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C-Reactive Protein, Obesity, and Colorectal Cancer Mortality : a Prospective Study of the NHANES III-NDI Dataset

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C-Reactive Protein, Obesity, and Colorectal Cancer Mortality: A Prospective Study of the NHANES III-NDI Dataset

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"I would maintain that thanks are the highest form of thought, and that gratitude is happiness doubled by wonder." G.K. Chesterton

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TABLE OF CONTENTS

ABSTRACT

BACKGROUND: Chronic inflammation has been implicated in the pathogenesis of many chronic diseases, including colorectal cancer. Obesity has been identified as a risk factor for colorectal cancer via induction of a chronic state of low-grade bowel inflammation due to excessive release of inflammatory cytokines such as C-Reactive protein (CRP) by adipocytes. Prior studies have produced evidence of positive associations between CRP and colon cancer risk but none to date have assessed if elevated CRP is an independent risk factor when controlling for obesity. Also, controversy exists about which measure of adiposity best predicts risk of colon cancer. **METHODS:** We examined these questions using the National Health and Nutrition Examination Survey III (NHANES III) database linked to the National Death Index. In addition to CRP level, we studied the following four adiposity measures: body mass index, waist circumference, waist-to-hip ratio, and a new index developed by the NIH that stratifies BMI according to waist circumference. Outcome variables were: all-cause, colorectal cancer, other obesity related cancers, and all other causes. Dichotomous and Polytomous Logistic Regression were performed. **RESULTS:** CRP levels showed positive but weak correlations with adiposity measures. In the age-adjusted and multivariate Dichotomous Logistic Regression analyses, elevated CRP level was significantly associated with all-cause mortality (OR=1.63 95% CI 1.40-1.91; and OR=1.32, 95% CI 1.08-1.61; respectively.) Using age-adjusted and multivariate Polytomous Logistic Regression, elevated CRP level was associated with mortality from colorectal cancer (OR=2.72, 95% CI 1.30-5.72; OR= 2.44, 95% CI 1.20-4.94; respectively.) OR estimates did not change appreciably when adiposity measures were included in multivariate models. Further, none of the body measures of adiposity were significantly associated with cause-specific death in either age-adjusted or multivariate analyses. **CONCLUSIONS:** Our findings suggest that CRP may be an independent risk factor for all-cause and, more so, for colorectal cancer mortality. We speculate that the surprising effects related to body measures of adiposity may reflect misclassification related to the single baseline obesity measurement, taken during 1988-94, in light of the obesity epidemic that emerged during the follow-up time period. Further investigation of this relationship is warranted to determine of elevated CRP remains an independent risk factor when longitudinal adiposity history is known.

1.0 INTRODUCTION

1.1 Cancer

Cancer is a group of diseases characterized by uncontrollable cell growth and spread of abnormal cells (ACS, 2008.) Cancer is the second most common cause of death in the United States, accounting for 1 out of every 4 deaths (ACS, 2008.) 1,437,180 new cancer cases were diagnosed in the United States and 565,650 Americans died from cancer in 2008 alone (ACS, 2008.) The impact of cancer on society is seen not only in the rates of morbidity and mortality of Americans but also in terms of economic consequences as well. The National Institutes of Health estimates that the overall cost of cancer in 2007 was $219 billion dollars, with $89.0 billion used for direct medical costs, $18.2 billion from indirect morbidity costs, and $112.0 billion from indirect mortality costs (ACS, 2008.) To help relieve the heavy burden, the U.S. Department of Health and Human Services identified cancer as a primary focus area for research and programs to improve health in the country (DHHS, 2000.)

Overall cancer incidence and death rates have decreased steadily in the United States over the past few decades due to better screening techniques and advances in treatment methodologies. Yet, it may be possible to prevent or delay certain cancers as it has been estimated that two-thirds of cancers are caused by modifiable risk factors such as tobacco use, alcohol use, overweight, physical inactivity, and unprotected exposure to ultraviolet rays (ACS, 2008.) Furthermore, overall rates of cancer are expected to rise as the population ages. Also, there is some speculation that as more

people adopt habits and lifestyles which confer greater risk, cancer is expected to overtake cardiovascular disease as the leading cause of death worldwide by 2010 (IARC, 2008.) Hence, it is important that research on the modifiable risk factors and underlying mechanisms of cancer be advanced so that health professionals can develop effective practices to prevent and treat cancer.

1.2 Inflammation and Cancer

An emerging theory linking behavioral risk factors with cancer development postulates that chronic, systemic inflammation contributes to the carcinogenic process by promoting cellular injury and proliferation, processes that can produce a favorable environment for genetic mutations to occur (Helzlsouer et al., 2006.) The link between cancer and inflammation was first postulated in 1863 by Virchow who speculated that the origin of cancer was at sites of chronic inflammation (Hong et al., 2007.) Studies of chronic inflammation and cancer have provided promising evidence that individuals with inflammatory diseases are at greater risk for developing certain types of cancer specific to the site of inflammation, such as colorectal cancer among those with irritable bowel diseases, liver cancer among chronic Hepatitis C sufferers, and stomach cancer among those with chronic ulcers (Bernstein, 2006; Sherman, 2006; Schottenfeld et al., 2006.) Recent studies have shown that inflammatory proteins may induce repeated local cellular injury through oxidative damage which, in turn, may result in genetic mutations or disruption of the formation of proteins involved in DNA repair and apoptosis (Lu et al., 2006; Peisajovich et al, 2008; Heikkila et al., 2009.) These findings suggest that chronic inflammation may play a causal role in malignancy as well as in progression.

A number of markers have been identified as useful tools to measure chronic systemic inflammation. C-Reactive Protein (CRP), an acute-phase reactant produced by the liver and adipocytes, has emerged as a reliable, non-specific serologic marker of inflammation (Helzlsouer et al., 2006.) CRP is an innate opsonin, a protein that recognizes microbes and other potentially harmful matter inside the body and promotes their uptake and destruction by immune cells (Peisajovich et al., 2008.) CRP levels in the body may rise in response to many factors, including the presence of acute conditions such as burns and heart attacks or chronic conditions such as arthritis and diabetes. There is also evidence of variation in CRP level due to polymorphisms in genes that code for CRP production (Black et al., 2004; Heikkila et al., 2009.) The association of elevated CRP levels with outcomes such as cardiovascular disease, type II diabetes, and, most recently, certain types of cancer, has created growing interest in ascertaining how inflammation might contribute to etiology (Danesh et al., 2004; Peisajovich et al., 2008; Heikkila et al., 2009; Grootendorst et al., 2007.)

Several different theories have been proposed to explain why high CRP levels are associated with increased risk for cancer incidence. First, CRP could become elevated when the tissue surrounding a growing tumor becomes inflamed due to infringement upon the organ (Peisajovich et al., 2008.) Second, CRP elevation could be related to immune system response to tumor antigens which may be reflected by elevated systemic inflammation (Balkwill et al., 2001.) Another theory is that the production of inflammatory mediators such as prostaglandins or COX-2 by cancer cells may stimulate CRP production (Heikkila et al., 2007.) Lastly, a rise in CRP also could be a response to pre-malignant lesions (Peisajovich et al., 2008.) The temporal

significance of elevated markers of systemic inflammation has yet to be determined. A number of prospective studies, however, collected baseline measurements of CRP several years before the diagnosis of cancer and have provided evidence that CRP levels were elevated before any measurable signs of cancer were detected (Helzlsouer et al., 2006; Tsilidis et al., 2008.) This finding suggests that CRP may be useful as a marker to identify individuals at risk for cancer.

In addition, it has been postulated that C-reactive protein may have prognostic value as an indicator of mortality risk. Several studies have demonstrated an association between elevated CRP and risk of overall mortality as well as cause-specific death from cardiovascular disease and cancer (Suleiman et al., 2006; Cae et al., 2007.) In a cohort study conducted by Marsik et al. (2008) of almost 275,000 individuals, a 3.3 fold risk for all-cause death was found in individuals with the highest levels of CRP compared with individuals with the lowest level of CRP; a similar yet attenuated risk was noted for individuals with moderate levels of CRP compared to individuals with low CRP, indicating a dose-response relationship.

The link between CRP and mortality has been seen in both short-term and long-term prospective studies. A study by Makita et al. (2008) following patients for a mean of only 2.7 years found an odds ratio of 2.26 for overall mortality among individuals with CRP levels greater than 1 mg/L. Koenig et al. (2008) found significant associations between CRP levels greater than 3 mg/L and overall mortality (OR=1.88), cardiovascular disease mortality (OR=2.15) and cancer mortality (OR=1.74) for individuals with a mean follow-up time of 7.1 years. Therefore, CRP shows promise as

a potential marker for predicting negative health outcomes in both short- and long-term prospective studies.

1.3 Colorectal Cancer Burden

Colorectal cancer (CRC) is the third most common cancer in the United States, with 108,070 colon cancers and 40,740 rectal cancers documented in 2008 (ACS, 2008.) An estimated 49,960 deaths among males and females resulted from colorectal cancer in 2008, making it the second most lethal cancer in the United States following lung cancer (ACS, 2008.) Colorectal cancer incidence and death has decreased during the last two decades, primarily due to better detection at early stages from increases in colonoscopy screening and improved treatment modalities. A sharp increase in colorectal cancer, however, has been observed in rapidly developing countries and among migrant populations in the U.S., consistent with long-standing evidence that environmental and lifestyle factors to play a key role in colorectal carcinogenesis (Whittemore et al., 1990; IARC, 2008.)

1.4 Behavioral Risk Factors and Mortality from Colorectal Cancer

Several factors may increase the risk of developing and dying from colorectal cancer. Age is the most prominent risk factor for colorectal cancer, with over 90% of cases being diagnosed in people 50 years and older (ACS, 2008.) Familial or personal history of colorectal cancer, polyps, or inherited genetic syndromes such as familial adenomatous polyposis or hereditary non-polyposis colorectal cancer may also be strong indicators of risk. Personal history of chronic inflammatory bowel diseases such as

Irritable Bowel Syndrome and Crohns Disease also confers risk for colorectal cancer by increasing gut permeability to allow greater exposure of colonocytes to luminal antigens (Soderholm et al., 2004.)

