999-2002 NHANES, $p<0.001$).

Bonora et al.(8) investigated the prevalence of IR among individual metabolic disorders in a sample of 888 subjects from the Bruneck study. Insulin resistance was defined as the lower limit of the top quintile of HOMA-IR distribution. A significant positive trend was seen across quintiles of IR and prevalence of IGT ($p=0.011$), hypercholesterolemia ($p<0.001$), hypertriglyceridemia ($p<0.001$), low high-density lipoprotein cholesterol (HDL-C, $p=0.049$), and hypertension ($p=0.002$). The prevalence

of IR was 65.9% in IGT subjects, 53.5% in subjects with hypercholesterolemia, 84.2% in subjects with hypertriglyceridemia, 88.1% in subjects with low HDL cholesterol, and 58.0% in hypertensive subjects. Insulin resistance is a complex, multifactorial metabolic condition that is increasing in prevalence, even in euglycemic subjects. Furthermore, IR appears to be highly prevalent among several cardio-metabolic risk factors.

Homeostatic model assessment of insulin resistance

History and physiological rationale

In 1985, Matthews et al.(9) created a model known as the HOMA-IR to estimate both IR and β-cell function. The physiological basis for HOMA-IR utilizes the relationship between basal concentrations of glucose and insulin, reflecting the action of the negative feedback-loop between the liver and the β-cells(10). Hepatic IR can be estimated based on the effects of reduced insulin secretion capacity, leading to increased hepatic glucose efflux. This increase in basal plasma glucose stimulates increased secretion of insulin within the portal vein, until glucose levels return to normal: thus the "feed-back" loop between the liver and β-cells. The basal plasma insulin levels necessary to maintain normal glucose levels are directly proportional to the grade of IR(10). Based on these interactions between the liver and β-cells, a nonlinear computer model was created to allow for assessment of IR and β-cell function(9). This model allows for a prediction of either IR or β-cell function based solely on a subjects fasting insulin and basal glucose levels. The following represents the HOMA-IR equation: [fasting serum insulin (mU/ml) x fasting plasma glucose (mmol/l)]/22.5. It is important to note that

while HOMA-IR is primarily a reflection of hepatic IR, there is a 70% correlation between hepatic IR and peripheral IR.(2)

Comparison to other techniques

Values from HOMA-IR have been compared and validated against several other techniques for assessing IR,(9,11) such as the euglycemic-hyperinsulnemic clamp, the hyperglycemic clamp, and the continuous infusion of glucose with model assessment (CIGMA). In the original study conducted by Matthews et al.(9), HOMA-IR was validated (via the Spearman correlation coefficient test) against several other methods for assessing IR, both in euglycemic and subjects with diabetes. Strong correlations were seen between HOMA-IR and the euglycemic hyperinsulinemic clamp in subjects with (R_s=0.92,p<0.0001) and without diabetes (R_s=0.83,p<0.01), the hyperglycemic clamp in a combined sample of subjects with and without diabetes (R_s=0.69,p=0.0005), and the CIGMA method in subjects with (R_s=0.97, p<0.0001) and without (R_s=0.69,p<0.02) diabetes. Bonora et al.(12) compared insulin sensitivity, assessed by a four hour euglycemic and hyperinsulinemic clamp, to HOMA-IR in 115 subjects with varying level of insulin sensitivity and glucose tolerance. Sixty-two subjects had diagnosed diabetes and 53 subjects were without diabetes. Results showed strong correlations between clamp-measured total glucose disposal and HOMA-IR (r=0.820, p<0.0001). Furthermore, strong correlations were seen between clamp measurements and HOMA-IR in men (r=0.800), women (r=0.796), younger (aged 50 years, r=0.832) and older (r=0.800) subjects, non-obese (BMI<27 kg/m^2, r=0.800) and obese (r=0.765) subjects, subjects with (r=0.754) and without (r=0.695) diabetes, and normotensive (r=0.786) and hypertensive

(r=0.762) subjects. In 87 subjects with NGT, García-Estévez et al.(13) revealed a significant correlation (r=0.70, p=0.001) between HOMA-IR and CIGMA.

HOMA-IR Uses (Cross-sectional and Prospective)

HOMA-IR has been utilized as a measure of IR in over 500 published articles(11). Furthermore, greater than 50% of those articles have utilized the model in subjects without diabetes(11). Many cross-sectional studies have utilized HOMA-IR as a measurement of IR(14-16). Ausk et al.(14) revealed a significant relationship between all-cause and CVD mortality across quartiles of HOMA-IR in subjects without diabetes. Healy et al.(15) investigated the associations between increasing levels of sedentary time and cardio-metabolic risk in a sample of 4,757 adults (≥20 years) from the 2003-2006 NHANES. Results revealed a significant positive trend across quartiles of total sedentary time and HOMA-IR ($p<0.001$). Haffner et al.(16) investigated the correlations between HOMA-IR and fasting insulin in a cross-sectional analysis of 2,465 subjects from the San Antonio Heart Study. Results revealed a significant correlation between HOMA-IR and fasting insulin in subjects with (r=0.908) and without (r= 0.991) diabetes. Utilizing data from the NHANES III, Durward et al.(17) investigated the risk of mortality across varying definitions of metabolic health. Metabolically healthy was defined as either: 1) HOMA-IR <2.5; 2) ≤2 Adult Treatment Panel (ATP) III metabolic syndrome criteria; 3) combined definition using ≤1 of the following: HOMA-IR ≥1.95 (or diabetes medications), triglycerides ≥1.7 mmol/L, HDL-C <1.04 mmol/L (males) or <1.30 mmol/L (females), LDL-C ≥2.6 mmol/L, and total cholesterol ≥5.2 mmol/L (or cholesterol-lowering medications). Subjects considered metabolically unhealthy based on the HOMA-IR definition had a significantly greater hazard ratio for all-cause mortality

(2.07, p<0.01) compared to those who were considered metabolically healthy by HOMA-IR definition.

HOMA-IR has also been used as a measure of IR in many prospective studies(18-20). Bonora et al.(18) investigated the incidence rates and risk factors for type 2 diabetes in cohort of white individuals who participated in the Bruneck Study. Results revealed that subjects in the highest quartile of HOMA-IR had significantly higher odds of developing type 2 diabetes (OR 8.5, p<0.001). Furthermore, it was revealed that every one-standard deviation increase in HOMA-IR coincided with increased odds for developing type 2 diabetes (OR 1.7, p< 0.018). Another study conducted by Bonora et al.(20) revealed that a one-unit increase in HOMA-IR was associated with an increased odds for incident CVD during (OR 1.56, p<0.001) in subjects with type 2 diabetes. Sung et al.(19) investigated the relationship between HOMA-IR and incident hypertension in a sample of euglycemic, normotensive Korean adults (n= 10,894). Results revealed a significant trend across quartiles of HOMA-IR and incident hypertension after five years of follow-up (p<0.01). Furthermore, subjects in the third (OR 1.5, p<0.05) and fourth (OR 1.7, p<0.05) quartiles of HOMA-IR had significantly higher odds of developing hypertension compared to those in the first quartile.

Misuses of HOMA-IR

The use of HOMA-IR as a measure of IR is not appropriate for all assessments and study designs. The use of HOMA-IR in animal studies has not been validated and also violates some physiological assumptions made by the model(11). HOMA-IR also cannot be used to report β-cell function in isolation(11). Due to the relationship between β-cell secretion rate and insulin sensitivity it is possible to misinterpret the results of the

model as issues with β-cell function when in actuality it is attributable to high insulin sensitivity and not failing β-cells(11). An example of this is using HOMA-IR as a measure of IR in a fit athlete with 50% β-cell function and 200% insulin sensitivity. A subject with 50% β-cell function would intuitively be considered to have failing β-cells. However, the attenuated β-cell function is attributable to high levels of insulin sensitivity and not complications with β-cells(11). Thus, this means using HOMA-IR in one subject, specifically in a highly insulin sensitive subject, would elicit a possible misinterpretation of the function of their β-cells.

Muscular strengthening activities

Muscular strengthening activities (MSA) are exercise modalities that have been shown to help play a role in the prevention and management of multiple chronic diseases and metabolic risk factors. Currently the Department of Health and Human Services (DHHS) recommends participation in MSA at moderate or high intensity; involving all major muscle groups (the legs, hips, back, chest, abdomen, shoulders, and arms) ≥2 days/week(21). The DHHS defines MSA as participation in activities that overload the muscles. These include: resistance training (RT), such as weight training, working with resistance bands, doing calisthenics utilizing body weight for resistance (such as push-ups, pull-ups, and sit-ups), carrying heavy loads, or heavy gardening (such as digging or hoeing)(21).

The current prevalence estimates of MSA participation ranges from approximately 6%-31.7%(22-25). Utilizing data from the 2009 Health Styles survey, Loustalot et al.(25) reported that 31.7% of respondents reported participation in MSA ≥2 days/week. However, only 6.0% of respondents reported adequate MSA including all

seven major muscle groups. The Centers for Disease Control (CDC) examined the prevalence of meeting the DHHS MSA recommendations using data from the 1998-2004 National Health Interview Survey (NHIS)(24). Results revealed a prevalence of 19.4% (95% CI 19.0-20.3) in 2004. Using data from the 1998-2008 NHIS, Carlson et al.(22) reported a 21.9% (95% CI 21.2-22.7) prevalence of adequate MSA participation in 2008. The most recent estimates for MSA participation were reported by the CDC using data from the 2011 Behavior Risk Factor Surveillance Survey (BRFSS)(23). Analysis revealed a prevalence estimate of 29.3%. Based on these data it is estimated that the prevalence of meeting the DHHS MSA recommendations is approximately 20-30%.

Relationship to insulin resistance/glycemic control

Several studies have revealed significant inverse associations between IR and MSA in subjects that are euglycemic(26-31). Ahmadizad et al.(26) investigated the effect of resistance or endurance training on IR in 24 healthy males (35–48 years). Study subjects had no medical condition that would inhibit exercise participation. Furthermore, subjects had not participated in regular exercise for at least 12 months. Subjects were randomly assigned to one of three groups: endurance training group (n=8), RT group (n=8) or control group (n=8). Insulin resistance was assessed via HOMA-IR. Following intervention, significant reductions in IR were seen in both the resistance (38.5%, $p<0.05$) and endurance training groups (35.7%, $p<0.05$). No significant differences were seen between exercise intervention groups.

In a cross-sectional analysis conducted by Cheng et al.(27), investigators examined the associations between MSA and insulin sensitivity (measured via the qualitative insulin sensitivity check index [QUICKI](32)), fasting insulin, and fasting

glucose. Subjects (n=4,504) participated in the 1999-2004 NHANES and did not have diabetes. Muscular strengthening activity was divided into three categories: low (<1 day/week), moderate (1–2.9), or high (≥3). Following adjustment for covariates, women reporting moderate (p=0.025) or high (p=0.021) amounts of MSA had significantly higher QUICKI levels compared to those reporting low levels of MSA. Furthermore, women reporting high levels of MSA had significantly lowered fasting insulin levels (p= 0.007) compared to those reporting low amounts of MSA. In men, only those reporting high levels of MSA had significantly higher QUICKI levels (p=0.003) and significantly lowered fasting insulin levels (p=0.007) compared to those reporting low MSA levels.

Miller et al.(28) investigated the effects of a 10-week isotonic RT program on glucose tolerance, fasting insulin and the insulin response to an OGTT. College-aged subjects without diabetes were used. Following intervention, significant changes were seen in basal plasma insulin levels (37.5%, $p<0.05$), indicating significant decreases in IR. Moreover, the insulin response to a 100-g OGTT was significantly reduced (18.0% $p<0.05$), further illustrating significant reductions in IR. In another trial, Miller et al.(29) investigated the effects of a 16-week RT intervention on IR in 11 healthy men (50-63 years). Insulin resistance and action was assessed via a two-step hyperinsulinemic-euglycemic glucose clamp and an OGTT. Following the RT intervention, there were significant decreases in both fasting plasma insulin levels ($p<0.05$) and insulin levels in response to an OGTT ($p<0.05$). Glucose infusion rates during the hyperinsulinemic-euglycemic glucose clamp increased 24% ($p<0.05$) during low insulin infusion and increased 22% ($p<0.05$) during high insulin infusion; indicating increases in peripheral insulin sensitivity.

Craig et al.(30) investigated the insulin response to an OGTT following a 12-week RT intervention in six younger (23 ± 1 year) and nine older (63 ± 1 year) subjects. Insulin response to an OGTT was significantly reduced in both groups ($p<0.05$). The sum insulin response to an OGTT decreased by 31.8% in the younger group and decreased by 32.6% in the elderly group, indicating reductions in peripheral IR. Kodama et al.(31) investigated the effects of low-intensity and low-volume exercise training on IR in elderly subjects. Subjects (n=56, 64±6 years), participated in a 12-week exercise intervention that included aerobic and RT. Results revealed a significant reduction in IR (21%, $p<0.05$), independent of BMI changes.

