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UNIVERSITY OF CALIFORNIA, SAN DIEGO  
SAN DIEGO STATE UNIVERSITY

**The Influence of Adiposity on Mortality and Cardiovascular Risk**

A dissertation submitted in partial satisfaction of the  
requirements for the degree of Doctor of Philosophy in  
Public Health (Epidemiology)

by

Jared Paul Reis

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2007

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Chair

University of California, San Diego

San Diego State University

2007

## **DEDICATION**

To my wife, Rebecca.

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## PUBLICATIONS AND PRESENTATIONS

### Book Chapter

1. LaMonte M.J., Ainsworth B.E., **REIS J.P.** Measuring physical activity. In: Wood T.M., Zhu W., eds. 2006. *Measurement Theory and Practice in Kinesiology*. Champaign, IL: Human Kinetics Publishers.

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activity. Presented at the *North American Association for the Study of Obesity*, October 2003.

27. **REIS J.P.**, Durstine J.L., Ainsworth B.E., Wilcox S., Tudor-Locke C.E. Ambulatory activity during and after phase II cardiac rehabilitation. Presented at the *Southwest Chapter of the American College of Sports Medicine* annual meeting, Las Vegas NV, November 2003.

## **ABSTRACT OF THE DISSERTATION**

### **The Influence of Adiposity on Mortality and Cardiovascular Risk**

by

Jared Paul Reis

Doctor of Philosophy in Public Health (Epidemiology)

University of California, San Diego, 2007

San Diego State University, 2007

Professor Caroline A. Macera, Chair

**OBJECTIVES:** There were three objectives of the current dissertation: (1) to examine the influence of age and (2) race/ethnicity on the association of adiposity with mortality; and (3) to determine whether leptin or insulin mediate the association of obesity with metabolic, inflammatory, and thrombogenic cardiovascular disease (CVD) risk factors. **METHODS:** Two population-based cohort studies using data from the third National Health and Nutrition Examination Survey (NHANES III) were used to examine objectives one and two, and a cross-sectional study of NHANES III to examine objective three. NHANES III included a national, complex multistage, clustered, stratified probability sample of the civilian, noninstitutionalized US population. Data were collected at baseline between 1988-1994 during a home

interview, physical examination, and laboratory analysis. Mortality follow-up of the baseline cohort was performed through December 2000 with the use of the National Death Index. **RESULTS:** Age modified the relation of adiposity with mortality. In middle-aged adults (30-64 years), body mass index (BMI) demonstrated a U-shaped relation with mortality in men and a J-shaped relation in women, while positive associations, stronger among women than men, were observed between waist-to-hip ratio (WHR) and mortality. In older adults (65-102 years), decreased adiposity, in general, carried an increased risk for mortality. The association of BMI with mortality varied by sex and race/ethnicity; however, WHR demonstrated positive relations with mortality, stronger among white and black women than men, but of similar strength among white, black, and Mexican American men. Among Mexican Americans, an elevated WHR increased the risk of death only among US-born English speaking men, while no association was observed in women, regardless of migration, acculturation, or level of education. Insulin demonstrated significant ( $p < 0.05$ ) associations, independent of obesity, with several metabolic CVD risk factors, while leptin was associated only with fibrinogen levels in women. **CONCLUSIONS:** Age and race/ethnicity are important factors to consider when examining the relation of adiposity with mortality. Insulin may at least partly mediate the association of obesity with metabolic but not inflammatory or thrombogenic CVD risk factors, while leptin does not appear to influence cardiovascular risk through a shared association with CVD risk factors.

## I: INTRODUCTION

### **The Obesity Epidemic**

The prevalence of obesity in the U.S. and much of the industrialized world has reached epidemic proportions. In the U.S., estimates over the last several decades have shown a continual increase with much interest in determining the health-related consequences of this epidemic. In the first National Health Examination Survey (1960-1962), 13.4% of adults aged 20-74 years were obese based upon a BMI  $\geq 30$  kg/m<sup>2</sup> (1). During the first (1971-1974) and second (1976-1980) National Health and Nutrition Examination Surveys (NHANES) this prevalence increased to 14.5% and 15.0%, respectively. Results from the third NHANES (1988-1994) and NHANES 1999-2000, and NHANES 2001-2002 showed that this prevalence increased to 23.3%, 30.9%, and 30.6%, respectively (2,3). An estimated 300,000 excess deaths attributable to obesity occur in the US each year (4). The economic and health-related consequences of the obesity epidemic are substantial, although few true economic evaluations of obesity have been performed (5). Direct U.S. medical care costs attributed to obesity have been estimated at more than \$70 billion in 1995 (6). Obesity increases the risk of a number of chronic health conditions, including hypertension, type 2 diabetes, stroke, gallbladder disease, osteoarthritis, sleep apnea, respiratory problems, and several of the most common types of cancer. As the second leading cause of preventable death in the U.S., overweight and obesity pose a tremendous public health challenge.

The causal factors contributing to the increase in the prevalence of obesity in the U.S. and other developed countries have not been completely elucidated. A genetic component to the accumulation of excess body fat under conditions of overfeeding, and the ability to lose fat during periods of underfeeding has been shown (7-10). However, genetic factors are unlikely to explain the increases in obesity observed over the last four decades, since any genetic alteration at the population level would likely take several generations. Thus, the influence of the environment, personal behaviors, and social and cultural factors must play important roles. The wide-scale availability of calorically dense food and less participation in physical activity has likely influenced the increase in obesity. Poor eating habits are typically learned during childhood. In 2001, nearly 80% of school-aged children did not meet the federal guideline of at least five servings of fruits or vegetables per day (11). Similar data show decreases in the amount of physical activity performed by children, exacerbated by recent declines in the requirement of physical education in many school districts around the country (12).

### **BMI, Fat Patterning, and Mortality**

BMI is calculated using self-reported or measured height and weight, and routinely used in epidemiologic studies to provide an indirect means of estimating adiposity. The major reason for incorporating BMI as an estimate of total body fat in large studies relates to its low cost, feasibility, and reproducibility. Despite the fact that those who are obese have been shown to underestimate their body weight and men to overestimate their height, leading to an underestimation of BMI (13,14),

studies have shown that BMI from measured height and weight is highly correlated with percent body fat (15). The first Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (16), concluded that overweight and obesity are major risk factors for increased morbidity and mortality. The report adopted guidelines established by the World Health Organization, and defined a BMI of 25 to less than 30 kg/m<sup>2</sup> as overweight and obesity as a BMI greater than or equal to 30 kg/m<sup>2</sup>. However, these clinical guidelines for identifying overweight or obese individuals who may be at an increased risk of mortality were based predominately upon studies of younger to middle-aged populations.

Whether BMI is positively associated with mortality in older adults is controversial. Although there is a paucity of data relative to the association of overweight or obesity and their effects on all-cause or cardiovascular mortality in the elderly, the available studies do not consistently support a positive relation. The reasons for this are not entirely clear, but it may be that those who are susceptible to the deleterious effects of obesity suffer from increased mortality in middle-age leaving a healthier population of older obese adults (selective survival), and in older-age the protective effects of obesity counterbalance some negative effects (17). The potential beneficial effects may include energy reserves during times of stress, lower rates of injury due to falls, and lower rates of osteoporosis (18). However, it may also be that BMI in the elderly does not accurately estimate body fat and therefore does not correspond with a relative increase in the risk of death, as is observed in younger populations. Older adults face a progressive decline in fat-free mass and overall height shrinkage (19,20). In addition, fat mass tends to accumulate intra-muscularly



and intra-abdominally with age leading to an inaccurate reflection of body fatness with the use of BMI. Therefore, additional measures of body habitus other than BMI may prove more useful as predictors of adverse health conditions, especially mortality (21,22).

Waist circumference and waist-to-hip ratio, as opposed to BMI, may be more specific indicators of total body fat and may therefore provide an improved means of determining the risk of mortality associated with obesity, especially in the elderly. Many reports have shown that abdominal or central obesity is equally important as total adiposity, and may be a better indicator of CVD risk (23). Waist circumference, used as a surrogate of abdominal obesity, is highly correlated with visceral adipose tissue (24) and has been strongly linked with components of the metabolic syndrome, including glucose intolerance, hypertension, dyslipidemia, and insulin resistance (25). Few studies have evaluated the usefulness of waist circumference or waist-to-hip ratio, compared to BMI, when predicting mortality, and those that have, have been inconsistent (26-29).

### **Relevant Literature**

In a study of approximately 3,700 Japanese-American men aged 71-93 years from the Honolulu Heart Study, Kalmijn et al. (27) evaluated the predictive power of BMI, waist-to-hip ratio, and skinfold thickness when assessing the risk of mortality. All measures were assessed by trained technicians using a standardized protocol. The men were followed for a mean of 4.5 years with 766 deaths recorded. The authors found a significant *inverse* association of BMI with mortality. These results were

independent of waist-to-hip ratio, and did not change after exclusion of deaths that occurred in the first 1-2 years, or the removal of former or current smokers. The relation between waist-to-hip ratio and mortality initially appeared to be U-shaped; however, after adjustment for BMI, a higher waist-to-hip ratio was linearly associated with increased mortality. Among men with a high BMI, the positive relation of waist-to-hip ratio with death was especially pronounced. The results for skinfold thickness were similar to the results for BMI, but less strong. This study was able to account for differences in several potential confounding factors, including smoking and alcohol use. However, this study was limited by a relatively short follow-up period and the inability to study the relation of body composition with specific causes of death. Despite these limitations, an increased waist-to-hip ratio was shown to offer utility in predicting death from all causes among these elderly men.

Baik et al. (26), in an analysis of data from the Health Professionals Follow-Up Study, evaluated the predictive power of BMI, waist and hip circumferences, and waist-to-hip ratio when assessing the risk of all-cause, CVD, and cancer mortality in men aged 40-75 years. A total of 39,756 men who were free of known chronic disease at baseline in 1986 were followed for 10 years when 1,972 total deaths were reported. Weight and height were self-reported from a mailed questionnaire, as was waist and hip circumference, measured with a mailed paper measuring tape. Among all men, the authors found significant U-shaped age- and multivariate-adjusted relations of BMI with all-cause mortality. When men who experienced greater than a 10 pound weight loss in the last five years were excluded, the relative risk associated with a low BMI decreased and was no longer statistically significant; however, the risk of an elevated

BMI was not appreciably altered. When men were stratified by age (at age 65 years), BMI was linearly associated with all-cause and CVD mortality among the younger men, but was unrelated to death from cancer, CVD, or all-causes among the elderly men. Waist circumference, however, significantly predicted the risk of death from CVD among the older sample of men. Although limited by the self-report of weight, height, waist and hip circumferences, this study provided good evidence that the use of BMI for the prediction of mortality in older men may not be advisable. In contrast, an increased waist circumference proved capable of identifying men at an increased risk of CVD death.

Visscher et al. (29) used data from the Rotterdam Study of 6,296 men and women from The Netherlands to study the relation of BMI, waist circumference, and waist-to-hip ratio as predictors of all-cause mortality. Participants were aged 55-102 years at baseline between 1990 and 1993, and were followed for a mean of 5.4 years when a total of 956 deaths were reported. Weight, height, waist and hip circumferences were measured by trained technicians. The authors found no relation of BMI with all cause mortality among never, former, or current smoking men or women. However, never smoking men in the highest quintile of waist circumference were 1.6 (95% CI=0.8, 3.4) times more likely to die during follow-up than never smoking men in the second quintile of waist circumference. No association of body circumferences with death from all causes was found among women. The current study was limited by a short follow-up, the inability to evaluate the effect of occult or pre-existing disease, small numbers of deaths, and the inability to determine the risk of death from specific causes. Although this study had several methodological

limitations, it showed that waist circumference, and not BMI, may prove useful for the prediction of all-cause mortality in the elderly.

Recently, Price et al. (28) studied 14,833 participants from one arm of a randomized trial of a health and social assessment of older persons aged > 75 years who were recruited from 106 family practices in the UK. Participants were not known to live in long-term nursing institutions and were not terminally ill at baseline. Body habitus variables were measured and included BMI, waist and hip circumferences. Over a median follow-up of 5.9 years, a total of 6,649 deaths were tallied. The authors showed that the risk of all-cause mortality was *inversely* related to BMI among both nonsmoking men and women. Waist-to-hip ratio, however, was significantly *positively* related to all-cause and CVD mortality among nonsmoking men and women. Waist circumference was not associated with mortality from all-causes or CVD among men or women. The investigators were able to control for a wide range of potential confounders and effect modifiers. In addition, they evaluated the effect of occult disease by eliminating deaths occurring in the first 1-2 years of follow-up and repeated their analyses among participants who were defined as “healthy”. This study provides powerful evidence that BMI may not be indicative of increased adiposity and mortality in the elderly and waist-to-hip ratio may add clinical utility when recommending a healthy body size in older adults.

### **BMI, Fat Patterning, and Mortality in a Tri-Ethnic Sample of U.S. Adults**

Despite the fact that CVD is a global problem, our understanding of this disease has come largely from studies of Caucasians of European origin. Several

ethnic groups predispose to develop coronary heart disease (CHD) or CVD and thus have a higher prevalence of these diseases. Racial/ethnic disparities in cardiovascular health are among the most prominent public health problems in the U.S. In black adults the risks of CHD and stroke have been shown to be nearly two times higher than those of other ethnic origins (30). Black men and women also appear to be particularly susceptible to high blood pressure regardless of educational level (30). Mexican American adults suffer from much higher rates of hypercholesterolemia, compared to white adults. In 1988-1994, the prevalence of the metabolic syndrome in Mexican American men and women was approximately 12% and 50% higher than rates in white men and women, respectively (31).

There are noted racial/ethnic differences in the prevalence of obesity. Rates of obesity in the U.S. have been increasing over the last several decades across both sexes and all racial/ethnic groups; however, this rise has been especially pronounced among Black women with estimates suggesting over half are obese and over 80% are overweight or obese (32). Second to black women are Mexican American women, in whom 73% are overweight and 33% are obese (32). Similar trends have been observed in men; however, for black men the acceleration in weight gain does not occur until after age 30 years.

In addition to racial/ethnic differences in the prevalence of obesity which tend to be particularly high among black and Mexican American women compared to non-Hispanic white women (2), it appears that fat accumulation and body shape also differ by race/ethnicity. Individuals of South Asian ancestry have a much different distribution of body fat compared with Europeans. They have thinner limbs, which

would suggest a smaller muscle mass, and greater central obesity with increased visceral adipose tissue mass (33). Several investigators have shown that Blacks have less visceral fat compared to non-Hispanic whites of a similar level of BMI or waist circumference (34-37). Despite this decreased amount of visceral fat, which is believed to be more atherogenic and has a greater tendency to lead to insulin resistance, blacks have higher rates of CHD and type 2 diabetes. This finding leads one to question whether blacks have similar risks of disease as whites of a similar total body fat. The paucity of data relating visceral fat or body circumferences to disease in blacks has limited our understanding of this relationship. To the best of our knowledge no study has measured visceral fat in Mexican Americans.

Despite the fact that obesity is more common in blacks than in white populations, obesity with respect to mortality is more lethal for whites. Calle et al. (38) reported that nonsmoking white men and women with no history of disease at the highest level of BMI had relative risks of mortality of 2.58 and 2.00, respectively. black men and women at the highest BMI had much lower nonsignificant risks for death (1.35 and 1.21). Similar results have been found in the American Cancer Society Prevention Study (39) as well as the Charleston Heart Study (40). To our knowledge, the relation of adiposity with mortality has not been reported in Mexican Americans.

### **Relevant Literature**

Calle et al. (38) used data from the Cancer Prevention Study II to evaluate the association of BMI with mortality in a sample of more than 1 million U.S. adults.

Over the course of 14 years of follow-up, 201,622 deaths occurred. BMI was based upon self-reported height and weight. The authors reported a J-shaped association of BMI with all-cause mortality among the white men and women with the relative risks of mortality in the highest BMI groups of 2.58 and 2.00, respectively. However, BMI did not appear to be an important predictor of mortality among the black men and women, with nonsignificant relative risks in the highest BMI categories of 1.35 and 1.21 in men and women, respectively. These data suggest that obesity does not confer the same risk of mortality in black adults as compared to white men and women. This study was limited by the self-report of height and weight and the lack of data regarding weight patterning (i.e., waist circumference).

Stevens et al. (39) examined the association of BMI with all cause and CVD mortality in 100,000 white women and 8,142 black women. BMI was calculated from self-reported weight and height. Analyses were based upon 6,860 all cause and 310 CVD deaths in the white women and 682 all-cause and 310 CVD deaths in the black women. The authors stratified their analyses by smoking status and educational level. Generally, an elevated risk of mortality was found among the white women that was not corroborated among the black women. Their findings were limited by the self-report of weight and height, and the lack of information regarding weight patterning (i.e., waist circumference).

### **Leptin, Insulin, and Cardiovascular Disease**

Leptin is the protein product of the obesity gene produced by adipocytes and is responsible for the regulation of food intake and energy balance. When discovered by

Friedman in the early 1990's, leptin was believed to be the antidote for the increasing epidemic of obesity. Once released by adipocytes, leptin travels to the hypothalamus to reduce energy intake, and increase energy expenditure by enhancing sympathetic nervous system activity. In mice, daily intraperitoneal injection of leptin reduces body weight by increasing oxygen consumption, body temperature, and locomotor activity, as well as reducing food intake (41). Thus, by increasing endogenous levels, it was believed that leptin could stimulate weight loss in the obese. However, the paradoxical findings of the highest leptin levels in those with the greatest amounts of adipose tissue led scientists to question its usefulness as the cure for obesity. In fact, shortly after its discovery, the confirmation of leptin resistance, whereby obese individuals are resistant to the weight reducing actions of leptin, was shown (42). The site of leptin resistance is believed to be the blood-brain barrier where serum leptin concentrations above 20 ng/mL do not result in concomitant increases in cerebrospinal fluid leptin levels (43,44). To test the potential weight reducing effects of leptin, a large double-blind, placebo-controlled, escalating dose clinical trial was conducted in 54 lean and 73 obese, predominately white men and women with a mean age of 39 years (45). Participants were randomly assigned to escalating dose groups of recombinant methionyl human leptin or matching placebo administered by daily morning subcutaneous injection. Although individuals assigned to the highest dose group experienced the largest weight loss, overall, the reduction in weight was modest and highly variable.

Epidemiologic evidence has implicated elevated leptin levels as a significant predictor of a first ever myocardial infarction (46,47) and stroke (48-50), independent



of total adiposity and other classic cardiovascular risk factors. The widespread distribution of functioning leptin receptors on vascular cells provides a potential explanation for these epidemiologic findings and suggests an important role for leptin in angiogenesis (51-54). There are also data from several different populations suggesting strong positive associations between leptin and insulin concentrations, independent of obesity (55-58). Leptin correlates significantly with markers of the metabolic syndrome, including plasma triglyceride, high density lipoprotein levels, and systolic blood pressure, even after consideration of the level of adiposity (55,59). Leptin may also participate in the development of CVD by impairing fibrinolysis (60) and endothelial function (61,62). There is also evidence that leptin may have proinflammatory effects by increasing C-reactive protein (55,63,64), an acute phase reactant that has been consistently associated with an increased risk of cardiovascular events.

The association of obesity with CVD is mediated at least in part by the strong links between obesity and established cardiovascular risk factors, including hypertension, dyslipidemia, and type 2 diabetes. However, the mechanisms explaining these relations are poorly understood and highly complex. Since it is produced by adipose tissue and correlates positively with measures of total adiposity, leptin may be the endogenous link between obesity and these risk factors. However, previous studies investigating the relation of leptin with these factors have been limited by small clinic-based samples and the inclusion of only men. In addition, hyperinsulinemia as a result of obesity may represent a link with cardiovascular risk. Therefore, large population-based studies, utilizing a random sampling strategy

including both men and women are needed to confirm these preliminary findings, and evaluate whether increased leptin concentrations or fasting insulin may be important mediators of the relation between obesity and cardiovascular risk.

### **Relevant Literature**

Recently, Wannamethee et al. (55) assessed the association of plasma leptin concentrations with metabolic, inflammatory, and haemostatic risk factors for CVD in a sample of 3,600 non-diabetic men aged 60-79 years. Participants were recruited from general medical practices in 24 British towns. Leptin concentrations decreased significantly with increasing physical activity and were lower among current smokers. After adjusting for differences in lifestyle factors, the authors found that leptin levels were positively associated with triglycerides, insulin resistance, C-reactive protein, fibrinogen, interleukin-6, several of the haemostatic markers of cardiovascular risk, and inversely associated with HDL cholesterol levels. After adjusting for insulin resistance, the associations of leptin with the metabolic risk factors were largely attenuated; however, the associations of leptin with the inflammatory markers and haemostatic markers remained. The strong positive, independent associations of leptin with the inflammatory and haemostatic cardiovascular risk factors suggests that leptin may play an important role in potentiating the cardiovascular risk attributed to obesity. However, this study was limited by the inclusion of only men with a very small age range.

In a sub-sample of men from the Health Professionals Follow-up Study, Chu and colleagues (61) evaluated the associations of fasting insulin and two obesity

products, leptin and tumor necrosis factor-alpha, with metabolic and thrombogenic cardiovascular risk factors. The authors found significant positive associations of leptin with the total cholesterol-HDL ratio and thrombogenic markers of CVD as well as negative associations with apolipoprotein A1 and HDL cholesterol. The authors found that insulin levels and not leptin largely mediated the associations of BMI with the metabolic and thrombogenic cardiovascular risk factors. However, the associations of leptin with many of the metabolic factors remained significant after adjusting for insulin, suggesting that leptin may still play an important role in lipid metabolism.

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## **II: ADIPOSITY AND MORTALITY AMONG US ADULTS: RESULTS FROM THE NHANES III MORTALITY STUDY, 1988-2000**

### **ABSTRACT**

**OBJECTIVE:** This prospective study compared the relative importance of various measures of adiposity with total and cause-specific mortality. **METHODS:** Participants included 5,799 men and 6,429 women in the third National Health and Nutrition Examination Survey cohort, aged 30-102 years at enrollment in 1988-1994. **RESULTS:** During a follow-up of 12 years (through December 2000), there were 1,188 deaths in men and 925 in women. In middle-aged adults, body mass index (BMI) demonstrated a U-shaped relation with total mortality in men and a J-shaped association in women, while a positive association of waist-to-hip ratio with total mortality was observed in women ( $p_{\text{trend}}=0.003$ ), but not in men ( $p_{\text{trend}}=0.2$ ). Compared to BMI, an increased waist-to-hip ratio or waist circumference was more strongly associated with an increased risk of death due to cardiovascular disease in middle-aged men and women. In older adults, BMI and waist circumference were inversely associated with total mortality, largely attributed to death from respiratory disease in older men and cardiovascular disease in older women. **CONCLUSIONS:** The relation of adiposity with mortality appears to be modified by age, with waist-to-hip ratio providing a better health indicator of the risk for death from cardiovascular disease than BMI among middle-aged adults.

## INTRODUCTION

The association of body mass index (BMI) with mortality has been a topic of much debate since some have suggested that this relation is J-shaped (1-3), U-shaped (4-6), positive (7-10), nonexistent or even inverse (11-13). These inconsistent findings may be at least partly attributed to the ability of previous studies to account for strong confounding factors, such as smoking, and preexisting or occult disease (14). Not accounting for smoking or disease tends to overestimate the risk of mortality at the lower end of the BMI range, since both are associated with a reduced body weight and an increased risk of death (14). Frequently used methods of controlling for the effects of occult or subclinical disease have involved the exclusion of persons with an increased recent weight loss or the removal of deaths occurring early during follow-up (15-17). The inappropriate control for intermediate metabolic factors on the causal pathway from obesity to death, such as hypertension, type 2 diabetes, or hypercholesterolemia, may also contribute to the contradictory findings across studies (14).

The age of the sample population at baseline may also explain the inconsistent results of BMI with mortality. Age is likely to modify this relation since older adults face a progressive decline in lean muscle mass due to decreased physical activity and the effects of preexisting and subclinical disease (18-20). Since older adults also experience a redistribution of body fat from the subcutaneous depot to intra-abdominal and intramuscular sites (21), some researchers have suggested that abdominal obesity should be assessed to evaluate mortality risk among the elderly (22). Waist circumference and waist-to-hip ratio are frequently used to estimate central adiposity

and have shown strong relations with metabolic cardiovascular disease risk factors, incident coronary events, and type 2 diabetes (23-25). Few studies have assessed the association of abdominal obesity with mortality (1,26-30), and none, to the best of our knowledge, has included a nationally representative sample of U.S. adults. The purpose of the present study was to examine the prospective association of several measures of adiposity, including BMI, waist circumference, and waist-to-hip ratio with total and cause-specific mortality, and how these relations may be influenced by age.