From a population-based perspective, the majority of risk for colon cancer, however, has been attributed to modifiable risk factors such as obesity, physical inactivity, smoking, heavy alcohol consumption, a diet high in red meat and processed foods, and inadequate dietary fiber intake (Chao et al., 2005; Park et al., 2005; Frezza et al., 2006; ACS, 2008.) These preventable risk factors play significant roles in the etiology of colorectal cancer, and it is projected that colorectal cancer rates will rise as the world realizes the consequences borne of the "Westernized" trend in globalization, which to date has been associated with concomitant increases in obesity and physical inactivity.

1.5 Adiposity and Colorectal Cancer

As mentioned, a key risk factor for colorectal cancer is obesity. A significant dilemma traditionally encountered in most studies of obesity and health outcomes is deciding which body measurement of adiposity best reflects risk of disease. Dozens of studies have evaluated the relationship of various adiposity measures (i.e. body mass index, waist circumference, waist-to-hip ratio), finding a moderate positive relationship between increasing obesity and increasing risk of CRC incidence and mortality (Russo et al., 1998; Moore et al., 2004; MacInnis et al., 2006; Pischon et al., 2006; Larsson et al., 2007; Wang et al., 2008.) Odds ratios for obesity and development of or death from colorectal cancer ranged from 1.07 to 1.79, depending on the adiposity measure used

and the population under study (Larsson et al., 2007; Moghaddam et al., 2007; Wang et al., 2008.) Crude body weight and body mass index were more strongly related to CRC incidence and death in men than in women, while waist circumference and waist-to-hip ratio were more strongly correlated with CRC incidence and death among women than among men (Russo et al., 1998; Pischon et al., 2006; Larsson et al., 2007; Wang et al., 2008.) The relationship between adiposity and risk of colon cancer appears to be stronger with advancing age and among individuals with low levels of physical activity (Moore et al., 2004.) No statistically significant relationships were found between adiposity measures and rectal cancer incidence or death among men or women (MacInnis et al., 2006; Pischon et al., 2006.)

Several hypotheses have emerged to explain the underlying mechanisms linking obesity with colorectal cancer. Two schools of thought currently dominate the research: (1) hyperinsulinemia pathway, and (2) chronic bowel inflammation by release of inflammatory cytokines from visceral adipose tissue into the lumen of the bowel (Wisse, 2004; Calabro et al., 2008; Kim K et al., 2008; Kim S et al., 2008.) Adipose tissue was long thought to be a passive storage facility for excess calories within the body (Visser et al., 1999; Fantuzzi, 2005; Calabro et al., 2008), but recent research provides evidence that adipose tissue, particularly central fat, is an active participant in regulating endocrine and pathologic processes, including immunity and inflammation (Fantuzzi, 2005; Calabro et al., 2008.) Evidence has shown that adipose tissue regularly releases cytokines (referred to as adipocytokines in this situation) such as C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Tumor Necrosis Factor-alpha (TNF-α), that create a chronic low-grade inflammatory environment in the body locations proximal to fat

cells (Visser et al., 1999; Khaodhiar et al., 2004.) Furthermore, it has been observed that macrophages tend to accumulate in the adipose tissue of obese individuals, leading to an even greater inflammatory response by prompting an increase in adipocytokine secretion by fat calls (Gunter et al., 2006.) Visceral adipose tissue, or fat cells that are located around the waist and in between abdominal organs, seems to be more active and release more cytokines than subcutaneous adipose tissue located in the extremities (Kim K et al., 2008.) Numerous studies have shown that higher adiposity measures correlate well with increased serum levels of inflammatory proteins (Fantuzzi, 2005; Kim K et al., 2008; Wee et al., 2008.) Correlations were more remarkable when measures of visceral adiposity (i.e. waist circumference) were compared with inflammatory marker levels than when measures of systemic adiposity (i.e. body mass index) were analyzed (Park H et al., 2005; Kim S et al., 2008; Wee et al., 2008.)

To illustrate the lability of this association, several prospective longitudinal studies on weight change and subsequent changes in inflammatory marker levels have produced evidence that those participants who lost weight concomitantly lowered their inflammatory marker levels and those who gained weight experienced an increase in their inflammatory marker levels (Fogarty et al., 2008; Kim K et al., 2008.) Also, regular use of non-steroidal anti-inflammatory drugs has been shown to confer a markedly decreased risk of colorectal cancer, providing evidence that chemoprevention of bowel inflammation protects against colon carcinogenesis (IARC, 1997; Grau et al., 2009.) It is postulated that the chronic bowel inflammation induced by high visceral obesity may promote an environment in which cell growth becomes dysregulated

through oxidative DNA damage, eventually overriding apoptotic controls and increasing likelihood of carcinogenesis (Gunter et al., 2006.)

1.6 C-Reactive Protein and Obesity

C-Reactive protein has been found to be a very promising biomarker for studying the relationship between obesity and inflammation (Erlinger et al., 2004.) Park et al. (2005) studied CRP levels in relation to several adiposity measures among Asian adults, finding that CRP levels correlated strongly with abdominal obesity (Spearman's coefficient for waist circumference=0.75) and moderately with other measures of obesity (Spearman's coefficient= 0.65 for crude weight, 0.69 for body mass index, and 0.68 for waist-to-hip ratio.) C-reactive protein produced more significant correlations with adiposity measures than any other inflammatory markers evaluated in the study. Similar yet divergent results for the correlation of CRP and obesity were concluded in a study of European adults by Rexrode et al. (2003.) This study also found a direct positive relationship between CRP and obesity; however, the strongest correlation observed was between CRP and body mass index, possibly indicating a difference in risk between the two demographically diverse study populations. Overall, CRP proved to be a stronger correlate of obesity than all other inflammatory markers measured in these two studies.

1.7 C-Reactive Protein and Colorectal Cancer

In addition to being a relatively consistent correlate of obesity, CRP has also been found to be a more highly associated marker for colorectal cancer risk than other inflammatory markers. A study by Il'yasova et al. (2005) examined the associations of

several inflammatory markers (C-Reactive Protein, Interleukin-6, and Tumor Necrosis Factor-alpha) with the risk of site-specific cancers and found that the association of CRP with colorectal cancer was more precise than the other two markers. Another study by Groblewska et al. (2008) found C-Reactive Protein to be a better predictor for colorectal cancer death than other inflammatory markers. Results of these studies suggest that, to date, CRP may be the most useful inflammatory marker to study when assessing risk of colorectal cancer incidence and death.

1.8 Conclusion

Ample evidence has linked higher levels of both obesity and C-Reactive Protein to increased risk for colorectal cancer incidence and death. Furthermore, C-Reactive Protein levels and adiposity measures have shown a moderate positive correlation, indicating that CRP may be linked with colorectal cancer through an obesity-induced inflammation pathway. However, it remains unknown how the relationship between CRP and obesity measures indicate risk of mortality and colorectal cancer among the National Health and Nutrition Examination Survey III (NHANES III) participants. Is CRP a risk factor for all-cause mortality, and more specifically death from colorectal cancer, independent of obesity? It is hypothesized that NHANES III participants having C-reactive protein levels greater than 0.50 mg/dL will incur a greater risk of all-cause mortality and colorectal cancer mortality than participants with normal CRP values, and that this relationship will persist after adjustment for adiposity measures. Using data from NHANES III and the National Death Index, this investigation aims to:

(1) Describe demographic and lifestyle attributes of those with normal and elevated levels of serum C-Reactive Protein,

(2) Determine whether individuals with elevated C-Reactive Protein levels have a greater risk of all-cause mortality and death from colorectal cancer compared to individuals with normal CRP levels, and,

(3) Assess whether the relationship between CRP and all-cause mortality and death from colorectal cancer is modified by controlling for different measures of obesity (body mass index, BMI-W, waist circumference, and waist-to-hip ratio.)

2.0 METHODS

2.1 Study Population

We analyzed data from the National Health and Nutrition Examination Survey III (NHANES III), the seventh of a series of studies conducted by the National Center for Health Statistics designed to estimate the nation's health status, assess the nationwide prevalence of risk factors for disease, and contribute to an understanding of disease etiology (NCHS, 1992; DHHS, 1996.) The NHANES III sample population was carefully constructed as a complex multistage probability sample to represent the total civilian non-institutionalized US population aged 2 months and older (NCHS, 1992.) 39,695 persons were selected from 81 primary sampling units to be interviewed and examined, with oversampling employed among the young, the elderly, and minorities to facilitate statistically-powered investigations of these subsamples. In two stages conducted from 1988-1994, 33,994 people were interviewed (14% non-response) and, of these, 30,818 participated in intensive physical examinations and blood draws for laboratory measures (9% non-response) at the NHANES mobile examination center (Mohadjer et al., 1996.) Additionally, because NHANES III was the first in the series

to investigate individuals older than 75 years of age, a new home examination technique was developed to minimize non-response among this population (NCHS, 1994.) Ultimately, 31,311 examinations were recorded in the NHANES III database, with due care being exercised on the part of medical examiners and laboratory personnel to ensure continuity of exam protocol and proper handling and storage of body fluid specimens (Gunter et al., 1990.) NHANES III methodologies and study participants have been described in detail elsewhere (Mohadjer et al., 1996.)