In a cross-sectional analysis conducted by Churilla et al.(33), investigators sought to determine the associations between meeting the current DHHS MSA recommendations and components of metabolic syndrome. Subjects (n=5,618, ≥20 years) participated in the 1999-2004 NHANES. Metabolic syndrome was defined using the American Heart Association/ National Heart, Lung, and Blood Institute cut-points. Following adjustment for potential confounding, subjects reporting meeting the DHHS MSA recommendations had lower odds of having IFG (OR 0.71, $p<0.05$) compared to subjects reporting no MSA. Furthermore, the prevalence of IFG was significantly lower in subjects meeting the DHHS MSA recommendations (28.3%, 95% CI 24.8-32.1) compared to those reporting no MSA (38.0%, 95% CI 35.2-40.9).

Relationship to lean body mass and insulin resistance

Intuitively, routine participation in sufficient amounts of MSA will lead to increases in lean body mass (LBM). Several studies have shown inverse associations between LBM and IR(28,34). Miller et al.(28) investigated the effects of a 10-week

isotonic RT on insulin response to and OGTT and basal insulin levels in college aged men without diabetes. A significant increase in LBM (3.5%, $p<0.05$) was seen following intervention. Furthermore, the increase in LBM was highly correlated with the reductions in insulin in response to an OGTT ($r = -0.89$, $p<0.05$). In a study using NHANES III, Srikanthan et al.(34) investigated the associations between skeletal muscle index (SMI, a measure of LBM) and IR in subjects with and without diabetes. Insulin resistance was investigated using HOMA-IR. Skeletal muscle index was categorized into quartiles. Following adjustment for covariates, results revealed a significant inverse dose-response relationship between quartiles of SMI and IR ($p<0.0001$). After exclusion of subjects with diabetes, the results remained significant ($p<0.0001$). Furthermore, results revealed that for every 10% increment increase in SMI, there was a 14% reduction in HOMA-IR in subjects without diabetes.

Relationship between muscular strength and insulin resistance

Some studies have shown an inverse association between IR and muscular strength, a physiological adaptation to MSA(35,36). Barzilay et al.(35) investigated the associations between quadriceps muscle strength and IR. Subjects (n= 2,006, ≥70 years) were without diabetes and were considered to be well-functioning (self-reported no difficulty with walking one-quarter mile or walking up 10 steps without stopping). Insulin resistance was measured via HOMA-IR. A significant inverse association was seen between strength per kilogram of muscle mass and IR in white and black males and females ($p<0.001$). A significant inverse association was also seen between quadriceps muscle mass and IR ($p<0.001$).

Karelis et al.(36) examined the associations between a muscular strength index

(MSI, calculated by dividing the subject's leg press 1-RM and LBM in kg) and insulin sensitivity in a cohort of obese and overweight postmenopausal women. Study subjects (n=82) were diabetes-free. Insulin resistance was assessed via the hyperinsulinemic-euglycemic glucose clamp. The MSI was categorized into quartiles. Following covariate adjustment, a significant positive association was seen between MSI and insulin sensitivity ($r=0.37$, $p<0.001$). Furthermore, subjects in the highest quartile of MSI had higher levels of insulin sensitivity ($p<0.05$) compared to those in the first and second quartiles.

Postulated mechanisms

There are several postulated mechanisms by which muscle contraction, and acute and chronic participation in exercise may play a role in the reduction of IR or the prevention of reaching an insulin resistive state(37-41). Several studies and reviews have discussed the effect of muscle contraction and exercise as a whole on IR. These mechanisms include: increased insulin sensitivity attributable to the effect of exercise on Glut4 expression and activation, the effect of exercise on glycogen synthase, effects on muscle fiber type, calcium levels, and increases in LBM.

Muscle contraction has been shown to lead to increases in tissue permeability and sensitivity to glucose(38). More specifically, several studies have revealed that both acute and chronic participation in exercise leads to an increase in insulin sensitivity via effects on Glut4 expression and activation(37,39,41-43). Glut4 plays a primary role in the uptake of glucose into tissue for use as fuel or for storage(37). The specific cellular mechanisms in which muscle contraction effects Glut4 activation and expression are not fully understood(37) but advances in microscopy techniques have given further insight into

these mechanisms(44). In a study conducted by Gjovaag et al.(39), investigators reported significant increases in Glut4 concentration ($p<0.01$) in the triceps brachii following a five to eight week strength protocol. Furthermore, Glut4 concentration was higher ($p<0.01$) in subjects participating in high loading (60% 1-RM) compared to lower loading (30% 1-RM); suggesting higher intensity training leads to increased exercise stimulated glucose uptake. Goodyear et al.(43) reported significant increases in the number of glucose transporters following electrically stimulated muscle contractions in the hindquarters of male rats. Exercise has been shown to stimulate the increase in the activity of glycogen synthase, an enzyme that stimulates the synthesis of glycogen from glucose-6-phosphate, following exercise(42). This increase in enzyme concentration is attributable to increased permeability of muscle tissue and increased expression of Glut4(42).

Routine participation in RT has been shown to increase the number of type IIa (fast twitch red) fibers(45,46). In earlier research, Ivy et al.(38) revealed that insulin sensitivity is increased in both fast and slow twitch red fiber types. Similarly, Richter et al.(47) revealed the highest insulin sensitivity to be fast twitch red fibers and the lowest being fast twitch white fibers(47). This is due primarily to the high glycolytic and oxidative capacity of the fast twitch red fiber types(38). More recently, Mackrell et al.(48) revealed a two-fold increase in insulin-mediated glucose uptake in myosin heavy chain (MyHC) IIa fibers in rats compared to MyHC IIx fibers. Gjovaag et al.(39) investigated the effects of RT on the conversion of MyHC IIx fibers to MyHC IIa. Results revealed significant increases in MyHC IIa fibers ($p<0.05$) as well as significant decreases in MyHC IIx fibers ($p<0.05$). Furthermore, a significant positive correlation

($r=0.73$, $p<0.01$) was found between increases in MyHC IIa fibers and Glut4 concentration.

Calcium may also contribute to the increases in insulin sensitivity due to exercise(37,38). Youn et al.(49) revealed calcium to stimulate glucose transport independent of muscle contraction. However, Goodyear et al.(37) noted that this activation of glucose transport is most likely not a direct effect of calcium but attributable to the activation of Protein Kinase C. Protein Kinase C is a calcium-dependent signaling kinase that could contribute to the regulation of contraction-stimulated glucose transport(37). Miller et al.(28) revealed a strong inverse association ($r=-0.89$, $p<0.05$) between insulin response to an OGTT and LBM in subjects without diabetes. This is indicative of a decrease in peripheral IR. One possible explanation is an increase in the clearance of insulin attributable to the increase in insulin sensitive tissues. Due to the rate of clearance for insulin being directly proportional to its binding capacity(50), an increase in availability of binding sites could potentially lead to increased sensitivity. The increases in LBM may also contribute to decreased IR due to increased area for glycogen storage(28).

Summary

It is evident in the literature that IR is highly prevalent even in subjects without diabetes: approximately one-fourth to one-third depending upon the specific study(5-7). Furthermore, research has shown that the prevalence of IR in euglycemic subjects is following a positive trend(7). Insulin resistance is also highly prevalent among individuals with various metabolic health conditions(8). HOMA-IR has been shown to be a validated method of assessing IR in euglycemic subjects in both cross-sectional and

prospective subjects. It has also been shown to have a strong correlation with peripheral insulin sensitivity thus allowing for its use as a proxy measure for studies specifically investigating peripheral IR(2). Moreover, over 50% of studies utilizing the HOMA-IR method have investigated subjects without diabetes(11).

In the 11 studies identified in the literature investigating the association between MSA and IR, all have consistently shown an inverse relationship with participation in adequate volumes of MSA and IR levels in euglycemic subjects. Furthermore, studies have shown that physiological adaptations due to MSA participation (increases in LBM and increases in muscular strength) are inversely associated with IR. Many mechanisms have been proposed and investigated as to why these favorable associations are seen; however they are not fully understood. Nonetheless, it is evident that there is a significant inverse relationship between MSA and IR, even in euglycemic subjects.

References

1. Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J. Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? Diabetes Care 2008;31 Suppl 2:S262-8.
2. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of beta-cell dysfunction and insulin resistance to the pathogenesis of impaired glucose tolerance and impaired fasting glucose. Diabetes Care 2006;29:1130-9.
3. Himsworth HP. Diabetes mellitus: its differentiation into insulin-sensitive and insulin-insensitive types. Diabet Med 2011;28:1440-4.
4. YALOW RS, BERSON SA. Immunoassay of endogenous plasma insulin in man. J Clin Invest 1960;39:1157-75.
5. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595-607.
6. Ioannou GN, Bryson CL, Boyko EJ. Prevalence and trends of insulin resistance, impaired fasting glucose, and diabetes. J Diabetes Complications 2007;21:363-70.
7. Li C, Ford ES, McGuire LC, Mokdad AH, Little RR, Reaven GM. Trends in hyperinsulinemia among nondiabetic adults in the U.S. Diabetes Care 2006;29:2396-402.
8. Bonora E, Kiechl S, Willeit J et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes 1998;47:1643-9.
9. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from

fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

10. Turner RC, Holman RR, Matthews D, Hockaday TD, Peto J. Insulin deficiency and insulin resistance interaction in diabetes: estimation of their relative contribution by feedback analysis from basal plasma insulin and glucose concentrations. Metabolism 1979;28:1086-96.

11. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care 2004;27:1487-95.

12. Bonora E, Targher G, Alberiche M et al. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57-63.

13. García-Estévez DA, Araújo-Vilar D, Fiestras-Janeiro G, Saavedra-González A, Cabezas-Cerrato J. Comparison of several insulin sensitivity indices derived from basal plasma insulin and glucose levels with minimal model indices. Horm Metab Res 2003;35:13-7.

14. Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the U.S. Diabetes Care 2010;33:1179-85.

15. Healy GN, Matthews CE, Dunstan DW, Winkler EA, Owen N. Sedentary time and cardio-metabolic biomarkers in US adults: NHANES 2003-06. Eur Heart J 2011;32:590-7.

16. Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. Diabetes Care 1997;20:1087-92.

17. Durward CM, Hartman TJ, Nickols-Richardson SM. All-cause mortality risk of metabolically healthy obese individuals in NHANES III. J Obes 2012;2012:460321.

18. Bonora E, Kiechl S, Willeit J et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes 2004;53:1782-9.

19. Sung KC, Lim S, Rosenson RS. Hyperinsulinemia and homeostasis model assessment of insulin resistance as predictors of hypertension: a 5-year follow-up study of Korean sample. Am J Hypertens 2011;24:1041-5.

20. Bonora E, Formentini G, Calcaterra F et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002;25:1135-41.

21. US Department of Health and Human Services. 2008 physical activty guidelines for Americans, http://www.health.gov/paguidelines.pdf 2008.

22. Carlson SA, Fulton JE, Schoenborn CA, Loustalot F. Trend and prevalence estimates based on the 2008 Physical Activity Guidelines for Americans. Am J Prev Med 2010;39:305-13.

23. Centers for Disease Control and Prevention. Adult Participation in Aerobic and Muscle-Strengthening Physical Activities-United States, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6217a2.htm, 2013.

24. Centers for Disease Control and Prevention.Trends in strength training--United States, 1998-2004. MMWR Morb Mortal Wkly Rep 2006;55:769-72.

25. Loustalot F, Carlson SA, Kruger J, Buchner DM, Fulton JE. Muscle-strengthening activities and participation among adults in the United States. Res Q Exerc Sport 2013;84:30-8.

26. Ahmadizad S, Haghighi AH, Hamedinia MR. Effects of resistance versus endurance training on serum adiponectin and insulin resistance index. Eur J Endocrinol 2007;157:625-31.

27. Cheng YJ, Gregg EW, De Rekeneire N et al. Muscle-strengthening activity and its association with insulin sensitivity. Diabetes Care 2007;30:2264-70.

28. Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. Med Sci Sports Exerc 1984;16:539-43.

29. Miller JP, Pratley RE, Goldberg AP et al. Strength training increases insulin action in healthy 50- to 65-yr-old men. J Appl Physiol (1985) 1994;77:1122-7.

30. Craig BW, Everhart J, Brown R. The influence of high-resistance training on glucose tolerance in young and elderly subjects. Mech Ageing Dev 1989;49:147-57.

31. Kodama S, Shu M, Saito K et al. Even low-intensity and low-volume exercise training may improve insulin resistance in the elderly. Intern Med 2007;46:1071-7.

32. Katz A, Nambi SS, Mather K et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-10.

33. Churilla JR, Magyari PM, Ford ES, Fitzhugh EC, Johnson TM. Muscular strengthening activity patterns and metabolic health risk among US adults. J Diabetes 2012;4:77-84.

34. Srikanthan P, Karlamangla AS. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J Clin Endocrinol Metab 2011;96:2898-903.