## **METHODS**

### **Sample design and population**

The current study utilized data from the third National Health and Nutrition Examination Survey (NHANES III) conducted in the U.S. from 1988-1994 by the Centers for Disease Control and Prevention (CDC). NHANES III included a national, complex multistage, clustered, stratified probability sample of the civilian, noninstitutionalized population aged two months and older. Data collection occurred during a home interview and a physical examination conducted in a mobile examination center (31). The Institutional Review Board at the CDC approved the study design and all participants provided written informed consent.

A total of 13,065 adults aged 30-102 years completed a physical examination as part of NHANES III. We excluded pregnant women ( $n=70$ ), and individuals who were missing height ( $n=25$ ), weight ( $n=17$ ), waist ( $n=698$ ), or hip circumference ( $n=20$ ) data. Persons who refused to provide sufficient personal identifying information were also excluded since they were ineligible for vital status follow-up

( $n=7$ ). The remaining 12,228 adults (5,799 men and 6,429 women) were eligible in this analysis for mortality follow-up.

### **Baseline measurements**

Race/ethnicity was self-reported and categorized as non-Hispanic white, non-Hispanic black, Mexican American, and other. Education was classified as less than high school, high school, some college, or college. Current, former, or never smoking was based upon the use of cigarettes, cigars, or pipe tobacco. Individuals who smoked at least 100 cigarettes, 20 cigars, or 20 pipes of tobacco in their lifetime but no longer smoked were considered former smokers. The consumption frequency of alcoholic beverages (beer, wine, liquor) and the type and frequency of leisure-time physical activities over the past month were assessed. Heart disease included angina, a physician's diagnosis of congestive heart failure, or myocardial infarction. Angina was determined with a series of questions as described elsewhere (32). A history of respiratory disease (chronic bronchitis, emphysema, or asthma), cancer (except non-melanoma skin cancer), or stroke was also queried.

Body weight to the nearest 0.1 kilogram and standing height to the nearest 0.1 centimeter were measured using a Toledo electronic scale and Seca stadiometer. BMI was calculated as weight in kilograms divided by the square of height in meters. Body weight ten years prior to the physical examination was requested. Weight change was calculated as the difference between measured weight at baseline and recalled weight. BMI ten years prior to baseline was calculated as recalled weight in kilograms divided by the square of height in meters assessed during the physical examination. Trained technicians measured waist circumference to the nearest 0.1 centimeter using a steel

measuring tape at the level of the iliac crest at the end of a normal expiration. Hip circumference was measured at the widest circumference around the buttocks. BMI, waist circumference, and waist-to-hip ratio were classified into quintiles and tertiles by using cutting points defined by the sex-specific distribution of these variables in the population.

Hypertension was defined as an average of six seated blood pressure readings by a trained technician or physician  $\geq 140/90$ , or use of antihypertensive medication (33,34). Diabetes was defined by history (type 1 or type 2), use of diabetes medications, or a fasting plasma glucose level  $\geq 126$  mg/dL (35). High cholesterol included a total cholesterol concentration  $\geq 240$  mg/dL or use of lipid lowering medication (36). Hormone replacement therapy use in women was based upon self-report and defined as current or not current use.

#### **Ascertainment of mortality**

We merged baseline data from NHANES III with follow-up data from the NHANES III Mortality Study. As part of the NHANES III Mortality Study, data from the National Death Index, which has been shown to capture 93 to 98 percent of all U.S. deaths (37-39), were used to ascertain the vital status of each cohort member through December 31, 2000. Information obtained from the Mortality Study data included the month, day, and year in which a person was last known to be alive and the *International Classification of Diseases (ICD)*, 9<sup>th</sup>/10<sup>th</sup> revision codes for the underlying cause of death. Since our interests were in the health effects of adiposity, we chose not to include deaths attributed to external causes (e.g., accidents, homicides, poisoning; 81 deaths), including ICD-9 codes E800-E999 for deaths occurring

between 1988-1998 and ICD-10 codes V01-Y98, thereafter, in our analyses of total deaths. Cardiovascular disease deaths included codes 390-448 and I00-I99; cancer deaths, codes 140-203 and C00-C97; and respiratory disease deaths, codes 466-519 and J00-J99.

### **Data analyses**

Data were analyzed using SAS (version 9.1, SAS Institute Inc, Cary, NC) and SUDAAN (version 9.0, Research Triangle Institute, Research Triangle Park, NC) software. Analyses included sample weights that account for the complex sample design and the unequal probabilities of selection. We computed length of follow-up as the time elapsed between the physical examination and the date of death for cases or December 31, 2000 for non-cases. Age-adjusted rates and means were derived by the direct method using ten-year age categories of the total population as the standard and analysis of covariance, respectively. Multivariable logistic regression models were fit to examine the relation of adiposity with total and cause-specific mortality. We did not adjust for physical activity or possible mediators of obesity effects, such as diabetes, hypertension, or high cholesterol, since doing so would have resulted in overadjustment because of their position on the causal pathway (14). Adjustment for estrogen use in women had very little, if any, effect on the associations of adiposity with mortality and was therefore not included. Linear trends were examined with the inclusion of adiposity as an ordinal variable within the multivariable models. A multiplicative interaction term of age group (30-64 and 65-102 years) and adiposity was tested. All hypothesis tests were two-sided and based upon a type one error rate of 0.05.



## RESULTS

Mean age of men at baseline was 54.6 years (standard error, 0.2) and 53.8 years (standard error, 0.2) for women (range 30-102 years). Proportions of men who were white, black, and Mexican American were 79.1, 9.4, and 4.4 percent, respectively, and 78.2, 10.6, and 3.8 percent among women. During a maximum of 12 years of follow-up (102,172 person-years), 1,188 men died from non-external causes of death (including 417 from cardiovascular disease, 311 from cancer, 117 from respiratory disease, and 343 from other causes) and 925 women died (including 319 from cardiovascular disease, 207 from cancer, 88 from respiratory disease, and 399 from other causes). In general, men and women who died were older, less educated, less physically active, more likely to have been a current smoker, and to have existing disease, hypertension, and diabetes at baseline (table 1). Men alive at the end of follow-up gained more weight in the ten years before baseline than men who died, while women who died had a higher waist circumference and waist-to-hip ratio at baseline, and higher BMI ten years before enrollment. The weighted Pearson correlations of BMI with waist circumference and waist-to-hip ratio were 0.92 and 0.55, respectively, for men, and 0.91 and 0.40 for women; waist circumference with waist-to-hip ratio was 0.74 in men and 0.67 in women.

In table 2 reverse J-shaped multivariable relations of BMI with total mortality were observed among men and women, while waist circumference demonstrated nonsignificant inverse associations. A nonsignificant inverse association of waist-to-hip ratio with total mortality was noted in men, and a J-shaped relation was observed in women.

Table 3 shows the relation of adiposity with total mortality differed significantly between middle-aged and older adults (table 3). In middle-aged men and women (30-64 years), curvilinear relations of BMI with mortality were noted. Waist circumference was associated in a U-shaped fashion with mortality in middle-aged men, whereas a nonsignificant positive association was observed in middle-aged women. In contrast, a graded risk of mortality across increasing quintiles of waist-to-hip ratio was noted in middle-aged women ( $p$  for trend=0.003). In middle-aged men, this trend was nonsignificant ( $p$  for trend=0.2), though risk increased 2.0-fold across quintiles. Total mortality decreased significantly across increasing quintiles of BMI and waist circumference in older men and women (65-102 years), and waist-to-hip ratio in men. In older women, the lowest and highest quintiles of waist-to-hip ratio modestly increased mortality.

The relation of adiposity with cardiovascular disease mortality differed between middle-aged and older adults (table 4). Only the highest quintile of BMI in middle-aged men and women carried an elevated risk of cardiovascular death. In middle-aged men and women, cardiovascular mortality increased 3.3- and 3.4-fold across quintiles of waist circumference, respectively, and 5.6- and 4.1-fold across quintiles of waist-to-hip ratio. In older men, no association of BMI with cardiovascular mortality was observed, while modest inverse associations with waist circumference and waist-to-hip ratio were noted. Death from cardiovascular disease decreased with increasing BMI and waist circumference, but not waist-to-hip ratio in older women.

In general, there was little association between adiposity and mortality from total cancer (not shown). However, increased relative risks for total cancer mortality in each quintile of BMI compared to quintile two in middle-aged women were noted; relative risks (95 percent confidence intervals) across increasing quintiles were 4.47 (1.44, 13.88), 1.00 (referent), 6.67 (2.25, 20.30), 4.21 (1.28, 13.90), and 3.87 (1.18, 12.74) ( $p$  for trend=0.6). There were too few deaths from respiratory conditions to examine this cause of death in younger adults, however, BMI and waist circumference were inversely associated with respiratory disease mortality ( $p$  for trend<0.05, for both) in older men and U-shaped among older women (not shown). Waist-to-hip ratio showed no association with respiratory disease mortality in either older men or women. There was not sufficient power to examine other causes of death separately, but collectively, BMI and waist circumference demonstrated U-shaped associations in younger men, positive associations in younger women, and no relation in older adults (not shown). Waist-to-hip ratio showed no relation with other causes of death.

Since BMI and waist-to-hip ratio were modestly correlated, we also determined their associations with total and cardiovascular disease mortality while concurrently adjusting for each measure. These individual relations were virtually unaffected by simultaneous adjustment among the middle-aged and older adults (not shown). In addition, we determined their combined association with total mortality by jointly classifying middle-aged and older adults separately by sex-specific tertiles of BMI and waist-to-hip ratio. Mortality was highest among middle-aged adults in the lowest tertile of BMI and the highest tertile of waist-to-hip ratio, while lowest mortality was evident in the highest tertile of BMI and lowest tertile of waist-to-hip

ratio (figure 1A). Among older adults, lowest mortality was observed in the highest tertile of BMI and middle tertile of waist-to-hip ratio (figure 1B).

Repeating analyses after excluding persons who died during the first three years of follow-up or those who experienced a weight loss of greater than 4.5 kilograms (10 pounds) in the 10 years prior to enrollment ( $n=2,288$ ) had little influence on the results presented in Table 3 (not shown), except for the relation of waist-to-hip ratio with mortality in middle-aged men. After exclusion, multivariable relative risks (95 percent confidence intervals) across increasing quintiles of waist-to-hip ratio were 1.00 (referent), 2.89 (1.10, 7.59), 2.31 (1.12, 4.78), 2.30 (0.86, 6.12), and 5.03 (2.23, 11.36) ( $p$  for trend=0.006).

## **DISCUSSION**

Results of this 12-year prospective cohort study of U.S. adults suggest that the relation of adiposity with mortality is modified by age. In middle-aged adults (30-64 years), BMI was associated in a curvilinear fashion with total mortality. In contrast, waist-to-hip ratio demonstrated a positive association independent of overall adiposity (i.e., BMI), although this relation did not reach statistical significance in middle-aged men. In older adults (65-102 years), BMI and waist circumference were each inversely associated with mortality. These observed associations were not explained to any great extent by numerous potential confounders, existing disease, bias from recent weight loss, or increased early deaths among the leanest adults.

Despite positive associations of BMI with numerous diseases (40), the shape of the association between BMI and all-cause mortality across studies has been U-shaped, J-shaped, positive, nonexistent, and inverse. However, waist-to-hip ratio has

shown a positive linear relation with mortality in middle-aged adults (1,41,42). In the Iowa Women's Health Study, the relative risk of mortality increased 2.6-fold across increasing quintiles of waist-to-hip ratio among all women, while BMI showed a J-shaped relation (1). In the current study, relative risks for total mortality across quintiles of waist-to-hip ratio in all middle-aged men and women increased 2.0- and 2.5-fold, respectively. Similar to findings of Iowa women (1) and middle-aged Swedish men (43), middle-aged adults with a low BMI and a high waist-to-hip ratio had the highest risk of mortality. Due to a close correlation, jointly classifying BMI and waist circumference resulted in too few subjects in some categories to provide meaningful risk estimates.

The increased risk of mortality among middle-aged adults in the highest quintiles of waist-to-hip ratio was largely explained by an increased risk of death from cardiovascular disease. An increased waist circumference also conveyed a higher risk of cardiovascular mortality, albeit not as strongly as waist-to-hip ratio; while only the highest quintile of BMI carried an elevated risk. Research over the last three decades has revealed the importance of abdominal fat measures in predicting an adverse metabolic risk factor profile (44-47), which increases the risk of cardiovascular disease. In the current study, high cholesterol, hypertension, and diabetes together explained approximately one-third of the risk of cardiovascular mortality associated with an elevated waist-to-hip ratio (not shown). Abdominal obesity, including an increased waist-to-hip ratio has predicted an increased risk of cardiovascular disease in several cohorts (48-52). Interventions which reduce total adiposity through diet and/or exercise in middle-aged adults have proven effective in reducing measures of

abdominal fat and improve cardiovascular disease risk factors (53-56), though waist-to-hip ratio may not be a sensitive indicator of change in abdominal obesity (57). Our findings suggest increased abdominal obesity in general and waist-to-hip ratio in particular are important predictors of mortality from cardiovascular disease in middle-aged adults.

Although computed tomography or magnetic resonance imaging measure body fat with a high degree of validity and precision, these methods are prohibitive for routine clinical use or field epidemiology due to cost and accessibility (58). For simplicity, clinical guidelines recommend assessing overall and abdominal adiposity via BMI and waist circumference, respectively (40). However, waist circumference largely reflects total adiposity as estimated by BMI ( $r=0.92$  in men and  $0.91$  in women in the current study), explaining the similar relations observed with mortality between these two adiposity measures. The correlation of BMI with waist-to-hip ratio was modest ( $r=0.55$  in men and  $0.40$  in women). Validation studies have shown that waist-to-hip ratio correlates significantly with intra-abdominal fat assessed by computed tomography (59,60). It appears that the information provided by waist-to-hip ratio regarding body shape or lower trunk adiposity is more strongly associated with an increased risk of mortality among middle-aged adults than that provided by waist circumference alone.

Similar to previous studies (19,61-64), we found the relation between adiposity and mortality in older adults was different than the relation observed in younger populations, regardless of the measure of adiposity. Although numerous studies have assessed the association of BMI with mortality, few have included the very old or

additional measures of body composition (27-29,65-67). In one of the largest studies conducted to date comparing various measures of adiposity among non-institutionalized adults aged  $\geq 75$  years, Price et al. (28) found a higher BMI or waist circumference reduced the risk of all-cause mortality, while a higher waist-to-hip ratio modestly increased mortality. Additional studies support an inverse association of BMI with mortality among older adults (27,65,68,69). In the current study, we confirmed this inverse association; however, an elevated waist-to-hip ratio modestly increased mortality risk only among older women.

The lower risk of mortality observed among older adults in the highest quintiles of BMI and waist circumference was largely attributable to reduced mortality from respiratory disease in men and cardiovascular disease in women. An inverse association between adiposity and cardiovascular mortality in older women, and no relation in older men, has been previously reported (28). To limit the potential for reverse causation, which is a concern in older adults due in part to higher levels of comorbidity, we adjusted for existing disease, excluded deaths in the first three years of follow-up, and removed those who experienced an increased recent weight loss. Results were similar with and without the exclusion of these persons. Although these analytic techniques may be effective if the underlying disease causes rapid weight loss leading to death, reverse causation may still influence the risk of mortality if the course of disease is lengthy. Regardless, in studies of chronic obstructive pulmonary disease that measure pulmonary function, BMI has been shown to be an independent predictor of death, highlighting the importance of body composition in respiratory disease prognosis (70,71).

The divergent relation of adiposity with mortality between middle-aged and older adults may be due to several reasons. The first may be a selective survival effect, whereby individuals who are susceptible to the adverse health effects of obesity due to environmental or genetic factors suffer from increased mortality during middle age, leaving a more resistant overweight elderly population. The second may be that the protective effects of obesity in older age outweigh the potential negative effects. Heavier persons have lower rates of osteoporosis due likely to greater weight-bearing bone formation (72). This may reduce the risk of falls and protect older adults from the acute trauma that can occur as a result of falling. In addition, obesity may provide energy reserves during periods of stress, including illness or trauma (73,74).

The external validity of our findings is strengthened by the nationally representative sample of non-institutionalized U.S. adults. Anthropometric indices were measured by trained technicians as opposed to self-report, and we controlled for numerous confounding and health factors which may distort the association of adiposity with mortality. However, we relied upon simple estimates of anthropometry that are unable to distinguish fat from fat-free mass. Many have suggested that smokers and those with clinical evidence of chronic illness or recent weight loss at baseline, and early deaths should be excluded in studies of adiposity and mortality (10,14,26,75). Nevertheless, studies still report a curvilinear relation between BMI and mortality after employing these analytic techniques (1,4,26,76,77). In contrast, waist-to-hip ratio demonstrated a positive relation with mortality among middle-aged adults in the current study after controlling for smoking and existing disease.



Concurrently excluding early mortality and recent weight loss had little influence in middle-aged women, and enhanced this relation in middle-aged men.

In conclusion, we provided evidence on the relative importance of three commonly used estimates of adiposity, namely BMI, waist circumference, and waist-to-hip ratio in assessing the risk of total and cause-specific mortality in a nationally representative sample of U.S. adults. We found evidence to suggest that the relation of adiposity with mortality is modified by age. In middle-aged adults, waist-to-hip ratio provided a better health indicator of cardiovascular disease mortality than BMI. While among the elderly, reduced adiposity in general carried an increased risk of mortality. Future studies of adiposity and mortality should carefully consider the influence of age.

Table 1. Sex-specific age-adjusted baseline characteristics of adults aged 30-102 years by vital status, NHANES III† Mortality Study, 1988-2000.

Baseline characteristic‡	Men				Women			
	Died during follow-up		Died during follow-up		Died during follow-up		Died during follow-up	
	Yes	No	Yes	No	Yes	No	Yes	No
Sample size§	1,188	4,611	925	5,504	925	5,504	925	5,504
Age (years)	67.6 (0.6)	46.9 (0.3)*	70.4 (0.8)	49.1 (0.5)*	70.4 (0.8)	49.1 (0.5)*	70.4 (0.8)	49.1 (0.5)*
Height (cm)	174.3 (0.4)	174.8 (0.2)	160.4 (0.6)	161.2 (0.1)	160.4 (0.6)	161.2 (0.1)	160.4 (0.6)	161.2 (0.1)
Weight (kg)	81.2 (1.4)	82.7 (0.3)	71.0 (1.2)	70.2 (0.4)	71.0 (1.2)	70.2 (0.4)	71.0 (1.2)	70.2 (0.4)
BMI† (kg/m <sup>2</sup> )	26.7 (0.4)	27.0 (0.1)	27.6 (0.4)	27.0 (0.2)	27.6 (0.4)	27.0 (0.2)	27.6 (0.4)	27.0 (0.2)
BMI† 10 years before baseline (kg/m <sup>2</sup> )	26.2 (0.3)	26.2 (0.1)	26.0 (0.4)	24.6 (0.1)*	26.0 (0.4)	24.6 (0.1)*	26.0 (0.4)	24.6 (0.1)*
Weight change (kg)	-0.74 (2.2)	5.8 (0.7)*	9.6 (2.7)	14.2 (0.7)	9.6 (2.7)	14.2 (0.7)	9.6 (2.7)	14.2 (0.7)
Waist circumference (cm)	98.0 (1.0)	98.2 (0.3)	93.1 (1.0)	91.1 (0.4)*	93.1 (1.0)	91.1 (0.4)*	93.1 (1.0)	91.1 (0.4)*
Hip circumference (cm)	99.4 (0.8)	100.0 (0.2)	103.3 (0.9)	103.1 (0.3)	103.3 (0.9)	103.1 (0.3)	103.3 (0.9)	103.1 (0.3)
Waist-to-hip ratio	0.982 (0.004)	0.983 (0.002)	0.903 (0.007)	0.887 (0.002)*	0.903 (0.007)	0.887 (0.002)*	0.903 (0.007)	0.887 (0.002)*
Education (years)	11.2 (0.2)	12.3 (0.1)*	11.3 (0.3)	12.1 (0.1)*	11.3 (0.3)	12.1 (0.1)*	11.3 (0.3)	12.1 (0.1)*
Physical activity (times/month)	23.7 (1.6)	27.2 (0.9)*	15.0 (1.7)	21.1 (0.7)*	15.0 (1.7)	21.1 (0.7)*	15.0 (1.7)	21.1 (0.7)*
Alcohol use (days/month)	12.8 (1.6)	12.0 (0.5)	5.5 (1.7)	5.2 (0.4)	5.5 (1.7)	5.2 (0.4)	5.5 (1.7)	5.2 (0.4)
Current smoker (%)	44.6	28.2*	34.6	20.1*	34.6	20.1*	34.6	20.1*
Heart disease (%)	23.0	10.2*	15.4	8.6*	15.4	8.6*	15.4	8.6*
Stroke (%)	6.3	2.5*	6.0	2.1*	6.0	2.1*	6.0	2.1*
Respiratory disease (%)	13.5	8.2*	19.4	8.9*	19.4	8.9*	19.4	8.9*
Cancer (%)	6.6	3.8*	10.4	6.5	10.4	6.5	10.4	6.5
Hypertension (%)	42.5	34.7*	42.0	34.1*	42.0	34.1*	42.0	34.1*
High cholesterol (%)	22.3	22.8	30.0	28.9	30.0	28.9	30.0	28.9
Diabetes (%)	16.6	8.4*	15.6	6.3*	15.6	6.3*	15.6	6.3*

Table 1, continued. Sex-specific age-adjusted baseline characteristics of adults aged 30-102 years by vital status, NHANES III† Mortality Study, 1988-2000.

\* $p < 0.05$  for the sex-specific comparison of those who died to those who were alive at the end of follow-up.

†NHANES III indicates the third National Health and Nutrition Examination Survey; BMI, body mass index.

‡Values shown are the age-adjusted weighted mean (standard error) or percent.

Table 2. Sex-specific adjusted relative risks for total mortality by quintile of body mass index, waist circumference, and waist-to-hip ratio in U.S. adults aged 30-102 years at baseline, NHANES III\* Mortality Study, 1988-2000.

Quintiles†	Men					Women				
	No. of deaths‡	Person-years of follow-up‡	Age-adjusted mortality rate§,¶	Multi-variate RR*,#	95% CI*	No. of deaths‡	Person-years of follow-up‡	Age-adjusted mortality rate§,¶	Multi-variate RR*,#	95% CI*
Body mass index										
1	332	8789	36.4	1.99	1.37, 2.91	231	10560	20.2	1.13	0.82, 1.56
2	223	10109	21.6	1.00	referent	181	10897	15.3	1.00	referent
3	225	9423	22.6	1.18	0.81, 1.71	207	10898	16.2	1.04	0.76, 1.43
4	222	9752	23.2	1.14	0.79, 1.64	169	10913	15.3	0.85	0.58, 1.23
5	186	10004	23.1	1.25	0.82, 1.89	137	10826	18.1	1.08	0.74, 1.58
<i>p</i> for linear trend 0.09										
Waist circumference										
1	234	9524	34.5	1.18	0.74, 1.88	152	10858	19.4	1.32	0.93, 1.88
2	216	9687	25.3	1.00	referent	177	10979	15.2	1.00	referent
3	221	9728	22.2	0.70	0.50, 0.99	202	10634	16.7	1.28	0.93, 1.76
4	261	9547	22.8	0.80	0.57, 1.14	224	10882	17.1	1.22	0.85, 1.75
5	256	9592	25.7	0.87	0.61, 1.25	170	10741	18.4	1.04	0.72, 1.52
<i>p</i> for linear trend 0.2										
Waist-to-hip ratio										
1	131	8695	32.2	1.00	0.65, 1.52	82	11200	15.7	1.09	0.69, 1.72
2	254	11587	28.8	1.00	referent	136	11005	15.4	1.00	referent
3	203	8424	23.8	0.70	0.48, 1.01	175	10827	15.6	1.23	0.76, 1.98
4	278	10127	21.0	0.74	0.53, 1.04	246	10538	18.7	1.34	0.92, 1.96
5	322	9245	26.7	0.88	0.59, 1.30	286	10525	18.8	1.48	1.05, 2.09
<i>p</i> for linear trend 0.7										

Table 2, continued. Sex-specific adjusted relative risks for total mortality by quintile of body mass index, waist circumference, and waist-to-hip ratio in U.S. adults aged 30-102 years at baseline, NHANES III\* Mortality Study, 1988-2000.

\*NHANES III indicates the third National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

†Sex-specific quintile cutting points for body mass index ( $\text{kg}/\text{m}^2$ ), 23.1, 25.5, 27.5, 30.3 in men and 22.6, 25.6, 28.6, 32.9 in women; waist circumference (cm), 87.2, 94.0, 99.8, 107.2 in men and 80.5, 88.7, 96.2, 105.2 in women; waist-to-hip ratio, 0.921, 0.963, 0.997, 1.035 in men and 0.827, 0.874, 0.917, 0.965 in women.