2.2 Sample Weights in NHANES III

The complex multistage probability sample employed in NHANES III requires that statistical analyses take into account: differential probabilities of selections among subgroups, bias from non-response, and need to reflect the dimensions of target population make-up (Mohadjer et al., 1996.) This adjustment is accomplished by assignment of multiple weights to each individual, thereby allowing generalization of findings to the U.S. population as a whole. Sample weighting was carried out in three stages. First, a basic weight was calculated to compensate for three factors: the individual's age/sex/race-ethnicity domain, the density stratum, and the primary sampling unit (Mohadjer et al., 1996.) Second, a weight was applied to account for non-response (Figure 1) of individuals at both the interview and examination stages after allocating non-responding individuals to classes such as race/ethnicity, age, household size, and self-reported health status (NCHS, 1992.) A third weight was applied to all survey participants based on post-stratification of the sample weights in accordance with 1990 census bureau estimates of the U.S. population (Mohadjer et al., 1996.)

Combining the basic weight, non-response adjustment weight, and post-stratification adjustment weight with a 4th weight that compensated for differences between Phase 1 (1988-1991) and Phase II (1991-1994) samples created the overall weight for each individual studied in NHANES III. For the purposes of this investigation, final weight "Final MEC+Home exam" (SAS weight code wtpfhx6) was employed to individuals who were interviewed and examined either at the mobile examination center or at home, and who were surveyed during either phase of the sampling periods (Mohadjer et al., 1996; DHHS 1996.)

2.3 NHANES III database linked with the National Death Index

In order to transform NHANES III from a cross-sectional study into a prospective study with an outcome endpoint, the National Center for Health Statistics linked the NHANES III database with mortality data records from the National Death Index (NDI) through December 31, 2000, resulting in a follow-up time for mortality status ranging from 6 to 12 years (Madans et al., 2006; NCHS, 2005.) This data linkage was performed through probabilistic matching, with one or more of these criteria sufficing to produce a match: (1) social security number, (2) first and last name, exact month of birth, year of birth within 1 year, (3) last name, first and middle initials, exact month of birth, year of birth within 1 year, (4) first and last name, exact month and day of birth, (5) last name, first and middle initials, exact month and day of birth, (6) first name, father's surname, exact month and year of birth, and (7) for females only, first name, exact month and year of birth, and last name from the survey record matching the birth surname on the NDI record (NCHS, 2005.) Mortality status of NHANES III participants could also be

determined if a death certificate was directly received by NCHS and matched with a NHANES III survey record based on name and other linkable information such as occupation (NCHS, 2006.) We used the public data files accessible on the NCHS website which included information on follow-up eligibility status, mortality status, mortality status source (NDI or death certificate), person-months of follow-up time from interview and exam, and underlying cause of death (NCHS, 2006.) Underlying cause of death was established through use of ICD-9 codes through 1998 and ICD-10 codes for 1999-2000, but final cause of death data were organized via ICD-10 codes after adjusting for changes between the coding systems (NCHS, 2006.) At the end of the follow-up period, 3,384 adult NHANES III participants were assumed to be deceased through NDI linkage (NCHS, 2005.)

2.4 Eligibility Criteria

Individuals in the NHANES III population were determined to be eligible for this study if they were 50 years of age or older, had a known mortality status, and had valid data on covariates and outcomes. Values of "blank but applicable," "blank," and "I don't know" were re-categorized as missing data. From the initial NHANES III sample of 33,994, our study included 7,589 participants with valid baseline data, laboratory assay results for CRP, and NDI mortality follow-up (Figure 1.)

2.5 Study Groups

This study compares two study groups: (1) individuals with a serum C-reactive protein (CRP) level of <.50 mg/dL (normal) and (2) individuals with a serum C-reactive

protein level of .50 mg/dL or greater (high.) This cutoff point for normal versus high C-reactive protein was employed in colon cancer studies conducted by Koike et al., (2008) and Shiu et al., (2008.) C-reactive protein was measured during the NHANES III laboratory examination (DHHS, 2007.) Serum C-reactive protein was analyzed using a fully automated Behring Nephelometer Analyzer System (Behring Diagnostics, Inc, Somerville, NJ.) Extensive details about the specific methods for obtaining C-reactive protein levels for the NHANES III population are provided elsewhere (Gunter et al., 1996.)

Participants were further classified according to three commonly used adiposity measures: body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR.) We also employed an adiposity measure developed in 1998 by the National Heart, Lung, and Blood Institute that stratifies BMI categories by waist circumference, which we refer to as BMI-W (NHLBI, 1998; Figure 3.) Body measurements were taken by trained NHANES III examiners using specified protocols (DHHS, 1996.) Body mass index was calculated by dividing an individual's weight in kilograms by height in meters squared. Categorization of BMI in our study used standard breakdowns (NHLBI 1998), as follows: [1] normal (BMI 18.5-24.9), [2] overweight (BMI 25.0-29.9) and [3] obese (BMI 30.0+.) Underweight individuals (BMI < 18.5) were excluded from analysis. Waist circumference was calculated by measuring the circumference of the abdomen in centimeters at the natural waist, around the bellybutton. Per accepted criteria (NHLBI 1998), waist circumference was classified as high if a male participant's waist circumference measured >102 cm at the bellybutton or a female participants' waist circumference measure >88 cm at the bellybutton. Waist-to-hip ratio was calculated

by dividing the waist circumference in centimeters by the hip circumference (measured at the widest point of the hips) in centimeters. A WHR greater than 1.0 was considered high for males and a WHR greater than 0.9 was considered high for females in this study (NHLBI, 1998.) As depicted in Figure 3, BMI-W consists of five categories: [1-normal] BMI (18.5-24.9) and any waist circumference); [2-increased] BMI (25.0-29.9) and waist circumference (normal); [3-high] BMI (25.0-29.9) and waist circumference (high) or BMI (30.0-34.9) and waist circumference (normal); [4-very high] BMI (30.0-34.9) and waist circumference (high) or BMI (35.0-39.9) and any waist circumference); and [5-extremely high] BMI (40.0+) and any waist circumference.

2.6 Outcomes

Mortality status (i.e., dependent variable) was categorized according to two schemes: [1] alive and deceased from any cause, and [2] alive, deceased from colorectal cancer (CRC), deceased from other obesity-related cancers (oORC), and deceased from other causes (Other.) The first scheme used the existing variable (mortstat) in the NDI-linked data file. The second was created using ICD-10 codes for underlying cause of death (ucod_113) in the NDI-linked mortality data file. The "alive" category was assigned when "mortstat"=0 and "ucod_113"=missing. The "CRC" category was assigned to values where "mortstat"=1 and "ucod_113"=023, representing codes C18-C21 (malignant neoplasms of the colon, rectum, and anus) in the ICD-10 codes (NCHS, 2006.) The "oORC" category was assigned to values where "mortstat"=1 and "ucod_113"= 025 (representing ICD-10 code C25, malignant neoplasms of the pancreas), 029 (representing ICD-10 code C50, malignant neoplasms of the breast),

031 (representing ICD-10 codes C54-55, malignant neoplasms of the corpus uteri and uterus), and 033 (representing ICD-10 cod C61, malignant neoplasms of the prostate; NCHS, 2006.) The "Other" category was assigned to all values where "mortstat"=1 and "ucod_113" did not equal satisfy any of the above values (023, 025, 029, 031, 033.)

2.7 Statistical Analyses

All statistical analyses for this study were performed using SURVEY procedures available in SAS that incorporate essential survey information such as sample weights and stratification in analyses of data sets from complex multistage probability sampling techniques (An, 2002; Jones et al., 2006.) Descriptive analyses (Aim 1) were performed for: age, gender, race/ethnicity, tobacco use, alcohol use, non-steroidal anti-inflammatory drug use, and personal history of selected diseases in relation to CRP level, using t-tests for continuous data and chi-square tests for proportions.

Mortality risk related to CRP level (Aim 2) was assessed by Dichotomous Logistic Regression for any cause of death, and, Polytomous Logistic Regression when multiple outcomes were studied (i.e., death from colorectal cancer, death for other obesity-related cancers, death from all other causes.) We performed univariate, age-adjusted and multivariate-adjusted odds ratios. Separate analyses also were performed to examine the relationships between each of the adiposity measures and mortality risk. Covariates in the multivariate models are defined as follows: Age was considered as a continuous variable in the multivariate model; Sex (male and female); Race/ethnicity (white non-Hispanic, black non-Hispanic, Mexican-America, and other.)This unconventional categorization comes from an existing variable in the original

NHANES survey, which purposefully oversampled Mexican-Americans; Cigarette use (never, past, or current) according to answers given to the interview questions "Have you smoked more than 100 cigarettes in your lifetime?" and "Do you smoke now?"; Alcohol use (never, past, or present) according to answers given to the interview questions "Have you had more than 12 alcoholic drinks in your lifetime?" and "Have you had more than 12 alcoholic drinks within the last year?"; Physical Activity (more active than others, less active than others, or about the same as others) according to answers given to the question, "Compared to others your age, how would you rate your physical activity level?"; NSAID (yes or no) according to responses given to the question "Have you taken NSAIDS (aspirin, acetaminophen, ibuprofen, naproxen, etc.) within the last month?"; and, Personal History (yes, no) of cancer, cardiovascular disease, and diabetes was determined by responses to multiple questions specifically asking the respondents if they had been told by a doctor that they had cancer, cardiovascular disease (heart attack, congestive heart failure, etc), or diabetes. To determine if observations regarding CRP held when controlling for body measures of adiposity (Aim 3), multivariate models defined above also included adiposity measures as covariates each in a separate analysis.

Results for all tests were considered statistically significant if $p<0.05$ or results within the confidence intervals (95%) did not include 1.0. SAS 9.2 was used to perform all statistical analyses of NHANES III data in this investigation (SAS, 2008.)