35. Barzilay JI, Cotsonis GA, Walston J et al. Insulin resistance is associated with decreased quadriceps muscle strength in nondiabetic adults aged >or=70 years. Diabetes Care 2009;32:736-8.

36. Karelis AD, Tousignant B, Nantel J et al. Association of insulin sensitivity and muscle strength in overweight and obese sedentary postmenopausal women. Appl Physiol Nutr Metab 2007;32:297-301.

37. Goodyear LJ, Kahn BB. Exercise, glucose transport, and insulin sensitivity. Annu Rev Med 1998;49:235-61.

38. Ivy JL. The insulin-like effect of muscle contraction. Exerc Sport Sci Rev 1987;15:29-51.

39. Gjøvaag TF, Dahl HA. Effect of training with different mechanical loadings on MyHC and GLUT4 changes. Med Sci Sports Exerc 2009;41:129-36.

40. Tabata I, Suzuki Y, Fukunaga T, Yokozeki T, Akima H, Funato K. Resistance training affects GLUT-4 content in skeletal muscle of humans after 19 days of head-down bed rest. J Appl Physiol (1985) 1999;86:909-14.

41. Holten MK, Zacho M, Gaster M, Juel C, Wojtaszewski JF, Dela F. Strength training increases insulin-mediated glucose uptake, GLUT4 content, and insulin

signaling in skeletal muscle in patients with type 2 diabetes. Diabetes 2004;53:294-305.

42. Ivy JL, Kuo CH. Regulation of GLUT4 protein and glycogen synthase during muscle glycogen synthesis after exercise. Acta Physiol Scand 1998;162:295-304.

43. Goodyear LJ, King PA, Hirshman MF, Thompson CM, Horton ED, Horton ES. Contractile activity increases plasma membrane glucose transporters in absence of insulin. Am J Physiol 1990;258:E667-72.

44. Lauritzen HP, Galbo H, Toyoda T, Goodyear LJ. Kinetics of contraction-induced GLUT4 translocation in skeletal muscle fibers from living mice. Diabetes 2010;59:2134-44.

45. Wilson JM, Loenneke JP, Jo E, Wilson GJ, Zourdos MC, Kim JS. The effects of endurance, strength, and power training on muscle fiber type shifting. J Strength Cond Res 2012;26:1724-9.

46. Claflin DR, Larkin LM, Cederna PS et al. Effects of high- and low-velocity resistance training on the contractile properties of skeletal muscle fibers from young and older humans. J Appl Physiol (1985) 2011;111:1021-30.

47. Richter EA, Garetto LP, Goodman MN, Ruderman NB. Enhanced muscle glucose metabolism after exercise: modulation by local factors. Am J Physiol 1984;246:E476-82.

48. Mackrell JG, Cartee GD. A novel method to measure glucose uptake and myosin heavy chain isoform expression of single fibers from rat skeletal muscle. Diabetes 2012;61:995-1003.

49. Youn JH, Gulve EA, Holloszy JO. Calcium stimulates glucose transport in skeletal muscle by a pathway independent of contraction. Am J Physiol 1991;260:C555-61.

50. Terris S, Steiner DF. Binding and degradation of 125I-insulin by rat hepatocytes. J Biol Chem 1975;250:8389-98.

Chapter Three: Methodology

Data Collection

Data were obtained utilizing the National Health and Nutrition Examination Survey (NHANES). The NHANES is conducted by the National Center for Health Statistics (NCHS) and is a continuous survey that regularly releases public-use data files(1). Originally introduced in the 1960's, the NHANES began as a series of surveys focusing on select populations and health outcomes. There are five series that have been conducted. NHANES I began in 1971 and ended in 1974. NHANES II began in 1976 and ended in 1980. NHANES III (phase 1) began in 1988 and continued through 1991. NHANES III (phase 2) began in 1991 and finished in 1994. In 1999, NHANES became a continuous survey, producing data sets in two-year cycles. The continuous NHANES changed its focus to a variety of health and nutrition measurements with respect to emerging disease and adverse health conditions. The NHANES is cross-sectional in nature and is characterized by a complex, multi-stage sampling design in order to obtain a representative sample of the U.S. population(2). The sampling technique is divided into four distinct stages to obtain a representative sample of the non-institutionalized U.S. population aged two months and older living in households(2). During stage 1 specific primary sampling units (PSUs) are selected. These are mostly single counties or, in a few cases, groups of contiguous counties with probability proportional to a measure of size (PPS). Stage 2 is characterized by the division of the PSUs into segments (generally city blocks or their equivalent). Like the PSUs, these segments are divided with PPS. Stage 3 is characterized by households within each segment being listed, and a sample is randomly drawn. In geographic areas where the proportion of groups selected for oversampling is high, the probability of selection for those groups is greater than in other

areas. In stage 4 individuals are chosen to participate in NHANES from a list of all persons residing in selected households. Individuals are drawn at random within designated age-sex-race/ethnicity screening subdomains(2).

A component of the NHANES is oversampling of specific demographics and characteristics of the population. The purpose for this technique is to ensure an adequate representation of certain minority groups (subjects) as well as increasing the reliability and precision estimates for these specific groups(2). Examples of oversampled subgroups in the 1999-2004 NHANES include: African Americans, Mexican Americans, families with low income, adolescents aged 12-19 years, and persons age ≥60 years.

The NHANES was designed to provide national estimates of the health and nutritional status of non-institutionalized U.S. civilians two months of age and older through both objective (examination) and subjective (interview) measures(1). The NHANES assesses demographic, socioeconomic, dietary and health-related aspects of life through interview. The examination takes place at a mobile examination center (MEC) where both physiological measurements and laboratory tests are administered by trained medical personnel(1).

Subjects

The total 1999-2004 NHANES sample N was 31,126. Of those, 15,332 subjects were ≥20 years of age, the population of interest for this study. We excluded 833 women who reported being pregnant, and 8,781 subjects who were non-fasted. Subjects with diabetes (n=617) or pre-diabetes (n=833) were excluded from the study as well. Following exclusion of those with missing data (n=1,640) for any variable included in the analysis, 2,543 remained in our analysis as eligible study subjects. The final sample met

the following conditions: 1) adult men and women ≥20 years of age; 2) attended a morning MEC following an overnight fast; 3) if female, non-pregnant; 4) had complete data on all the variables of interest and 5) were without diabetes (glycosylated hemoglobin <5.7%, and answered no to the question DIQ010: (Other than during pregnancy, have you ever been told by a doctor or health care professional that you have diabetes or sugar diabetes?).

Measures

Dependent Variable: Muscular Strengthening Activity

Current recommendations set forth by the Department of Health and Human Services (DHHS) state that the healthy population should participate in MSA two or more days per week(3). The dependent variable in this study was calculated from 'self-reported' MSA patterns. The final sample provided responses to the following items, which came from the PA questionnaire file item PAD440: "Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles such as lifting weights, push-ups or sit-ups?) Include all such activities even if you have mentioned them before in the past 12 months." No self-reported MSA was used as the dependent variable in this study.

Independent Variable: HOMA-IR

The primary independent variable was IR. We used the homeostatic model assessment of insulin resistance (HOMA-IR) as a measure for IR, calculated via the equation by Matthews et al.(4): [fasting serum insulin (mU/ml) x fasting plasma glucose (mmol/l) /22.5]. Age-adjusted quartiles of log-transformed HOMA-IR were created using

every 25th percentile based on weights specific to NHANES: Q1 (<0.20), Q2 (≥0.20 and <0.37), Q3 (≥0.37 and <0.55) and Q4 (≥0.55). HOMA-IR was log transformed due to the the data not being normally distributed following a test for normality.

Other independent variables:

Other independent variables or potential mediating factors include age, gender, race/ethnicity, education, smoking, alcohol, waist circumference, and non-MSA specific leisure-time physical activity (LTPA).

Age:

Five categories of age were created: 20-29, 30-39, 40-49, 50-59 and ≥60.

Gender:

Gender was dichotomized as male or female.

Race/Ethnicity:

Four categories of race were created: non-Hispanic White, non-Hispanic Black, Mexican American and Other.

Education:

Education was categorized into four groups: less than high school, high school graduate, some college, and college graduate.

Smoking:

Three categories of smoking were created: current smoker, former smoker (quit within last six months), and non-smoker.

Alcohol:

Three categories of alcohol consumption were created based on the United States Department of Agriculture (USDA) and DHHS gender specific cut-points(5): non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day).

Waist circumference:

Waist circumference (WC) was used as a measure for adiposity and dichotomized by gender specific cut-points(6): men (elevated: ≥102cm, desirable <102cm), women (elevated: ≥88cm, desirable <88cm).

Non-MSA specific Leisure-time physical activity

Leisure time physical activity was categorized into three levels based on the 2008 DHHS PA guidelines(3): none (0 min/week), insufficient (1-149 min/week) and meeting the recommendations (≥150 min/week). The LTPA variable was created from a compendium of activities within the 1999-2004 NHANES. These activities are primarily aerobic activities. However, some activities, such as rock climbing or wrestling incorporate both anaerobic (resistance) and aerobic pathways. Within the NHANES, MSA is defined exclusively using the PAD440 question. The LTPA variable used in this study is mutually exclusive of the PAD440 question and has been used as a measure of aerobic PA in several studies(7,8).

Data Analysis

The NHANES data are weighted to account for the complex survey design, oversampling, survey non-response, and post-stratification to match 2000 U.S. Census

population control totals. Subjects participating in the NHANES are assigned a weight that is equivalent to the reciprocal of their probability of selection. Due to the complex survey design, these base weights must be calculated utilizing the reciprocal of their final probability of selection. The final probability incorporates the following: the probability of the PSU being selected; the probability of a segment of the PSU being selected; probability of a household being selected; and the probability of an individual being selected. Base weights are also adjusted for non-response to the in-home interview when creating interview weights. They are further adjusted for non-response to the MEC exam when creating exam weights(9).

Compared to earlier NHANES cycles, the sample size in the two-year continuous cycle is smaller. Thus the use of a statistical software program, capable of handling the increased sampling variation is necessary. SAS-callable SUDAAN(12) was used to handle to complex survey design and create an unbiased estimate of the variance(10).

Statistical Analysis

The data in this study were initially managed using SAS 9.2(11). SAS was used to conduct both complex variable recodes and validation of data coding. SAS-callable SUDAAN(12) was then used to conduct the analysis, incorporating sampling weights within the context of the correlated multi-stage complex sampling design inherent to NHANES. Age-adjusted prevalence estimates were calculated using PROC DESCRIPT. Non-overlapping 95% confidence intervals (CI) with coinciding p-values illustrate significance ($p<0.05$). Logistic regression (PROC RLOGIST) analysis was used to test the null hypotheses that individual regression coefficients are equal to zero for each quartile of HOMA-IR. The three logistic regression models created included the primary

independent variable HOMA-IR unadjusted; a second model adjusting for age, race, gender, education, smoking, alcohol consumption, WC and HOMA-IR; and a third model further adjusting for LTPA.

Limitations

Aspects of the 1999-2004 NHANES may limit the findings of this study. A portion of this survey is based on self-reported data. These self-reported variables are subject to recall bias. Furthermore, the self-reported data is subject to social-desirability bias (a response provided to please the interviewer). The nature of the survey can be subject to interview bias. Due to the cross-sectional study design, causality cannot be established between variables. Measurement errors, coding errors, and sampling errors may also occur in survey designs. The final limitation is residual confounding, which is inherent to all survey research.

References

1. National Center for Health Statistics Centers for Disease Control and Prevention. NHANES Analytic and Reporting Guidelines September 2006 Version.
2. National Center for Health Statistics Centers for Disease Control and Prevention. Key Concepts About NHANES Survey Design. http://www.cdc.gov/nchs/tutorials/NHANES/SurveyDesign/SampleDesign/Info1.html.
3. US Department of Health and Human Services. 2008 physical activty guidelines for Americans, http://www.health.gov/paguidelines.pdf 2008.
4. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
5. U.S. Department of Agriculture, U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2010. Washington, DC: U.S. Government Printing Office, December 2010.
6. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
7. Churilla JR, Fitzhugh EC. Relationship between leisure-time physical activity and metabolic syndrome using varying definitions: 1999-2004 NHANES. Diab Vasc Dis Res 2009;6:100-9.

8. Churilla JR, Fitzhugh EC. Total physical activity volume, physical activity intensity, and metabolic syndrome: 1999-2004 National Health and Nutrition Examination Survey. Metab Syndr Relat Disord 2012;10:70-6.

9. National Center for Health Statistics Centers for Disease Control and Prevention. Key Concepts About Weighting in NHANES. http://www.cdc.gov/nchs/tutorials/NHANES/SurveyDesign/Weighting/OverviewKey.html.

10. National Center for Health Statistics Centers for Disease Control and Prevention. Key Concepts About Variance Estimation Within NHANES. http://www.cdc.gov/nchs/tutorials/NHANES/SurveyDesign/VarianceEstimation/Info1.html.