‡Unweighted.

§Weighted.

¶Per 1,000 person-years.

#Data were adjusted for the following variables assessed at baseline: age (years), race/ethnicity (white, African American, Mexican American, other), education (< high school, high school, some college, college), smoking status (current, former, never), alcohol use (none, once per week or less, more than once per week but less than every day, every day), heart disease (yes/no), stroke (yes/no), respiratory disease (yes/no), and cancer (except non-melanoma skin cancer) (yes/no).

Table 3. Sex-specific adjusted relative risks for total mortality by quintile of body mass index, waist circumference, and waist-to-hip ratio according to age group (30-64 and 65-102 years), NHANES III\* Mortality Study, 1988-2000.

Quintiles of body mass index or abdominal adiposity†	Body mass index				Waist circumference				Waist-to-hip ratio			
	No. of deaths‡	Multi-variate RR*.§	95% CI*	No. of deaths‡	Multi-variate RR*.§	95% CI*	No. of deaths‡	Multi-variate RR*.§	95% CI*	No. of deaths‡	Multi-variate RR*.§	95% CI*
<i>Men aged 30-64 years (n = 3,966)</i>												
1	77	1.95	0.99, 3.81	67	1.04	0.60, 1.80	33	1.00	referent	33	1.00	referent
2	46	1.00	referent	49	1.00	referent	81	1.71	0.94, 3.10	81	1.71	0.94, 3.10
3	47	1.08	0.58, 2.01	45	0.53	0.31, 0.91	40	1.01	0.51, 1.99	40	1.01	0.51, 1.99
4	52	1.10	0.57, 2.11	61	1.01	0.56, 1.82	62	1.41	0.76, 2.62	62	1.41	0.76, 2.62
5	77	1.96	1.06, 3.60	77	1.37	0.80, 2.34	83	1.99	0.97, 4.07	83	1.99	0.97, 4.07
<i>p for linear trend</i>												
0.6												
<i>Men aged 65-102 years (n = 4,514)</i>												
1	255	2.04	1.22, 3.44	167	1.38	0.63, 3.02	98	2.08	1.04, 4.18	98	2.08	1.04, 4.18
2	177	1.00	referent	167	1.00	referent	173	1.00	referent	173	1.00	referent
3	178	1.26	0.70, 2.28	176	0.82	0.47, 1.42	163	0.83	0.51, 1.35	163	0.83	0.51, 1.35
4	170	1.17	0.73, 1.87	200	0.69	0.41, 1.18	216	0.75	0.49, 1.15	216	0.75	0.49, 1.15
5	109	0.78	0.48, 1.27	179	0.64	0.38, 1.08	239	0.80	0.52, 1.24	239	0.80	0.52, 1.24
<i>p for linear trend</i>												
0.0002												
<i>p for interaction by age group (men)</i>												
0.0007												
<i>Women aged 30-64 years (n = 1,833)</i>												
1	42	1.39	0.69, 2.82	30	0.94	0.47, 1.88	22	1.00	referent	22	1.00	referent
2	26	1.00	referent	33	1.00	referent	31	1.17	0.53, 2.57	31	1.17	0.53, 2.57
3	50	1.67	0.79, 3.52	45	1.59	0.84, 3.00	42	1.77	0.84, 3.73	42	1.77	0.84, 3.73
4	48	1.53	0.73, 3.24	51	1.26	0.64, 2.51	53	1.99	0.94, 4.24	53	1.99	0.94, 4.24
5	55	2.06	1.07, 3.96	62	1.60	0.89, 2.86	73	2.50	1.20, 5.17	73	2.50	1.20, 5.17
<i>p for linear trend</i>												
0.1												
<i>Women aged 65-102 years (n = 1,915)</i>												
1	189	1.05	0.71, 1.55	122	1.63	1.07, 2.47	60	1.40	0.76, 2.58	60	1.40	0.76, 2.58
2	155	1.00	referent	144	1.00	referent	105	1.00	referent	105	1.00	referent
3	157	0.83	0.59, 1.17	157	1.14	0.80, 1.61	133	1.15	0.65, 2.02	133	1.15	0.65, 2.02
4	121	0.62	0.39, 0.96	173	1.18	0.78, 1.78	193	1.25	0.83, 1.88	193	1.25	0.83, 1.88
5	82	0.71	0.44, 1.13	108	0.76	0.47, 1.23	213	1.28	0.86, 1.90	213	1.28	0.86, 1.90
<i>p for linear trend</i>												
0.009												
<i>p for interaction by age group (women)</i>												
0.003												
<i>p for interaction by age group (men)</i>												
0.002												
<i>p for interaction by age group (women)</i>												
0.002												

Table 3, continued. Sex-specific adjusted relative risks for total mortality by quintile of body mass index, waist circumference, and waist-to-hip ratio according to age group (30-64 and 65-102 years), NHANES III\* Mortality Study, 1988-2000.

\*NHANES III indicates the third National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

†Sex-specific quintile cutting points can be found in the footnote of table 2.

‡Unweighted.

§Adjusted for the same variables used in the multivariable analyses presented in table 2.

Table 4. Sex-specific adjusted relative risks for death from cardiovascular disease by quintile of body mass index, waist circumference, and waist-to-hip ratio according to age group (30-64 and 65-102 years), NHANES III\* Mortality Study, 1988-2000.

Quintiles of body mass index or abdominal adiposity†	Body mass index				Waist circumference				Waist-to-hip ratio			
	No. of deaths‡	Multi-variate RR*,§	95% CI*	No. of deaths‡	Multi-variate RR*,§	95% CI*	No. of deaths‡	Multi-variate RR*,§	95% CI*	No. of deaths‡	Multi-variate RR*,§	95% CI*
<i>Men aged 30-64 years (n = 3,966)</i>												
1	17	0.89	0.31, 2.52	13	1.00	referent	7	1.00	referent	7	1.00	referent
2	21	1.00	referent	19	2.32	0.72, 7.50	29	2.72	0.80, 9.25	29	2.72	0.80, 9.25
3	16	0.65	0.22, 1.94	14	1.24	0.38, 4.08	13	2.04	0.50, 8.38	13	2.04	0.50, 8.38
4	22	0.93	0.41, 2.12	31	3.35	1.09, 10.28	19	2.69	0.77, 9.44	19	2.69	0.77, 9.44
5	37	1.99	0.90, 4.37	36	3.27	1.02, 10.53	45	5.61	1.50, 20.9	45	5.61	1.50, 20.9
<i>p for linear trend</i>												
			0.09			0.04						0.02
<i>Men aged 65-102 years (n = 4,514)</i>												
1	121	1.81	0.98, 3.35	86	1.26	0.55, 2.89	63	2.78	1.54, 5.02	63	2.78	1.54, 5.02
2	83	1.00	referent	80	1.00	referent	79	1.00	referent	79	1.00	referent
3	90	1.52	0.85, 2.72	81	0.68	0.37, 1.25	79	0.91	0.55, 1.50	79	0.91	0.55, 1.50
4	73	1.25	0.73, 2.16	89	0.84	0.45, 1.54	88	0.83	0.50, 1.35	88	0.83	0.50, 1.35
5	59	1.16	0.62, 2.20	90	0.77	0.42, 1.39	117	1.02	0.62, 1.65	117	1.02	0.62, 1.65
<i>p for linear trend</i>												
			0.3			0.1						0.03
<i>p for interaction by age group (men)</i>												
			0.009			0.0005						<0.0001
<i>Women aged 30-64 years (n = 1,833)</i>												
1	6	0.79	0.20, 3.20	5	1.00	referent	4	1.00	referent	4	1.00	referent
2	9	1.00	referent	5	0.86	0.17, 4.25	6	2.05	0.33, 12.5	6	2.05	0.33, 12.5
3	9	0.80	0.27, 2.36	9	1.55	0.27, 8.86	12	2.28	0.40, 13.1	12	2.28	0.40, 13.1
4	15	0.65	0.22, 1.93	16	1.36	0.30, 6.06	17	2.91	0.58, 14.5	17	2.91	0.58, 14.5
5	21	2.23	0.67, 7.41	25	3.37	0.70, 16.15	21	4.11	0.71, 23.8	21	4.11	0.71, 23.8
<i>p for linear trend</i>												
			0.3			0.08						0.09
<i>Women aged 65-102 years (n = 1,915)</i>												
1	100	0.87	0.54, 1.39	62	1.20	0.72, 2.01	27	1.05	0.53, 2.11	27	1.05	0.53, 2.11
2	86	1.00	referent	82	1.00	referent	59	1.00	referent	59	1.00	referent
3	90	0.88	0.60, 1.29	93	1.33	0.86, 2.05	71	1.32	0.69, 2.51	71	1.32	0.69, 2.51
4	61	0.70	0.42, 1.19	90	1.17	0.71, 1.92	107	1.47	0.93, 2.31	107	1.47	0.93, 2.31
5	35	0.53	0.31, 0.89	45	0.57	0.33, 0.98	108	1.12	0.68, 1.81	108	1.12	0.68, 1.81
<i>p for linear trend</i>												
			0.08			0.1						0.6
<i>p for interaction by age group (women)</i>												
			0.07			0.007						0.09



Table 4, continued. Sex-specific adjusted relative risks for death from cardiovascular disease by quintile of body mass index, waist circumference, and waist-to-hip ratio according to age group (30-64 and 65-102 years), NHANES III\* Mortality Study, 1988-2000.

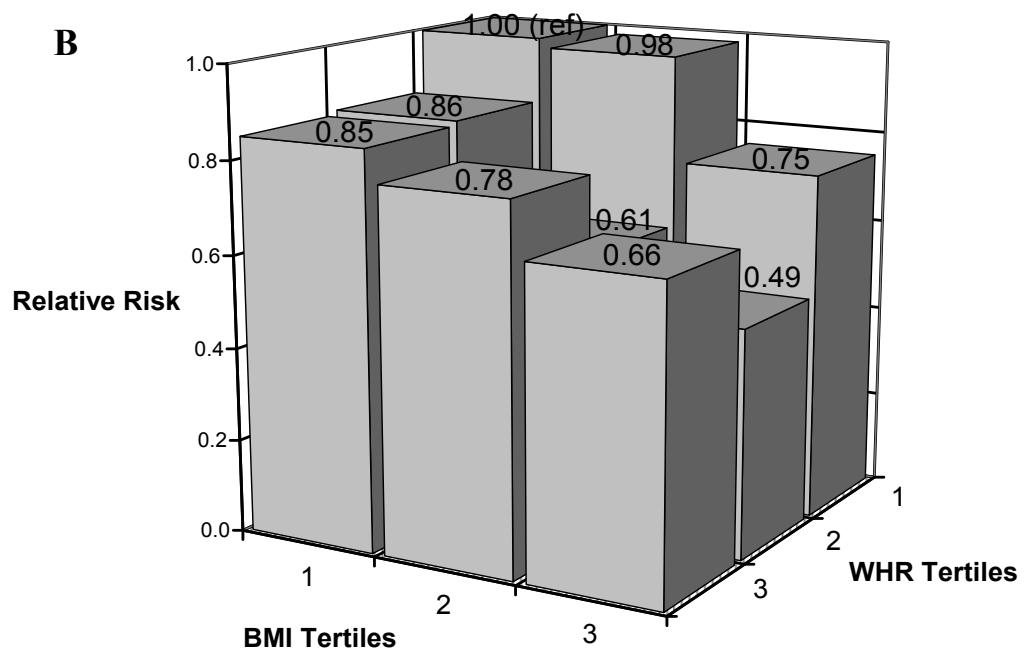
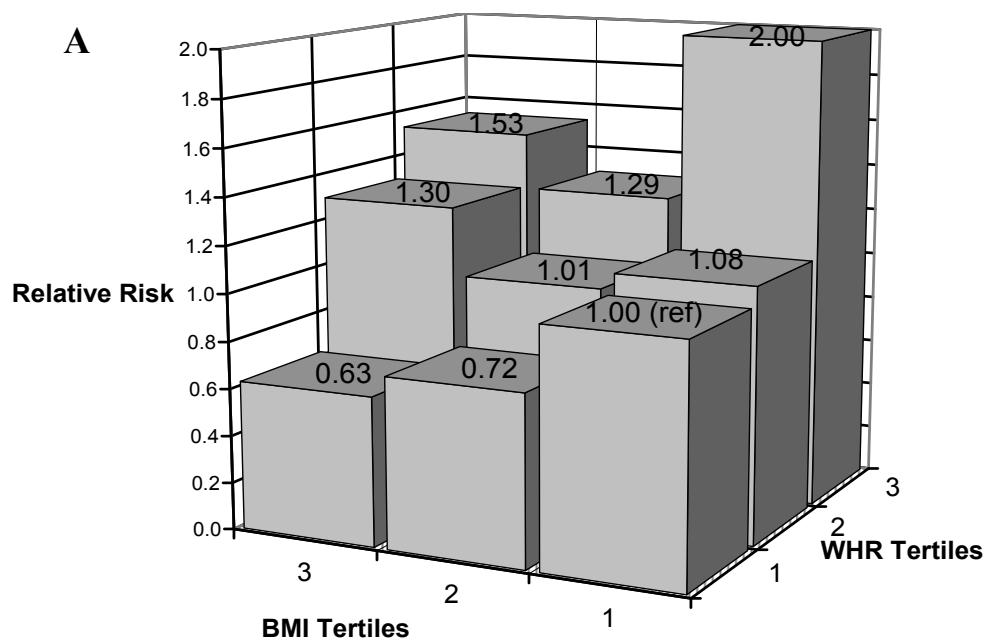
\*NHANES III indicates the third National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

†Sex-specific quintile cutting points can be found in the footnote of table 2.

‡Unweighted.

§Adjusted for the same variables used in the multivariable analyses presented in tables 2-3.

**Figure 1.** Adjusted relative risks for total mortality according to tertiles of body mass index (BMI) and waist-to-hip ratio (WHR) among (A) adults aged 30-64 years, and (B) adults aged 65-102 years, NHANES III Mortality Study, 1988-2000. Adjusted for variables listed in the footnote of table 2. Note differences in the orientation of the BMI and WHR tertiles between graphs A and B and differences in scale. The sex-specific tertile cutting points for BMI ( $\text{kg}/\text{m}^2$ ) were 24.7 and 28.4 in men and 24.6 and 29.9 in women; and WHR were 0.950 and 1.010 in men and 0.859 and 0.933 in women. Ref indicates referent group; NHANES III, the third National Health and Nutrition Examination Survey.



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**III: RACIAL/ETHNIC DIFFERENCES IN THE RELATION OF  
ADIPOSIITY WITH MORTALITY:  
RESULTS FROM THE NHANES III MORTALITY STUDY, 1988-2000**

**ABSTRACT**

**OBJECTIVE:** Examine whether adiposity is similarly associated with all-cause mortality among adults of varying race/ethnicity, and explore the influence of migration and acculturation on this relation in Mexican Americans (MA).

**METHODS:** This prospective study included a national sample of 3,212 white, 2,558 black, and 2,330 MA adults, aged 30-64 years at baseline in 1988-1994. Mortality was assessed through December 2000 via the National Death Index. **RESULTS:** The strength and shape of the association of body mass index (BMI) with mortality varied by sex and race/ethnicity. In contrast, waist-to-hip ratio (WHR) showed a positive association with mortality, stronger among white and black women than men, but of similar strength among white, black, and MA men. Among MAs, an elevated WHR increased the risk of death only among U.S.-born English speaking men, while no evidence of an increased risk of mortality attributed to obesity in women was found, irrespective of country of birth, level of acculturation, or education.

**CONCLUSIONS:** An elevated WHR increased the risk for mortality in white and black, but not MA women, and modestly increased this risk among men from each racial/ethnic group. Migration and acculturation in MA adults, particularly men, may influence this relation.

## INTRODUCTION

Racial/ethnic differences in the health complications associated with obesity have been widely reported. Black adults have higher rates of hypertension, coronary heart disease, and stroke, and are at greater risk of death from diabetes, cardiovascular disease, and other causes, compared with white adults (1,2). In addition, Mexican Americans are at a greater risk of type 2 diabetes than non-Hispanic whites (3,4), and compared to whites and blacks, have been shown to have a higher prevalence of metabolic syndrome (5). Despite early research which suggested Mexican American adults had a low risk of death despite a poor cardiovascular disease risk factor profile, lower socioeconomic status, and barriers to healthcare, more recent evidence has shown that Mexican Americans suffer from higher rates of all-cause and cardiovascular disease mortality compared to whites (6,7). Furthermore, black women and Mexican American adults are more likely to be overweight or obese compared to their white counterparts (8).

Although several studies have compared the relation of overall adiposity (i.e., body mass index, BMI) with mortality among white and black adults (9-14), few have examined measures of central adiposity, including waist circumference or waist-to-hip ratio (12,13), and even fewer have included Mexican Americans (15). Studies of blacks and whites have shown an increased BMI may not be as strong a risk factor for mortality among blacks (9,12), however, all of these studies do not agree (10). Interestingly, even though black adults, particularly black women, have high rates of obesity and increased waist girths, black adults have less visceral adipose tissue mass

determined through imaging techniques than whites at the same level of obesity (16-19). Since central obesity is a known risk factor for type 2 diabetes and coronary heart disease (20-22), this would suggest that at the same level of waist circumference or waist-to-hip ratio, black adults may have a lower risk of mortality compared to white adults.

Of the Hispanics living in the U.S., Mexican Americans represent the largest ethnically distinct subpopulation and are one of the fastest growing ethnic groups (23). Mexican Americans are a diverse group, reflected by differences in educational attainment, country of birth, primary language use, and other indicators of acculturation, which influence obesity and health status. For example, cross-sectional analyses of data from the third National Health and Nutrition Examination Survey (NHANES III) showed Mexican Americans born in Mexico had a more favorable heart disease risk factor profile, a lower risk of heart disease, and less abdominal obesity than their counterparts born in the U.S. (24,25) Furthermore, Mexican Americans born in the U.S. with a preference for speaking English had an intermediate risk, while those born in the U.S. and predominately spoke Spanish had the greatest risk and the highest waist circumference values (24,25). Other studies have confirmed the importance of birthplace and acculturation when describing obesity levels and examining the risk for mortality among Mexican Americans (6,26-28).

The purpose of the present study was to prospectively examine whether measures of overall and central adiposity are similarly associated with mortality among a national sample of white, black, and Mexican American men and women. In

addition, we explored the influence of migration and acculturation on these relations in Mexican American adults.

## **METHODS**

### **Sample design and population**

The current study utilized data from NHANES III, conducted in the U.S. from 1988-1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). NHANES III included a national, complex multistage, clustered, stratified probability sample of the civilian, noninstitutionalized population aged two months and older. Oversampling of non-Hispanic blacks and Mexican Americans during NHANES III was performed so the sample could produce statistically reliable health estimates for the two largest racial/ethnic minority groups in the U.S. Data were collected by standardized questionnaires administered at home by bilingual interviewers and a physical examination conducted in a mobile examination center (29). The Institutional Review Board at the CDC approved the study design and all participants provided written informed consent.

A total of 3,344 white, 2,754 black, and 2,476 Mexican American adults aged 30-64 years completed a physical examination as part of NHANES III. We excluded women who were pregnant during the examination (16 whites, 23 blacks, 29 Mexican Americans), as well as individuals who were missing height, weight, waist, or hip circumference (106 whites, 168 blacks, 108 Mexican Americans). Persons with insufficient personal identifying information were excluded since they were ineligible for vital status follow-up (3 whites, 2 blacks, 2 Mexican Americans). The remaining 3,212 whites (1,486 men and 1,726 women), 2,558 blacks (1,145 men and 1,413

women), and 2,330 Mexican Americans (1,172 men and 1,158 women) were eligible in this analysis for follow-up for all-cause mortality.

### **Baseline measurements**

Body weight to the nearest 0.1 kilogram and standing height to the nearest 0.1 centimeter were measured using a Toledo electronic scale and Seca stadiometer. BMI was calculated as weight in kilograms divided by the square of height in meters. Self-reported body weight ten years prior to the physical examination was requested. Weight change was calculated as the difference between measured weight at baseline and recalled body weight. Trained technicians measured waist circumference to the nearest 0.1 centimeter using a steel measuring tape at the level of the iliac crest at the end of a normal expiration. Hip circumference was measured at the widest circumference around the buttocks. Waist-to-hip ratio was calculated as waist divided by hip circumference. We classified the measures of overall and central adiposity into quartiles by using cutting points defined by the sex-specific distribution of these variables among Mexican American adults in order to maximize statistical power in this understudied ethnic group.

The highest grade or year of school completed was used to classify education as less than high school, or greater than or equal to a high school education. Current, former, or never smoking was based upon the use of cigarettes, cigars, or pipe tobacco. Individuals who reported smoking at least 100 cigarettes, 20 cigars, or 20 pipes of tobacco in their lifetime but no longer smoked were considered former smokers. The consumption frequency of alcoholic beverages (beer, wine, liquor) and the type and frequency of leisure-time physical activities over the past month were



assessed. Migration and acculturation status among Mexican Americans were indicated by country of birth and primary language spoken at home. Country of birth and language use are two factors which have high levels of validity and reliability (30) and reflect the strength of cultural beliefs and practices (31). The presence or absence of major chronic illness at baseline was assessed as heart disease, including angina, a physician's diagnosis of congestive heart failure, or myocardial infarction; respiratory disease, including chronic bronchitis, emphysema, or asthma; stroke; or cancer, except non-melanoma skin cancer. The presence of angina was determined with a series of questions described elsewhere (32).

Hypertension was defined as an average of six seated blood pressure readings by a trained technician or physician  $\geq 140/90$ , or use of antihypertensive medication (33,34). Diabetes was defined by history (type 1 or type 2), use of diabetes medications, a fasting plasma glucose value  $\geq 126$  mg/dL, or a 2-hour post-load glucose value  $\geq 200$  mg/dl (35). High cholesterol included a total cholesterol concentration  $\geq 240$  mg/dL or use of lipid lowering medication (36). Women were defined as postmenopausal if they reported not having had a period during the previous 12 months, a hysterectomy, both ovaries removed, or if they were 60 years of age or older. Hormone replacement therapy use in women was based upon self-report and defined as current or not current use.

### **Ascertainment of mortality**

We merged baseline data from NHANES III with follow-up data from the NHANES III Mortality Study. As part of the NHANES III Mortality Study, data from the National Death Index (NDI), which has been shown to capture 93-98% of all U.S.

deaths (37-39), were used to ascertain the vital status of each cohort member through December 31, 2000. Information obtained from the Mortality Study data included the month, day, and year in which a person was last known to be alive.

### **Data analyses**

Data were analyzed using SAS (version 9.1, SAS Institute Inc, Cary, NC) and SUDAAN (version 9.0, Research Triangle Institute, Research Triangle Park, NC) software. All analyses included sample weights that account for the complex sample design and the unequal probabilities of selection because of oversampling and nonresponse. We computed length of follow-up as the time elapsed between the physical examination and the date of death for cases or December 31, 2000 for non-cases. Age-adjusted rates and means were derived by the direct method using ten-year age categories of the total population as the standard and analysis of covariance, respectively. Sex-specific multivariable logistic regression models were fit to examine the relation of adiposity with mortality from all-causes, adjusting for age, education, smoking status, illness at baseline, and race/ethnicity (except when stratified). We did not adjust for physical activity or possible mediators of obesity effects, such as diabetes, hypertension, or high cholesterol, since doing so would have resulted in overadjustment because of their position on the causal pathway (40). We also did not adjust for alcohol use in either sex or estrogen use in women due to problems with model convergence owing to the low number of deaths in Mexican Americans and women of each race/ethnicity. Sensitivity analyses conducted in models which combined individuals from each racial/ethnic group showed these factors had very little, if any, effect on the sex-specific association of adiposity with mortality. We

examined linear trends in the relative risks across quartiles of adiposity by including these variables as ordinal terms within the multivariable models. All hypothesis tests were two-sided and based upon a type one error rate of 0.05. No adjustments were made for multiple comparisons.

## **RESULTS**

White men and women were older than black and Mexican American men and women (Table 1). White men and black women were the heaviest, while Mexican American men and black women had the highest BMI. Mexican American men and white women had the lowest waist circumference, and black men and white women had the lowest waist-to-hip ratio. Hip circumference was highest among white men and black women. Education was highest among white adults and Mexican Americans were the least physically active. Mexican American men reported a lower frequency of alcohol consumption compared to black men, but had a similar frequency as white men. Among women, alcohol use was lowest among Mexican Americans. Black women were more likely than white or Mexican American women to be postmenopausal, while the use of postmenopausal hormones was more frequent among white women. Black men and women were more likely than white and Mexican American men and women to smoke and to be hypertensive. Mexican American men and women tended to have the lowest rates of illness at baseline; however, they also had the highest prevalence of diabetes. Almost half of all Mexican American men and women (47.4% and 45.0%, respectively) were born in Mexico, approximately 15% were born in the U.S. and primarily spoke Spanish, and the

remainder was born in the U.S. and spoke English (37.6% of men and 39.6% of women).