3.0 RESULTS

3.1 Participant Characteristics

CRP Status. Baseline characteristics for all eligible participants (n=7192) according to CRP level (Normal vs. High) are shown in Table 1. Proportionately there were more females than males in the High-CRP group (29.34% vs. 23.29%, p=.0007.) Non-Hispanic blacks and Mexican Americans were more likely to be in the High-CRP group than Non-Hispanic whites and those categorized as "other" (38.01% and 28.93% vs 25.75% and 21.76%, respectively, p<.0001.) There were more current drinkers in the normal-CRP group than in the high-CRP group (77.12% vs. 22.88%p=.0020.) Participants in the normal CRP-group were much more likely than those in the high-CRP group to consider themselves physically active (44.23% vs. 28.79%, p<.0001.) A marginal difference between the two groups was observed in relation to tobacco use (p=.06.) Age, non-steroidal anti-inflammatory use, and having a personal history of cancer did not differ significantly between the two study groups.

Participants with higher levels of adiposity were more likely than those with normal weight to exhibit elevated CRP levels (Table 2.) For example, participants with categorized as having normal or overweight BMI were more likely to have normal CRP levels compared to obese individuals (82.16%,, 75.13%, 40.14%, respectively, p<.001.) Participants in the high-CRP group were also more likely to have a high waist circumference and waist-to-hip ratio than did the normal-CRP group (p<.0001.) Similarly, participants with high-CRP levels were more likely to have higher-risk BMI-W values (3-high, 4-very high, 5-extremely high) than the normal-CRP group.

Spearman's correlation coefficients between CRP level and adiposity measures showed a weak positive relationship (Table 3.)

All-Cause Mortality. Table 4 illustrates patient characteristics according to mortality status based on the National Death Index linkage with the NHANES III database. Participants varied according to mortality status on almost all demographic and behavioral factors, as well as CRP level. For example, males were more likely to be deceased than were females, and Non-Hispanic Whites and non-Hispanic Blacks were more likely to be deceased than Mexican Americans and those categorized as Other. As expected, increasing age was a significant correlate of mortality with the youngest age group (50-54) being much less likely to be deceased than the oldest age group (80+; 6.55% vs. 70.79%, respectively) with increasing mortality continually observed as age group increased (<.0001.)

With regard to CRP status and mortality, individuals with elevated CRP levels at baseline were much more likely to be deceased at the end of follow-up than those with normal CRP levels. Participants who had classified themselves as current or past smokers were more likely to be deceased at end of follow-up (27.63% and 26.64% vs. 22.35%, respectively), while current alcohol drinkers and those who reported taking NSAIDS within the last month were more likely to be alive at the end of follow-up. High physical activity rates also seemed to be protective against death. Individuals reporting a personal history of cancer, cardiovascular disease and diabetes were more likely to die than those who had not. Contrary to evidence citing high adiposity as a risk factor for mortality, participants with high BMI, BMI-W, and waist circumference values were more likely to be alive at the end of follow-up than those with normal

values (p<.0001.) Those with high waist-to-hip ratio values were slightly more likely to die by the end of follow-up than those with normal waist-to-hip ratio, but this relationship was not significant (p=0.72.)

***Cause-Specific Mortality*.** In Table 5, we broke down mortality into four specific outcomes: Alive, Death from colorectal cancer (CRC), Death from other obesity-related cancers (Other-ORC), and death from all other causes (All Other Causes.) Compared to females, males were more likely to die (p=.0408) from other obesity-related cancers (1.39% vs. 0.98%), colorectal cancer (0.64% vs. 0.53%) and all other causes (24.84% vs. 21.96%.) A higher proportion of Individuals with high-CRP died from CRC, other obesity-related cancers and all other causes compared to those with normal CRP level (p<.0001.) Surprisingly, individuals with normal BMI, waist circumference, BMI-W, WHR levels tended to die in greater proportions than individuals with higher values (p<.0001.) Although the specific cause of death varied somewhat according to tobacco smoking history (p=.0005), there appeared to be no coherent trend between ever use (past or current) and never use. Similarly, cause of death varied according to alcohol use (p<.0001) but with no clear trend in relation to ever (past or current) versus never use. Current NSAID use was not associated with a consistently greater proportion of deaths across the types of deaths.

3.2 CRP Status and Mortality Risk

All-Cause Mortality. Crude, age-adjusted, and multivariate-adjusted odds ratios for mortality are shown in Table 6. Part A of Table 6 displays results from the conventional dichotomous logistic regression. Compared to patients with normal CRP levels, those

with high CRP levels had an approximately 60% increase in risk of death as seen in both the crude and age-adjusted analyses. This risk was attenuated to approximately a 30% increased risk of death after adjustment for the following suspected confounders: sex, age, race/ethnicity, tobacco use, alcohol use, physical activity level, NSAID use, and personal history of cancer, cardiovascular disease, or diabetes. Analyses were conducted with each adiposity measure added as a covariate in separate multivariate models. Odds Ratios for mortality risk in relation CRP levels did not appreciably change (See Table 7 Part A) when controlling for adiposity measures. Most of the adiposity measures were associated with increased risk of death in the multivariate models. Some measures, however, were associated with a decreased risk of death.

Cause-Specific Mortality. Part B of Table 6 includes the odds ratios for CRP level in relation to the four outcome groups (Alive, CRC, Other-ORC, and All Other Causes.) Due to having more than two outcomes, Polytomous Logistic Regression was employed using a referent group consisting of participants with normal CRP level (versus high CRP) who were still alive at the end of follow-up which was compared, in parallel, to normal-versus-high CRP with respect to each mortality outcome. Participants with elevated CRP levels had a greater than two-fold risk of dying from colorectal cancer (2.66 OR, 95% CI=1.28-5.24) compared to participants with normal CRP levels who were still alive. Age adjusted odds ratios for cause-specific mortality among the high-CRP group were 2.723 (95%CI=1.297-5.719) for death from colorectal cancer, 1.403 (.810-2.430) for other obesity-related cancers, and 1.619 (1.375-1.906) for the death from all other causes. After adjusting for the same confounders as those in the dichotomous logistic regression, individuals with high CRP were two and half times as

likely to die from colorectal cancer (2437, 95%CI= 1.203-4.938), 21% more likely to die from other obesity-related cancers (1.212, 95%CI= 0.626-2.344), and 30% more likely to die from other causes (1.304, 95%CI= 1.059-1.607.)

Part B of Table 7 shows the odds ratios for cause-specific mortality after adding adiposity measures to the multivariate model used above. Adjustment for BMI indicated odds ratios for cause-specific mortality among the high-CRP group of 2.462 (95% CI=1.191-5.088) for deaths from colorectal cancer, 1.174 (95% CI= 0.610-2.260 NS) for deaths from other obesity-related cancers, and 1.392 (95% CI=1.123-1.725) for death from all other causes. Adjustment for BMI-W resulted in the high-CRP group having a 2.765 times (95%CI=1.295-5.904) increased risk for death from colorectal cancer, a 26% (1.261, 95% CI=0.645-2.63 NS) increased risk for death from other obesity-related cancers, and a 42% (1.418; 95% CI= 1.155-1.741) increased risk for death from all other causes. Adjustment for waist circumference resulted in odds ratios of 2.849 (95%CI=1.313-6.183) for death from colorectal cancer, 1.295 (95% CI=0.672-2.494) for death from other obesity-related cancers, and 1.349 (95% CI= 1.099-1.656) for death from all other causes. Finally, after adjusting for waist-to-hip ratio, the odds ratios for the individuals in the high-CRP group were found to be 2.867 (95% CI=1.317-6.243) for death from colon cancer, 1.214 (95%CI= .621-2.372) for death from other obesity-related cancers, and 1.302 (95% CI=1.047-1.618.)

Regarding adiposity as an independent risk factor for all-cause mortality (Table 8), we found in multivariate analyses that BMIs in the range of overweight and obese were significantly associated with reduced risk of death (OR=0.79, 95% CI 0.63-0.99; OR=0.65 95% CI 0.52-0.81, respectively.) Likewise, BMI-W levels tended to be

associated with reduced risk of death as was waist circumference in multivariate analyses (OR=0.81, 95% CI 0.69-0.94.) On the other hand, elevated waist-to-hip ratio was associated with increased risk of death in both crude and age-adjusted analyses, but this effect was attenuated in the multivariate analysis. When examining adiposity as a risk factor for specific causes of death (Table 9), we observed no consistent patterns. Surprisingly, in some analyses, data suggested that adiposity may be protective for various causes of death.

4.0 DISCUSSION

4.1 Key Findings

In this study, we examined the effect of C-reactive protein level on colorectal cancer mortality, and if this relationship remained independent of obesity status. In terms of correlates of CRP (Aim 1), we found that individuals with elevated CRP differed from individuals with normal CRP in terms of sex, race/ethnicity, alcohol use, physical activity level, and personal history of cardiovascular disease and diabetes. Tobacco use marginally different among the two groups (p=.06.) Age, non-steroidal anti-inflammatory drug use, and personal history of cancer, however, did not differ significantly between the two study groups.

We found evidence that individuals with elevated C-reactive protein levels were at greater risk for both all-cause mortality and death from colorectal cancer (Aim 2) in both univariate and age-adjusted analyses. An attenuated but still statistically significant risk of all-cause mortality and colorectal cancer mortality was maintained in multivariate

analyses controlling for logistic regression to account for differences in covariates between the two study groups found through study aim 1. These findings are consistent with results reported in a recent study by Heikkila et al. (2009) examining the association between CRP and colorectal cancer risk among English men aged 45-59 and English women aged 60-80.

Consistent with our hypotheses, we found that elevated CRP levels were associated with a statistically significant increase in risk of all-cause death and death from colorectal cancer independent of obesity status, regardless of which body measure of adiposity was analyzed. Controlling for body mass index, BMI-W, and waist circumference yielded slightly attenuated odds ratios, while controlling for waist-to-hip ratio slightly increased the odds ratio estimates.