11. SAS Institute Inc 2009. Base SAS 9.2 Procedures Guide.

12. Research Triangle Institute (2012). SUDAAN User's Manual, Release 11.0.

Chapter Four: The Associations between HOMA-IR and Muscular Strengthening Activity in euglycemic U.S. Adults

Background: Muscular strengthening activity (MSA) has been shown to be inversely associated with insulin resistance (IR). We examined the associations between quartiles of the homeostatic model assessment of insulin resistance (HOMA-IR) and self-reported MSA in a nationally representative sample of euglycemic U.S. adults.

Methods: Sample included adult participants (≥20 years of age [n=2,543]) from the 1999-2004 National Health and Nutrition Examination Survey (NHANES). HOMA-IR was categorized into quartiles based on every 25th percentile. No self-reported MSA was the dependent variable.

Results: Following adjustment for covariates, those with HOMA-IR values in third ($p<0.01$) and fourth ($p<0.001$) quartiles were found to have significantly greater odds of reporting no MSA. Following further adjustment for non-MSA specific leisure time physical activity, results remained significant ($p<0.05$ third, $p<0.001$ fourth). A significant positive trend was seen across quartiles of HOMA-IR ($p=0.01$) for odds of reporting no MSA.

Conclusions: Having a higher HOMA-IR value is associated with greater odds of reporting no MSA in euglycemic U.S. adults.

The homeostatic model for insulin resistance (HOMA-IR) has been extensively used as a measure for insulin resistance (IR) in epidemiological studies. Greater levels of IR have been shown to be highly associated with incidence of type 2 diabetes(1,2) and cardiovascular disease (CVD)(3-6). Interestingly, previous studies using surveillance data have also estimated that HOMA derived IR(7) and hyperinsulinemia(8) are highly prevalent in subjects who are apparently healthy.

Traditionally, muscular strengthening activity (MSA) has been examined as an independent predictor of IR in subjects without diabetes. Several studies have investigated these associations(9-16). Miller et al.(9) reported a significant reduction (37.5%, $p<0.05$) in basal insulin levels and insulin levels in response to an oral glucose tolerance test (OGTT) ($p<0.05$) in eight young healthy male subjects following a 10-week high-resistance, isotonic weight-lifting program. Cheng et al.(13) investigated the associations between volumes of MSA and IR, measured via the quantitative insulin sensitivity check index (QUICKI), in subjects without diabetes utilizing data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES). Results revealed significantly higher QUICKI levels in subjects reporting ≥1 day/week of MSA ($p<0.05$). Following adjustment for covariates, results remained significant in females but not males. Significance was only seen in volumes of MSA ≥3 days/week ($p<0.05$) in males.

Currently, no studies have examined these associations using HOMA-IR as the independent variable. This novel approach, defined as using a disease or adverse metabolic condition as the independent variable and physical activity (PA) as the dependent varibale, has been used in few studies(17-21). Moreover, this approach allows

for a clinical interpretation of surevillance data, providing potential insight into PA patterns in diseased subjects. The purpose of this study was to invesitgate the associations between quartiles of HOMA-IR and self-reported MSA in a representative sample of euglycemic adults in the United States (U.S.). To the extent of our knowledge, this is the first study to examine the assocations between quartiles of HOMA-IR and MSA in a representative sample of euglycemic U.S. adults.

Methods

This study utilized six years of data from the 1999-2004 NHANES, a continuous survey conducted by the National Center for Health Statistics(22). The NHANES was designed to provide national estimates of the health and nutritional status of non-institutionalized U.S. civilians over the age of two months. The total 1999-2004 NHANES sample N was 31,126, ages two months and above. Out of the 15,332 subjects (≥20 years of age) who participated in the 1999-2004 NHANES, we excluded 833 women who reported being pregnant, and 8,781 subjects who were non-fasted. Subjects with diabetes (n=617) or pre-diabetes (n=833) were excluded from the study as well. Following exclusion of those with missing data (n=1,640) for any variable included in the analysis, 2,543 remained in our analysis as eligible study subjects. The final sample met the following conditions: 1) adult men and women ≥20 years of age; 2) attended a morning medical exam in a mobile examination center following an overnight fast; 3) if female, non-pregnant; 4) had complete data on all the variables of interest and 5) were without diabetes (glycosylated hemoglobin <5.7%, and answered no to the question DIQ010: (Other than during pregnancy, have you ever been told by a doctor or health care professional that you have diabetes or sugar diabetes?).

Muscle Strengthening Activity

Current recommendations set forth by the Department of Health and Human Services (DHHS) state that the healthy population should participate in MSA two or more days per week(23). The dependent variable in this study was calculated from 'self-reported' MSA. The final sample provided responses to the following items which came from the physical activity (PA) questionnaire file item PAD440: Over the past 30 days, did you do any physical activities specifically designed to strengthen your muscles such as lifting weights, push-ups or sit-ups? Include all such activities even if you have mentioned them before in the past 12 months. No self-reported MSA was used as the dependent variable in this study.

Insulin Resistance

The independent variable was IR. We used the HOMA-IR as a measure for IR; calculated via the equation by Matthews et al.(24): [fasting serum insulin (mU/ml) x fasting plasma glucose (mmol/l)]/22.5. Age-adjusted log-transformed quartiles of HOMA-IR were created using every 25^{th} percentile based on weights specific to NHANES: Q1 (<0.20), Q2 (≥0.20 and <0.37), Q3 (≥0.37 and ≤0.55) and Q4 (>0.55).

Covariates

Five categories of age were created: 20-29, 30-39, 40-49, 50-59 and ≥60. Four categories of race were created: non-Hispanic White, non-Hispanic Black, Mexican American and Other. Education was categorized into four groups: less than high school, high school graduate or GED, some college, and college graduate. Three categories of smoking were created: smoker, former smoker (quit within last six months), and non-

smoker. Three categories of alcohol consumption were created based on the United States Department of Agriculture and DHHS gender specific cut-points: non-drinker (0 drinks/day), moderate (>0 and ≤1 [women], >0 and ≤2 [men] drinks/day), and above moderate (>1 [women], >2 [men] drinks/day)(25). Waist circumference (WC) was used as a measure for adiposity and dichotomized by gender specific cut-points: men (elevated: ≥102cm, desirable <102cm), women (elevated: ≥88cm, desirable <88cm)(26). Leisure time physical activity (LTPA) was categorized into three levels: 0 min/week, >0 to <150 min/week, and meeting the 2008 DHHS PA recommendations ≥150 min/week(23).

Statistical Analysis

The data in this study were initially managed using SAS 9.2(27) which was used to conduct both complex variable recodes and data coding validation. SAS-callable SUDAAN(28) was then used to conduct the analysis, incorporating sampling weights within the context of the correlated multi-stage complex sampling design inherent to NHANES. Age-adjusted prevalence estimates were calculated using PROC DESCRIPT. Non-overlapping 95% confidence intervals (CI) with coinciding p-values illustrate significance ($p<0.05$). Logistic regression (PROC RLOGIST) analysis was used to test the null hypotheses that individual regression coefficients are equal to zero for each quartile of HOMA-IR. The three logistic regression models created included the primary independent variable HOMA-IR unadjusted, a second model adjusting for age, race, gender, education, smoking, alcohol consumption, WC and HOMA-IR, and a third model further adjusting for other non MSA specific LTPA.

Results

Following adjustment for covariates, those with HOMA-IR values in third ($p<0.01$) and fourth ($p<0.001$) quartiles were found to have significantly greater odds of reporting no MSA. Following further adjustment for non-MSA specific LTPA, results remained significant ($p<0.05$ third, $p<0.001$ fourth). A significant positive trend was seen across quartiles of HOMA-IR ($p=0.01$) for odds of reporting no MSA.

Table 1 provides a summary of the study sample characteristics.

Table 1. Characteristics of study sample: 1999-2004 NHANES

Covariates		N	Weighted % (SE)
HOMA-IR			
	Q1	731	31.60 (1.41)
	Q2	711	28.25 (0.97)
	Q3	618	23.48 (1.08)
	Q4	483	16.66 (0.99)
Age			
	20-29	512	22.18 (1.89)
	30-39	506	23.91 (1.37)
	40-49	505	20.18 (1.08)
	50-59	341	15.32 (0.94)
	≥60	679	16.31 (1.04)
Gender			
	Male	1281	48.87 (0.88)
	Female	1262	51.13 (0.88)
Race			
	Non-Hispanic White	1391	75.99 (2.05)
	Non-Hispanic Black	400	8.91 (1.18)
	Mexican American	596	6.85 (0.92)
	Other	156	8.25 (1.59)
Education			
	College graduate	520	25.37 (1.64)
	Some college	703	30.26 (1.14)
	High school/GED	580	25.93 (1.54)
	< High school	740	18.44 (0.91)
Smoking			
	Non-smoker	1309	49.95 (1.89)
	Former smoker	639	24.90 (1.35)
	Smoker	595	25.16 (1.51)
Alcohol consumption			
	Above Moderate	221	9.88 (1.05)
	Moderate	1610	65.73 (2.29)
	None	712	24.38 (2.31)
WC			
	Desirable	1446	59.77 (1.09)
	Elevated	1097	40.23 (1.09)
LTPA			
	Meets Recommendations	819	36.57 (2.08)
	Some	723	30.68 (1.69)
	None	1001	32.75 (1.57)

Table 1. Waist circumference: Men (elevated: ≥102cm, normal <102cm), Women (elevated: ≥88cm, normal <88cm). LTPA: None, Some (≥1 but <150 minutes/week.), Meets recommendations (≥150 minutes/week.) Q: Quartile; WC: Waist Circumference; MSA: Muscular strengthening activity; LTPA: Leisure-time physical activity.

Table 2 provides prevalence estimates for reporting no self-reported MSA. The prevalence of reporting no MSA was significantly higher in subjects in the third (76.02%, 95% confidence interval [CI] 71.06-80.36) and fourth (81.19%, 95% CI 76.56-85.09) quartiles of HOMA-IR compared to those in the first (63.64%, 95% CI 58.69-68.31). No significant differences were found for prevalence of no MSA in the second quartile of HOMA-IR compared to the first.

Table 3 illustrates the results of the logistic regression analysis of the associations between quartiles of HOMA-IR and no self-reported MSA in people without diabetes. The unadjusted odds of reporting no self-reported MSA were significantly greater in subjects in the third (Odds ratio [OR] 1.90, 95% CI 1.48-2.45) and fourth (OR 2.69, 95% CI 1.96-3.71) quartiles of HOMA-IR compared to those in the first. Following adjustment for age, gender, race, education, smoking status, alcohol consumption, and WC, results remained significant for the third (OR 1.59, 95% CI 1.13-2.23) and fourth (OR 2.00, 95% CI 1.37-2.91) quartiles. In the fully adjusted model, which included other non MSA specific LTPA, significance remained for the third (OR 1.51, 95% CI 1.07-2.14) and fourth (OR 2.10, 95% CI 1.43-3.08) quartiles.

Table 2. Prevalence estimates for subjects reporting no MSA - 1999-2004 NHANES.

Covariates	Prevalence	95% CI	p-for-trend
HOMA-IR			
Q1	63.64	58.69-68.31	
Q2	68.52	63.54-73.11	p<0.001
Q3	76.02	71.06-80.36	
Q4	81.19	76.56-85.09	
Age			
20-29	56.84	51.76-61.78	
30-39	66.55	60.60-72.01	
40-49	71.85	65.59-77.37	p<0.001
50-59	73.28	67.77-78.16	
≥60	83.45	78.30-87.57	
Gender			
Male	67.77	63.99-71.33	p<0.001
Female	73.87	70.71-77.27	
Race			
Non-Hispanic White	69.27	65.70--72.62	
Non-Hispanic Black	67.37	61.08-73.10	p<0.05
Mexican American	80.75	77.26-83.82	
Other	80.71	74.41-85.75	
Education			
College graduate	56.90	51.81-61.85	
Some college	68.54	64.65-72.18	p<0.001
High school/GED	78.40	74.12-82.14	
< High school	84.47	80.09-88.03	
Smoking			
Non-smoker	67.37	63.63-70.90	
Former smoker	71.14	64.14-77.26	p<0.001
Smoker	79.45	75.83-82.65	
Alcohol			
Above Moderate	67.34	60.57-73.45	
Moderate	67.49	64.36-70.47	p<0.001
None	80.80	76.57-84.43	
WC			
Desirable	65.12	61.54-68.55	p<0.001
Elevated	79.45	76.29-82.28	
LTPA			
Meets	46.17	46.17-53.73	
Some	75.66	71.27-79.57	p<0.001
None	90.08	87.63-92.09	

Table 2. Waist circumference: Men (elevated: ≥102cm, normal <102cm), Women (elevated: ≥88cm, normal <88cm). LTPA: None, Some (≥1 but <150 minutes/week.), Meets Recommendations (≥150 minutes/week.) Q: Quartile; WC: Waist Circumference; MSA: Muscular strengthening activity; LTPA: Leisure-time physical activity.