Weighted Pearson correlation analyses were used to examine the degree of correlation between the adiposity measures. Correlations of BMI and waist circumference were 0.92-0.93 across the races in men and 0.89-0.91 in women; BMI and WHR were 0.51-0.59 and 0.56-0.63; and waist circumference and WHR were 0.69-0.76 and 0.56-0.63. Due to the close correlation of BMI and waist circumference in men and women, we focused on BMI and waist-to-hip ratio as measures of overall and central adiposity, respectively.

During a maximum follow-up of 12 years (72,083 person-years), there were 103 (age-adjusted rate = 6.8 per 1,000 person-years), 136 (15.3 per 1,000), and 88 (8.3 per 1,000) deaths from all-causes in white, black, and Mexican American men, respectively, and 84 (4.9 per 1,000), 86 (7.7 per 1,000), and 60 (6.1 per 1,000) deaths in similar women. Table 2 displays the age-adjusted all-cause mortality rates per 1,000 person-years and adjusted relative risks according to the quartile of BMI and waist-to-hip ratio by sex and race/ethnicity. BMI showed a U-shaped relation with mortality in men of each race/ethnicity, however, lowest mortality was observed in the second to the highest quartile of BMI in black and Mexican American men, and the second to the lowest quartile in white men. Among white and black women, relative risks for mortality increased and decreased inconsistently across increasing quartiles of BMI. Nonsignificant relative risks for mortality less than 1.0 were noted in Mexican American women in each quartile of BMI compared to women in the second quartile.

All-cause mortality was increased by 64%, 81%, and 56% among white, black, and Mexican American men, respectively, in the top quartile of waist-to-hip ratio compared to similar men in the bottom quartile, although this risk was statistically significant only for black men (Table 2). Among white and black women, mortality increased in a positive dose-response fashion with increasing quartile of waist-to-hip ratio ( $p_{\text{trend}}=0.005$  for white women and  $p_{\text{trend}}=0.02$  for black women). White and black women in the top quartile of waist-to-hip ratio were 2.64 and 2.07 times more likely to die, respectively, compared to similar women in the lowest quartile of waist-to-hip ratio. We found no evidence to suggest that an elevated waist-to-hip ratio increased the relative risk for mortality in Mexican American women, since nonsignificant relative risks less than 1.0 were noted for women in each quartile when compared with women in the bottom quartile ( $p_{\text{trend}}=0.9$ ).

In Mexican American men, the relations of BMI and waist-to-hip ratio with mortality varied significantly by migration and language use ( $p_{\text{interaction}}=0.007$  for BMI and 0.03 for waist-to-hip ratio) (Table 3). In Mexican American men and women who were born in Mexico and men who were born in the U.S. whose primary language was Spanish, nonsignificant relative risks for mortality less than 1.0 were noted in each quartile of BMI when compared to the second to the lowest quartile. In general, similar results were found among U.S.-born Spanish speaking Mexican American women after collapsing women in the top two quartiles of BMI due a small number of deaths. In U.S.-born English speaking Mexican American men, BMI demonstrated a U-shaped relation with mortality, while BMI was inconsistently associated with mortality among similar Mexican American women. For waist-to-hip ratio, relative

risks for mortality increased with increasing quartile only among U.S.-born English speaking men, although this relation was of borderline significance ( $p_{\text{trend}}=0.06$ ). The relative risk for mortality increased 4.0-fold across quartiles among these men. There were too few deaths among U.S.-born Spanish speaking Mexican American women to reliably examine the relation of waist-to-hip ratio with mortality.

In secondary analyses, the relations of BMI and waist-to-hip ratio with mortality did not vary significantly by level of educational attainment in men or women from each racial/ethnic group (not shown). For analyses presented in Table 2, excluding those who died in the first year of follow-up or those who lost more than 4.5 kg (10 lbs) in the 10 years prior to enrollment had little influence on the results, except for the associations of waist-to-hip ratio with mortality in men. These exclusions tended to increase the strength of these relations, especially for men in the highest quartile of waist-to-hip ratio (relative risk (RR)=2.09, 95% confidence interval (CI)=1.01, 4.33,  $p_{\text{trend}}=0.06$ , highest vs. lowest quartile in white men; RR=2.12, 95% CI=0.93, 4.80,  $p_{\text{trend}}=0.1$  for black men; RR=2.64, 95% CI=1.06, 6.63,  $p_{\text{trend}}=0.04$  for Mexican American men).

## **DISCUSSION**

In this 12-year prospective cohort study, we compared the relative importance of overall and central adiposity (i.e., BMI and waist-to-hip ratio, respectively) with mortality from all-causes in a national sample of white, black, and Mexican American men and women. In general, we found the strength and shape of the relation between BMI and mortality varied by sex and race/ethnicity, however, waist-to-hip ratio showed positive associations with mortality that were stronger among white and black

women than men, but were of similar magnitude between white, black, and Mexican American men. When evaluating the influence of migration and acculturation on this relation among Mexican Americans, an elevated waist-to-hip ratio increased the risk for mortality only among U.S.-born English speaking men. An increased BMI or waist-to-hip ratio did not increase the risk for death among Mexican American women, regardless of country of birth, level of acculturation, or educational attainment.

To our knowledge, this is the first study to compare the relation of overall and central adiposity with mortality among white, black, and Mexican American adults. Previous studies of adiposity and mortality have suggested that blacks may better tolerate obesity; however, these studies have focused almost exclusively on BMI as a measure of adiposity and have included only whites and blacks. Among 290,178 white and 12,055 black adults from the Cancer Prevention Study II cohort, the highest levels of BMI increased the relative risk for all-cause mortality by 2.58 and 2.00 in white men and women, respectively, compared to 1.35 and 1.21 in black men and women (9). The Charleston Heart Study showed BMI, midarm, and waist circumferences were associated with mortality in black men (13), but not black women (12). In contrast, Durazo-Arvizu (10) showed the relation between BMI and all-cause mortality was similar in a U.S. national sample of white and black adults, although BMI associated with minimum mortality was on-average 3.1 and 1.5 kg/m<sup>2</sup> higher in black men and women, respectively, compared to similar whites. The strength and shape of the relation of BMI with mortality varied between white and black men and women in the current study, however, numerous studies have shown

that BMI is an inconsistent indicator of mortality risk as evidenced by findings suggesting this relation is J-shaped, U-shaped, positive, non-existent and even inverse (41-45). On the other hand, waist-to-hip ratio demonstrated positive associations with mortality in whites and blacks that were stronger for women than for men. Thus, even though imaging studies suggest black adults have less intra-abdominal fat than whites at the same level of obesity (16,18,19), there appears to be little difference in the sex-specific relative risk for death between whites and blacks at the same level of waist-to-hip ratio.

We found evidence to suggest that country of birth and acculturation may modify the relation of adiposity with mortality among Mexican Americans, more clearly for men than for women. Among Mexican American men who were born in the U.S. and were the most acculturated (defined as speaking English), BMI and waist-to-hip ratio demonstrated U-shaped and positive associations with mortality, respectively; findings similar to those observed among white and black men. However, no association of BMI or waist-to-hip ratio with mortality was noted among similar men who were born in Mexico and men born in the U.S. whose primary language was Spanish. It is challenging to explain this differential influence of adiposity on the risk of death between these three subpopulations of Mexican Americans. It is well known that migration influences factors related to diet, lifestyle, and health status (46,47). Previous studies of Mexican American men and women born in Mexico have suggested that they have a more heart healthy dietary intake, including significantly lower fat, and higher fiber, vitamin, and mineral consumption, low smoking rates among women, and low mortality, compared to similar adults born



in the U.S. (6,48-50) Mexican Americans born in Mexico and those born in the US who primarily spoke Spanish may have worked in occupations requiring greater amounts of physical activity than their U.S.-born counterparts. Sociocultural factors such as these may protect overweight or obese Mexican Americans from an increased risk of mortality. However, the number of deaths within subgroups of Mexican Americans was small, especially among women. Additional longitudinal follow-up of a larger number of deaths may allow better estimates of the relative risks for mortality associated with adiposity.

An alternative explanation for the varying results of adiposity with mortality in Mexican American men by migration and level of acculturation may be due to the “healthy migrant” effect, whereby those who immigrate to the U.S. are healthier than those who do not immigrate (51). A third explanation may be due to an incomplete ascertainment of deaths, which may have been differential with respect to ethnicity and birthplace (52,53). To collect vital status, this study linked social security numbers and other personal identifying information with the NDI, a centralized database of death record information collected from state offices of vital statistics. Misclassification may have occurred since Mexican Americans born in Mexico and their less acculturated counterparts born in the U.S. may have been less likely than whites, blacks, and U.S. born English speaking Mexican Americans to have or accurately report a social security number (54,55). In addition, if migrants or less acculturated Mexican Americans traveled back to Mexico during the follow-up period and died, death record information would not be transmitted to the NDI (54). This misclassification could have attenuated true associations of adiposity with mortality

among Mexican Americans born in Mexico and those born in the U.S. who spoke Spanish. Thus, it is unclear if migration and acculturation are phenomena that influence the biologic effects of obesity and the risk of mortality among Mexican Americans. Future cohort studies are needed that supplement or replace vital status obtained from the NDI with information collected from next-of-kin and/or other methodologies that do not rely solely upon the use of vital statistics.

We found that adiposity in Mexican American women, regardless of country of birth, level of acculturation, or education did not carry an increased risk for mortality. This was surprising since cross-sectional analyses of these Mexican American women participating in the baseline examination of NHANES III have shown abdominal obesity increases the odds of hypertension (56), type 2 diabetes (56), and metabolic syndrome (57). Additional cross-sectional studies from more recent survey years of NHANES (58,59) and prospective epidemiologic studies of Mexican American women from the San Antonio Heart Study have confirmed these results (60-63). It is well known that these metabolic complications of obesity increase the risk for mortality, especially death due to diabetes and cardiovascular disease (64). Thus, we are unable to explain why adiposity did not increase the risk for mortality in Mexican American women. Perhaps sociocultural factors or the previously suggested biases that may at least partly explain the differential influence of migration and acculturation on the relation of adiposity with mortality in Mexican American men affect all subpopulations of Mexican American women. Additional studies are needed to examine this relation.

The external validity of these findings is enhanced by the nationally representative sample of white, black, and Mexican American adults. In addition, this study included anthropometric indices measured by trained technicians as opposed to self-report. However, there are limitations of the current study in addition to those previously described. We relied upon simple estimates of anthropometry that are unable to distinguish fat from fat-free mass. In addition, we used a simple, static variable to quantify acculturation among Mexican American adults since this was the only indicator collected during NHANES III. Acculturation is a very complex adaptation process that involves attitudes, cognitive factors, and personality in addition to language (65). However, language use is one of the most important factors in the acculturation process and has been used in numerous studies as a proxy measure of acculturation (24,25,28,30,50). As mentioned earlier, the small number of deaths hindered our ability to examine the relation of adiposity with specific causes of death. In addition, many have suggested that those with clinical evidence of chronic illness or recent weight loss at baseline, smokers, and early deaths should be excluded to improve internal validity in studies of BMI with mortality (40,66-68). Nevertheless, studies still report a curvilinear relation after performing these exclusions (41,42,66,69,70). In the current study, excluding those who died in the first year of follow-up and those who experienced an increased recent weight loss enhanced the strength of the relation of waist-to-hip ratio with mortality in men and had little impact on the relation with BMI in both men and women.

In conclusion, the results of this study fail to support the use of BMI as a means by which to assess the risk for mortality from all-causes in white, black, and

Mexican American adults. In contrast, waist-to-hip ratio may provide an improved indicator of mortality among these racial/ethnically diverse populations. The modifying influence of country of birth and acculturation on the relation of adiposity with mortality among Mexican American men, and the failure of adiposity to predict mortality in Mexican American women demands confirmation from additional research. These findings have implications for future studies designed to examine risk factors for mortality among racial/ethnically diverse populations of U.S. adults.

Table 5. Age-adjusted baseline characteristics of participants aged 30-64 years by sex and race/ethnicity, NHANES III\* Mortality Study, 1988-2000.

Baseline characteristic†	Men			Women		
	White	Black	Mexican American	White	Black	Mexican American
Sample size§	1,486	1,145	1,172	1,726	1,413	1,158
Age (years)	44.1 (0.3)	42.8 (0.3)‡	41.6 (0.3)‡¶	44.9 (0.3)	43.2 (0.3)‡	42.6 (0.3)‡
Height (cm)	177.1 (0.2)	176.3 (0.2)	169.8 (0.2)‡¶	163.3 (0.2)	163.5 (0.2)	156.5 (0.2)‡¶
Weight (kg)	85.2 (0.5)	83.5 (0.5)‡	80.6 (0.4)‡¶	70.8 (0.7)	79.2 (0.6)‡	71.7 (0.6)¶
BMI* (kg/m <sup>2</sup> )	27.1 (0.1)	26.8 (0.2)	27.9 (0.1)‡¶	26.6 (0.2)	29.6 (0.2)‡	29.2 (0.2)‡
Waist circumference (cm)	97.9 (0.3)	93.7 (0.4)‡	97.8 (0.3)¶	89.0 (0.6)	95.7 (0.5)‡	94.6 (0.6)‡
Hip circumference (cm)	100.8 (0.2)	99.4 (0.3)‡	98.8 (0.4)‡	103.3 (0.5)	107.9 (0.4)‡	104.6 (0.4)¶
Waist-to-hip ratio	0.969	0.940	0.990	0.860	0.885	0.904
Education (years)	(0.002)	(0.002)‡	(0.002)‡¶	(0.003)	(0.002)‡	(0.003)‡¶
Physical activity (times/month)	13.2 (0.1)	11.6 (0.1)‡	8.5 (0.2)‡¶	13.0 (0.1)	11.9 (0.1)‡	8.5 (0.3)‡¶
Alcohol use (days/month)	25.6 (0.9)	26.6 (1.3)	20.4 (1.2)‡¶	21.6 (1.0)	16.4 (0.9)‡	13.5 (0.8)‡¶
Postmenopausal (%)	12.5 (0.5)	14.8 (1.1)	11.9 (0.8)¶	6.2 (0.6)	5.0 (0.5)	2.5 (0.2)‡¶
Current hormone use (%)	--	--	--	41.4	47.7‡	40.4¶
Current smoker (%)	--	--	--	31.9	15.0‡	16.3‡
Existing disease (%)	34.5	49.1‡	30.4¶	27.4	32.7‡	15.5‡¶
Hypertension (%)	14.6	14.5	10.3‡¶	18.3	20.5	16.7¶
High cholesterol (%)	23.8	34.7‡	23.3¶	17.8	35.0‡	20.1¶
Diabetes (%)	23.2	18.3‡	22.8	22.5	20.3	18.5‡
Acculturation (%)	10.1	11.1	16.6‡¶	8.6	12.7‡	18.5‡¶
Born in Mexico	--	--	47.4	--	--	45.0
Born in U.S., Spanish speaking	--	--	15.1	--	--	15.4
Born in U.S., English speaking	--	--	37.6	--	--	39.6

Table 5, continued. Age-adjusted baseline characteristics of participants aged 30-64 years by sex and race/ethnicity, NHANES III\* Mortality Study, 1988-2000.

\*NHANES III indicates the third National Health and Nutrition Examination Survey; BMI, body mass index.

†Values shown are the weighted mean (standard error) or percent.

§Unweighted.

‡ $p < 0.05$  vs. whites, within the same sex.

¥ $p < 0.05$  vs. blacks, within the same sex.

Table 6. Age-adjusted all-cause mortality rates and adjusted relative risks (95% confidence intervals) among adults aged 30-64 years according to quartiles of adiposity by sex and race/ethnicity, NHANES III\* Mortality Study, 1988-2000.

	Body Mass Index (kg/m <sup>2</sup> )									
	Men					Women				
	<24.8	24.8-27.3	27.4-30.4	>30.4	<i>P</i> <sub>trend</sub>	<24.8	24.8-28.3	28.4-32.3	>32.3	<i>P</i> <sub>trend</sub>
Overall	Deaths†	120	69	59	79	62	62	47	60	
	Rate‡	12.0	8.3	7.4	10.1	5.4	7.0	5.8	6.3	
	RR*§	1.40	1.00	1.03	1.72	0.64	1.00	0.70	1.07	0.1
	95%CI*	0.83, 2.36	referent	0.57, 1.84	0.96, 3.10	0.34, 1.18	referent	0.34, 1.44	0.54, 2.14	
White	Deaths†	34	20	21	28	30	24	11	20	
	Rate‡	8.3	5.5	6.7	9.2	5.3	6.4	4.1	6.7	
	RR*§	1.53	1.00	1.18	2.03	0.56	1.00	0.62	1.19	0.08
	95%CI*	0.77, 3.06	referent	0.55, 2.52	0.95, 4.32	0.27, 1.19	referent	0.25, 1.59	0.50, 2.83	
Black	Deaths†	63	25	21	27	22	17	21	26	
	Rate‡	17.9	12.8	9.3	12.9	7.7	6.8	7.3	6.4	
	RR*§	1.02	1.00	0.64	1.05	1.42	1.00	1.21	0.98	0.3
	95%CI*	0.54, 1.95	referent	0.30, 1.33	0.46, 2.36	0.58, 3.45	referent	0.55, 2.64	0.50, 1.91	
Mexican American	Deaths†	23	24	17	24	10	21	15	14	
	Rate‡	9.6	9.1	6.3	9.1	4.5	8.0	5.8	5.4	
	RR*§	1.04	1.00	0.70	0.99	0.76	1.00	0.70	0.66	0.5
	95%CI*	0.41, 2.61	referent	0.26, 1.89	0.47, 2.08	0.28, 2.07	referent	0.33, 1.50	0.31, 1.37	

Table 6, continued. Age-adjusted all-cause mortality rates and adjusted relative risks (95% confidence intervals) among adults aged 30-64 years according to quartiles of adiposity by sex and race/ethnicity, NHANES III\* Mortality Study, 1988-2000.

	Waist-to-Hip Ratio										
	Men					Women					
	<0.941	0.941-0.994	1.031	0.995-1.031	> 1.031	<i>P</i> <sub>trend</sub>	<0.852	0.852-0.901	0.954	>0.954	<i>P</i> <sub>trend</sub>
Overall	Deaths† Rate‡ RR*¥ 95%CI*	76 9.1 1.00 referent	85 9.2 1.10 0.64, 1.89	61 8.0 0.96 0.57, 1.61	105 12.2 1.58 0.95, 2.62	<i>P</i> <sub>trend</sub> 0.1	36 3.7 1.00 referent	40 4.6 1.37 0.73, 2.60	53 6.3 1.53 0.85, 2.77	102 8.8 2.43 1.38, 4.25	0.001
White	Deaths† Rate‡ RR*¥ 95%CI*	17 5.4 1.00 referent	30 7.7 1.23 0.58, 2.62	21 6.6 1.01 0.51, 1.97	35 9.8 1.64 0.86, 3.14	<i>P</i> <sub>trend</sub> 0.2	16 3.6 1.00 referent	16 4.5 1.40 0.63, 3.12	19 5.9 1.44 0.70, 2.95	34 9.3 2.64 1.34, 5.21	0.005
Black	Deaths† Rate‡ RR*¥ 95%CI*	49 13.2 1.00 referent	32 11.5 0.78 0.45, 1.37	20 12.1 0.81 0.45, 1.46	35 24.2 1.81 1.05, 3.12	<i>P</i> <sub>trend</sub> 0.1	10 3.3 1.00 referent	15 5.3 1.58 0.48, 5.20	25 9.1 2.48 1.16, 5.33	36 9.1 2.07 0.87, 4.89	0.02
Mexican American	Deaths† Rate‡ RR*¥ 95%CI*	10 6.6 1.00 referent	23 8.3 1.20 0.46, 3.17	20 7.6 0.97 0.34, 2.78	35 9.8 1.56 0.57, 4.22	<i>P</i> <sub>trend</sub> 0.4	10 4.9 1.00 referent	9 3.8 0.48 0.18, 1.25	9 3.6 0.39 0.15, 1.04	32 7.5 0.84 0.39, 1.85	0.9

\*NHANES indicates the third National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

†Unweighted

‡Weighted age-adjusted rate per 1,000 person-years.

¥Adjusted for age (years), smoking status (current, former, never), education (less than high school graduate, high school graduate or more), existing disease (yes, no), and race/ethnicity (except when stratified).



Table 7. Adjusted relative risks (95% confidence intervals) for all-cause mortality among Mexican American adults aged 30-64 years according to quartiles of adiposity by country of birth and language preference, NHANES III\* Mortality Study, 1988-2000.

	Body Mass Index (kg/m <sup>2</sup> )									
	Men					Women				
	<24.8	24.8-27.3	27.4-30.4	>30.4	<i>P</i> <sub>trend</sub>	<24.8	24.8-28.3	28.4-32.3	>32.3	<i>P</i> <sub>trend</sub>
Mexican Americans	Deaths† 10	23	20	35		10	21	15	14	
	RR*‡ 1.04	1.00	0.70	0.99	0.6	0.76	1.00	0.70	0.66	0.5
	95%CI* 0.41, 2.61	referent	0.26, 1.89	0.47, 2.08		0.28, 2.07	referent	0.33, 1.50	0.31, 1.37	
Mexico-born	Deaths† 10	14	5	5		5	12	5	8	
	RR*‡ 0.67	1.00	0.41	0.26	0.05	0.74	1.00	0.30	0.64	0.4
	95%CI* 0.19, 2.38	referent	0.12, 1.40	0.06, 1.09		0.18, 2.97	referent	0.07, 1.24	0.30, 1.34	
U.S.-born Spanish speaking	Deaths† 6	6	7	7		2	3	5‡		
	RR*‡ 0.87	1.00	0.54	0.75	0.8	1.04	1.00	0.77		0.7
	95%CI* 0.16, 4.81	referent	0.09, 3.41	0.11, 5.03		0.10, 10.36	referent	0.12, 4.82		
U.S.-born English speaking	Deaths† 7	4	4	11		3	5	5	3	
	RR*‡ 4.42	1.00	3.37	4.62	0.4	1.32	1.00	2.70	0.29	0.5
	95%CI* 0.81, 24.03	referent	0.60, 18.92	1.33, 16.12		0.20, 8.66	referent	0.53, 13.83	0.04, 1.86	

Table 7, continued. Adjusted relative risks (95% confidence intervals) for all-cause mortality among Mexican American adults aged 30-64 years according to quartiles of adiposity by country of birth and language preference, NHANES III\* Mortality Study, 1988-2000.

	Waist-to-Hip Ratio									
	Men					Women				
	<0.941	0.941-0.994	0.995-1.031	>1.031	$P_{\text{trend}}$	<0.852	0.852-0.901	0.902-0.954	>0.954	$P_{\text{trend}}$
Mexican Americans	Deaths† 10	23	20	35	0.4	10	9	9	32	0.9
	RR*‡ 1.00	1.20	0.97	1.56	0.4	1.00	0.48	0.39	0.84	0.9
	95%CI*	referent	0.46, 3.17	0.34, 2.78	0.57, 4.22	referent	0.18, 1.25	0.15, 1.04	0.39, 1.85	
Mexico-born	Deaths† 5	12	7	10	0.5	7	5	5	13	0.5
	RR*‡ 1.00	1.89	1.17	0.93	0.5	1.00	0.37	0.60	0.50	0.5
	95%CI*	referent	0.54, 6.62	0.26, 5.31	0.27, 3.25	referent	0.10, 1.36	0.20, 1.83	0.16, 1.51	
U.S.-born Spanish speaking	Deaths† 2	2	9	13	0.7	1	1	0	8	
	RR*‡ 1.00	0.07	0.39	0.67	0.7	-	-	-	-	
	95%CI*	referent	0.01, 0.84	0.07, 2.16	0.09, 4.78					
U.S.-born English speaking	Deaths† 3	8	3	12	0.06	2	2	3	9	0.6
	RR*‡ 1.00	1.83	1.36	3.96	0.06	1.00	0.81	0.20	1.63	0.6
	95%CI*	referent	0.29, 11.68	0.18, 10.14	0.95, 16.56	referent	0.10, 6.63	0.01, 4.16	0.21, 12.57	

\*NHANES III indicates the third National Health and Nutrition Examination Survey; RR, relative risk; CI, confidence interval.

†Unweighted

‡Adjusted for age, smoking status, education, and existing disease.

§Number of deaths, RR, and 95% CI for BMI  $\geq 28.4$  kg/m<sup>2</sup>.