Very surprisingly, we found either no association of obesity with mortality risk, or in some sub-analyses, results suggested that high anthropometric measures of adiposity may actually be protective against all-cause mortality and colorectal cancer death. These findings are in stark contrast to the overwhelming preponderance of evidence in the literature that states that obesity confers a greater risk of all-cause mortality and colorectal cancer mortality. To further explore these novel findings, we compared our findings of the correlates of CRP and adiposity measures with results obtained in previous studies. Correlations between CRP levels and adiposity measures performed in previous studies have shown strong positive relationships; however, correlations conducted in our investigation yielded much weaker associations. For example, Park et al. (2005) reported Spearman correlation coefficients of 0.69 between CRP and BMI, 0.75 between CRP and waist circumference, and 0.68 between CRP

and waist-to-hip ratio among an Asian population with no pre-existing inflammatory conditions or symptoms. The correlation between CRP and BMI-W was not performed in the study by Park. Correlations between CRP and adiposity measures in our study were much lower, ranging from 0.07 to 0.17. We speculate that our unusual findings may be due to a number of causes. Park et al. (2005) excluded individuals who had very high CRP levels (mg/dL > 10.0), which are indicative of acute infection or trauma. Inclusion of these very high values in our study may have resulted in a lack of correlation between very high CRP levels and very high adiposity measures, especially since those with acute sickness tend to lose body mass over time and exhibit normal or even below normal adiposity measurements (Flegal et al., 2007; Manson et al., 2007.) To demonstrate the possible effect that the inclusion of individuals with very high CRP levels may have had on the correlations, we performed another correlation excluding all participants with CRP levels greater than 10 mg/dL. This exclusion resulted in slightly higher correlation coefficients but did not increase them sufficiently to match the correlations observed in other studies. On the other hand, we suspected that the preponderance of CRP values labeled as "undetectable" (<.22 mg/dL), that resulted from the relative low-sensitivity of the assay used to measure CRP, may have also diluted the correlation coefficients. However, upon exclusion of participants with undetectable levels of CRP, we found that the correlation coefficients between adiposity measures and CRP became marginally negative. Although we did not ascertain an explanation of our unusual findings with respect to correlation coefficients, the results of the categorical analyses between adiposity measures and CRP levels in our study did show statistically

significant associations between increased CRP level and increasing adiposity measures.

Another possible reason for the null effects of increasing adiposity on mortality may be that the increased risk of obesity-related negative outcomes may be eliminated by the use of treatment modalities that decrease the negative effects of obesity on one's health. For example, increased use of anti-inflammatory drugs during the follow-up period may have distorted the relationship between CRP and obesity measures by controlling inflammation brought upon by increased adiposity. Consistent with this hypothesis, Wee et al. (2008) observed CRP levels to be only weakly correlated with adiposity measures when a large proportion of the study population was on a low-dose NSAID regimen. Due to the increase in attention by the media advocating use of a low-dose aspirin regimen for prevention of multiple diseases since baseline data were collected, participants that may have started to use NSAIDS during follow-up time may not have reported regular NSAID use at baseline.

A third possible explanation for lack of correlation between CRP and adiposity measures is misclassification of adiposity in the NHANES III cohort due to longitudinal changes in participants' obesity levels after the baseline measurement. In the time period following the data collection for NHANES III (1988-1994), there was a substantial surge in obesity prevalence throughout the country (CDC, 2008.) The baseline measurements of adiposity, hence, may not accurately represent the obesity status of NHANES III individuals during the follow-up period, which occurred between 6 and 12 years from collection of baseline data.

If misclassification is at play, is it possible, however, that obesity-related sequelae would be manifest so quickly? Research documenting the effects of weight

loss on improved short-term health outcomes provides evidence that alterations in body size such as weight gain could have immediate deleterious effects on health. An example of this is the effect seen in a study by Eliassen et al. (2006) among women aged 30-55 with a mean follow-up time of 24 years that found a 2 kg weight gain since age 18 conferred a 24.2% greater risk breast cancer (long-term risk), while a 2 kg weight gain among the same women within a few years after menopause conferred a 7.6% increase in risk of developing breast cancer. It is possible that many of the NHANES III participants whose adiposity measures were "normal" at baseline gained sufficient body mass over the course of follow-up to confer increased risk of mortality from obesity-related diseases such as colorectal cancer. Therefore, differences in outcomes across the study groups converged towards the null. Misclassification of individuals as having had "normal" body size when they should have been characterized as having high adiposity later in the study may account for a null or protective effect of increased body size on mortality risk.

We posit that that the hypothesis of misclassification of adiposity measures in NHANES III participants is supported by results from a study by Flegal et al. (2007), who found that overweight and obesity was a risk factor for deleterious outcomes among the NHANES I cohort (1971-75), a longitudinal study with repeated measurements and conducted in an earlier and more weight-stable time period yet overweight status was found to be a protective factor against death in the NHANES II and III cohorts. Flegal (2007) speculated that a large proportion of the difference between cohorts could be explained through increased use of treatment modalities that are superb for managing chronic conditions associated with obesity, such as blood sugar-stabilizing drugs for

obese diabetics and prophylactic low-dose aspirin use among obese individuals who are at risk for inflammation-related diseases such as cardiovascular disease. On the other hand, obesity rates are higher among lower socio-economic classes and the underserved (Stunkard et al., 1993.) Hence, use of beneficial treatments might not fully explain the lack of relationship between obesity and mortality observed in the NHANES III cohort.

It remains unknown to what extent these different hypotheses explain the unusual relationships between obesity and mortality risk observed in our study. We must also ask the question about reliability of the participants' CRP levels over time as well. CRP level is well-known to increase with age and thus follow-up time (Rumley et al., 2006.) Furthermore, CRP has been documented to be a marker for both long- and short-term mortality risk, while the time-based effects of adiposity and weight gain remain inconclusive. Therefore, it is plausible that relative levels of CRP likely remained consistent. Hence, the risks of all-cause and colorectal cancer-specific mortality conferred by high levels of CRP might have remained relatively consistent through follow-up period.

4.2 Strengths and Limitations

A major strength of this investigation is the use of data from the NHANES III study, a complex multi-stage probability sample that is representative of the U.S. population enabling generalization of study results to all Americans. Meticulously constructed linkage standards for connecting NHANES III baseline data with National Death Index data assured that individuals who were assumed to be alive at the end of follow-up were correctly classified. Furthermore, the comprehensiveness of methods for collecting

baseline measurements used in NHANES III lends credence to the reliability of the anthropometric measures and lab-assigned values for C-reactive protein (Gunter et al., 1990; NCHS, 1992.) Lastly, ample follow-up time (mean=96.5 months) was allotted so that a sufficient numbers of deceased participants (n=3384) accrued.

There are several important limitations to be considered. First, as discussed, NHANES III collected baseline measurements of all variables only once, while more reliable findings may have been observed if repeated measurements of the independent variables had been accumulated. This limitation is especially pertinent when analyzing adiposity values in the context of a rapidly growing obesity epidemic.

Another limitation of this study is that only mortality status, not disease incidence, was obtained during the follow-up period. Therefore, the results of this study cannot be assumed to reflect risk of colon cancer incidence, which is more common than colorectal cancer death and may produce serious quality of life issues independent of mortality risk. Also, the multivariate model might have benefited from inclusion of more key risk factors for colorectal cancer death not available in the NHANES III data sets we analyzed, such as history of use of statins or dietary history (e.g., high red meat intake.) Furthermore, numerous studies have shown that increased CRP and adiposity is associated with colon cancer but not significantly associated with rectal or anal cancers (MacInnis et al., 2006; Larsson et al., 2007.) However, mortality data for death from the National Death Index was only available for 113 aggregated groups of ICD-10 code subgroups. Only mortality from colorectal cancers (as a group) was available for analysis in this investigation. Therefore, we speculate that the findings in our study may

be underestimated when compared to results that would have been observed if only death from colon cancer had specifically been analyzed.

4.3 Conclusions

Findings from this investigation suggest that individuals with high levels of serum C-reactive protein may have an increased risk of all-cause mortality, colorectal cancer death, and death from other obesity-related cancers. This increased risk seems to persist even after adjusting for many potential confounding variables including anthropometric measures of adiposity. We speculate that the negligible change in mortality risk after controlling for baseline adiposity status may be due, in part, to increased adiposity of participants over time and subsequent misclassification of participants based on baseline data. More research using different study populations is warranted to further investigate the links between C-reactive protein, obesity, and colorectal cancer. Several opportunities for future analysis of this topic have been identified:

1. Continue to review and analyze extant published findings using NHANES III data regarding risk of mortality in relation to adiposity measures to determine if our findings are consistent.

2. Perform survival analyses to identify any differences in the length of time to mortality
outcomes.

4. Explore genetic determinants of CRP serum levels among NHANES III participants using the restricted-access polymorphism database available through the Research Data Center at the National Center for Health Statistics.

5. Identify an existing longitudinal cohort study in which CRP, obesity status, and long-term outcomes can be analyzed.

Further exploration of these topics may provide a greater understanding of the inter-relationships of C-Reactive Protein, adiposity measures, and colorectal cancer, leading to effective preventive programs that will improve the public health.