Table 3. Odds for reporting no MSA in those without diabetes - 1999-2004 NHANES.

Variable	Model 1[a]	Model 2[b]	Model 3[c]
HOMA-IR			
Q1	1.00	1.00	1.00
Q2	1.27 (CI 0.96-1.68)	1.21 (CI 0.89-1.64)	1.25 (CI 0.88-1.77)
Q3	1.90 (CI 1.48-2.45)**	1.59 (CI 1.13-2.23)**	1.51 (CI 1.07-2.14)*
Q4	2.69 (CI 1.96-3.71)**	2.00 (CI 1.37-2.91)***	2.10 (CI 1.43-3.08)***
Age			
20-29		1.00	1.00
30-39		1.61 (CI 1.15-2.26)**	1.33 (CI 0.98-1.80)
40-49		2.34 (CI 1.67-3.28)***	2.23 (CI 1.59-3.13)***
50-59		2.22 (CI 1.67-3.28)***	1.96 (CI 1.39-2.78)***
≥60		3.69 (CI 2.67-5.09)***	3.10 (CI 2.26-4.24)***
Gender			
Male		1.00	1.00
Female		1.43 (CI 1.14-1.80)**	1.51 (CI 1.06-1.63)*
Race			
Non-Hispanic White		1.00	1.00
Non-Hispanic Black		0.74 (CI 0.51-1.06)**	0.58 (CI 0.40-0.84)**
Mexican American		1.36 (CI 0.94-1.98)	1.14 (CI 0.77-1.67)
Other		1.58 (CI 0.94-2.65)	1.31 (CI 0.76-2.27)
School			
College graduate		1.00	1.00
Some college		1.53 (CI 1.16-2.03)**	1.32 (CI 0.97-1.80)
High school or GED		2.41 (CI 1.84-3.16)***	1.94 (CI 1.45-2.60)***
< High school		3.40 (CI 2.07-5.57)***	2.28 (1.41-3.67)**
Smoking			
Non-smoker		1.00	1.00
Former smoker		1.19 (CI 0.89-1.60)	1.25 (CI 0.93-1.68)
Smoker		1.94 (CI 1.46-2.58)***	1.64 (CI 1.26-2.14)***
Alcohol			
Above moderate		1.00	1.00
Moderate		1.19 (CI 0.83-1.59)	1.05 (CI 0.73-1.49)
None		1.94 (CI 1.42-3.13)***	1.90 (CI 1.28-2.82)**
WC			
Desirable		1.00	1.00
Elevated		1.55 (CI 1.30-1.84)***	1.44 (CI 1.17-1.77)***
LTPA			
Meets Recommendations			1.00
Insufficient			3.16 (CI 2.49-4.01)***
None			8.02 (CI 5.92-10.87)***

Table 3. Waist circumference: Men (elevated: ≥102cm, normal <102cm), Women (elevated: ≥88cm, normal <88cm). LTPA: None, Some (≥1 but <150 minutes/week.), Meets Recommendations (≥150 minutes/week.) ***p<0.001, **p<0.01, *p<0.05

[a]Model 1: unadjusted. [b]Model 2: adjusted for age, race, gender, education, smoking status, alcohol consumption, WC, and MSA. [c]Model 3: all covariates plus LTPA. WC: Waist Circumference; MSA: Muscular strengthening activity; Q: Quartile; LTPA: Leisure-time physical activity

Discussion

The results of this analysis show a positive association between quartiles of HOMA-IR and the prevalence no self-reported MSA in euglycemic U.S. adults. This study adds to previous traditional work investigating the relationship between MSA and IR in healthy populations(9-16). Miller et al.(9) investigated the effects of a 10-week resistance training (RT) program on basal insulin levels and insulin response to an OGTT. Results revealed significant reductions in basal insulin levels ($p<0.05$) and insulin levels in response to an OGTT ($p<0.05$) following the intervention. Another study conducted by Craig et al.(12) revealed significant decreases in insulin response ($p<0.05$) to an OGTT independent of age (31.8% younger, 32.6% elderly) in healthy subjects completing a 12-week RT program. The current study findings support previous prospective work, which indicates that MSA is inversely associated with IR.

Two cross-sectional studies have also shown an association between IR and MSA(13,29). Churilla et al.(29) reported a significantly lowered odds (OR 0.71; 95% CI 0.54-0.93) for having impaired fasting glucose (IFG), suggesting normal β-cell function in subjects reporting meeting the DHHS MSA recommendation compared to subjects reporting no MSA. In another analysis using NHANES 1999-2004, Cheng et al.(13) investigated the associations between MSA and insulin sensitivity (measured via QUICKI(30)) in euglycemic subjects. Results revealed a significant difference in QUCIKI levels for men and women reporting ≥1 day/week of MSA ($p<0.05$) compared to those reporting none. Following adjustment for age, race/ethnicity, physical activity other than MSA, BMI, smoking, alcohol consumption, and daily total caloric intake, results remained significant in females but not males. Significance was only seen in

volumes of MSA ≥3 days/week ($p<0.05$) in males. The results of these studies further indicate that MSA may be favorably associated with insulin sensitivity and glucose control.

The aforementioned studies have all shown inverse associations between MSA and IR in subjects without diabetes. However, our study investigated the associations between increasing HOMA-IR quartiles and no self-reported MSA. This approach allows for the potential clinical examination and interpretation of surveillance data. Few studies have examined population based data using this method(17-21). Churilla et al.(21) reported the prevalence of meeting the 2008 DHHS PA recommendations to 59.1% among participants reporting high-cholesterol (HC) and 68.3% among participants not reporting HC ($p<0.05$), suggesting those with elevated cholesterol levels may not be as physically active as individuals with desirable levels. Another study by Churilla et al.(20) reported significantly lowered odds (OR 0.85, 95% CI 0.82-0.88) for meeting the DHHS PA recommendations in subjects with hypertension compared to those without hypertension, again suggesting lower physical activity levels among hypertensive individuals compared to those with desirable blood pressure values. Similar studies have investigated diabetes and PA patterns(17,18). In a cross-sectional analysis using the behavioral risk factor surveillance system (BRFSS), Zhao et al.(18) revealed that subjects with diabetes reported lower levels of PA compared to those without diabetes. Also, subjects with diabetes were less likely to report meeting the 2008 DHHS PA recommendations compared to those without. These data suggest that subjects with diabetes, high cholesterol, CHD, and hypertension may be less likely to engage in a volume of PA that may prevent chronic diseases and promote health. Furthermore, the

use of this novel clinical approach in surveillance research may allow clinicians (e.g., physicians, physician assistants, nurse practitioners) to better utilize their time with patients who need lifestyle counseling and coaching. Our study suggests that subjects with higher levels of IR (specifically the upper 50^{th} percentile) have greater odds of reporting no MSA. Results from the few clinical analyses and the current analysis may begin to provide clinicians an understanding of behavioral patterns in population data, thus revealing an increased need for recommendations in therapeutic lifestyle interventions (PA, MSA, and dietary changes) within high risk or diseased populations.

The current prevalence estimates for engaging in adequate amounts of MSA are approximately 21.9%-31.7%(31-34). Loustalot et al.(32) reported that 31.7% of respondents reported participation in MSA ≥2 days/week. The most recent estimate, using the 2011 BRFSS, is approximately 29.3%(34). From these data it can be estimated that approximately 70% of U.S. adults are not engaging in adequate amounts of MSA. Our study adds to these results specifically suggesting that eugluycemic subjects in the upper quartile (81.19%, 95% CI 76.56-85.09) and third quartile (76.02%, 95% CI 71.06-80.36) of IR have a significantly higher prevalence of reporting no MSA compared to subjects in the lowest quartile (63.64%, 95% CI 58.69-68.31).

According to Barnes et al.(35) the prevalence of physicians recommending exercise or PA to adult patients is approximately 32.4%. Moreover, subjects with disease (e.g., diabetes, cardiovascular disease, cancer, hypertension) and subjects who were obese had a greater prevalence compared to those without disease or those with a desirable BMI. Despite this higher prevalence, Zhao et al.(18) showed that subjects with diabetes have lower odds of reporting participation adequate PA. Interestingly, subjects with IR,

who may have normal glucose levels, are in a state of increased risk for disease development and there is no data currently reporting the prevalence of physician recommended PA, specifically with IR status. Furthermore, our study results reveal the importance of continuing research into this area in order to combat the increasing incidence and prevalence of IR which has been shown to be highly associated with increased risk for CVD(3,4), diabetes(1,36) and a number of adverse metabolic conditions including obesity(37,38), dyslipidemia(39,40), inflammation(41) and hypertension(42).

A recent review(43) investigating the role of MSA and the risk of CVD revealed that MSA can improve insulin action, glucose response, reduce body fat and reduce visceral adipose tissue; all of which are risk factors for CVD at abnormal levels. A recent study by Grontved et al.(44), investigating the effects of MSA on type 2 diabetes, revealed that men who participate in aerobic training (AT) and MSA for at least 150 minutes per week have a 59% reduction in risk for diabetes. Furthermore, a study investigating MSA and risk for CHD by Tanasescu et al.(45) reported a 23% (RR 0.77, $p<0.05$) reduction in risk for CHD in men who participated in at least 30 minutes of MSA per week compared with men who did no MSA. These results suggest that participation in routine PA, inclusive of MSA, could have a favorable impact on the risk for diabetes (which has been shown to be a possible vascular equivalent to CVD) as well as CVD. Due to the relationship between CVD and diabetes, as shown in a review by Grundy et al.(46), it is imperative for health care professionals to suggest PA, inclusive of MSA, to everyone capable of safely participating. Furthermore, due to the preventive effect MSA has on diabetes and CVD risk, it is vital that adults in higher risk categories (i.e., higher

levels of IR despite normal glucose levels), be counseled on therapeutic lifestyle changes, including engaging in MSA.

The strengths of our study include strong external validity owing to the use of a large representative sample and the use of validated assays to measure insulin, glucose and glycosylated hemoglobin. Moreover, the novel approach to this study design, characterized by utilizing IR as a predictor variable rather than an outcome, provides insight into this relationship utilizing IR as the independent variable and health behavior (MSA) as the dependent variable. The limitations of our study include the cross-sectional study design, which does not allow for causation to be established, residual confounding, and the use of questionnaires for the assessment of MSA, which may be subject to recall bias.

Conclusions

Euglycemic adults that fall in the upper 50^{th} percentile of HOMA-IR were more likely to report no MSA independent of several covariates. Muscular strengthening activity has been shown to improve insulin action, glycemic control, and reduce the risk for CVD and type 2 diabetes. Thus, it may become increasingly important for health care professionals to advocate MSA participation in all populations that can safely participate, specifically those with higher levels of IR.

References

1. Bonora E, Kiechl S, Willeit J et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes 2004;53:1782-9.
2. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999;104:787-94.
3. Bonora E, Formentini G, Calcaterra F et al. HOMA-estimated insulin resistance is an independent predictor of cardiovascular disease in type 2 diabetic subjects: prospective data from the Verona Diabetes Complications Study. Diabetes Care 2002;25:1135-41.
4. Bonora E, Kiechl S, Willeit J et al. Insulin resistance as estimated by homeostasis model assessment predicts incident symptomatic cardiovascular disease in caucasian subjects from the general population: the Bruneck study. Diabetes Care 2007;30:318-24.
5. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177-84.
6. Hedblad B, Nilsson P, Engström G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002;19:470-5.
7. Ioannou GN, Bryson CL, Boyko EJ. Prevalence and trends of insulin resistance, impaired fasting glucose, and diabetes. J Diabetes Complications 2007;21:363-70.

8. Li C, Ford ES, McGuire LC, Mokdad AH, Little RR, Reaven GM. Trends in hyperinsulinemia among nondiabetic adults in the U.S. Diabetes Care 2006;29:2396-402.

9. Miller WJ, Sherman WM, Ivy JL. Effect of strength training on glucose tolerance and post-glucose insulin response. Med Sci Sports Exerc 1984;16:539-43.

10. Miller JP, Pratley RE, Goldberg AP et al. Strength training increases insulin action in healthy 50- to 65-yr-old men. J Appl Physiol (1985) 1994;77:1122-7.

11. Ahmadizad S, Haghighi AH, Hamedinia MR. Effects of resistance versus endurance training on serum adiponectin and insulin resistance index. Eur J Endocrinol 2007;157:625-31.

12. Craig BW, Everhart J, Brown R. The influence of high-resistance training on glucose tolerance in young and elderly subjects. Mech Ageing Dev 1989;49:147-57.

13. Cheng YJ, Gregg EW, De Rekeneire N et al. Muscle-strengthening activity and its association with insulin sensitivity. Diabetes Care 2007;30:2264-70.

14. Kodama S, Shu M, Saito K et al. Even low-intensity and low-volume exercise training may improve insulin resistance in the elderly. Intern Med 2007;46:1071-7.