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**IV. THE RELATION OF LEPTIN AND INSULIN  
WITH OBESITY-RELATED CARDIOVASCULAR RISK FACTORS  
IN US ADULTS**

**ABSTRACT**

**OBJECTIVE:** Accumulating evidence suggests that leptin may mediate the association of obesity with cardiovascular disease (CVD) through an association with CVD risk factors; however, data have been virtually limited to clinical samples, which may be prone to selection bias. This cross-sectional study examined whether leptin or insulin may mediate the endogenous relation of obesity with metabolic, inflammatory, and thrombogenic cardiovascular risk factors. **METHODS:** Participants included 522 men and 514 women aged  $\geq 40$  years who completed a morning physical examination after an overnight fast between 1988 and 1991 during the first phase of the third National Health and Nutrition Examination Survey. Participants were free of existing CVD, cancer (except non-melanoma skin cancer), diabetes, or respiratory disease. **RESULTS:** In multivariate analyses adjusted for race/ethnicity and lifestyle factors, waist circumference (WC) was positively associated with blood pressure, triglyceride, LDL cholesterol, total cholesterol:HDL ratio, apolipoprotein B, C-reactive protein (CRP), and fibrinogen concentrations, and negatively associated with HDL cholesterol and apolipoprotein A1 levels. The associations of WC with the metabolic CVD risk factors were largely attenuated after adjustment for insulin levels, while the associations of WC with the inflammatory and thrombogenic factors (CRP and fibrinogen, respectively) were largely explained by adjustment for leptin

concentrations. However, leptin levels were not independently associated with CRP and fibrinogen in men ( $\beta=0.02$  and  $3.13$ , respectively;  $p>0.05$ , for both) and CRP in women ( $\beta=0.03$ ;  $p>0.05$ ) when adjusted for WC. Positive associations of leptin ( $\beta=1.27$ ;  $p<0.05$ ) and insulin ( $\beta=1.53$ ;  $p<0.05$ ) with fibrinogen in women, independent of WC, were noted. **CONCLUSIONS:** Insulin may be an important mediator of the association of obesity with metabolic but not inflammatory or thrombogenic CVD risk factors, while leptin does not appear to influence cardiovascular risk through a shared association with these risk factors. However, we cannot rule out the possibility that leptin and insulin influence cardiovascular risk in women through independent effects on fibrinogen concentrations.

## INTRODUCTION

The prevalence of overweight and obesity are increasing dramatically in the US and worldwide (1,2). Obesity and weight gain are strong independent predictors of incident cardiovascular events (3,4) and predispose to numerous risk factors for cardiovascular disease (CVD), including hypertension (5), dyslipidemia (6), and type 2 diabetes (7). Randomized clinical trials have shown that weight reduction in obese adults can lead to short-term improvements in these metabolic conditions (8-11). However, despite these consistent epidemiologic findings, the endogenous mechanism linking obesity with CVD remains largely elusive.

Leptin is a hormone produced by the adipocyte and is widely recognized for its effects on food intake and energy balance. However, more recent research has implicated leptin in the development of CVD and as an independent predictor of incident cardiovascular events, in most, but not all studies (12). Increased leptin levels have been associated with a first-ever stroke (13-15) and coronary event (16,17), independent of traditional cardiovascular risk factors. The widespread distribution of functioning leptin receptors on vascular cells provides a potential explanation for these epidemiologic findings and suggests an important role for leptin in angiogenesis (18-21). Indirect relations of leptin with traditional and nontraditional cardiovascular risk factors may also explain these findings (22-27); however, these studies have been limited by clinical samples and lack of representation of the general population.

Obesity, especially increased visceral adiposity, is strongly associated with marked reductions in insulin sensitivity and increased fasting insulin concentrations (28,29). In the Insulin Resistance and Atherosclerosis Study, an increased waist

circumference, a marker of visceral fat, was strongly associated with reduced insulin sensitivity and increased fasting insulin, independent of body mass index (BMI) and glucose tolerance (29). Insulin resistance and fasting hyperinsulinemia have been implicated as independent risk factors for type 2 diabetes (30-32) and coronary heart disease (33,34), and have been proposed as the metabolic precursors of the metabolic syndrome, a condition characterized by increased visceral adiposity, dyslipidemia, hypertension, inflammation, and a prothrombotic state (35). However, the role of insulin in the pathogenesis of CVD remains controversial since several prospective studies have failed to confirm a direct association (36-38).

The current study was designed to investigate the endogenous mechanism by which obesity may increase the risk of CVD by examining whether fasting leptin or insulin mediate the association of obesity with metabolic, inflammatory, and thrombogenic cardiovascular risk factors in a national population-based cohort of US adults. A second purpose was to determine whether leptin and insulin are associated with these CVD risk factors, independent of obesity.

## **METHODS**

### **Study design**

The current study utilized data from the third National Health and Nutrition Examination Survey (NHANES III), conducted in the United States from 1988-1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). Recruitment and data collection occurred during two three-year phases, each consisting of a home interview, a physical examination, and laboratory analysis. Each phase included a cross-sectional, national, complex multistage,

clustered, stratified probability sample of the civilian, noninstitutionalized population aged two months and older. Oversampling of young children (< 5 years), older persons (> 60 years), non-Hispanic blacks, and Mexican Americans during NHANES III was conducted to increase the representation of individuals from these groups.

### **Study population**

Participants were randomly assigned by household to be examined in the morning at a mobile examination center after an overnight fast. We limited the current study to adults aged 40 years and older who completed phase 1 (1988 to 1991) of NHANES III since the measurement of apolipoprotein A1 (apo-A1) and apolipoprotein B (apo-B) occurred only during this phase. We further excluded those who had fasted for < 9 hours (n = 186), > 24 hours (n = 3), or who had an unknown fasting time (n = 34), those who were pregnant (n = 1), those with an insufficient quantity of serum to perform the leptin assay (n = 238), and those who had missing insulin (n = 95), or waist circumference data (n = 120). Since the presence of chronic conditions may influence both cardiovascular risk factors and body weight, we excluded those who reported a diagnosis of congestive heart failure or a previous myocardial infarction (n = 191), stroke (n = 41), angina (n = 76), cancer (except non-melanoma skin cancer) (n = 89), respiratory disease (bronchitis, emphysema, or asthma) (n = 143), or diabetes (n = 184). The presence of angina was determined with a series of questions described elsewhere (39). Diabetes was defined by history (type 1 or type 2 diabetes), use of diabetes medications, or a fasting plasma glucose level  $\geq$  126 mg/dL. The final analytic sample consisted of 522 men and 514 women. The

Institutional Review Board at the CDC approved the study design and all participants provided written informed consent.

### **Physical examination**

During the physical examination, anthropometric measurements and blood pressure readings were obtained. Waist circumference was measured to the nearest 0.1 cm using a steel measuring tape at the level of the iliac crest at the end of a normal expiration. Hip circumference was measured at the widest circumference around the buttocks. Waist-to-hip ratio was calculated as waist divided by hip circumference. Body weight to the nearest 0.1 kg and standing height to the nearest 0.1 cm were measured using a Toledo electronic self-zeroing scale and Seca stadiometer while participants were wearing undergarments, a paper robe, and foam slippers. BMI was calculated as weight in kg divided by the square of height in m. Three seated blood pressure readings were obtained by a trained technician during the home interview and another three readings by a physician during the physical examination, according to the standardized measurement protocols recommended by the American Heart Association (40). Systolic (SBP) and diastolic blood pressures (DBP) were recorded as the first and fifth Korotkoff sounds, respectively. The average of all available blood pressure readings were used in analyses.

### **Laboratory methods and biochemical measures**

A fasting venous blood sample was collected using a standard protocol (41). Sera were separated, frozen at -20°C and transferred on dry ice to the CDC central laboratory for priority analyses. Surplus serum specimens were stored at -70°C and went through at least one freeze-thaw cycle during an average of eight years of storage

before leptin concentrations were measured. Leptin has been previously shown to remain stable through five freeze-thaw cycles (42) and after storage for as long as 29 years (43). Serum leptin concentrations were measured by radioimmunoassay (RIA) (Linco Research, Inc, St Charles, MO) (42); intra- and interassay coefficients of variation were both  $< 5\%$ . Serum insulin was measured by RIA (Pharmacia Diagnostics).

Plasma glucose was measured using a hexokinase enzymatic method (Hexokinase System/Roche COBAS MIRA Chem System). Serum cholesterol and triglyceride levels were measured enzymatically (Hitachi 704 analyzer, Boehringer Mannheim, Mannheim, Germany). HDL-cholesterol was assessed following the precipitation of the other lipoproteins with a polyanion/divalent cation mixture. LDL cholesterol was calculated using the Friedewald equation (serum total cholesterol – HDL cholesterol – serum triglyceride/5) (44). We calculated the total cholesterol:HDL-ratio (TCHR) as a measure of dyslipidemia by dividing total cholesterol concentration by HDL-cholesterol concentration. Serum apo-A1 and apo-B were measured by radial immunodiffusion in the first 8.2% of the specimens collected during the first five months of NHANES III, and by rate immunonephelometry for the remaining specimens, as previously described (45). Serum C-reactive protein was measured by using latex-enhanced nephelometry (Behring Diagnostics Inc, Somerville, NJ). Fibrinogen was measured using a quantitative assay of clotting time compared to a known standard (Coag-A-Mate XC Plus/Organon-Teknika/General Diagnostics). Analytical methods and quality control protocols for NHANES III have been described in detail elsewhere (41,46).



**Covariates**

Race/ethnicity was based upon self-reported race and ethnicity, and was categorized as non-Hispanic white, non-Hispanic black, Mexican American, and other. The other category included all Hispanics, regardless of race, who were not Mexican American, and also all non-Hispanics from racial groups other than white or black. Smoking status was categorized as current, former, or never, based upon the use of cigarettes, cigars, or pipe tobacco. Individuals who reported smoking at least 100 cigarettes, 20 cigars, or 20 pipes of tobacco in their lifetime but no longer smoked were classified as former smokers. A standardized questionnaire was used to determine the type and frequency of leisure-time physical activities performed over the past 30 days. These activities included walking, jogging or running, biking, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, as well as a category for other activities. To capture long term alcohol use, the consumption frequency of alcoholic beverages (beer, wine, liquor) during the past month was assessed with the use of a food frequency questionnaire. Women were defined as postmenopausal if they reported not having had a period during the previous 12 months, a hysterectomy, both ovaries removed, or if they were 60 years of age or older. Hormone replacement therapy use in women was based upon self-report and defined as current or not current use.

**Statistical analyses**

Due to sex differences in leptin concentrations, body composition, and some CVD risk factors, we conducted all analyses separately for men and women. Since leptin, insulin, and some risk factors were non-normally distributed, these variables

were log-transformed prior to hypothesis testing when considered dependent variables; untransformed means are reported for ease of interpretation. For each continuous characteristic we tested whether a linear trend existed across the sex-specific quintile groups of waist circumference by treating waist circumference as an ordinal variable in age-adjusted linear regression models. For categorical characteristics, the chi-square test was used to test for independence.

Weighted Pearson partial correlations examined the relation of waist circumference, log-transformed leptin, and insulin with each of the CVD risk factors after adjusting for covariates. To evaluate whether leptin or insulin may be the biological mediator between obesity and CVD risk factors we assessed the change in the beta coefficient for waist circumference (used as a marker of fat mass) when adding untransformed leptin or insulin, both individually and together, to multivariable linear regression models. Multivariable linear regression evaluated the relation of leptin and insulin with the CVD risk factors after adjusting for waist circumference and covariates. Waist circumference, as opposed to BMI or waist-to-hip ratio, was used as a measure of obesity since stronger correlations were observed with leptin, insulin, and the CVD risk factors. Covariates included age (40-54, 55-69,  $\geq 70$  years), race/ethnicity, smoking, physical activity (times/month), alcohol use (days/month), and fasting time (two categories: 9- < 12 and 12-24 hours). The addition of menopausal status and hormone therapy as covariates to the multivariable models in women had very little, if any, effect on the associations of waist circumference, leptin, and insulin with the CVD risk factors and were therefore not included.

To assess compliance with the assumption of linearity we viewed graphical plots and tested the significance of including higher order leptin and insulin terms to the multivariable models. We found no evidence of non-linearity and present only results from the linear models. In addition, we repeated all analyses after excluding individuals with leptin and insulin values  $\pm 3$  standard deviations from the sex-specific mean values. Results were similar with and without the exclusion of these persons and therefore we present findings from the full sample. Statistical significance was defined at the  $p < 0.05$  level using two-sided tests and all analyses were conducted using SAS (version 9.1, SAS Institute Inc, Cary, NC) and SUDAAN (version 9.0, RTI International, Research Triangle Park, NC) to account for the complex sampling strategy and weighting of the NHANES III population.

## **RESULTS**

The characteristics for the 522 men and 514 women in the current study sample according to the quintile of waist circumference are displayed in Table 1. In men, no association was observed between age and waist circumference, while in women, waist circumference increased with increasing age. White men were generally more likely to have a higher waist circumference than racial/ethnic minority men, while in women, no association was noted between waist circumference and race/ethnicity. Men and women who smoked were more likely to have a lower waist circumference. Overall, in both men and women, a higher waist circumference was associated with less physical activity, higher leptin, insulin, SBP, DBP, total cholesterol, triglyceride, LDL, TCHR, apo-B, C-reactive protein, and fibrinogen concentrations, and lower HDL and apo-A1 levels; all  $p < 0.05$ .

Table 2 displays the weighted Pearson partial correlations of waist circumference, log-transformed leptin, and insulin concentrations with each of the metabolic, inflammatory, and thrombogenic cardiovascular risk factors after adjusting for age, race/ethnicity, smoking, physical activity, alcohol use, and fasting time. In men and women, waist circumference, leptin, and insulin were positively correlated with SBP, DBP, total cholesterol, triglyceride, LDL, TCHR, apo-B, C-reactive protein, and fibrinogen, and negatively correlated with HDL and apo-A1. Nearly all correlations were statistically significant at  $p < 0.05$ , except for the associations of insulin with fibrinogen in men, and leptin with apo-A1 in women.

To evaluate whether leptin or insulin may be the biological mediator between obesity and CVD risk factors, we examined the change in the beta coefficient for waist circumference when adding leptin or insulin to a base model including waist circumference and covariates. Waist circumference was independently associated in men and women with each CVD risk factor (all  $p < 0.05$ ), with the exception of total cholesterol in men (Table 3). In men, the associations of waist circumference with SBP, DBP, total cholesterol, and triglyceride were reduced by 9% to 60% when adjusting for leptin levels, however, the relations with the remaining metabolic factors were either unchanged or increased in strength, providing no evidence that leptin mediated these relations. The associations of waist circumference with C-reactive protein and fibrinogen in men were reduced by 62% and 86%, respectively, when leptin was included in the multivariable models. After adjusting for insulin levels, all associations of waist circumference with the metabolic factors were reduced; by 8% for LDL to 95% for triglyceride. Beta coefficients for the associations of waist

circumference with C-reactive protein and fibrinogen were reduced by 17% and 19%, respectively, when adjusting for insulin levels. When adjusting for leptin and insulin levels together in men, the associations of waist circumference with the CVD risk factors were reduced (except for LDL and apo-A1) by 7% for apo-B to 99% for triglyceride.

In women, the associations of waist circumference with all of the metabolic risk factors, except for HDL and apo-A1 were reduced when adjusting for leptin levels; these reductions ranged from 5% for DBP to 23% for total cholesterol (Table 3). Associations of waist circumference with C-reactive protein and fibrinogen were reduced by 19% and 56%, respectively, when including leptin concentrations. Associations of waist circumference with the metabolic factors were reduced by a greater extent when adjusting for insulin levels as compared to leptin, except for the associations with total cholesterol, LDL, and TCHR. Adjusting for insulin levels reduced the relation of waist circumference with the metabolic factors by 1% for LDL to 32% for SBP. Relations with C-reactive protein and fibrinogen were reduced by 15% and 33%, respectively, when adjusting for insulin levels. Relations between waist circumference and the CVD risk factors in women when adjusting for leptin and insulin levels together were reduced by 13% for LDL to 74% for fibrinogen.

Multivariable linear regression models were fit to examine whether leptin and insulin were independently associated with each of the CVD risk factors after adjusting for waist circumference and covariates (Table 4). In men, no significant associations of leptin with the CVD risk factors were noted when adjusting for waist circumference and covariates, while in women, leptin remained positively associated

with only fibrinogen levels. In contrast, insulin levels remained positively associated with DBP, triglyceride, TCHR, and apo-B and negatively associated with HDL and apo-A1 in men and positively associated with SBP, triglyceride, TCHR, apo-B, and fibrinogen and negatively associated with HDL in women when adjusted additionally for waist circumference.

## **DISCUSSION**

In this national population-based sample of adults, insulin levels largely mediated the association of waist circumference with metabolic CVD risk factors, while leptin largely explained the association of waist circumference with inflammatory and thrombogenic factors. The magnitude of these reductions was generally greater for men than for women. However, leptin levels were not independently associated with CRP and fibrinogen in men and CRP in women when adjusted for waist circumference, suggesting that leptin itself may not be an important determinant of these inflammatory and thrombogenic factors. These findings are in agreement with a cross-sectional analysis of a sub-sample of men from the Health Professionals Follow-up Study, which found plasma leptin levels were not an important predictor of several metabolic and thrombogenic CVD risk factors (47). However, our findings differ from a recent cross-sectional study of older men from the British Regional Heart Study which reported significant associations of leptin with inflammatory and thrombogenic factors, independent of waist circumference (25). The reasons for the differences between studies are unknown, but may be due to differences in sampling and sample size.

Previous research has shown that leptin may participate in the inflammatory response (48) and clinical studies have reported positive associations of leptin with CRP, a marker of systemic inflammation (23,24,48). Inflammation is widely proposed as an important factor in all stages of atherosclerotic plaque formation and eventual rupture (49) and elevated CRP has predicted the long-term risk of cardiovascular disease in several prospective cohorts (50). While the underlying mechanisms supporting an association of leptin with increased CRP are unclear, there are potential pathways. CRP is produced largely by the liver in response to interleukin (IL)-6 and to a lesser extent by other proinflammatory cytokines, including IL-1 and tumor necrosis factor (TNF)- $\alpha$  (51). The leptin receptor shares structural and functional similarities with the IL-6 family of cytokines (52) and leptin has been shown to increase the in vitro expression of IL-6 and TNF- $\alpha$  (53). However, adipocytes also synthesize IL-6 and TNF- $\alpha$ , (54,55) and may therefore serve as a common source for the production of leptin and cytokines responsible for the expression of hepatic CRP. Thus, leptin may increase CRP levels directly through IL-6 or TNF- $\alpha$ , or through a shared association with body fat. Results of the current study may suggest the latter, since the relation of leptin with CRP did not retain significance in either men or women when adjusted for waist circumference.

Fibrinogen is a hepatic protein involved in platelet aggregation, blood coagulation, as well as the acute inflammatory response (56). Elevated fibrinogen concentrations are associated with obesity (57,58) and an increased risk of ischemic coronary events in asymptomatic individuals, independent of established cardiovascular risk factors (59). These findings support a role for obesity in

thrombogenesis and CVD. In the current study, leptin levels largely mediated the association of waist circumference with fibrinogen concentrations in men and women compared to insulin. However, when adjusted for waist circumference and covariates the association of leptin with fibrinogen was attenuated and no longer statistically significant in men, while in women, the relation was attenuated, but statistical significance persisted. These results suggest that leptin may not be independently associated with fibrinogen concentrations, confirming the results of previous studies showing the relation of leptin with fibrinogen is reduced and no longer statistically significant when controlled for obesity (47,60). Since few studies of leptin with CVD risk factors have been performed in women, future studies are necessary to confirm the significant association observed between leptin and fibrinogen concentrations.

Although we used standard effect decomposition methods to assess the potential for leptin and insulin to mediate the relation of obesity with metabolic, inflammatory, and thrombotic CVD risk factors, this approach is limited in the presence of unmeasured confounding and/or interaction (61). For example, we found that leptin largely mediated the association of obesity with CRP and fibrinogen; however, an independent association between leptin and these factors was only confirmed for fibrinogen in women after adjusting for obesity. Since adipose tissue is a potent producer of leptin and cytokines responsible for the hepatic synthesis of CRP and fibrinogen (e.g. IL-6 and TNF- $\alpha$  (51,62)), a positive correlation of leptin with waist circumference, CRP, and fibrinogen would be expected. This may have inflated the proportion of the effect of obesity on CRP and fibrinogen explained by leptin. Consequently, this may also explain why leptin was not independently associated with



CRP in both sexes and fibrinogen in men when adjusted for obesity. Recently, Chu et al. (47) showed that controlling for the confounding effects of soluble TNF receptors dramatically reduced the mediating influence of leptin on the association of obesity with fibrinogen concentrations. In addition, these researchers found no evidence of an independent association of leptin with fibrinogen after multivariable adjustment for TNF receptors and BMI (47).

In the current study, insulin largely explained the association of waist circumference with several metabolic risk factors for CVD. In addition, the associations of insulin with these factors were independent of waist circumference and confounders. The relation of obesity with insulin resistance, hyperinsulinemia, and dyslipidemia is complex. Obesity is closely linked with decreased insulin sensitivity and increased fasting insulin concentrations; however, individuals of normal weight can also be insulin resistant (63). Nevertheless, adipose tissue triglyceride stores are a rich source of free fatty acids that stimulate the hepatic synthesis of glucose, triglycerides, and very low density lipoproteins, and contribute to a decrease in circulating HDL concentrations and insulin sensitivity (64-66). One of the most responsive functions of insulin is to inhibit lipolysis in adipose tissue (67); however, in the presence of insulin resistance, an increased amount of lipolysis of stored triglyceride molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin and promote additional lipolysis (35). Chronic hyperinsulinemia has also been shown to raise blood pressure through increased sympathetic nervous system activation (68). Our results support an important role for insulin in the development of obesity-related metabolic CVD risk factors.

The national population-based sampling strategy of NHANES III decreases the influence of selection bias and improves external validity. In addition, appropriate blood collection procedures allowed us to control for the diurnal variability and effect of food intake on leptin and insulin levels (69-71). However, the cross-sectional design complicates drawing a causal inference due to the absence of a temporal relation. In addition, although several metabolic CVD risk factors were examined, only a single inflammatory or thrombogenic factor was assessed during NHANES III. Furthermore, an indication of long-term exposure to the biochemical factors may have been reduced, since only a single baseline measurement was obtained. It is generally recommended to take several measurements to account for short-term variability and monitor long-term or cumulative exposure. However, this measurement error is unlikely to be associated with any of the factors assessed in the current study and therefore the significance of the associations or lack of associations reported here may be conservative.

In conclusion, this cross-sectional, population-based study suggests that insulin levels are an important mediator of the association of obesity with metabolic, but not inflammatory or thrombogenic CVD risk factors. Despite the evidence that leptin concentrations mediated to a greater degree than insulin the association of waist circumference with CRP and fibrinogen, the associations of leptin with both of these factors in men and CRP in women were not independent of waist circumference. Therefore, the present study suggests that leptin does not indirectly influence cardiovascular risk through a shared association with obesity-related metabolic, inflammatory, and thrombogenic CVD risk factors. However, we cannot rule out the

possibility that leptin and insulin influence cardiovascular risk in women through independent effects on fibrinogen concentrations.

Table 8. Characteristics of men and women aged 40 years and older according to quintile of waist circumference, NHANES III.