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6.0 FIGURES and TABLES

Fig. 1 Formation of Study Sample Size in NDI-linked NHANES III Database

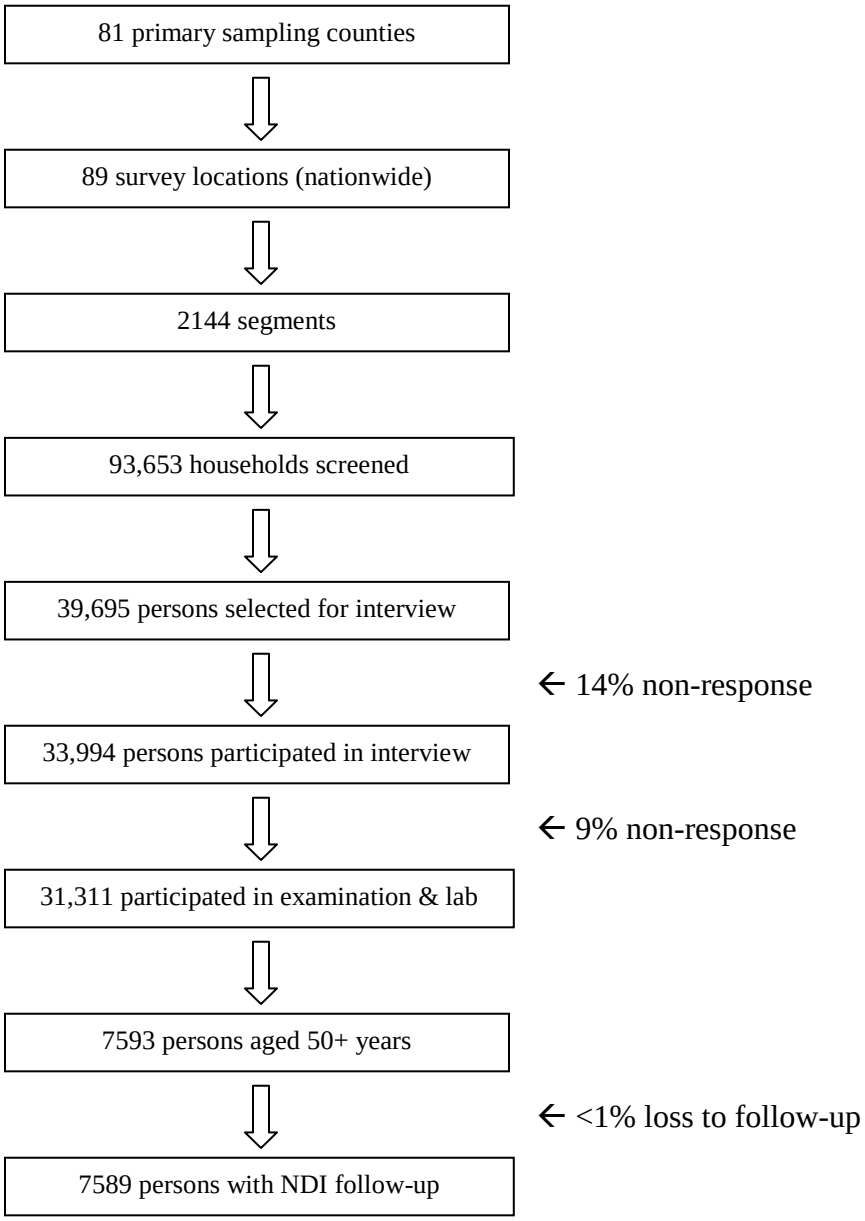
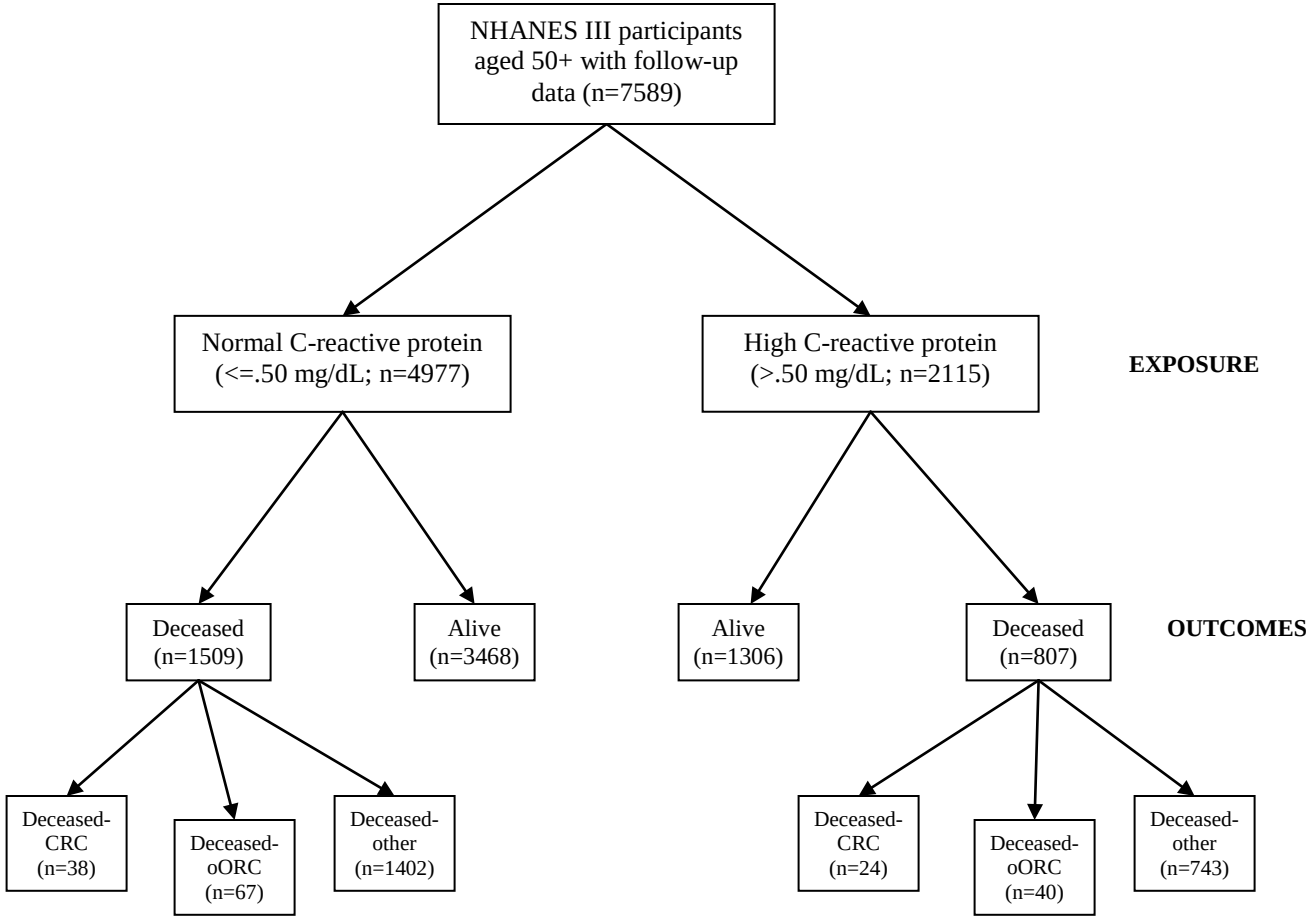


Fig. 2 Study Design



Key:
CRC- colorectal cancer
oORC= other obesity-other obesity related cancers

Fig. 3 Classification of the NIHLB BMI-W Index

BMI-W[1] (disease risk)	Waist Circumference[2,3]	BMI[3]	BMI Label[3]
Average (1)	Any	< 18.5	Underweight (1)
	Any	18.5-24.9	Normal (2)
Increased (2)	Normal	25.0-29.9	Overweight (3)
High (3)	High	25.0-29.9	Overweight (3)
	Normal	30.0-34.9	Obese I (4)
Very High (4)	High	30.0-34.9	Obese I (4)
	Any	35.0-39.9	Obese II (5)
Extremely High (5)	Any	40.0+	Obese III (6)

1. *High waist circumference defined as: Males > 40 in (102 cm); Females > 35 in (88 cm)*
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Table 1 Participant Characteristics according to C-Reactive Protein Level

	C-Reactive Protein		Chi-sq[2]	p-Value
	Normal (n=4977)	High (n=2115)		
Sex				
Male	2457 (76.71)[1]	940 (23.29)		
Female	2520 (70.66)	1175 (29.34)	11.46	.0007
Race/Ethnicity				
Non-Hispanic White[1]	2925 (74.25)	1104 (25.75)		
Non-Hispanic Black	897 (61.99)	534 (38.01)		
Mexican American	963 (71.07)	418 (28.93)		
Other	192 (78.24)	59 (21.76)	23.96	<.0001
Age				
Mean (SD)	67.79 (10.76)	68.00 (10.63)	-0.77[2]	.4426
Age				
50-54	656 (75.11)	257 (24.89)		
55-59	617 (74.73)	253 (25.27)		
60-64	806 (73.09)	360 (26.91)		
65-69	739 (73.02)	333 (26.98)		
70-74	741 (72.50)	310 (27.50)		
75-79	474 (72.31)	198 (27.69)		
80+	944 (70.89)	404 (29.11)	3.79	.7056
Smoking Status				
Never	2332 (75.39)	893 (24.61)		
Past	1799 (72.54)	771 (27.46)		
Current	846 (70.67)	451 (29.33)	5.68	.0585
Alcohol Use				
Never	988 (71.52)	437 (28.48)		
Past	2015 (71.33)	932 (28.67)	12.40	.0020
Current	1657 (77.12)	565 (22.88)		
Physical Activity Level				
More active than others	1971 (80.91)	568 (19.09)		
About the same as others	2045 (71.42)	938 (28.58)		
Less active than others	816 (61.09)	554 (38.31)	99.43	<.0001
Current NSAID use				
Yes	3354 (72.79)	1449 (27.21)	2.38	.1233
No	1578 (74.83)	650 (25.17)		
Positive Personal History				
Cancer	764 (73.18)	315 (28.81)	0.02	.8886
Cardiovascular Disease	767 (63.35)	475 (36.65)	31.65	<.0001
Diabetes	612 (61.60)	421 (38.40)	31.59	<.0001

[1] *n(%); percentages are weighted and rounded.*
[2] *Rao-Scott Chi-square used to correct for weighted frequencies except for age as a continuous variable, where t-test is used.*