15. Abbatecola AM, Ferrucci L, Ceda G et al. Insulin resistance and muscle strength in older persons. J Gerontol A Biol Sci Med Sci 2005;60:1278-82.

16. Hernán Jiménez O, Ramírez-Vélez R. [Strength training improves insulin sensitivity and plasma lipid levels without altering body composition in overweight and obese subjects]. Endocrinol Nutr 2011;58:169-74.

17. Zhao G, Ford ES, Li C, Balluz LS. Physical activity in U.S. older adults with diabetes mellitus: prevalence and correlates of meeting physical activity recommendations. J Am Geriatr Soc 2011;59:132-7.

18. Zhao G, Ford ES, Li C, Mokdad AH. Compliance with physical activity recommendations in US adults with diabetes. Diabet Med 2008;25:221-7.

19. Zhao G, Ford ES, Li C, Mokdad AH. Are United States adults with coronary heart disease meeting physical activity recommendations? Am J Cardiol 2008;101:557-61.

20. Churilla JR, Ford ES. Comparing physical activity patterns of hypertensive and nonhypertensive US adults. Am J Hypertens 2010;23:987-93.

21. Churilla JR, Johnson TM, Zippel EA. Association of physical activity volume and hypercholesterolemia in US adults. QJM 2013;106:333-40.

22. National Center for Health Statistics Centers for Disease Control and Prevention. NHANES Analytic and Reporting Guidelines September 2006 Version.

23. US Department of Health and Human Services. 2008 physical activty guidelines for Americans, http://www.health.gov/paguidelines.pdf 2008.

24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

25. U.S. Department of Agriculture USDoHaHS. Dietary Guidelines for Americans, 2010. Washington, DC: U.S. Government Printing Office, December 2010.

26. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.

27. SAS Institute Inc 2009. Base SAS 9.2 Procedures Guide.

28. Research Triangle Institute (2012). SUDAAN User's Manual, Release 11.0.

29. Churilla JR, Magyari PM, Ford ES, Fitzhugh EC, Johnson TM. Muscular strengthening activity patterns and metabolic health risk among US adults. J Diabetes 2012;4:77-84.

30. Katz A, Nambi SS, Mather K et al. Quantitative insulin sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-10.

31. Carlson SA, Fulton JE, Schoenborn CA, Loustalot F. Trend and prevalence estimates based on the 2008 Physical Activity Guidelines for Americans. Am J Prev Med 2010;39:305-13.

32. Loustalot F, Carlson SA, Kruger J, Buchner DM, Fulton JE. Muscle-strengthening activities and participation among adults in the United States. Res Q Exerc Sport 2013;84:30-8.

33. Centers for Disease Control and Prevention.Trends in strength training--United States, 1998-2004. MMWR Morb Mortal Wkly Rep 2006;55:769-72.

34. Centers for Disease Control and Prevention. Adult Participation in Aerobic and Muscle-Strengthening Physical Activities-United States, 2011. http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6217a2.htm, 2013.

35. Barnes PM, Schoenborn CA. Trends in adults receiving a recommendation for exercise or other physical activity from a physician or other health professional. NCHS Data Brief 2012:1-8.

36. Zavaroni I, Bonora E, Pagliara M et al. Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance. N Engl J Med 1989;320:702-6.

37. Reaven G, Abbasi F, McLaughlin T. Obesity, insulin resistance, and cardiovascular disease. Recent Prog Horm Res 2004;59:207-23.

38. McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G. Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. Metabolism 2004;53:495-9.

39. Kim JS, Kang HT, Shim JY, Lee HR. The association between the triglyceride to high-density lipoprotein cholesterol ratio with insulin resistance (HOMA-IR) in the general Korean population: based on the National Health and Nutrition Examination Survey in 2007-2009. Diabetes Res Clin Pract 2012;97:132-8.

40. Bonora E, Kiechl S, Willeit J et al. Prevalence of insulin resistance in metabolic disorders: the Bruneck Study. Diabetes 1998;47:1643-9.

41. Chen J, Wildman RP, Hamm LL et al. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2960-5.

42. Ferrannini E, Buzzigoli G, Bonadonna R et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350-7.

43. Braith RW, Stewart KJ. Resistance exercise training: its role in the prevention of cardiovascular disease. Circulation 2006;113:2642-50.

44. Grøntved A, Rimm EB, Willett WC, Andersen LB, Hu FB. A prospective study of weight training and risk of type 2 diabetes mellitus in men. Arch Intern Med 2012;172:1306-12.

45. Tanasescu M, Leitzmann MF, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Exercise type and intensity in relation to coronary heart disease in men. JAMA 2002;288:1994-2000.

46. Grundy SM, Benjamin IJ, Burke GL et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. Circulation 1999;100:1134-46.

Appendix A: University of North Florida IRB Approval Letter

UNF
UNIVERSITY of
NORTH FLORIDA.

Office of Research and Sponsored Programs
1 UNF Drive
Jacksonville, FL 32224-2665
904-620-2455 FAX 904-620-2457
Equal Opportunity/Equal Access/Affirmative Action Institution

MEMORANDUM

DATE: February 7, 2014

TO: Mr. William Boyer

FACULTY: Dr. James Churilla
Clinical and Applied Movement Sciences

FROM: Dr. Jennifer Wesely
On behalf of the UNF Institutional Review Board

RE: Project outline review on behalf of the UNF Institutional Review Board IRB

This is to advise you that your projects, as outlined below, were discussed and reviewed on behalf of the UNF Institutional Review Board. Projects as outlined are declared "not human subjects research" based on the federal definition of "research" as stated in the U.S. Department of Health and Human Services Code of Federal Regulations 45 Part 46. Therefore, it is not necessary for projects fitting the description below to be reviewed and approved by the UNF IRB.

Based on conversations with the Dr. Churilla, UNF's IRB understands that Mr. Boyer works with publicly available data from CDC's NHANES (National Health and Nutrition Exam Survey) and conducts secondary data analysis. All data sets received are fairly large and de-identified. Although the PI conducts systematic investigations with the intent to generalize and the information obtained is about living individuals, the PI neither intervenes nor interacts with the individuals. Therefore, this work is not human subject research and is not subject to 45 CFR 46. An IRB submission and review is not necessary.

This waiver should be kept for your records and applies to your project in the form and content as submitted to the IRB for review. Any variations or modifications to waived projects as related to dealing with human subjects must be cleared with the IRB prior to implementing such changes. Any unanticipated problems involving risk and any occurrence of serious harm to subjects and others shall be reported promptly to the IRB.

Thank you for submitting your work for IRB review. We appreciate that you understand the value of IRB review of human subject research conducted at UNF.

Should you have any questions or if we can be of further service, please contact Office of Research and Sponsored Programs at 904.620.2455.

Research Integrity Staff

Appendix B: Associations between HOMA-IR and adiposity measurements in euglycemic U.S. adults: NHANES 1999-2004

Background: Waist circumference (WC) and body mass index (BMI) have been shown to be positively associated with insulin resistance (IR). The objective of this study was to examine the associations between quartiles of the IR (using the homeostatic model assessment of insulin resistance [HOMA-IR]) and BMI and WC in a nationally representative sample of euglycemic U.S. adults.

Methods: Sample included adult participants (≥20 years of age) (N=2,442 [BMI model], N=2,438 [WC model]) from the 1999-2004 National Health and Nutrition Examination Survey (NHANES). HOMA-IR was categorized into quartiles. BMI and WC were examined continuously as the dependent variables.

Results: Following adjustment for covariates, those with HOMA-IR values in the second, third and fourth quartiles had significantly higher BMI's ($p<0.001$) compared to subjects in the first quartile. In the model using WC, significantly higher WC's were found in subjects in the second, third, and fourth quartiles of HOMA-IR ($p<0.001$) compared to those in the first quartile. A significant linear trend was seen analyzing HOMA-IR linearly ($p<0.001$) in both models.

Conclusions: Having a higher HOMA-IR value is associated with higher BMI and WC values in euglycemic subjects.

Insulin resistance (IR) is characterized by the inability of the body to properly utilize endogenous insulin in an effective manner to maintain glucose homeostasis. The homeostatic model assessment of IR (HOMA-IR) has been utilized as a measure for IR in several epidemiological studies. Many studies have shown a significant association between higher levels of IR and cardiovascular disease (CVD)(1-3); all-cause mortality(4) as well as several cardio metabolic risk factors such as: inflammation(5,6) high blood pressure(7,8) and dyslipidemia(7,9) in subjects without diabetes. Furthermore, IR has been shown to be inversely associated with healthy lifestyle behaviors such as physical activity (PA)(10,11). Balkau et al.(11) revealed a significant inverse association between IR and PA independent of BMI and WC.

Insulin resistance is associated with adiposity, characterized by both body mass index (BMI) (9,12-14) and waist circumference (WC)(14-17). In a study conducted by Racette et al.(17), results revealed WC to be a stronger predictor of insulin sensitivity compared to fitness. Riserus et al.(13) showed BMI to be a stronger predictor of insulin sensitivity compared to PA, high-density lipoprotein cholesterol (HDL-C), saturated fat, fasting glucose, triglycerides, diastolic blood pressure (DBP) and socioeconomic status. Results from Nilsson et al.(16) revealed an elevated WC in women (>88 cm) to have a similar predictive value for IR as the National Cholesterol Education Program (NCEP) metabolic syndrome (MetS) definition.

While the relationship of adiposity and IR has been studied extensively, these studies have utilized adiposity as an explanatory variable rather than the dependent variable. This study investigated the associations between increasing levels of IR and adiposity (BMI and WC) in nationally representative sample of euglycemic United States

(U.S.) adults. To the extent of the author's knowledge, this is the first study to investigate these associations using a nationally representative sample from the National Health and Nutrition Examination Survey (NHANES).

Methods

This study utilized six years of data from the 1999-2004 NHANES, a continuous survey conducted by the National Center for Health Statistics(18). The NHANES was designed to provide national estimates of the health and nutritional status of non-institutionalized U.S. civilians over the age of two months. The final samples for this study (N=2,475 [BMI model], N=2,475 [WC model]) met the following conditions: 1) adult men and women ≥20 years of age; 2) attended a morning medical exam in a mobile examination center following an eight to nine hour overnight fast; 3) if female, non-pregnant; 4) had complete data on all the variables of interest and 5) were without diabetes (glycosylated hemoglobin <5.7%, and answered no to the question "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?").

Insulin Resistance

The independent variable was IR. We used the HOMA-IR as a measure for IR; calculated via the equation by Matthews et al.(19): [fasting serum insulin (mU/ml) x fasting plasma glucose (mmol/l)]/22.5. Age-adjusted quartiles of log-transformed HOMA-IR were created using every 25th percentile based on weights specific to NHANES: Q1 (<0.20), Q2 (≥0.20 and <0.37), Q3 (≥0.37 and <0.55) and Q4 (≥0.55).

Adiposity

The dependent variables in the study were adiposity characterized by WC (cm) and BMI (kg/m^2). Body mass index and WC were taken from the ***BMX Body Measures*** file (20) in NHANES and examined continuously. Adiposity measurements were collected using methods from the Anthropometric Standardization Reference Manual (21).

Covariates

Five categories of age were created: 20-29, 30-39, 40-49, 50-59 and ≥60. Gender was categorized as either male or female. Four categories of race were created: non-Hispanic White, non-Hispanic Black, Mexican American, and Other. Education was categorized into four groups: less than high school, high school graduate or GED, some college, and college graduate. Three categories of smoking were created: never smoked, former smoker (quit within the last six-months), and current smoker. C-reactive protein (CRP) was dichotomized: elevated (>3 and ≤10 mg/L) or normal (≤3 mg/L) (22). Hypertension was defined as having a systolic blood pressure (SBP) ≥135mmHg or a DBP ≥85mmHg or currently undergoing pharmacological treatment for hypertension (23). Triglycerides were dichotomized as either elevated (≥150 mg/dl) or normal (<150 mg/dl)(23). Physical activity was categorized into three levels: none (0 min/week), insufficient PA (1-150 min/week), and meeting the 2008 Department of Health and Human Services (DHHS) PA recommendations (≥150 min/week) (24).

Statistical Analysis

The data in this study were initially managed using SAS 9.2 (25). SAS was used to conduct both complex variable recodes and data coding validation. SAS-callable SUDAAN (26) was then used to conduct the analysis, incorporating sampling weights within the context of the correlated multi-stage complex sampling design inherent to NHANES. Non-overlapping 95% confidence intervals (CI) and corresponding p-values illustrate significance ($p<0.05$). Linear regression (PROC REGRESS) analysis was used to test the null hypotheses that individual regression coefficients are equal to zero for each quartile of HOMA-IR. Two regression models were created; one for WC and one for BMI. The model examining WC adjusted for age, race, gender, CRP, hypertension, triglycerides, PA and HOMA-IR. The model examining BMI adjusted for age, race, education, CRP, smoking, hypertension, triglycerides, PA and HOMA-IR. These two models differed in the specific covariates used in order to achieve a parsimonious model for each.