	Waist Circumference Quintile					<i>P</i> <sub>trend</sub>
	I	II	III	IV	V	
<b>MEN (n = 522)</b>	104	103	106	104	105	
n						
Waist circumference (cm)	82.4 (0.6)	90.3 (0.2)	96.8 (0.3)	102.4 (0.2)	113.0 (1.3)	< 0.0001
Waist-to-hip ratio	0.90 (0.001)	0.95 (0.005)	0.97 (0.003)	1.00 (0.005)	1.04 (0.006)	< 0.0001
BMI (kg/m <sup>2</sup> )	22.0 (0.2)	23.8 (0.2)	26.0 (0.2)	28.1 (0.3)	32.0 (0.6)	< 0.0001
Age (years), (%)						0.1*
40-54	70.1	65.1	56.4	62.9	50.3	
55-69	22.0	28.0	32.8	23.5	35.0	
≥ 70	7.9	7.0	10.8	13.6	14.7	
Race/ethnicity, n (%)						0.0002*
white	74.2	75.4	88.0	82.3	84.2	
African-American	14.2	9.9	6.5	5.8	4.7	
Mexican-American	1.5	2.6	2.1	4.6	4.6	
other	10.1	12.1	3.4	7.2	6.5	
Tobacco use, n (%)						0.03*
Never	33.5	28.2	32.8	22.0	25.5	
Former	28.3	38.4	33.9	44.1	56.5	
Current	38.2	33.4	33.3	33.9	18.0	
Physical activity (times/month)	34.3 (3.8)	26.2 (2.2)	34.6 (6.4)	23.6 (1.7)	18.2 (1.8)	0.0007
Alcohol (days/month)	17.4 (3.4)	20.3 (4.9)	16.7 (5.7)	12.0 (3.4)	13.5 (3.3)	0.2
Biochemical variables						
Leptin (µg/L)	2.9 (0.2)	4.0 (0.2)	4.9 (0.2)	7.2 (0.6)	11.3 (1.0)	< 0.0001
Insulin (µU/ml)	6.4 (0.3)	7.7 (0.4)	9.2 (0.2)	11.4 (0.8)	16.5 (1.6)	< 0.0001
SBP (mmHg)	125.2 (1.8)	124.1 (2.0)	128.0 (1.0)	127.0 (2.1)	136.5 (1.3)	0.0003
DBP (mmHg)	76.3 (1.1)	76.0 (1.3)	79.4 (1.0)	78.4 (1.0)	83.2 (1.4)	< 0.0001
Cholesterol (mg/dL)	207.6 (3.9)	217.3 (5.3)	206.1 (5.0)	217.8 (4.2)	227.9 (6.5)	0.01
Triglyceride (mg/dL)	107.0 (9.8)	136.0 (14.2)	147.1 (9.7)	152.7 (9.0)	192.9 (20.1)	< 0.0001
LDL (mg/dL)	130.0 (3.7)	140.3 (4.7)	133.4 (6.4)	142.0 (4.3)	150.2 (5.2)	0.002
HDL (mg/dL)	56.1 (2.3)	49.4 (1.8)	43.8 (1.3)	45.2 (1.7)	40.9 (1.5)	< 0.0001
TCHR	4.0 (0.2)	4.7 (0.2)	5.0 (0.2)	5.1 (0.2)	6.0 (0.3)	< 0.0001
Apo-A1 (mg/dL)	148.7 (3.6)	141.5 (2.5)	133.0 (3.0)	136.9 (2.9)	130.7 (2.2)	< 0.0001
Apo-B (mg/dL)	104.2 (2.9)	112.7 (3.2)	113.4 (3.1)	117.4 (3.2)	124.3 (4.2)	< 0.0001
C-reactive protein (mg/dL)	0.3 (0.03)	0.3 (0.05)	0.4 (0.07)	0.4 (0.03)	0.5 (0.09)	0.006
Fibrinogen (mg/dL)	272.6 (9.3)	293.2 (12.1)	287.5 (18.4)	296.4 (11.1)	323.2 (17.8)	0.02



Table 8, continued. Characteristics of men and women aged 40 years and older according to quintile of waist circumference, NHANES III.

BMI, body mass index; NHANES III, National Health and Nutrition Examination Survey III; SBP, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein-cholesterol; HDL, high density lipoprotein-cholesterol; TCHR, total cholesterol:HDL ratio; Apo-A1, apolipoprotein A1; Apo-B, apolipoprotein B. All data presented as mean (standard error) unless noted. All *p*-values (except for age, race/ethnicity, and tobacco use) are age-adjusted. \**p*-value for independence. Waist circumference (cm) quintile cutting-points: 87.6, 93.3, 99.6, 106.1 (men); 81.8, 88.4, 95.3, 103.3 (women).

Table 9. Weighted Pearson partial correlation coefficients for waist circumference, log-transformed leptin, and insulin versus metabolic, inflammatory, and thrombogenic cardiovascular risk factors among men and women aged 40 years and older, NHANES III.

	Men			Women		
	Waist	Leptin	Insulin	Waist	Leptin	Insulin
<i>Metabolic</i>						
SBP (mmHg)	0.19 <sup>c</sup>	0.14 <sup>b</sup>	0.14 <sup>b</sup>	0.28 <sup>c</sup>	0.22 <sup>c</sup>	0.29 <sup>c</sup>
DBP (mmHg)	0.27 <sup>c</sup>	0.20 <sup>c</sup>	0.29 <sup>c</sup>	0.28 <sup>c</sup>	0.27 <sup>c</sup>	0.21 <sup>c</sup>
Cholesterol (mg/dL)	0.14 <sup>b</sup>	0.11 <sup>a</sup>	0.12 <sup>a</sup>	0.22 <sup>c</sup>	0.27 <sup>c</sup>	0.19 <sup>c</sup>
Triglyceride (mg/dL)	0.32 <sup>c</sup>	0.27 <sup>c</sup>	0.38 <sup>c</sup>	0.36 <sup>c</sup>	0.27 <sup>c</sup>	0.40 <sup>c</sup>
LDL (mg/dL)	0.15 <sup>c</sup>	0.12 <sup>a</sup>	0.13 <sup>b</sup>	0.26 <sup>c</sup>	0.25 <sup>c</sup>	0.19 <sup>c</sup>
HDL (mg/dL)	-0.32 <sup>c</sup>	-0.24 <sup>c</sup>	-0.37 <sup>c</sup>	-0.31 <sup>c</sup>	-0.13 <sup>b</sup>	-0.27 <sup>c</sup>
TCHR	0.35 <sup>c</sup>	0.24 <sup>c</sup>	0.38 <sup>c</sup>	0.36 <sup>c</sup>	0.25 <sup>c</sup>	0.33 <sup>c</sup>
Apo-A1 (mg/dL)	-0.21 <sup>c</sup>	-0.13 <sup>b</sup>	-0.21 <sup>c</sup>	-0.20 <sup>c</sup>	-0.04	-0.14 <sup>b</sup>
Apo-B (mg/dL)	0.23 <sup>c</sup>	0.17 <sup>c</sup>	0.24 <sup>c</sup>	0.35 <sup>c</sup>	0.27 <sup>c</sup>	0.31 <sup>c</sup>
<i>Inflammatory</i>						
C-reactive protein (mg/dL)	0.25 <sup>c</sup>	0.18 <sup>c</sup>	0.13 <sup>b</sup>	0.35 <sup>c</sup>	0.23 <sup>c</sup>	0.28 <sup>c</sup>
<i>Thrombogenic</i>						
Fibrinogen (mg/dL)	0.14 <sup>c</sup>	0.13 <sup>b</sup>	0.03	0.22 <sup>c</sup>	0.22 <sup>c</sup>	0.21 <sup>c</sup>

<sup>a</sup>  $p < 0.05$ ; <sup>b</sup>  $p < 0.01$ ; <sup>c</sup>  $p < 0.001$

Waist, waist circumference; see footnote of Table 1 for the definition of remaining abbreviations.

Adjusted for age (40-54, 55-69,  $\geq 70$  years), race/ethnicity (non-Hispanic white, non-Hispanic African American, Mexican American, other), smoking (current, former, never), physical activity (times/month), alcohol use (days/month), and fasting time (two categories: 9- < 12, 12-24 hours).

Table 10. Various multivariable models assessing the effect of leptin and insulin on the association of waist circumference with metabolic, inflammatory, and thrombotic cardiovascular risk factors among men and women aged 40 years and older, NHANES III.

	Waist		Waist + Leptin		Waist + Insulin		Waist + Leptin + Insulin						
	$\beta$	se	$\beta$	se	$\beta$	se	$\beta$	se					
<b>MEN</b>													
<i>Metabolic</i>													
SBP (mmHg)	0.30 <sup>f</sup>	0.06	0.26 <sup>b</sup>	0.08	-13	0.08	0.25 <sup>b</sup>	0.08	-17	0.08	0.24 <sup>a</sup>	0.09	-20
DBP (mmHg)	0.22 <sup>c</sup>	0.05	0.20 <sup>f</sup>	0.22	-9	0.22	0.11	0.06	-50	0.06	0.15 <sup>a</sup>	0.06	-32
Cholesterol (mg/dL)	0.36	0.19	0.29	0.33	-19	0.33	0.05	0.22	-86	0.22	0.13	0.33	-64
Triglyceride (mg/dL)	2.20 <sup>b</sup>	0.71	0.88 <sup>c</sup>	0.87	-60	0.87	0.10	0.74	-95	0.74	0.01 <sup>a</sup>	0.99	-99
LDL (mg/dL)	0.39 <sup>b</sup>	0.13	0.70 <sup>f</sup>	0.27	+79	0.27	0.36 <sup>a</sup>	0.17	-8	0.17	0.62 <sup>d</sup>	0.27	+59
HDL (mg/dL)	-0.42 <sup>c</sup>	0.10	-0.50 <sup>f</sup>	0.09	+19	0.09	-0.28 <sup>b</sup>	0.09	-33	0.09	-0.41 <sup>c</sup>	0.09	-2
TCHR	0.05 <sup>b</sup>	0.01	0.05 <sup>c</sup>	0.01	0	0.01	0.02	0.01	-60	0.01	0.03 <sup>b</sup>	0.01	-40
Apo-AI (mg/dL)	-0.45 <sup>c</sup>	0.10	-0.60 <sup>f</sup>	0.11	+33	0.11	-0.32 <sup>b</sup>	0.09	-29	0.09	-0.50 <sup>f</sup>	0.10	+11
Apo-B (mg/dL)	0.46 <sup>b</sup>	0.16	0.60 <sup>b</sup>	0.18	+30	0.18	0.21	0.18	-54	0.18	0.43 <sup>a</sup>	0.19	-7
<i>Inflammatory</i>													
C-reactive protein (mg/dL)	0.0103 <sup>b</sup>	0.0060	0.0039 <sup>f</sup>	0.0020	-62	0.0020	0.0085 <sup>f</sup>	0.0047	-17	0.0047	0.0043	0.0025	-58
<i>Thrombotic</i>													
Fibrinogen (mg/dL)	1.09 <sup>f</sup>	0.47	0.15	0.77	-86	0.77	0.88	0.77	-19	0.77	0.24	0.95	-78



Table 10, continued. Various multivariable models assessing the effect of leptin and insulin on the association of waist circumference with metabolic, inflammatory, and thrombogenic cardiovascular risk factors among men and women aged 40 years and older, NHANES III.

<b>WOMEN</b>											
<i>Metabolic</i>											
SBP (mmHg)	0.31 <sup>c</sup>	0.07	0.25 <sup>b</sup>	0.08	-19	0.21 <sup>c</sup>	0.06	-32	0.18 <sup>a</sup>	0.06	-42
DBP (mmHg)	0.20 <sup>c</sup>	0.03	0.15 <sup>b</sup>	0.04	-5	0.18 <sup>c</sup>	0.04	-10	0.14 <sup>b</sup>	0.04	-30
Cholesterol (mg/dL)	0.61 <sup>c</sup>	0.15	0.47 <sup>a</sup>	0.21	-23	0.61 <sup>b</sup>	0.18	0	0.49 <sup>a</sup>	0.23	-20
Triglyceride (mg/dL)	1.98 <sup>c</sup>	0.48	1.79 <sup>c</sup>	0.54	-10	1.39 <sup>b</sup>	0.49	-30	1.34 <sup>a</sup>	0.56	-32
LDL (mg/dL)	0.71 <sup>c</sup>	0.17	0.62 <sup>a</sup>	0.23	-13	0.70 <sup>b</sup>	0.21	-1	0.62 <sup>a</sup>	0.25	-13
HDL (mg/dL)	-0.45 <sup>c</sup>	0.07	-0.46 <sup>c</sup>	0.07	+2	-0.33 <sup>c</sup>	0.08	-27	-0.36 <sup>c</sup>	0.09	-20
TCHR	0.05 <sup>c</sup>	0.01	0.04 <sup>c</sup>	0.01	-20	0.04 <sup>b</sup>	0.01	-20	0.04 <sup>b</sup>	0.01	-20
Apo-AI (mg/dL)	-0.53 <sup>c</sup>	0.12	-0.56 <sup>c</sup>	0.13	+6	-0.43 <sup>b</sup>	0.13	-19	-0.48 <sup>b</sup>	0.14	-17
Apo-B (mg/dL)	0.70 <sup>c</sup>	0.11	0.66 <sup>c</sup>	0.15	-6	0.56 <sup>c</sup>	0.12	-20	0.56 <sup>b</sup>	0.16	-20
<i>Inflammatory</i>											
C-reactive protein (mg/dL)	0.0072 <sup>c</sup>	0.0018	0.0058 <sup>c</sup>	0.0022	-19	0.0061 <sup>c</sup>	0.0018	-15	0.0051 <sup>c</sup>	0.0020	-29
<i>Thrombogenic</i>											
Fibrinogen (mg/dL)	1.12 <sup>b</sup>	0.36	0.49	0.37	-56	0.75	0.45	-33	0.29	0.44	-74

<sup>a</sup> $p < 0.05$ ; <sup>b</sup> $p < 0.01$ ; <sup>c</sup> $p < 0.001$ . Waist, waist circumference; se, standard error; see footnote of Table 8 for the definition of remaining abbreviations. All models adjusted for variables listed in the footnote of Table 9.

Table 11. Multivariable association of leptin and insulin with metabolic, inflammatory, and thrombogenic cardiovascular risk factors among men and women aged 40 years and older, NHANES III.

	Men				Women			
	Leptin		Insulin		Leptin		Insulin	
	$\beta$	se	$\beta$	se	$\beta$	se	$\beta$	se
<i>Metabolic</i>								
SBP (mmHg)	0.13	0.23	0.13	0.18	0.12	0.08	0.39 <sup>a</sup>	0.15
DBP (mmHg)	0.06	0.22	0.31 <sup>b</sup>	0.11	0.10	0.06	0.09	0.12
Cholesterol (mg/dL)	0.26	1.03	0.91	0.49	0.29	0.20	0.02	0.36
Triglyceride (mg/dL)	4.41	3.95	5.98 <sup>c</sup>	1.63	0.38	0.32	2.44 <sup>c</sup>	0.81
LDL (mg/dL)	-1.08	0.71	0.08	0.40	0.18	0.20	0.03	0.34
HDL (mg/dL)	0.29	0.20	-0.37 <sup>a</sup>	0.13	0.03	0.07	-0.49 <sup>a</sup>	0.18
TCHR	-0.002	0.052	0.07 <sup>a</sup>	0.03	0.005	0.007	0.05 <sup>a</sup>	0.02
Apo-A1 (mg/dL)	0.49	0.27	-0.37 <sup>a</sup>	0.17	0.07	0.15	-0.40	0.28
Apo-B (mg/dL)	-0.49	0.62	0.71 <sup>a</sup>	0.34	0.07	0.13	0.57 <sup>a</sup>	0.22
<i>Inflammatory</i>								
C-reactive protein (mg/dL)	0.0214	0.0144	0.0050	0.0073	0.0028	0.0040	0.0045	0.0061
<i>Thrombogenic</i>								
Fibrinogen (mg/dL)	3.13	2.54	0.60	2.06	1.27 <sup>c</sup>	0.25	1.53 <sup>a</sup>	0.64

<sup>a</sup>  $p < 0.05$ ; <sup>b</sup>  $p < 0.01$ ; <sup>c</sup>  $p < 0.001$ .

se, standard error; see footnote of Table 8 for the definition of the remaining abbreviations.

Adjusted for waist circumference (cm) in addition to the variables listed in the footnote of Table 9.

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## V: DISCUSSION

There were three objectives of the current dissertation. The first was to compare the relative importance of overall and central adiposity with the risk for total and cause-specific mortality among a national sample of US adults, while also paying particular attention to the potential modifying influence of age. The second objective was to compare the relative importance of overall and central adiposity in predicting the risk of all-cause mortality among white, black, and Mexican American men and women, while also examining the influence of migration and acculturation on these relations in Mexican Americans. The third objective was to examine whether leptin or insulin mediate the association of obesity with metabolic, inflammatory, and thrombogenic cardiovascular disease risk factors.

A prospective cohort study was conducted to examine objective one. Participants were adults aged 30-102 years who completed the baseline physical examination as part of the third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994. NHANES III included a national, complex multistage, clustered, stratified probability sample of the civilian, noninstitutionalized population aged two months and older. Overall adiposity was estimated by body mass index (BMI) calculated from measured height and weight. Central obesity was estimated by waist circumference and waist-to-hip ratio. Vital status was ascertained by linking the baseline cohort with the National Death Index through December 31,

2000. Results suggested that the relation of adiposity with mortality is modified by age. In middle-aged adults (30-64 years), BMI was associated in a U-shaped fashion with total mortality in men and in a J-shaped fashion in women. In contrast, waist-to-hip ratio demonstrated a positive association with mortality independent of overall adiposity (i.e., BMI), although this relation did not reach statistical significance in middle-aged men. In middle-aged men and women, waist-to-hip ratio was more strongly associated with the risk of mortality due to cardiovascular disease than BMI or waist circumference alone. In older adults (65-102 years), BMI and waist circumference were each inversely associated with mortality. These observed associations were not explained to any great extent by numerous potential confounders, existing disease, bias from recent weight loss, or increased early deaths among the leanest adults.

Despite positive associations of BMI with numerous diseases (1), the shape of the association between BMI and all-cause mortality across studies has been U-shaped, J-shaped, positive, nonexistent, and inverse. However, waist-to-hip ratio has shown a positive linear relation with mortality in most studies of middle-aged adults (2-4). In the Iowa Women's Health Study, the relative risk of mortality increased 2.6-fold across increasing quintiles of waist-to-hip ratio among all women, while BMI showed a J-shaped relation (2). In the current dissertation, relative risks for total mortality across quintiles of waist-to-hip ratio in all middle-aged men and women increased 2.0- and 2.5-fold, respectively. Similar to findings of Iowa women (2) and middle-aged Swedish men (5), middle-aged adults with a low BMI and a high waist-to-hip ratio had the highest risk of mortality. Due to a close correlation, jointly

classifying BMI and waist circumference resulted in too few subjects in some categories to provide meaningful risk estimates.

One of the primary findings of the first study of this dissertation was that the increased risk of mortality among middle-aged adults in the highest quintiles of waist-to-hip ratio was largely explained by an increased risk of death from cardiovascular disease. An increased waist circumference also conveyed a higher risk of cardiovascular mortality, albeit not as strongly as waist-to-hip ratio; while only the highest quintile of BMI carried an elevated risk. Research over the last three decades has revealed the importance of abdominal fat measures in predicting an adverse metabolic risk factor profile (6-9), which increases the risk of cardiovascular disease. In the current dissertation, high cholesterol, hypertension, and diabetes together explained approximately one-third of the risk of cardiovascular mortality associated with an elevated waist-to-hip ratio. Abdominal obesity, including an increased waist-to-hip ratio has predicted an increased risk of cardiovascular disease in several cohorts (10-14). Interventions which reduce total adiposity through diet and/or exercise in middle-aged adults have proven effective in reducing measures of abdominal fat and improve cardiovascular disease risk factors (15-18), though waist-to-hip ratio may not be a sensitive indicator of change in abdominal obesity (19). These findings suggest increased abdominal obesity in general and waist-to-hip ratio in particular are important predictors of mortality from cardiovascular disease in middle-aged adults.

Another primary finding of study one was that the relation between adiposity and mortality differed between middle-aged and older adults. This finding has generally been confirmed in previous cohorts that have differed widely in age (20-24).

Although numerous studies have assessed the association of BMI with mortality, few have included the very old or additional measures of body composition (25-30). In one of the largest studies conducted to date comparing various measures of adiposity among non-institutionalized adults aged  $\geq 75$  years, Price et al. (26) found a higher BMI or waist circumference reduced the risk of all-cause mortality, while a higher waist-to-hip ratio modestly increased mortality. Additional studies support an inverse association of BMI with mortality among older adults (25,28,31,32). In the current dissertation, an elevated waist-to-hip ratio did not increase the risk of mortality.

The lower risk of mortality among older adults in the highest quintiles of BMI and waist circumference was largely attributable to reduced mortality from respiratory disease in men and cardiovascular disease in women. An inverse association between adiposity and cardiovascular mortality in older women, and no relation in older men, has been previously reported (26). To limit the potential for reverse causation, which is a concern in older adults due in part to higher levels of comorbidity, those who died in the first three years of follow-up or those who experienced an increased recent weight loss were excluded. Results were similar with and without the exclusion of these persons. Although these analytic techniques may be effective if the underlying disease causes rapid weight loss leading to death, reverse causation may still influence the risk of mortality if the course of disease is lengthy. Regardless, in studies of chronic obstructive pulmonary disease that measure pulmonary function, BMI has been shown to be an independent predictor of death, highlighting the importance of body composition in respiratory disease prognosis (33,34).

The divergent relation of adiposity with mortality between middle-aged and older adults may be due to several reasons. The first may be a selective survival effect, whereby individuals who are susceptible to the adverse health effects of obesity due to environmental or genetic factors suffer from increased mortality during middle age, leaving a more resistant overweight elderly population. The second may be that the protective effects of obesity in older age outweigh the potential negative effects. Heavier persons have lower rates of osteoporosis due likely to greater weight-bearing bone formation (35). This may reduce the risk of falls and protect older adults from the acute trauma that can occur as a result of falling. In addition, obesity may provide energy reserves during periods of stress, including illness or trauma (36,37).

A similar prospective cohort study was used to examine objective two using the NHANES III population. This time, however, men and women were stratified by race/ethnicity when determining the relation of overall and central adiposity with mortality. In addition, only those aged 30-64 years were included due to the modifying influence of age on the relation of adiposity with mortality. In general, results suggested that the strength and shape of the relation between BMI and mortality varied by sex and race/ethnicity, however, waist-to-hip ratio showed positive associations with mortality that were stronger among white and black women than men, but were of similar magnitude between white, black, and Mexican American men. When evaluating the influence of migration and acculturation on this relation among Mexican Americans, an elevated waist-to-hip ratio increased the risk for mortality only among U.S.-born English speaking men. An increased BMI or waist-

to-hip ratio did not increase the risk for death among Mexican American women, regardless of country of birth, level of acculturation, or educational attainment.

Previous studies of adiposity and mortality have suggested that blacks may better tolerate obesity; however, these studies have focused almost exclusively on BMI as a measure of adiposity and have included only whites and blacks. Among 290,178 white and 12,055 black adults from the Cancer Prevention Study II cohort, the highest levels of BMI increased the relative risk for all-cause mortality by 2.58 and 2.00 in white men and women, respectively, compared to 1.35 and 1.21 in black men and women (38). The Charleston Heart Study showed BMI, midarm, and waist circumferences were associated with mortality in black men (39), but not black women (40). In contrast, Durazo-Arvizu (41) showed the relation between BMI and all-cause mortality was similar in a U.S. national sample of white and black adults, although BMI associated with minimum mortality was on-average 3.1 and 1.5 kg/m<sup>2</sup> higher in black men and women, respectively, compared to similar whites. The strength and shape of the relation of BMI with mortality varied between white and black men and women in the current dissertation, however, numerous studies have shown that BMI is an inconsistent indicator of mortality risk as evidenced by findings suggesting this relation is J-shaped, U-shaped, positive, non-existent and even inverse (2,42-45). On the other hand, waist-to-hip ratio demonstrated positive associations with mortality in whites and blacks that were stronger for women than for men. Thus, even though imaging studies suggest black adults have less intra-abdominal fat than whites at the same level of obesity (46-48), there appears to be little difference in the



sex-specific relative risk for mortality between whites and blacks at the same level of waist-to-hip ratio.

There was evidence to suggest that country of birth and acculturation may modify the relation of adiposity with mortality among Mexican Americans, more clearly for men than for women. Among Mexican American men who were born in the U.S. and were the most acculturated (defined as speaking English), BMI and waist-to-hip ratio demonstrated U-shaped and positive associations with mortality, respectively; findings similar to those observed among white and black men. However, no association of BMI or waist-to-hip ratio with mortality was noted among similar men who were born in Mexico and men born in the U.S. whose primary language was Spanish. It is challenging to explain this differential influence of adiposity on the risk of death between these three subpopulations of Mexican Americans. It is well known that migration influences factors related to diet, lifestyle, and health status (49,50). Previous studies of Mexican American men and women living in Mexico have suggested that they have a more heart healthy dietary intake, including significantly lower fat, and higher fiber, vitamin, and mineral consumption, low smoking rates among women, and low mortality, compared to similar adults born in the U.S. (51-54) Mexican Americans born in Mexico and those born in the US who primarily spoke Spanish may have worked in occupations requiring greater amounts of physical activity than their U.S.-born counterparts. Sociocultural factors such as these may protect overweight or obese Mexican American immigrants and those who maintain this lifestyle (i.e., U.S.-born Spanish speakers) from an increased risk of mortality. However, the number of deaths within subgroups of Mexican Americans

was small, especially among women. Additional longitudinal follow-up of a larger number of deaths may allow better estimates of the relative risks for mortality associated with adiposity and more clearly elucidate whether this relation differs between these subgroups of Mexican Americans.