Table 2 Adiposity Measures according to C-Reactive Protein Level

	C-Reactive Protein		Chi-sq[2]	p-Value
	Normal n= 4843	**High** n=2063		
Body Mass Index				
Normal	1803 (82.16)[1]	498 (17.84)		
Overweight	1990 (75.13)	786 (24.87)		
Obese	1050 (59.86)	779 (40.14)	149.05	<.0001
Waist Circumference[3]				
Normal	2453 (81.82)	722 (18.18)		
High	2376 (66.65)	1314 (33.35)	85.17	<.0001
BMI-W[4]				
1- Normal	1803 (82.16)	498 (17.84)		
2- Elevated	828 (82.09)	260 (17.91)		
3- High	1141 (70.64)	526 (29.36)		
4- Very High	932 (62.83)	620 (37.17)		
5- Extremely High	62 (32.46)	120 (67.54)	186.72	<.0001
Waist-to-Hip Ratio[5]				
Normal	2141 (78.79)	745 (21.21)		
High	2585 (69.66)	1216 (30.34)	28.80	<.0001

[1] *n(%); percentages are weighted and rounded.*
[2] *Rao-Scott Chi-square used to correct for weighted frequencies.*
[3] *High waist circumference >= 102 cm for men, >= 88 cm for women*
[4] *Body Mass Index stratified by waist circumference (BMI-W)*
[5] *High waist-to-hip ratio >= 1.0 for men, >=0.9 for women*

Table 3 Correlations[1] between C-Reactive Protein and Adiposity Measures

[1] Spearman correlations for ordinal data

	C-Reactive Protein	P-Value
Body Mass Index	0.17	<.0001
BMI-W[2]	0.19	<.0001
Waist Circumference	0.14	<.0001
Waist-to-Hip Ratio	0.07	<.0001

[2] Body Mass Index stratified by waist circumference (BMI-W)

Table 4 Participant Characteristics and All-Cause Mortality

[1] *n (%); weighted and rounded percentages.*

	Alive (n=5028)	Deceased-CRC (n=68)	Deceased-CRC (n=122)	Deceased-Other (n=2379)	Chi-sq	P-Value
	Alive n=5022		**Deceased** n=2567		**Chi-Square**[2]	**P-Value**
Sex						
Male	2237 (73.12)[1]		1378 (26.88)[1]		7.04	.0080
Female	2785 (76.49)		1189 (23.51)			
Race/Ethnicity						
Non-Hispanic White	2645 (74.37)		1621 (25.63)			
Non-Hispanic Black	1076 (69.26)		544 (30.74)		50.96	<.0001
Mexican American	1075 (81.29)		362 (18.71)			
Other	226 (89.06)		40 (10.94)			
Age at Interview						
Mean (SD)	64.47 (9.38)		75.14 (9.77)		-46.22[2]	<.0001
Age at Interview						
50-54	872 (93.45)		78 (6.55)			
55-59	794 (88.34)		124 (11.66)			
60-64	1013 (84.93)		216 (15.07)		712.68	<.0001
65-69	833 (75.13)		304 (24.87)			
70-74	743 (69.59)		382 (30.41)			
75-79	363 (51.74)		378 (48.26)			
80+	404 (29.21)		1085 (70.79)			
Body Mass Index[3]						
Normal (18.5-24.9)	1500 (72.12)		975 (27.88)			
Overweight (25.0-29.9)	196 (76.07)		950 (23.93)		24.58	<.0001
Obese (30.0+)	1481 (80.17)		480 (19.83)			
BMI-W[4]						
1- Normal	1516 (72.12)		1039 (27.88)			
2- Elevated	767 (76.24)		378 (23.76)			
3- High	1202 (76.95)		547 (23.05)		37.95	<.0001
4- Very high	1253 (81.00)		393 (19.00)			
5- Extremely high	158 (80.20)		44 (19.80)			
Waist Circumference[5]						
Normal	2111 (72.97)		1303 (27.03)		20.64	<.0001
High	2786 (78.25)		1118 (421.75)			
Waist-to-Hip Ratio[6]						
Normal	2026 (76.53)		1106 (23.47)		.13	.7202
High	2780 (75.99)		1185 (24.01)			
C-reactive Protein (mg/dL)						
Normal- (<0.5)	3468 (78.25)		1509 (21.74)		42.62	<.0001
Elevated- (>0.5)	1306 (69.38)		807 (30.62)			
Smoking Status						
Never	2374 (77.65)		1080 (22.35)		13.57	.0011
Past	1718 (73.36)		1028 (26.64)			
Current	930 (72.37)		459 (27.63)			
Alcohol Use						
Never	981 (73.23)		546 (26.77)		49.80	<.0001
Past	2041 (72.58)		1065 (27.43)			
Current	1734 (82.29)		563 (17.41)			
Physical Activity Level						
More active than others	1896 (79.76)		782 (20.24)		64.75	<.0001
About the same as others	2150 (76.37)		1022 (23.63)			
Less active than others	854 (62.93)		667 (37.07)			
Current NSAID use						
Yes	3404 (75.66)		1697 (24.34)		2.79	.0950
No	1580 (73.26)		842 (26.74)			
Positive Personal History						
Cancer	602 (14.22)		550 (24.02)		51.57	<.0001
Cardiovascular Disease	593 (9.90)		772 (28.32)		428. 67	<.0001
Diabetes	595 (9.00)		510 (17.56)		76.53	<.0001
Follow-up Time in Months						
Mean (SE)[7]	108.60 (20.58)		58.45 (34.42)		79.20[2]	<.0001
Median	108.00		66.00			

[2] *Rao-Scott Chi-square used to correct for weighted frequencies except for age as a continuous variable, where t-test is used.*
[3] *BMI I<18.5 not included in analyses*
[4] *Body Mass Index stratified by waist circumference (BMI-W),*
[5] *High waist circumference >= 102 cm for men, >= 88 cm for women*
[6] *High waist-to-hip ratio >= 1.0 for men, >=0.9 for women*
[7] *SE= Standard Error of the Mean*

Table 5- Participant Characteristics and Cause-Specific Mortality

Sex						
Male	2238 (73.13)[1*]	46 (0.64)[1*]	77 (1.39)[1*]	1254 (24.84)[1*]	8.27	**.0408**
Female	2790 (76.53)	22 (0.53)	45 (0.98)	1121 (21.96)		
Race/Ethnicity						
Non-Hispanic White	2649 (74.40)	37 (0.55)	78 (1.18)	1504 (23.87)		
Non-Hispanic Black	1076 (69.26)	20 (1.14)	33 (1.66)	491 (27.93)	§	§
Mexican American	1077 (81.31)	11 (0.76)	9 (0.46)	342 (17.48)		
Other	226 (89.06)	0 (0.00)	2 (0.50)	38 (10.44)		
Age						
Mean (SD)	64.49 (9.40)	73.06 (9.10)	74.42 (10.00)	75.23 (9.77)	§	§
Age Group						
50-54	873 (93.45)	2 (0.06)	3 (0.14)	73 (6.34)		
55-59	794 (88.34)	5 (0.35)	8 (0.84)	111 (10.46)		
60-64	1013 (84.93)	3 (0.16)	14 (0.99)	199 (13.92)		
65-69	833 (75.13)	15 (0.92)	16 (1.51)	273 (22.44)	935.52	**<.0001**
70-74	743 (69.59)	13 (0.91)	16 (1.29)	353 (28.22)		
75-79	363 (51.74)	8 (0.89)	18 (1.67)	352 (45.70)		
80+	409 (29.72)	22 (1.32)	47 (2.71)	1014 (66.25)		
Body Mass Index[3]						
Normal	1503 (72.18)	27 (0.78)	46 (1.23)	900 (25.81)	31.96	**<.0001**
Overweight	1967 (76.08)	26 (0.46)	50 (1.38)	874 (22.07)		
Obese	482 (80.17)	13 (0.52)	23 (0.84)	23 (18.47)		
BMI-W[4]						
1- Normal	1503 (72.18)	27 (0.78)	46 (1.23)	900 (25.81)		
2- Elevated	768 (76.27)	15 (0.61)	27 (2.09)	336 (21.02)	48.79	**<.0001**
3- High	1202 (76.95)	11 (0.36)	22 (0.85)	514 (21.84)		
4- Very High	1254 (81.01)	11 (0.57)	19 (0.86)	363 (17.57)		
5- Extremely High	158 (80.20)	2 (0.39)	3 (0.97)	39 (18.44)		
Waist Circumference[5]						
Normal	2115 (73.03)	38 (0.61)	69 (1.52)	1194 (24.84	23.37	**<.0001**
High	2788 (78.26)	28 (0.53)	51 (0.88)	1039 (20.34		
Waist-to-hip Ratio[6]						
Normal	2031 (76.59)	32 (0.64)	61 (1.32)	1011 (21.46)	2.10	.5523
High	2781 (75.99)	30 (0.45)	54 (1.06)	1101 (22.51)		
C-reactive Protein (mg/dL)						
Normal	3470 (78.27)	38 (0.41)	67 (1.03	1402 (20.28)	47.01	**<.0001**
High	1308 (69.38)	24 (0.97)	40 (1.26)	743 (28.38)		
Smoking Status						
Never	2378 (77.68)	29 (0.49)	58 (1.29)	991 (20.55)		
Past	1720 (73.40)	28 (0.74)	45 (0.83)	955 (25.02)	23.90	**.0005**
Current	930 (72.37)	11 (0.44)	19 (1.56)	429 (25.63)		
Alcohol Use						
Never	981 (73.23)	14 (0.62)	24 (0.94)	508 (25.21)		
Past	2043 (72.60)	30 (0.67)	47 (1.11)	987 (25.63)	71.13	**<.0001**
Current	1736 (82.60)	22 (0.54)	26 (0.94)	514 (15.92)		
Physical Activity Level						
More active than others	1897 (79.78)	21 (0.43)	42 (0.98)	718 (18.82)		
Less active than others	856 (32.98)	9 (0.35)	30 (1.55)	628 (35.12)	97.43	**<.0001**
About the same as others	2153 (76.40)	33 (0.73)	48 (1.24)	940 (21.63)		
Current NSAID use						
Yes	3407 (75.68)	49 (0.60)	83 (1.08)	1564 (22.64)		
No	1583 (73.29)	19 (0.54)	39 (1.42)	783 (24.76)	4.43	**<.0001**
Positive Personal History						
Cancer	603 (14.22)	25 (33.60)	45 (41.05)	479 (22.91)	83.79	**<.0001**
Cardiovascular Disease	596 (9.96)	14 (18.62)	24 (12.44)	734 (29.38)	300.87	**<.0001**
Diabetes	596 (9.02)	11 (11.66)	17 (11.70)	482 (18.01)	102.23	**<.0001**
Follow-up time in Months						
Mean (SE)[7]	108.43 (1.47)	58.31 (4.65)	55.42 (4.02)	61.07 (1.57)	§	§
Median	108.00	57.00	52.00	57.00		