Results

Subjects with HOMA-IR values in the second, third and fourth quartiles had significantly higher BMI's ($p<0.001$) compared to subjects in the first quartile. In the model using WC, significantly higher WC's were found in subjects in the second, third, and fourth quartiles of HOMA-IR ($p<0.001$) compared to those in the first quartile. A significant linear trend was seen analyzing HOMA-IR linearly ($p<0.001$) in both models. Table 1 summarizes the population characteristics.

Table 1. Population characteristics of study sample, National Health and Nutrition Examination Survey 1999-2004

	N	Weighted % (SE)
HOMA-IR		
Q1	2195	58.09 (1.52)
Q2	774	18.35 (0.83)
Q3	674	15.46 (0.80)
Q4	533	11.10 (0.72)
Age		
20-29	513	22.35 (1.88)
30-39	517	24.71 (1.41)
40-49	497	22.52 (1.17)
50-59	319	14.94 (0.91)
≥60	629	15.48 (1.03)
Gender		
Male	1279	50.30 (0.94)
Female	1196	49.70 (0.94)
Race		
Non-Hispanic White	1329	75.01 (2.05)
Non-Hispanic Black	394	9.02 (1.18)
Mexican American	594	7.18 (0.92)
Other	158	8.78 (1.67)
Education		
College graduate	510	25.69 (1.68)
Some college	672	29.93 (1.10)
High school graduate/GED	563	25.78 (1.56)
< High school	730	18.60 (0.88)
Smoking		
Never smoked	1298	50.88 (1.90)
Former smoker	613	24.73 (1.42)
Current smoker	564	24.39 (1.50)
C-reactive protein		
Normal	1759	73.83 (1.36)
Elevated	716	26.17 (1.36)
Hypertension		
Normotensive	1536	67.25 (1.08)
Hypertension	939	32.75 (1.08)
Triglycerides		
Normal	1871	76.29 (1.27)
Elevated	604	23.71 (1.27)
Physical Activity		
Meets recommendations	976	33.15 (1.67)
Insufficient	691	29.88 (1.70)
None	808	36.97 (2.11)

Q1 (<0.20), Q2 (≥0.20 and <0.37), Q3 (≥0.37 and <0.55) and Q4 (≥0.55). Hypertension: SBP ≥135mmHg or a DBP ≥85mmHg. Normotensive: SBP <135mmHg and a DBP <85mmHg. CRP: elevated (>3 and ≤10 mg/L) or normal (≤3 mg/L). Triglycerides: elevated (≥150 mg/dl) or normal (<150 mg/dl) PA: None, Insufficient (≥1 but <150 min/wk.), Meets Recommendations (≥150 min/wk.) HOMA-IR: homeostatic model assessment of insulin resistance. SE: Standard error.

Table 2 illustrates the results of the linear regression analysis examining the associations between WC and independent variables among those without diabetes. Following adjustment for covariates, significantly greater WC levels (β=19.44, $p<0.001$) were observed in subjects in the greatest quartile of IR when compared to the other quartiles. Subjects in the third quartile of IR, had significantly greater WC levels (β=11.93, $p<0.001$) compared to the referent group and second quartile. Furthermore, subjects in the second quartile of IR had significantly higher WC values (β=6.63, $p<0.001$) compared to the referent group. When examining HOMA-IR linearly, a significant relationship was revealed with WC (β=3.75, $p<0.001$).

Table 2. β coefficients for regression analysis examining associations between HOMA-IR and waist circumference in centimeters

Categorical Regression		Linear Regression	
Covariates	**Waist Circumference (95% CI) β**	**Covariates**	**Waist Circumference (95% CI) β**
HOMA-IR		**HOMA-IR**	
Q1	0.00		
Q2	6.63 (5.51,7.76)***	HOMA-IR	3.75 (2.75-4.76)***
Q3	11.93 (10.64,13.21)***		
Q4	19.44 (17.73,21.14)***		
Age		**Age**	
20-29	0.00	20-29	0.00
30-39	2.32 (0.64,3.99)**	30-39	2.30 (0.74,3.86)**
40-49	3.48 (1.85,5.10)***	40-49	3.68 (1.99,5.36)***
50-59	5.61 (4.02,7.20)***	50-59	5.99 (4.25,7.74)***
≥60	4.58 (2.64,6.51)***	≥60	4.85 (2.92,6.79)***
Gender		**Gender**	
Male	0.00	Male	0.00
Female	-7.21 (-8.34,-6.07)***	Female	-7.27 (-8.50,-6.04)***
Race		**Race**	
Non-Hispanic White	0.00	Non-Hispanic White	0.00
Non-Hispanic Black	-1.30 (-2.83,0.22)	Non-Hispanic Black	-1.62 (-3.29,0.06)
Mexican American	-2.43 (-4.02,-0.84)*	Mexican American	-2.05 (-3.75,-0.34)*
Other	-2.44 (-5.05,0.16)	Other	-2.27 (-4.84,0.29)*
C-reactive protein		**C-reactive protein**	
Normal	0.00	Normal	0.00
Elevated	5.78 (4.53,7.02)***	Elevated	5.90 (4.62,7.18)***
Hypertension		**Hypertension**	
Normotensive	0.00	Normotensive	0.00
Hypertension	2.38 (1.10,3.67)***	Hypertension	2.51 (1.28,3.75)***
Triglycerides		**Triglycerides**	
Normal	0.00	Normal	0.00
Elevated	0.68 (-0.67,2.02)	Elevated	1.45 (0.23,2.67)*
Physical Activity		**Physical Activity**	
Meets recommendations	0.00	Meets recommendations	0.00
Insufficient	0.70 (-0.53,1.92)	Insufficient	1.15 (-0.22,2.52)
None	1.19 (0.41,1.97)**	None	1.75 (0.71,2.80)***

Table 2. Q1 (<0.20), Q2 (≥0.20 and <0.37), Q3 (≥0.37 and <0.55) and Q4 (≥0.55). Hypertension: SBP ≥135mmHg or a DBP ≥85mmHg. Normotensive: SBP <135mmHg and a DBP <85mmHg. CRP: elevated (>3 and ≤10 mg/L) or normal (≤3 mg/L). Triglycerides: elevated (≥150 mg/dl) or normal (<150 mg/dl) PA: None, Insufficient (≥1 but <150 min/wk.), Meets Recommendations (≥150 min/wk.) ***p<0.001, **p<0.01, *p<0.05. Model: adjusted for age, race, gender, CRP, hypertension, triglycerides, PA, HOMA-IR. PA: Physical activity. CRP: C-reactive protein. HOMA-IR: homeostatic model assessment of insulin resistance, CI: Confidence interval. β: Beta.

Table 3 illustrates the results of the linear regression analysis examining the associations between BMI and independent variables among those without diabetes. Significant differences in BMI were revealed in subjects in the second ($\beta=2.58$, $p<0.001$), third ($\beta=4.37$, $p<0.001$) and fourth ($\beta=7.63$, $p<0.001$) quartiles for IR compared to the referent group. Furthermore, significant differences in BMI levels were found between the second, third and fourth quartiles of HOMA-IR ($p<0.001$). Similar to WC, when examining HOMA-IR linearly, a significant relationship was revealed with BMI ($\beta=1.46$, $p<0.001$).

Table 3. β coefficients for regression analysis examining associations between HOMA-IR and body mass index in kg/m^2

Categorical Regression		Linear Regression	
Covariates	**Body Mass Index (95% CI) β**	**Covariates**	**Body Mass Index (95% CI) β**
HOMA-IR		**HOMA-IR**	
Q1	0.00		
Q2	2.58 (0.21,3.01)***	HOMA-IR	1.46 (1.08,1.84)***
Q3	4.37 (3.86,4.88)***		
Q4	7.63 (6.92,8.34)***		
Age		**Age**	
20-29	0.00	20-29	0.00
30-39	0.36 (-0.27,0.98)	30-39	0.39 (-0.22,1.01)
40-49	0.33 (-0.40,1.06)	40-49	0.43 (-0.33,1.18)
50-59	0.52 (-0.08,1.13)	50-59	0.68 (0.04,1.33)*
≥60	-0.81 (-1.55,-0.06)*	≥60	-0.70 (-1.40,-0.00)*
Race		**Race**	
Non-Hispanic White	0.00	Non-Hispanic White	0.00
Non-Hispanic Black	0.94 (0.28,1.60)**	Non-Hispanic Black	0.77 (0.11,1.44)*
Mexican American	-0.23 (-0.92,0.46)	Mexican American	-0.15 (-0.85,0.55)
Other	-0.17 (-1.24,0.91)	Other	-0.23 (-1.28,0.83)
Education		**Education**	
College graduate	0.00	College graduate	0.00
Some college	0.21 (-0.34,0.75)	Some college	0.37 (-0.24,0.97)
High school graduate/GED	0.37 (-0.12,0.87)	High school graduate/GED	0.43 (-0.08,0.94)
< High school	0.15 (-0.44,0.74)	< High school	0.33 (-0.42,1.07)
C-reactive protein		**C-reactive protein**	
Normal	0.00	Normal	0.00
Elevated	2.28 (1.72,2.84)***	Elevated	2.32 (1.71,2.59)***
Smoking		**Smoking**	
Never smoked	0.00	Never smoked	0.00
Former smoker	0.14 (-0.48,0.76)	Former smoker	0.10 (-0.50,0.70)
Current smoker	-0.81 (-1.49,-0.13)*	Current smoker	-0.96 (-1.71,-0.21)*
Hypertension		**Hypertension**	
Normotensive	0.00	Normotensive	0.00
Hypertension	1.03 (0.55,1.51)***	Hypertension	1.07 (0.56,1.59)***
Triglycerides		**Triglycerides**	
Normal	0.00	Normal	0.00
Elevated	-0.02 (-0.47,0.44)	Elevated	0.26 (-0.18,0.70)
Physical Activity		**Physical Activity**	
Meets recommendations	0.00	Meets recommendations	0.00
Insufficient	0.03 (-0.43,0.50)	Insufficient	0.19 (-0.37,0.76)
None	0.04 (-0.34,0.42)	None	0.24 (-0.27,0.74)

Table 3. Q1 (<0.20), Q2 (≥0.20 and <0.37), Q3 (≥0.37 and <0.55) and Q4 (≥0.55). Hypertension: SBP ≥135mmHg or a DBP ≥85mmHg. Normotensive: SBP <135mmHg and a DBP <85mmHg. CRP: elevated (>3 and ≤10 mg/L) or normal (≤3 mg/L). Triglycerides: elevated (≥150 mg/dl) or normal (<150 mg/dl). PA: None, Insufficient (≥1 but <150 min/wk.), Meets Recommendations (≥150 min/wk.) ***p<0.001, **p<0.01, *p<0.05. Model: adjusted for age, race, education, smoking, CRP, hypertension, triglycerides, PA, HOMA-IR. PA: Physical activity. CRP: C-reactive protein. HOMA-IR: homeostatic model assessment of insulin resistance, CI: Confidence interval. β: Beta.

Table 4 illustrates the mean WC and BMI level percentages across quartiles of HOMA-IR. Furthermore, a significant difference was found in mean levels of WC (second: third: 96.02, fourth: 102.92, $p<0.01$) and BMI (second: 26.35, third: 27.92, fourth: 30.97, $p<0.001$) in the third and fourth quartiles of HOMA-IR compared to those in the first quartile (WC: 91.14, BMI: 23.77). Moreover, significant differences were found between subjects in the fourth quartile compared to those in the third quartile of HOMA-IR ($p<0.01$) as well as between the second and third quartiles ($p<0.01$). Trend analysis revealed a significant positive trend between BMI and quartiles of HOMA-IR ($p<0.001$) as well as WC and quartiles of HOMA-IR ($p<0.001$). When examining the relationship between adiposity measurement and HOMA-IR linearly, both BMI ($p<0.001$) and WC ($p<0.001$) were found to have a significant positive linearly relationship with HOMA-IR.

Table 4. Means values of Waist Circumference (cm) and Body Mass Index (kg/m^2) across quartiles of HOMA-IR

HOMA-IR Quartile	WC means (95% CI)	BMI means (95% CI)
Q1	84.59 (83.87,85.32)	23.77 (23.53,24.00)
Q2	91.23 (90.55,91.90)	26.35 (26.00,26.69)
Q3	96.52 (95.41,97.63)	28.14 (27.67,28.60)
Q4	104.03 (102.40,105.66)	31.40 (30.73,32.07)
p-for-trend (categorical HOMA-IR)	p<0.001	p<0.001
p-for-trend (linear HOMA-IR)	p<0.001	p<0.001

Q: Quartile; WC: Waist Circumference; BMI: Body Mass Index; kg/m^2: Body weight in kilograms divided by height in meters squared; HOMA-IR: Homeostatic model assessment of insulin resistance; CI: Confidence interval; cm: Centimeters.