An alternative explanation for the varying results of adiposity with mortality in Mexican American men by migration and level of acculturation may be due to the “healthy migrant” effect, whereby those who immigrate to the U.S. are healthier than those who do not immigrate (55). A third explanation may be due to an incomplete ascertainment of deaths, which may have been differential with respect to ethnicity and birthplace (56,57). To collect vital status this dissertation linked social security numbers and other personal identifying information from individuals who participated in NHANES III with the NDI, a centralized database of death record information collected from state offices of vital statistics. Misclassification may have occurred since Mexican Americans born in Mexico and their less acculturated counterparts born in the U.S. may have been less likely than whites, blacks, and U.S. born English speaking Mexican Americans to have or accurately report a social security number (58,59). In addition, if migrants or less acculturated Mexican Americans traveled back to Mexico during the follow-up period and died, death record information would not be transmitted to the NDI (58). These factors would obviously underestimate mortality and may have resulted in nondifferential misclassification, biasing the associations of adiposity with mortality among Mexican Americans born in Mexico and those born in the U.S. who spoke Spanish toward the null hypothesis. Thus, it is unclear if migration and acculturation are phenomena that influence the biologic

effects of obesity and risk for mortality among Mexican Americans. Future cohort studies are needed that supplement or replace death record information contained in the NDI with information obtained from next-of-kin and/or other methodologies that do not rely solely upon the use of vital statistics.

Adiposity in Mexican American women, regardless of country of birth, level of acculturation, or education did not carry an increased risk for all-cause mortality. This was surprising since cross-sectional analyses of these Mexican American women participating in the baseline examination of NHANES III have shown abdominal obesity increases the odds of hypertension (60), type 2 diabetes (60), and the metabolic syndrome (9). Additional cross-sectional studies from more recent survey years of NHANES (61,62) and prospective epidemiologic studies of Mexican American women from the San Antonio Heart Study have confirmed these results (63-66). It is well known that these metabolic complications of obesity increase the risk for mortality, especially death due to diabetes and cardiovascular disease (67). Perhaps sociocultural factors or the previously suggested biases that may at least partly explain the differential influence of migration and acculturation on the relation of adiposity with mortality in Mexican American men affect all subpopulations of Mexican American women. Additional studies are needed to examine this relation.

A cross-sectional study of apparently healthy adults aged 40 years and older who completed a physical examination during the first phase of NHANES III 1988-1991 was conducted to examine objective three. Results suggested that insulin levels largely mediated the association of waist circumference with metabolic CVD risk factors, while leptin seemed to largely explain the association of waist circumference

with inflammatory and thrombogenic factors. The magnitude of these reductions was generally greater for men than for women. However, leptin levels were not independently associated with CRP and fibrinogen in men and CRP in women when adjusted for waist circumference, suggesting that leptin itself may not be an important determinant of these inflammatory and thrombogenic factors. These findings are in agreement with a cross-sectional analysis of a sub-sample of men from the Health Professionals Follow-up Study, which found plasma leptin levels were not an important predictor of several metabolic and thrombogenic CVD risk factors (68). However, these findings differ from a recent cross-sectional study of older men from the British Regional Heart Study which reported significant associations of leptin with inflammatory and thrombogenic factors, independent of waist circumference (69).

Previous research has shown that leptin may participate in the inflammatory response (70) and clinical studies have reported positive associations of leptin with CRP, a marker of systemic inflammation (70-72). Inflammation is widely proposed as an important factor in all stages of atherosclerotic plaque formation and eventual rupture (73) and elevated CRP has predicted the long-term risk of cardiovascular disease in several prospective cohorts (74). While the underlying mechanisms supporting an association of leptin with increased CRP are unclear, there are potential pathways. CRP is produced largely by the liver in response to interleukin (IL)-6 and to a lesser extent by other proinflammatory cytokines, including IL-1 and tumor necrosis factor (TNF)- $\alpha$  (75). The leptin receptor shares structural and functional similarities with the IL-6 family of cytokines (76) and leptin has been shown to increase the *in vitro* expression of IL-6 and TNF- $\alpha$  (77). However, adipocytes also

synthesize IL-6 and TNF- $\alpha$ , (78,79) and may therefore serve as a common source for the production of leptin and cytokines responsible for the expression of hepatic CRP. Thus, leptin may increase CRP levels directly through IL-6 or TNF- $\alpha$ , or through a shared association with body fat. Results of the current dissertation may suggest the latter, since the relation of leptin with CRP did not retain significance in either men or women when adjusted for waist circumference.

Fibrinogen is a hepatic protein involved in platelet aggregation, blood coagulation, as well as the acute inflammatory response (80). Elevated fibrinogen concentrations are associated with obesity (81,82) and an increased risk of ischemic coronary events in asymptomatic individuals, independent of established cardiovascular risk factors (83). These findings support a role for obesity in thrombogenesis and CVD. In the current dissertation, leptin levels largely mediated the association of waist circumference with fibrinogen concentrations in men and women compared to insulin. However, when adjusted for waist circumference and covariates the association of leptin with fibrinogen was attenuated and no longer statistically significant in men, while in women, the relation was attenuated, but statistical significance persisted. These results suggest that leptin may not be independently associated with fibrinogen concentrations, confirming the results of previous studies showing the relation of leptin with fibrinogen is reduced and no longer statistically significant when controlled for obesity (68,84). Since few studies of leptin with CVD risk factors have been performed in women, future studies are necessary to confirm the significant association observed between leptin and fibrinogen concentrations.

Our findings of leptin largely mediating the association of obesity with CRP and fibrinogen may be influenced by confounding by cytokines such as IL-6 and TNF- $\alpha$ . These cytokines are produced by adipose tissue, in addition to leptin, and are responsible for the hepatic synthesis of CRP and fibrinogen (75,85). This may at least partly explain why leptin levels largely mediated the association of waist circumference with CRP and fibrinogen, since a positive correlation of IL-6 and TNF- $\alpha$  with leptin, CRP, and fibrinogen concentrations would be expected. This may also explain why leptin was not significantly associated with CRP in both sexes and fibrinogen in men following adjustment for waist circumference. Chu et al. (68) recently showed that controlling for the confounding effects of soluble TNF receptors dramatically reduced the mediating influence of leptin on the association of obesity with fibrinogen concentrations. In addition, these researchers found no evidence of an independent association of leptin with fibrinogen after multivariable adjustment for TNF receptors and BMI (68).

In the current dissertation, insulin largely explained the association of waist circumference with several metabolic risk factors for CVD. In addition, the associations of insulin with these factors were independent of waist circumference and confounders. The relation of obesity with insulin resistance, hyperinsulinemia, and dyslipidemia is complex. Obesity is closely linked with decreased insulin sensitivity and increased fasting insulin concentrations; however, individuals of normal weight can also be insulin resistant (86). Nevertheless, adipose tissue triglyceride stores are a rich source of free fatty acids that stimulate the hepatic synthesis of glucose, triglycerides, and very low density lipoproteins, and contribute to a decrease in

circulating HDL concentrations and insulin sensitivity (87-89). One of the most responsive functions of insulin is to inhibit lipolysis in adipose tissue (90); however, in the presence of insulin resistance, an increased amount of lipolysis of stored triglyceride molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin and promote additional lipolysis (91). Chronic hyperinsulinemia has also been shown to raise blood pressure through increased sympathetic nervous system activation (92). These results suggest an important role for insulin in the development of obesity-related metabolic CVD risk factors.

The strengths of the current dissertation include the population-based sampling strategy providing a nationally representative sample of the US population, anthropometric indices measured by trained technicians as opposed to self-report, and the ability to control for numerous confounding and health factors which may distort the association of adiposity with mortality. However, there are limitations of the current dissertation that should be appreciated. This dissertation used indicators of adiposity that are unable to distinguish fat from fat-free mass. In addition, due to the small number of deaths, this dissertation was unable to examine the relation of adiposity with specific causes of deaths within each of the three racial/ethnic groups. The cross-sectional design of study three impedes the ability to infer causality due to the absence of a temporal relation.

In conclusion, there was evidence to suggest that the relation of adiposity with mortality is modified by age. In middle-aged adults, waist-to-hip ratio provided a better health indicator for the risk of death due to cardiovascular disease than BMI. While among the elderly, reduced adiposity in general carried an increased risk for

mortality. In addition, results failed to support the use of BMI as a means by which to assess the risk for all-cause mortality in white, black, and Mexican American adults. In contrast, waist-to-hip ratio may provide an improved indicator of mortality risk among these racial/ethnically diverse populations. The modifying influence of country of birth and acculturation on the relation of adiposity with mortality among Mexican American men, and the failure of adiposity to predict mortality in Mexican American women demands confirmation from additional research. Furthermore, insulin levels may be an important mediator of the association of obesity with metabolic, but not inflammatory or thrombogenic CVD risk factors. Despite the evidence that leptin concentrations mediated to a greater degree than insulin the association of waist circumference with CRP and fibrinogen, the associations of leptin with both of these factors in men and CRP in women were not independent of waist circumference. Therefore, the present dissertation suggests that leptin does not indirectly influence cardiovascular risk through a shared association with obesity-related metabolic, inflammatory, and thrombogenic CVD risk factors. However, we cannot rule out the possibility that leptin and insulin influence cardiovascular risk in women through independent effects on fibrinogen concentrations.



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**APPENDIX – Application to the Research Data Center**

December 13, 2006

Research Data Center  
National Center for Health Statistics  
3311 Toledo Rd.  
Suite 4113  
Hyattsville, MD 20782

To Whom It May Concern:

The following application is for a research project entitled “The Influence of Adiposity on Mortality.” This project will be conducted as part of dissertation requirements for the degree of Doctor of Philosophy in Epidemiology at San Diego State University for the principal investigator, Jared Reis. The theme of the current application is to study the influence of adiposity on the risk of all-cause and cardiovascular disease mortality among adult participants of the third National Health and Nutrition Examination Survey, 1988-1994. Two separate studies are proposed: the first will assess the associations of body mass index (BMI), waist circumference, and waist-to-hip ratio with mortality; the second study will compare the associations of BMI, waist circumference, and waist-to-hip ratio with mortality among Black, Mexican American, and white men and women. The final product of this research will include two manuscripts that will be submitted for publication in the peer-reviewed literature.

In order to accomplish this research, a linkage of the NHANES III dataset provided by the principal investigator with the mortality file for NHANES III will be required. After this linkage is performed, the principal investigator proposes to use the remote access system to analyze the data.

Kind regards,

Jared P. Reis, PhD(c)  
Doctoral Candidate in Epidemiology  
San Diego State University

**B. Project Title**

THE INFLUENCE OF ADIPOSITY ON MORTALITY

**C. Abstract**

The first purpose of this proposed research application for use of NCHS data through the RDC is to study the associations of body mass index (BMI), waist circumference, and waist-to-hip ratio with the risk of mortality in participants 45 years and older who completed the physical examination during NHANES III, 1988-1994. The second purpose is to compare the associations of BMI, waist circumference, and waist-to-hip ratio with mortality among Black, Mexican American, and white men and women. In order to accomplish this research, a SAS dataset from NHANES III will be provided to the RDC from the principal investigator to link with outcome information from the mortality file from NHANES III, which contains vital status for all adult participants through December 31, 2000.

**D. Personal identification**

Jared P. Reis, PhD(c)  
Doctoral Candidate in Epidemiology  
Graduate School of Public Health  
San Diego State University

**E. Dates proposed to use remote system**

The start date for use of the remote system would be ASAP and would continue uninterrupted through April 30, 2007. Additional analysis through the remote system will then be needed on an interim or month to month basis (e.g., required re-analysis after co-author or reviewer input).

**F. Source of funding**

A personal check will be used for payment.

## **G. Background of study**

### **BMI, Fat Patterning, and Mortality**

Body mass index (BMI) is calculated using self-reported or measured height and weight, and routinely used in epidemiologic studies to provide an indirect means of estimating adiposity. The major reason for incorporating BMI as an estimate of total body fat in large studies relates to its low cost, feasibility, and reproducibility. Despite the fact that those who are obese have been shown to underestimate their body weight and men to overestimate their height, leading to an underestimation of BMI (1,2), studies have shown that BMI from measured height and weight is highly correlated with percent body fat (3). The first Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults (4), concluded that overweight and obesity are major risk factors for increased morbidity and mortality. The report adopted guidelines established by the World Health Organization, and defined a BMI of 25 to less than 30 kg/m<sup>2</sup> as overweight and obesity as a BMI greater than or equal to 30 kg/m<sup>2</sup>. However, these clinical guidelines for identifying overweight or obese individuals who may be at an increased risk of mortality were based predominately upon studies of younger to middle-aged populations.

Whether BMI is positively associated with mortality in older adults is controversial. Although there is a paucity of data relative to the association of overweight or obesity and their effects on all-cause or cardiovascular mortality in the elderly, the available studies do not consistently support a positive relation. The reasons for this are not entirely clear, but it may be that those who are susceptible to the deleterious effects of obesity suffer from increased mortality in middle-age leaving a healthier population of older obese adults (selective survival), and in older-age the protective effects of obesity counterbalance some negative effects (5). The potential beneficial effects may include energy reserves during times of stress, lower rates of injury due to falls, and lower rates of osteoporosis (6). However, it may also be that BMI in the elderly does not accurately estimate body fat and therefore does not correspond with a relative increase in the risk of death, as is observed in younger populations. Older adults face a progressive decline in fat-free mass and overall height shrinkage (7,8). In addition, fat mass tends to accumulate intra-muscularly and intra-abdominally with age leading to an inaccurate reflection of body fatness with the use of BMI. Therefore, additional measures of body habitus other than BMI may prove more useful as predictors of adverse health conditions, especially mortality (9,10).

Waist circumference and waist-to-hip ratio, as opposed to BMI, may be more specific indicators of total body fat and may therefore provide an improved means of determining the risk of mortality associated with obesity, especially in the elderly. Many reports have shown that abdominal or central obesity is equally important as total adiposity, and may be a better indicator of cardiovascular disease (CVD) risk (11). Waist circumference, used as a surrogate of abdominal obesity, is highly correlated

with visceral adipose tissue (12) and has been strongly linked with components of the metabolic syndrome, including glucose intolerance, hypertension, dyslipidemia, and insulin resistance (13). Few studies have evaluated the usefulness of waist circumference or waist-to-hip ratio, compared to BMI, when predicting mortality, and those that have, have been inconsistent (14-17).

#### BMI, Fat Patterning, and Mortality in a Tri-Ethnic Sample of U.S. Adults

Despite the fact that CVD is a global problem, our understanding of this disease has come largely from studies of Caucasians of European origin. Several ethnic groups predispose to develop coronary heart disease (CHD) or CVD and thus have a higher prevalence of these diseases. Racial/ethnic disparities in cardiovascular health are among the most prominent public health problems in the U.S. In Black adults the risks of CHD and stroke have been shown to be nearly two times higher than those of other ethnic origins (18). Black men and women also appear to be particularly susceptible to high blood pressure regardless of educational level (18). Mexican American adults suffer from much higher rates of hypercholesterolemia. In 1988-1994, the prevalence of the metabolic syndrome in Mexican American men and women was approximately 12% and 50% higher than rates in white men and women, respectively (19).

There are noted racial/ethnic differences in the prevalence of obesity. Rates of obesity in the U.S. have been increasing over the last several decades across both sexes and all racial/ethnic groups; however, this rise has been especially pronounced among black women with estimates suggesting over half are obese and over 80% are overweight or obese (20). Second to black women are Mexican American women, in whom 73% are overweight and 33% are obese (20). Similar trends have been observed in men; however, for black men the acceleration in weight gain does not occur until after age 30 years.

In addition to racial/ethnic differences in the prevalence of obesity which tend to be particularly high among black and Mexican American women compared to non-Hispanic women (21), it appears that fat accumulation and body shape also differ by race/ethnicity. Individuals of South Asian ancestry have a much different distribution of body fat compared with Europeans. They have thinner limbs, which would suggest a smaller muscle mass, and greater central obesity with increased visceral adipose tissue mass (22). Several investigators have shown that blacks have less visceral fat compared to non-Hispanic whites of a similar level of BMI or waist circumference (23-26). Despite this decreased amount of visceral fat, which is believed to be more atherogenic and has a greater tendency to lead to insulin resistance, blacks have higher rates of CHD and type 2 diabetes. This finding leads one to question whether blacks have similar risks of disease as whites of a similar total body fat. The paucity of data relating visceral fat or body circumferences to disease in blacks has limited our

understanding of this relationship. To the best of our knowledge no study has measured visceral fat in Mexican Americans.

Despite the fact that obesity is more common in Blacks than in white populations, obesity with respect to mortality is more lethal for whites. Calle et al. (27) reported that nonsmoking white men and women with no history of disease at the highest level of BMI had relative risks of mortality of 2.58 and 2.00, respectively. Black men and women at the highest BMI had much lower nonsignificant risks for death (1.35 and 1.21). Similar results have been found in the American Cancer Society Prevention Study (28) as well as the Charleston Heart Study (29). To our knowledge, the relation of adiposity with mortality has not been reported in Mexican Americans.

### **1. Research questions**

Study #1: Associations of BMI, Waist Circumference, and Waist-to-Hip Ratio with Mortality

Research Question 1. What are the associations of BMI, waist circumference, and waist-to-hip ratio with all cause and cardiovascular disease mortality?

Question 2. What are the associations of BMI, waist circumference, and waist-to-hip ratio with all cause and cardiovascular disease mortality in younger and older adults?

Study #2: BMI, Waist Circumference, and Waist-to-Hip Ratio as predictors of mortality in a tri-ethnic sample of U.S. adults

Research Question 1. What are the associations of BMI, waist circumference, and waist-to-hip ratio with all cause and cardiovascular disease mortality in Black, Mexican American, and white adults?

### **2. Public health benefits**

The epidemic of obesity among US adults is a major public health problem. Estimating the health risks associated with this increase in obesity is of primary importance. This research will contribute significantly to the public health literature by estimating the risk of death associated with being underweight, overweight, and obese as defined by BMI. In addition, the associations of additional measures of adiposity (waist circumference and waist-to-hip ratio) that have been understudied as predictors of death will be tested to determine if they add clinical utility when evaluating the risk of mortality.

## H. A summary of the data requirements for the proposed research along with an explanation of why the data are needed for the proposed study

### 1. Identification of cases to be included in the analytic file

The mortality file from NHANES III is requested to be merged with a dataset supplied by the researcher. The supplied dataset includes information contained within the publicly available NHANES III data downloaded from the CDC website.

### 2. Identification of variables to be included in the analytic file

<b><u>Variable</u></b>	<b><u>Variable Description</u></b>
SEQN	NHANES III sequence number
ELIGSTAT	Eligibility status for mortality follow-up
MORTSTAT	Final mortality status
MORTSRCE	Final mortality source
DODMONTH	Month of death
DODDAY	Day of death
DODYEAR	Year of death
AGEDEATH	Age at death
AGEPRALV	Age when last presumed alive
CAUSEAVL	Cause of death data available
ICD_9REV	Underlying cause of death code ICD-9
ICD_10REV	Underlying cause of death code ICD-10
UCOD_282 (ICD-9)	282 Underlying cause of death recode groups 1986-1998
UCOD_72 (ICD-9)	72 Underlying cause of death recode groups 1986-1998
UCOD_34 (ICD-9)	34 Underlying cause of death recode groups 1986-1998
UCOD_358 (ICD-10)	358 Underlying cause of death recode groups 1999-2000
UCOD_113 (ICD-10)	113 Underlying cause of death recode, all years (ICD-10)
UCOD_39 (ICD-10)	39 Underlying cause of death recode groups 1999-2000
DODMONTH	Month of birth
DOBDAY	Day of birth
DOBYEAR	Year of birth
MECMONTH	Month of MEC exam
MECDAY	Day of MEC exam
MECYEAR	Year of MEC exam
AGEMEC	Age at MEC exam
HMEMONTH	Month of home exam
HOMEXDAY	Day of home exam



HOMEXYEAR	Year of home exam
AGEHOMEX	Age at home exam

3. Data to be supplied by the researcher and merged with NCHS data.

A SAS dataset containing the adult participants of the physical exam conducted during NHANES III will be supplied by the researcher to merge with the mortality file housed at the RDC. A complete data dictionary detailing the variables included in this supplied dataset can be found in the appendix. The SAS dataset was downloaded from the NHANES website and appropriately scored to include the variables of interest in the analyses.

4. A description of why publicly available data are insufficient.

Publicly available mortality information for NHANES III participants is not available. Therefore, if researchers are interested in studying the effects of obesity on the risk of death using NHANES III participants, they must coordinate their efforts through the RDC.

## I. Methods

### 1. Analytic strategy and statistical methods to be used

#### *Study #1*

Study one will utilize a prospective observational design to compare the relations of BMI, waist circumference, and waist-to-hip ratio with mortality. Participants will include men and women aged  $\geq 45$  years who completed the physical examination as part of NHANES III, 1988-1994. Body weight and standing height were measured to the nearest 0.1 lb and cm using a Toledo electronic self-zeroing scale and Seca stadiometer while participants were wearing undergarments, a paper robe, and foam slippers. BMI will be calculated as measured weight in kg divided by the square of measured height in m. Waist circumference was measured at the level of the iliac crest at the end of a normal expiration. Hip circumference was measured at the widest circumference around the buttocks. All circumference measures were recorded to the nearest mm. Waist-to-hip ratio will be calculated as waist divided by hip circumference. To account for the potential for non-linear relations with mortality and to facilitate interpretation, categorical variables (quintiles) will be formed based upon the sex-specific distribution of BMI and circumference measures in the total population.

Mortality information, including vital status (alive, deceased), date, and underlying cause of death assigned according to the *International Classification of Diseases, 10<sup>th</sup> Revision* (ICD-10) for those who died during the follow-up period

(1988-2000) will be obtained from the Research Data Center of the National Center for Health Statistics (NCHS). NCHS has linked the personal identifiers of all adult participants of NHANES III with the National Death Index to provide information on vital status until December 31, 2000. Therefore, the follow-up time for this study will range from 6 to 12 years. The primary endpoint of interest will be the time to mortality from all causes. The time to death from CVD, defined as ICD-10 codes I00 through I99, will serve as a secondary outcome.

Confounders will include age, race/ethnicity, education, alcohol use, smoking status, physical activity, and for women, menopausal status and use of hormone therapy. Race/ethnicity was based upon self-reported race and ethnicity, and will be categorized as non-Hispanic white, non-Hispanic Black, Mexican American, and other. The other category will include all Hispanics, regardless of race, who are not Mexican American, and also all non-Hispanics from racial groups other than white or Black. Educational level will be based upon the highest grade or year of school completed and will be categorized as less than high school, high school, some college, and a college degree. To capture long term alcohol use, the consumption frequency of alcoholic beverages (beer, wine, liquor) during the past month was assessed with the use of a food frequency questionnaire. Participants will be classified into those who consumed none of these three alcoholic beverages, those who drank up to once per week, more than once per week but less than once per day, and those who drank alcohol once per day or more. The history of cigarette, cigar, and pipe smoking was assessed and will be used to categorize participants as a current, past, or never tobacco user. A standardized questionnaire was used to determine the type and frequency of physical activities performed over the past 30 days. These activities included walking, jogging or running, biking, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, as well as a category for other activities. A metabolic frequency score will be created by multiplying the metabolic equivalent (MET) for each activity (30) by its reported frequency and summing across all activities. One MET is approximately equal to the energy expended during quiet sitting or about 1 kcal/kg/hr for a 60 kg person. Women will be defined as postmenopausal if they report not having had a period during the previous 12 months, a hysterectomy, both ovaries removed, or if they were 70 years of age or older at baseline. Hormone replacement therapy (HRT) will be based upon self-report (current user, not current user).

Pre-existing disease at study entry will be accounted for since the presence of disease is likely to influence body weight and the risk of mortality. These chronic conditions will include CVD, cancer, respiratory disease, and diabetes. CVD will be defined as physician diagnosed myocardial infarction, congestive heart failure, stroke, or angina pectoris. A series of questions were used to assess angina. Participants will be defined as having angina if they reported that they had ever had any chest pain or discomfort, that they got the pain or discomfort while walking uphill or in a hurry, that the pain caused them to stop or slow down, that the pain was relieved by standing still, that the pain was relieved within 10 minutes, and that the pain was precordial or radiated along the left arm. Participants who reported they never walked uphill or in a

hurry will be classified as having angina if they meet the other criteria. Cancer will include a previous diagnosis except non-melanoma skin cancer. Respiratory disease will be described as asthma, chronic bronchitis, or emphysema. Diabetes will be based upon a previous physician's diagnosis of type 1 or 2 diabetes, use of diabetes medications, or fasting glucose  $\geq 126$  mg/dL.

### *Statistical Analyses*

Proportional hazards regression models will be fit to evaluate the associations of BMI, waist circumference, and waist-to-hip ratio with mortality. The primary study endpoint will include time to mortality from all causes. Time to death from CVD will serve as a secondary endpoint. Participants will be censored at their date of death or December 31, 2000, depending upon vital status. Compliance with the proportional hazards assumption will be evaluated using graphical techniques. At least two sets of adjusted models will be examined, including those that are adjusted for confounders, and the additional adjustment for self-reported chronic disease at baseline. Since the association of body composition with mortality may differ by sex, all analyses will be performed separately for men and women. A second set of analyses will be performed among younger and older adults, since waist circumference and waist-to-hip ratio may provide a more specific indicator of body fat than BMI among older adults (14,16). A sensitivity analysis will be performed to account for the potential of confounding by occult disease by excluding deaths occurring early in follow-up. SAS (Cary, NC) and SUDAAN (Research Triangle Park, NC) will be used to analyze the data.

### *Study #2*

A prospective observational design will be used to compare the relations of BMI, waist circumference, and waist-to-hip ratio with mortality in Black, Mexican American, and white adults. The inclusion of participants will be limited to men and women from these racial/ethnic groups aged  $\geq 45$  years who completed the physical examination as part of NHANES III, 1988-1994. Participation from other racial/ethnic groups was too infrequent to calculate stable estimates of association within these populations. Body weight and standing height were measured to the nearest 0.1 lb and cm using a Toledo electronic self-zeroing scale and Seca stadiometer while participants were wearing undergarments, a paper robe, and foam slippers. BMI will be calculated as measured weight in kg divided by the square of measured height in m. Waist circumference was measured at the level of the iliac crest at the end of a normal expiration. Hip circumference was measured at the widest circumference around the buttocks. All circumference measures were recorded to the nearest mm. Waist-to-hip ratio will be calculated as waist divided by hip circumference. To account for the potential for non-linear relations with mortality and to facilitate interpretation, categorical variables (quartiles) will be formed based upon the sex-specific distribution of BMI and circumference measures in the total population.

Mortality information, including vital status (alive, deceased), date, and underlying cause of death assigned according to the *International Classification of Diseases, 10<sup>th</sup> Revision* (ICD-10) for those who died during the follow-up period (1988-2000) will be obtained from the Research Data Center of the National Center for Health Statistics (NCHS). NCHS has linked the personal identifiers of all adult participants of NHANES III with the National Death Index to provide information on vital status until December 31, 2000. Therefore, the follow-up time for this study will range from 6 to 12 years. The primary endpoint of interest will be the time to mortality from all-causes. The time to death from CVD, defined as ICD-10 codes I00 through I99, will serve as a secondary outcome.

Confounders will include age, education, alcohol use, smoking status, physical activity, and for women, menopausal status and use of hormone therapy. Educational level will be based upon the highest grade or year of school completed and will be categorized as less than high school, high school, some college, and a college degree. To capture long term alcohol use, the consumption frequency of alcoholic beverages (beer, wine, liquor) during the past month was assessed with the use of a food frequency questionnaire. Participants will be classified into those who consumed none of these three alcoholic beverages, those who drank up to once per week, more than once per week but less than once per day, and those who drank alcohol once per day or more. The history of cigarette, cigar, and pipe smoking was assessed and will be used to categorize participants as a current, past, or never tobacco user. A standardized questionnaire was used to determine the type and frequency of physical activities performed over the past 30 days. These activities included walking, jogging or running, biking, swimming, aerobics, dancing, calisthenics, gardening, lifting weights, as well as a category for other activities. A metabolic frequency score will be created by multiplying the metabolic equivalent (MET) for each activity (30) by its reported frequency and summing across all activities. One MET is approximately equal to the energy expended during quiet sitting or about 1 kcal/kg/hr for a 60 kg person. Women will be defined as postmenopausal if they report not having had a period during the previous 12 months, a hysterectomy, both ovaries removed, or if they are 70 years of age or older at baseline. Hormone replacement therapy (HRT) will be based upon self-report (current user, not current user).

Pre-existing disease at study entry will be accounted for since the presence of disease is likely to influence body weight and the risk of mortality. These chronic conditions will include CVD, cancer, respiratory disease, and diabetes. CVD will be defined as physician diagnosed myocardial infarction, congestive heart failure, stroke, or angina pectoris. A series of questions were used to assess angina. Participants will be defined as having angina if they reported that they had ever had any chest pain or discomfort, that they got the pain or discomfort while walking uphill or in a hurry, that the pain caused them to stop or slow down, that the pain was relieved by standing still, that the pain was relieved within 10 minutes, and that the pain was precordial or radiated along the left arm. Participants who reported they never walked uphill or in a

hurry will be classified as having angina if they meet the other criteria. Cancer will include a diagnosis of leukemia or cancer except non-melanoma skin cancer. Respiratory disease will be described as asthma, chronic bronchitis, or emphysema. Diabetes will be based upon a previous physician's diagnosis of type 1 or 2 diabetes, use of diabetes medications, or fasting glucose  $\geq$  126 mg/dL.

### *Statistical Analyses*

Proportional hazards regression models will be fit to evaluate the associations of BMI, waist circumference, and waist-to-hip ratio with mortality among Black, Mexican American, and white men and women. The primary endpoint of interest will be the time to mortality from all-causes. The time to death due to CVD will serve as a secondary outcome. Participants will be censored at their date of death or December 31, 2000, depending upon vital status. Compliance with the proportional hazards assumption will be evaluated using graphical techniques. At least two sets of adjusted models will be examined; those adjusted for confounders, and the additional adjustment for self-reported chronic disease at baseline. Since the association of body composition with mortality may differ by sex, all analyses will be performed separately for men and women. A sensitivity analysis will be performed in an attempt to account for confounding by occult disease by excluding those who died during the first few years of follow-up. SAS (Cary, NC) and SUDAAN (Research Triangle Park, NC) will be used to analyze the data.

## **2. Software requirements**

SAS (Cary, NC) and SUDAAN (Research Triangle Park, NC) will be used to analyze the data.

## **J. Disclosure review**

### Study #1

In study one means±standard deviations will be used for continuous variables and frequencies for discrete variables to describe the characteristics of the study sample according to sex and BMI. These demographic characteristics will include age, weight, height, waist circumference, waist-to-hip ratio, race/ethnicity, smoking status, alcohol use, physical activity, education, menopausal status, estrogen use, CVD, respiratory disease, cancer, and diabetes. Age-adjusted absolute all cause and CVD death rates will be calculated with SUDANN PROC RATIO for each category of BMI, waist circumference, and waist-to-hip ratio. The absolute death rates will be presented separately for men and women. As noted proportional hazards regression will be used to describe the association of BMI, waist circumference, and waist-to-hip ratio with all-cause and CVD mortality; hazard ratios (and 95% confidence intervals) adjusted for confounders and additionally for pre-existing disease status will be

reported. Additional analyses will report adjusted hazard ratios among younger and older men and women.

Example of output:

Body mass index* in 1986	Overall			Cardiovascular disease		
	No. of deaths	Multi-variate RR†,‡	95% CI†	No. of deaths	Multi-variate RR‡	95% CI
<b>Age &lt;65 years</b>						
<23	62	1.0		8	1.0	
23.0–24.9	112	1.21	0.88, 1.65	9	0.72	0.28, 1.88
25.0–26.9	110	1.19	0.87, 1.63	22	1.76	0.78, 3.97
27.0–29.9	87	1.39	1.00, 1.93	19	2.26	0.98, 5.21
≥30.0	57	1.97	1.36, 2.84	15	3.92	1.64, 9.36
<i>p</i> for trend			<0.001			<0.001
<b>Age ≥65 years</b>						
<23	61	1.0		11	1.0	
23.0–24.9	67	0.69	0.48, 0.99	11	0.58	0.25, 1.38
25.0–26.9	75	0.75	0.53, 1.08	17	0.95	0.43, 2.11
27.0–29.9	50	0.83	0.56, 1.23	11	0.94	0.39, 2.24
≥30.0	19	0.85	0.49, 1.46	3	0.70	0.19, 2.66
<i>p</i> for trend			0.59			0.98

## Study #2

In study two means±standard deviations will be used for continuous variables and frequencies for discrete variables to describe the characteristics of the study sample according to sex and race/ethnicity. These demographic characteristics will include age, weight, height, waist circumference, waist-to-hip ratio, smoking status, alcohol use, physical activity, education, menopausal status, estrogen use, CVD, respiratory disease, cancer, and diabetes. Age-adjusted absolute all cause and CVD death rates will be calculated with SUDANN PROC RATIO for each category of BMI, waist circumference, and waist-to-hip ratio. The absolute death rates will be stratified by sex and race/ethnicity. As noted proportional hazards regression will be used to describe the association of BMI, waist circumference, and waist-to-hip ratio with all-cause and CVD mortality by sex and race/ethnicity; hazard ratios (and 95% confidence intervals) adjusted for confounders and additionally for pre-existing disease status will be reported.

Example of output:

	Waist/hip ratio									
	Men					Women				
	<0.925	0.925- 0.961	0.962- 0.999	>1.00	<i>p</i> for trend	<0.835	0.835- 0.894	0.895- 0.954	>0.954	<i>p</i> for trend
Overall										
No. of cases	45	49	77	92		14	21	32	53	
RR†	1.0	1.06	1.70	1.80	0.002	1.0	1.13	1.57	2.10	0.008
95% CI†		0.7-1.6	1.2-2.5	1.2-2.6			0.6-2.2	0.8-3.0	1.1-3.8	
African-American										
No. of cases	19	14	16	13		3	9	12	29	
RR	1.0	1.08	1.87	1.68	0.064	1.0	2.07	2.33	4.22	0.019
95% CI		0.5-2.2	0.96-3.6	0.8-3.4			0.6-7.7	0.7-6.3	1.3-14	
White										
No. of cases	26	35	61	79		11	12	20	24	
RR	1.0	1.07	1.67	1.82	0.002	1.0	0.87	1.39	1.43	0.194
95% CI		0.6-1.8	1.1-2.6	1.2-2.8			0.4-2.0	0.7-2.9	0.7-3.0	

**K.****1. Curriculum vitae – JARED P. REIS, PhD(c)****EDUCATION**

- Present      **Ph.D. candidate** in Epidemiology  
University of California, San Diego / San Diego State University  
Academic advisors: Caroline Macera, Ph.D., Barbara Ainsworth, Ph.D.,  
M.P.H.  
Dissertation: The influence of adiposity on mortality and  
cardiovascular risk
- 2003          **M.S. in Exercise Science**, University of South Carolina  
Arnold School of Public Health, Columbia, S.C.  
Academic advisors: J. Larry Durstine, Ph.D., Barbara Ainsworth,  
Ph.D., M.P.H.  
Thesis: Pedometer-determined physical activity during and after a  
phase II cardiac rehabilitation program
- 2000          **B.S. in Exercise Science**, *University of Rhode Island*

**EMPLOYMENT HISTORY**

- 2005-present    Epidemiologist, Naval Health Research Center, San Diego, C.A.  
2005-2006      Teaching Assistant, San Diego State University, San Diego, C.A.  
2003-2005      Graduate Research Assistant, San Diego State University, San Diego,  
C.A.  
2002-2003      Teaching Assistant, University of South Carolina, Columbia, S.C.  
2001-2004      Graduate Research Assistant, University of South Carolina, Columbia,  
S.C.  
2000            Clinical Exercise Physiologist, Richland Palmetto Hospital, Columbia,  
S.C.  
2000            Clinical Exercise Physiologist-Intern, South County Hospital,  
Wakefield, R.I.  
1998-2000      Certified Personal Trainer, University of Rhode Island, Kingston, R.I.

**PROFESSIONAL AFFILIATIONS**

- 2005-present    Society for Epidemiologic Research  
2003-present    Southwest Chapter of the American College of Sports Medicine  
2002-present    American College of Sports Medicine  
2002-2003      Southeast Chapter of the American College of Sports Medicine  
1999-2004      Kappa Delta Pi—International Honor Society in Education  
1999-2000      Northeast Chapter of the American College of Sports Medicine



1998-2000 American Council on Exercise

### **SCHOLARLY ACTIVITIES**

Peer Reviewer

2005-present Preventive Medicine

2003-present Medicine & Science in Sports & Exercise

### **RESEARCH INTERESTS**

- Etiology and prevention of cancer and cardiovascular disease
- Physical activity, obesity, and health
- Measurement of physical activity
- The role of biomarkers in epidemiologic research

### **TEACHING EXPERIENCE**

2006 Graduate Teaching Assistant  
Graduate School of Public Health, San Diego State University

#### **Course taught:**

Fall 2006 PH 302 Epidemiology of Communicable and Chronic Diseases

2005 Graduate Teaching Assistant  
Dept. of Exercise and Nutritional Sciences, San Diego State University

#### **Course taught:**

Spring 2005 ENS 434 Promoting Exercise Behavior

2002-2003 Graduate Teaching Assistant  
Department of Exercise Science, University of South Carolina

#### **Courses taught:**

Spring 2003 EXSC 531 Physiology of Muscular Activity Laboratory II

Fall 2002 EXSC 530 Physiology of Muscular Activity Laboratory I

## PUBLICATIONS AND PRESENTATIONS

### Book Chapter:

1. LaMonte M.J., Ainsworth B.E., REIS J.P. Measuring physical activity. In: Wood T.M., Zhu W., eds. 2006. *Measurement Theory and Practice in Kinesiology*. Champaign, IL: Human Kinetics Publishers.

### Published/In Press Journal Articles:

1. Tudor-Locke C., Williams J.E., **REIS J.P.**, Pluto D. Utility of pedometers for assessing physical activity: Convergent validity. *Sports Medicine*. 2002;32(12):795-808.
2. **REIS J.P.**, Bowles H.R., Ainsworth B.E., DuBose K.D., Smith S., Laditka J.N. Nonoccupational physical activity by degree of urbanization and US geographic region. *Medicine & Science in Sports & Exercise*. 2004;36(12):2093-2098.
3. VanVrancken C., Bopp C., **REIS J.P.**, DuBose K.D., Kirtland K., Ainsworth B.E. The prevalence of leisure-time physical activity among diabetics in South Carolina. *The Southern Medical Journal*. 2004;Feb;97(2):141-4.
4. Tudor-Locke C., Williams J.E., **REIS J.P.**, Pluto D. Utility of pedometers for assessing physical activity: Construct validity. *Sports Medicine*. 2004;34(5):281-291.
5. Tudor-Locke C., Ham S., Macera C.A., Ainsworth B.E., Kirtland K.A., **REIS J.P.**, Kimsey C.D. Jr. Descriptive epidemiology of pedometer-determined physical activity. *Medicine & Science in Sports & Exercise*. 2004;36(9):1567-1573.
6. Tudor-Locke C., Lind K.A., **REIS J.P.**, Ainsworth B.E., Macera C.A. Using a pedometer in a self monitoring survey to assess physical activity. *Field Methods*. 2004;16(4):422-438.
7. Tudor-Locke C., Bassett D.R. Jr., Swartz A., Strath S., Parr B., **REIS J.P.**, DuBose K.D., Ainsworth B.E. A preliminary study of one year of pedometerself-monitoring. *Annals of Behavioral Medicine*. 2004;Dec;28(3):158-62.
8. Tudor-Locke C., Burkett L., **REIS J.P.**, Ainsworth B.E., Macera C.A., Wilson D.K. How many days of pedometer monitoring predict weekly physical activity? *Preventive Medicine*. 2005 Mar;40(3):293-298.

9. **REIS J.P.**, DuBose K.D., Ainsworth B.E., Macera C.A., Yore M.M. Reliability and validity of the Occupational Physical Activity Questionnaire. *Medicine & Science in Sports & Exercise*. 2005;38(12):2075-2083.
10. Ainsworth B.E., Sallis J.F., Jones D.A., **REIS J.P.**, Addy C.L., Bowles H.R., Macera C.A., Bull F.C., Kohl H.W. Neighborhood environment and physical activity: A national survey of U.S. adults. *American Journal of Preventive Medicine*. *In press*.
11. Ainsworth B.E., Macera C.A., Jones D.A., **REIS J.P.**, Addy C.L., Bowles H.R., Kohl H.W. Comparison of the 2001 BRFSS and the Short IPAQ Physical Activity Questionnaires. *Medicine & Science in Sports & Exercise*. 2006;38(9):1584-1592.
12. Ham S.A., **REIS J.P.**, Strath S.J., DuBose K.D., Ainsworth B.E. Discrepancies between methods of identifying objectively determined physical activity. *Medicine & Science in Sports & Exercise*. *In press*.
13. Marshall S.J., Jones D.A., Ainsworth B.E., **REIS J.P.**, Levy S., Macera C.A. Race/ethnicity and leisure time physical inactivity: moderating effects of social class and occupational physical activity. *Medicine & Science in Sports & Exercise*. *In press*.
14. DuBose K.D., Edwards S., Ainsworth B.E., **REIS J.P.**, Slattery M.L. Validation of a historical physical activity questionnaire in middle-aged women. *Journal of Physical Activity and Health*. *In press*.

#### **Journal Articles-In Progress:**

1. Macera C.A., Rauh M.J., Trone D.W., **REIS J.P.**, Shaffer R.A. Activity related injuries among women in military, civilian, and competitive settings: Are there common risk factors? Target journal: *British Journal of Sports Medicine*. Under review.
2. **REIS J.P.**, Macera C.A., Ainsworth B.E., Jones D.A. Prevalence of total walking in the United States: Results of a national survey, 2002-2003. Target journal: *Medicine & Science in Sports & Exercise*.
3. **REIS J.P.**, von Muhlen D.G., Kritz-Silverstein D., Wingard D. Barrett-Connor E. Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults. Target journal: *Diabetes Care*. Under review.
4. **REIS J.P.**, Trone D.W., Macera C.A. Factors associated with discharge from Marine Corps basic training. Target Journal: *Military Medicine*. Under review.

5. Ham S.A., Yore M.M., Ainsworth B.E., Kruger J., **REIS J.P.**, Kohl H.W., Macera C.A. Reliability and Validity of a Short Multiple-Domain Physical Activity Questionnaire. Target journal: *Medicine & Science in Sports & Exercise*.
6. Ainsworth B.E., Sallis J.F., Jones D.A., **REIS J.P.**, Addy C.L., Macera C.A., Kohl H.W. Associations between the neighborhood environment and self-reported walking: Results from a U.S. national survey. Target journal: *Preventive Medicine*.
7. Yore M.M, Ham S.A., Ainsworth B.E., Kruger J., **REIS J.P.**, Kohl H.W., Macera C.A. Reliability and validity of the instrument used in BRFSS to assess physical activity. Target journal: *Medicine & Science in Sports & Exercise*. Under review.
8. Taylor M.K., Sausen K.P., Mujica-Parodi L.R., Potterat E., **REIS J.P.** Physiologic stress reactivity to military survival training. Target journal: *Aviation, Space, and Environmental Medicine*.

#### **Technical Report:**

1. Yore M.M., Ham S., Kohl H.W., Kruger J., Ainsworth B.E., Macera C.A., **REIS J.P.**, Strath S. Evaluation of the Behavioral Risk Factor Surveillance System – Physical Activity Indicators. Division of Nutrition and Physical Activity, Centers for Disease Control and Prevention, Summer 2004.

#### **Conference Papers:**

1. **REIS J.P.**, LaMonte M.J., Ainsworth B.E., Durstine J.L. C-reactive protein and cardiorespiratory fitness in an adult population. *Medicine & Science in Sports & Exercise* 2003;35(5 Suppl):S361.
2. Taylor J.K., Grandjean P.W., DuBose K.D., LaMonte M.J., Davis P.G., **REIS J.P.**, Ainsworth B.E., Durstine J.L. Triglyceride concentrations, LDL particle size & profile scores in women: the Cross Cultural Activity Participation Study. *Medicine & Science in Sports & Exercise* 2003;35(5 Suppl):S468.
3. Grandjean P.W., Taylor J.K., DuBose K.D., LaMonte M.J., Davis P.G., **REIS J.P.**, Ainsworth B.E., Durstine J.L. Triglyceride concentrations, HDL particle size, and HDL profile scores in women: the Cross-Cultural Activity Participation Study. *Medicine & Science in Sports & Exercise* 2003;35(5 Suppl):S460.

4. LaMonte M.J., Durstine J.L., Szymanski L.M., DuBose K.D., Davis P.G., **REIS J.P.**, Ainsworth B.E. Cardiorespiratory fitness and hemostatic factors: the Cross-Cultural Activity Participation Study. *Medicine & Science in Sports & Exercise* 2003;35(5 Suppl):S365.
5. Ham S.A., Bassett D.R., **REIS J.P.**, Strath S., DuBose K.D., Jones D.A., Ainsworth B.E., Kohl H.W. Defining relative intensity physical activity bouts from accelerometer data. *Medicine & Science in Sports & Exercise* 2003;35(5 Suppl):S615.
6. Lemay K., **REIS J.P.**, DuBose K.D., Bowles H.R. Feasibility of concurrent heart rate and CSA accelerometer assessment. Second Place, Undergraduate Research Seminar, Department of Exercise Science, University of South Carolina. May 2003.
7. Tudor-Locke C., Ham S., Macera C., Ainsworth B.E., Kirtland K., **REIS J.P.**, Kimsey C.D. Descriptive epidemiology of pedometer-determined physical activity. Presented at the *North American Association for the Study of Obesity*, October 2003.
8. **REIS J.P.**, Durstine J.L., Ainsworth B.E., Wilcox S., Tudor-Locke C.E. Ambulatory activity during and after phase II cardiac rehabilitation. Presented at the *Southwest Chapter of the American College of Sports Medicine* annual meeting, Las Vegas NV, November 2003.
9. Ainsworth B.E., Jones D.A., Macera C.A., **REIS J.P.**, Addy C.L., Bull F.C., Pratt M. Comparison of the BRFSS Physical Activity Module and the International Physical Activity Questionnaire (IPAQ). *Medicine & Science in Sports & Exercise* 2004;36(5 Suppl):S110-S111.
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2. Letter from dissertation committee chair, Caroline A. Macera, PhD

December 13, 2006

Research Data Center  
National Center for Health Statistics  
3311 Toledo Rd.  
Suite 4113  
Hyattsville, MD 20782

To Whom It May Concern:

I am writing this letter on behalf of Jared Reis, who is a PhD candidate in Epidemiology at San Diego State University. Jared is completing this project to fulfill dissertation requirements for his doctoral program. He will be conducting this research under my direct supervision as his dissertation committee chair. I have full confidence in his abilities to work with the RDC in carrying out the research described in this application. Please do not hesitate to contact me if you have any questions or concerns.

Sincerely,

Caroline A. Macera, PhD  
Professor of Epidemiology  
Graduate School of Public Health  
San Diego State University  
619-594-3813 (office)  
cmacera@mail.sdsu.edu



**3. Data dictionary – Requesting NHANES III mortality file in SAS format to be linked with researcher supplied data using SEQN as the matching variable.**

<u>Variable</u>	<u>Variable Description</u>
SEQN	NHANES III sequence number
ELIGSTAT	Eligibility status for mortality follow-up
MORTSTAT	Final mortality status
MORTSRCE	Final mortality source
DODMONTH	Month of death
DODDAY	Day of death
DODYEAR	Year of death
AGEDEATH	Age at death
AGEPRALV	Age when last presumed alive
CAUSEAVL	Cause of death data available
ICD_9REV	Underlying cause of death code ICD-9
ICD_10REV	Underlying cause of death code ICD-10
UCOD_282	282 Underlying cause of death recode groups 1986-1998 (ICD-9)
UCOD_72	72 Underlying cause of death recode groups 1986-1998 (ICD-9)
UCOD_34	34 Underlying cause of death recode groups 1986-1998 (ICD-9)
UCOD_358	358 Underlying cause of death recode groups 1999-2000 (ICD-10)
UCOD_113	113 Underlying cause of death recode, All years (ICD-10)
UCOD_39	39 Underlying cause of death recode groups 1999-2000 (ICD-10)
DODMONTH	Month of birth
DOBDAY	Day of birth
DOBYEAR	Year of birth
MECMONTH	Month of MEC exam
MECDAY	Day of MEC exam
MECYEAR	Year of MEC exam
AGEMEC	Age at MEC exam
HMEMONTH	Month of home exam
HOMEXDAY	Day of home exam
HOMEXYEAR	Year of home exam
AGEHOMEX	Age at home exam

5. A description of the computer and email system to be used to receive output from the remote access system as well as security provisions established for them.

The computer that will be accessed to receive the output from the analyses is located in the home office of the principal investigator. The door to this office is locked when I am not at home. The computer is a desktop Gateway with Windows XP operating system. A complex password is required at log-on. The email address to receive output will be [jpreis@ucsd.edu](mailto:jpreis@ucsd.edu). A complex password is also required to log-on to this email system.

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