Discussion

The results of this study illustrate a positive dose-response relationship between HOMA-IR and two commonly utilized health indicators that have been shown to be highly correlated with adiposity in euglycemic U.S. adults. Significantly greater values for WC were seen in subjects falling in the second, third and fourth quartiles of HOMA-IR compared to the first quartile. Similarly, significantly higher mean values for BMI were seen in the second, third and fourth quartiles of HOMA-IR compared to the first quartile. Our results add to existing cross-sectional studies investigating these associations in U.S. adults(12,15-17,27). In a study of 4,800 Japanese men, Tabata et al.(15) investigated the associations between increasing levels of WC and elevated HOMA-IR. Compared to those with a WC <80 cm, subjects with a WC 80-84 cm (OR 3.2, 95% CI 2.3–4.3), 85-89 cm (8.2, 95% CI 6.1–11.0), 90-94 cm (15.2, 95% CI 11.1–20.8), or ≥95 cm (45.2, 95% CI 31.8–64.4) were significantly more likely to have an elevated HOMA-IR level.

The findings of this study are also consistent with several prospective(13,28,29) and retrospective studies(30) as well as a randomized control trial(14). Wahrenberg et al.(30) revealed that a WC ≥100 cm had a higher predictor value for IR measured by HOMA-IR in males and females compared to a WC <100 cm. Furthermore, a higher prevalence of IR (defined as HOMA-IR score >3.99) was found in subjects with a WC ≥100 cm (277 males; 388 females) compared to those <100 cm (7 males; 25 females). Another study conducted by Riserus et al.(13) found BMI to be a stronger predictor of insulin sensitivity compared to PA, HDL-C, saturated fat, fasting glucose, triglycerides, DBP and socioeconomic status. Following exclusion of overweight and obese subjects,

BMI remained the strongest predictor.

Increased levels of adiposity have been shown to be independently associated with increased risk for many adverse health conditions such as CVD(31-33), coronary heart disease(34), diabetes(33,35,36) as well as all-cause mortality(32). Furthermore, adiposity has been shown in several studies to be associated with several CVD risk factors such as hypertension(37,38), dyslipidemia(37,38), and MetS(37,39). Katzmarzyk et al.(40) revealed an augmented WC (≥102 cm) to be associated with increased risk for CVD, independent of having ≥2 MetS risk factors. Insulin resistance has also been shown to be independently associated with CVD(1-3), all-cause mortality(4), and diabetes(3) as well as several cardio metabolic risk factors such as: inflammation (5,6) high blood pressure(7,8) and dyslipidemia(7,9); in subjects without diabetes. These results illustrate the impact augmented levels of adiposity and IR can have on future CVD risk, even in euglycemic subjects.

The results of our study revealed strong associations between HOMA-IR and measurements of adiposity independent of PA. Several studies have shown inverse associations between IR and PA(10,11) as well as PA and adiposity(41-43). A cross-sectional analysis conducted by Balkau et al.(11) investigated the associations between insulin sensitivity and PA in subjects without CVD and not treated with pharmacotherapy for diabetes, hypertension, dyslipidemia, or obesity. Results revealed significant associations between total activity and increased insulin sensitivity independent of BMI and adiposity. While our study focused on the associations between IR and adiposity, no significant mediating effects were seen, attributable to PA. Thus, our results speak to the strength of association between IR and adiposity independent of PA, specifically in

euglycemic subjects.

The strengths of our study include strong external validity owing to the use of a large representative sample, consistent validated measurements for WC and BMI, and the use of validated assays to measure insulin, glucose and glycosylated hemoglobin. Additionally, our results are consistent with others demonstrating a positive relationship between IR and adiposity. Finally, the novel approach to this study design, characterized by utilizing HOMA-IR as the explanatory variable and adiposity measures as the dependent variables provides further insight into this relationship. The limitations of our study include the cross-sectional study design, which does not allow for causation to be established between variables, and the use of questionnaires for the assessment of PA, which is subject to recall bias.

Conclusions

In conclusion, adults without diabetes that fall in the 25th percentile and above of HOMA-IR had greater WC values and those falling into the 25th percentile or higher of HOMA-IR possessed greater BMI values compared to subjects in the lower 25th percentile. Insulin resistance and increased adiposity have been shown to be independently associated with increased risk for CVD, CHD, and diabetes. Our study revealed that higher levels of IR are associated with increased WC and BMI, independent of PA among euglycemic adults. Our study suggests that future research into the deleterious relationships between IR and increased adiposity should consider the effects in those considered euglycemic as well as the possible mediating effects of increased volumes of PA.

References

1. Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in relation to the incidence of cardiovascular disease: the San Antonio Heart Study. Diabetes Care 2002;25:1177-84.
2. Hedblad B, Nilsson P, Engström G, Berglund G, Janzon L. Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death. Diabet Med 2002;19:470-5.
3. Bonora E, Kiechl S, Willeit J et al. Population-based incidence rates and risk factors for type 2 diabetes in white individuals: the Bruneck study. Diabetes 2004;53:1782-9.
4. Ausk KJ, Boyko EJ, Ioannou GN. Insulin resistance predicts mortality in nondiabetic individuals in the U.S. Diabetes Care 2010;33:1179-85.
5. McLaughlin T, Abbasi F, Lamendola C et al. Differentiation between obesity and insulin resistance in the association with C-reactive protein. Circulation 2002;106:2908-12.
6. Chen J, Wildman RP, Hamm LL et al. Association between inflammation and insulin resistance in U.S. nondiabetic adults: results from the Third National Health and Nutrition Examination Survey. Diabetes Care 2004;27:2960-5.
7. Resnick HE, Jones K, Ruotolo G et al. Insulin resistance, the metabolic syndrome, and risk of incident cardiovascular disease in nondiabetic american indians: the Strong Heart Study. Diabetes Care 2003;26:861-7.
8. Ferrannini E, Buzzigoli G, Bonadonna R et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350-7.

9. McLaughlin T, Allison G, Abbasi F, Lamendola C, Reaven G. Prevalence of insulin resistance and associated cardiovascular disease risk factors among normal weight, overweight, and obese individuals. Metabolism 2004;53:495-9.

10. Goodpaster BH, Katsiaras A, Kelley DE. Enhanced fat oxidation through physical activity is associated with improvements in insulin sensitivity in obesity. Diabetes 2003;52:2191-7.

11. Balkau B, Mhamdi L, Oppert JM et al. Physical activity and insulin sensitivity: the RISC study. Diabetes 2008;57:2613-8.

12. Chen G, Liu C, Yao J et al. Overweight, obesity, and their associations with insulin resistance and β-cell function among Chinese: a cross-sectional study in China. Metabolism 2010;59:1823-32.

13. Risérus U, Arnlöv J, Berglund L. Long-term predictors of insulin resistance: role of lifestyle and metabolic factors in middle-aged men. Diabetes Care 2007;30:2928-33.

14. Farin HM, Abbasi F, Reaven GM. Body mass index and waist circumference both contribute to differences in insulin-mediated glucose disposal in nondiabetic adults. Am J Clin Nutr 2006;83:47-51.

15. Tabata S, Yoshimitsu S, Hamachi T, Abe H, Ohnaka K, Kono S. Waist circumference and insulin resistance: a cross-sectional study of Japanese men. BMC Endocr Disord 2009;9:1.

16. Nilsson G, Hedberg P, Jonason T et al. Waist circumference alone predicts insulin resistance as good as the metabolic syndrome in elderly women. Eur J Intern Med 2008;19:520-6.

17. Racette SB, Evans EM, Weiss EP, Hagberg JM, Holloszy JO. Abdominal adiposity is a stronger predictor of insulin resistance than fitness among 50-95 year olds. Diabetes Care 2006;29:673-8.

18. National Center for Health Statistics Centers for Disease Control and Prevention. NHANES Analytic and Reporting Guidelines September 2006 Version.

19. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.

20. National Center for Health Statistics Centers for Disease Control and Prevention. National Health and Nutrition Examination Survey, http://www.cdc.gov/nchs/nhanes/nhanes1999-2000/BMX.htm. (1999-2004, accessed 25 February 2014). .

21. Lohmann TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Champaign, Illinois: Human Kinetics Books, Jan 1, 1988.

22. Pearson TA, Mensah GA, Alexander RW et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003;107:499-511.

23. Grundy SM, Cleeman JI, Daniels SR et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.

24. US Department of Health and Human Services. 2008 physical activty guidelines for Americans, http://www.health.gov/paguidelines.pdf 2008.

25. SAS Institute Inc 2009. Base SAS 9.2 Procedures Guide.

26. Research Triangle Institute (2012). SUDAAN User's Manual, Release 11.0.

27. Martínez-Larrad MT, Lorenzo C, González-Villalpando C, Gabriel R, Haffner SM, Serrano-Ríos M. Associations between surrogate measures of insulin resistance and waist circumference, cardiovascular risk and the metabolic syndrome across Hispanic and non-Hispanic white populations. Diabet Med 2012;29:1390-4.

28. Trirogoff ML, Shintani A, Himmelfarb J, Ikizler TA. Body mass index and fat mass are the primary correlates of insulin resistance in nondiabetic stage 3-4 chronic kidney disease patients. Am J Clin Nutr 2007;86:1642-8.

29. Liu R, Brickman WJ, Christoffel KK et al. Association of adiposity trajectories with insulin sensitivity and glycemic deterioration: a longitudinal study of rural Chinese twin adults. Diabetes Care 2012;35:1506-12.

30. Wahrenberg H, Hertel K, Leijonhufvud BM, Persson LG, Toft E, Arner P. Use of waist circumference to predict insulin resistance: retrospective study. BMJ 2005;330:1363-4.

31. Staiano AE, Reeder BA, Elliott S et al. Body mass index versus waist circumference as predictors of mortality in Canadian adults. Int J Obes (Lond) 2012;36:1450-4.

32. Katzmarzyk PT, Reeder BA, Elliott S et al. Body mass index and risk of cardiovascular disease, cancer and all-cause mortality. Can J Public Health 2012;103:147-51.

33. Janiszewski PM, Janssen I, Ross R. Does waist circumference predict diabetes and cardiovascular disease beyond commonly evaluated cardiometabolic risk factors? Diabetes Care 2007;30:3105-9.

34. Flint AJ, Rexrode KM, Hu FB et al. Body mass index, waist circumference, and risk of coronary heart disease: a prospective study among men and women. Obes Res Clin Pract 2010;4:e171-e181.

35. Siren R, Eriksson JG, Vanhanen H. Waist circumference a good indicator of future risk for type 2 diabetes and cardiovascular disease. BMC Public Health 2012;12:631.

36. Siegel LC, Sesso HD, Bowman TS, Lee IM, Manson JE, Gaziano JM. Physical activity, body mass index, and diabetes risk in men: a prospective study. Am J Med 2009;122:1115-21.

37. Janssen I, Katzmarzyk PT, Ross R. Waist circumference and not body mass index explains obesity-related health risk. Am J Clin Nutr 2004;79:379-84.

38. Ashton WD, Nanchahal K, Wood DA. Body mass index and metabolic risk factors for coronary heart disease in women. Eur Heart J 2001;22:46-55.

39. Churilla JR, Fitzhugh EC, Thompson DL. The Metabolic Syndrome: How Definition Impacts the Prevalence and Risk in U.S. Adults: 1999-2004 NHANES. Metab Syndr Relat Disord 2007;5:331-42.

40. Katzmarzyk PT, Janssen I, Ross R, Church TS, Blair SN. The importance of waist circumference in the definition of metabolic syndrome: prospective analyses of mortality in men. Diabetes Care 2006;29:404-9.

41. Folsom AR, Caspersen CJ, Taylor HL et al. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample. The Minnesota Heart Survey. Am J Epidemiol 1985;121:570-9.

42. Jakicic JM, Otto AD. Physical activity considerations for the treatment and prevention of obesity. Am J Clin Nutr 2005;82:226S-229S.

43. Troisi RJ, Heinold JW, Vokonas PS, Weiss ST. Cigarette smoking, dietary intake, and physical activity: effects on body fat distribution--the Normative Aging Study. Am J Clin Nutr 1991;53:1104-11.

Vita

William Robert Boyer II is a graduate research assistant and instructor in the Clinical and Applied Movement Sciences department at the University of North Florida in Jacksonville, Florida. He also completed his undergraduate coursework at the University of North Florida where he earned his Bachelors of Science degree in Exercise Science.

His research studies have included the investigation of the associations between muscular strengthening activities and insulin resistance, specifically in subjects with normal glucose levels. He has also investigated associations between different measurements of adiposity and insulin resistance. Furthermore, he also has also examined associations between mental distress severity and physical activity participation. He is married to Hannah Boyer. They currently reside in Jacksonville, Florida and will be relocating to Knoxville, Tennessee where Bill will be pursuing his Ph.D. They also have a Jack Russell Terrier named Cooper.