[1] n (%); weighted and rounded percentages.
[2] Rao-Scott Chi-Square Test for weighted sample data
[3] BMI I<18.5 not included in analyses
[4] Body Mass Index stratified by waist circumference (BMI-W),
[5] High waist circumference >= 102 cm for men, >= 88 cm for women
[6] High waist-to-hip ratio >= 1.0 for men, >=0.9 for women
[7] SE= Standard Error of the Mean
§ values can not be obtained due to empty cells

Table 6 Crude, Age-adjusted, and Multivariate-adjusted Odds Ratios for Mortality in relation to C-reactive Protein Level

		n	Crude Odds Ratio (95% CI)	Age-adjusted OR (95% CI)	Multivariate-adjusted OR[1] (95% CI)
A	**C-Reactive Protein**				
	Normal	4977	1.0	1.0	1.0
	High	2115	1.589 (1.388-1.819)	1.628 (1.388-1.909)	1.318 (1.080-1.610)
B	**C-Reactive Protein**				
	Alive w/normal CRP[2]	3470	---	---	---
	CRC[3]	24	2.660 (1.277-5.539)	2.723 (1.297-5.719)	2.437 (1.203-4.938)
	Other ORC[4]	40	1.378 (0.798-2.380)	1.403 (0.810-2.430)	1.212 (0.626-2.344)
	All Other Causes	743	1.579 (1.373-1.816)	1.619 (1.375-1.906)	1.304 (1.059-1.607)

[1] *Adjusted for age, sex, race/ethnicity, tobacco use alcohol use, physical activity level, NSAID use, personal history of cancer, personal history of CVD, personal history of diabetes*
[2] *Referent group: Participants with normal CRP levels who were alive at the end of the study*
[3] *CRC= Colorectal Cancer*
[4] *oORC= Other Obesity-Related Cancer (i.e., breast, endometrial, pancreatic, prostate)*

Table 7 Addition of Adiposity Measures into Multivariate Models estimating Odds Ratios for All-Cause Mortality and Cause-Specific Mortality in relation to C-Reactive Protein

	n	BMI-adjusted OR[1,2] (95%CI)	n	BMI-W adjusted OR[1,2] (95%CI)	n	WC-adjusted OR[1,2] (95%CI)	n	WHR-adjusted OR[1,2] (95%CI)
C-Reactive Protein								
Normal	6201	1.0	6099	1.0	6146	1.0	6011	1.0
High		1.407 (1.140-1.736)		1.438 (1.175-1.759)		1.375 (1.127-1.678)		1.325 (1.073-1.636)
C-Reactive Protein								
Alive w/ Normal CRP[3]	6201	---	6099	---	6146	---	6011	---
CRC[4]		2.462 (1.191-5.088)		2.765 (1.295-5.904)		2.849 (1.313-6.183)		2.867 (1.317-6.243)
o-ORC[5]		1.174 (0.610-2.260)		1.261 (0.645-2.463)		1.295 (0.672-2.494)		1.214 (0.621-2.372)
All Other Causes		1.392 (1.123-1.725)		1.418 (1.155-1.741)		1.349 (1.099-1.656)		1.302 (1.047-1.618)

[1] *Adjusted for age, sex, race/ethnicity, tobacco use alcohol use, physical activity level, NSAID use, personal history of cancer, personal history of CVD, personal history of diabetes.*
[2] *Body Mass Index (BMI), Body Mass Index stratified by waist circumference (BMI-W), Waist Circumference (WC), Waist-Hip-Ratio (WHR)*
[3] *Referent group: Participants with normal CRP levels who were alive at the end of the study*
[4] *CRC= Colorectal Cancer*
[5] *o-ORC= Other Obesity-related Cancer (i.e., breast, endometrial, pancreatic, prostate)*

Table 8 Odds Ratios for All-Cause Mortality in relation to Adiposity

	n	Crude OR (95% CI)	Age-adjusted OR (95% CI)	Adjusted OR[1] (95% CI)
BMI	6200			
Normal		1.0	1.0	**1.0**
Overweight		**0.814 (0.692-0.957)**	0.913 (0.754-1.105)	**0.791 (0.627-0.997)**
Obese		**0.640 (0.539-0.759)**	0.910 (0.760-1.089)	**0.650 (0.521-0.811)**
BMI-W[2]	6098			
Normal		1.0	1.0	1.0
Elevated		0.806 (0.649-1.002)	0.989 (0.772-1.266)	0.784 (0.564-1.092)
High		**0.775 (0.651-0.922)**	0.838 (0.688-1.021)	**0.759 (0.598-0.963)**
Very High		**0.607 (0.511-0.721)**	0.859 (0.713-1.036)	**0.633 (0.505-0.792)**
Extremely High		0.639 (0.407-1.003)	1.130 (0.680-1.878)	0.634 (0.314-1.283)
Waist Circumference	6145			
Normal		1.0	1.0	1.0
High		1.031 (0.874-1.216)	0.986 (0.817-1.189)	**0.806 (0.688-0.944)**
Waist-to-hip Ratio	6010			
Normal		1.0	1.0	1.0
High		**1.589 (1.388-1.819)**	**1.628 (1.388-1.909)**	1.008 (.814-1.249)

[1] *Adjusted for age, sex, race/ethnicity, tobacco use alcohol use, physical activity level, NSAID use, personal history of cancer, personal history of CVD, personal history of diabetes, and CRP level.*

[2] *Body Mass Index stratified by waist circumference (BMI-W)*

Table 9 Odds Ratios for Cause-Specific Mortality in relation to Adiposity

	n	**Crude Odds Ratio** (95% CI)	**Age-adjusted OR** (95% CI)	**Multivariate OR[1]** (95% CI)
Body Mass Index: Overweight	7355			
Alive with Normal BMI[2]		---	---	---
CRC[3]		0.556 (0.275-1.123)	0.617 (0.299-1.275)	**0.427 (0.208-0.889)**
o-ORC[4]		1.066 (.639-1.778)	1.170 (.692-1.980)	1.024 (.548-1.912)
All Other Causes		**0.811 (0.684-0.963)**	0.912 (0.747-1.113)	**0.798 (0.639-0.996)**
Body Mass Index: Obese				
Alive and Normal BMI[2]		---	---	---
CRC		0.600 (0.271-1.327)	0.828 (0.357-1.921)	0.663 (0.259-1.696)
o-ORC		0.612 (0.295-1.270)	0.816 (0.392-1.699)	0.756 (0.345-1.654)
All Other Causes		**0.644 (0.542-0.766)**	0.922 (0.468-1.106)	**0.781 (0.631-0.968)**
Waist Circumference	7322			
Alive with Normal WC[2]		---	---	---
CRC		0.807 (0.407-1.602)	0.871 (0.428-1.774)	0.810 (0.329-1.996)
o-ORC		0.**538 (0.324-0.896)**	**0.577 (0.346-0.960)**	0.684 (0.375-1.246)
All Other Causes		**0.764 (0.677-0.862)**	**0.838 (0.731-0.961)**	0.883 (0.760-1.025)
BMI-W[5] Elevated	7220			
Alive and Normal BMI-W[2]		---	---	---
CRC		0.740 (0.329-1.666)	0.894 (0.388-2.059)	0.500 (0.244-1.026)
o-ORC		1.606 (0.874-2.954)	**1.920 (1.029-3.589)**	1.381 (0.563-3.386)
All Other Causes		**0.771 (0.611-0.972)**	0.942 (0.725-1.224)	0.728 (0.521-1.019)
BMI-W High				
Alive with Normal BMI-W[2]		---	---	---
CRC		0.435 (0.185-1.020)	0.467 (0.195-1.122)	0.397 (0.158-1.002)
o-ORC		0.648 (0.341-1.230)	0.691 (0.361-1.325)	0.740 (0.379-1.446)
All Other Causes		**0.794 (0.663-0.950)**	0.862 (0.703-1.056)	0.**792 (0.633-0.991)**
BMI-W Very High				---
Alive with Normal BMI-W[2]		---	---	0.672 (0.261-1.730)
CRC		0.647 (0.284-1.475)	0.893 (0.371-2.146)	0.797 (0.362-1.757)
o-ORC		0.621 (0.302-1.277)	1.144 (0.680-1.926)	**0.751 (0.604-0.933)**
All Other Causes		**0.607 (0.509-0.723)**	1.156 (0.163-8.202)	
BMI-W Extremely High				---
Alive with Normal BMI-W[2]		---	----	0.810 (0.111-5.890)
CRC		0.452 (0.087-2.352)	0.766 (0.138-4.236)	**0.145 (0.028-0.743)**
o-ORC		0.710 (0.105-4.776)	**1.156 (1.101-1.125)**	0.895 (0.445-1.798)
All Other Causes		0.643 (0.404-1.024)	1.144 (0.680-1.926)	
Waist-to-Hip Ratio	7101			---
Alive with Normal WHR[2]		---	---	0.547 (0.258-1.158)
CRC		0.711 (0.351-1.438)	0.680 (0.330-1.402)	0.929 (0.523-1.650)
o-ORC		0.809 (0.515-1.272)	0.770 (0.490-1.209)	1.054 (0.860-1.291)
All Other Causes		1.057 (0.893-1.252)	1.016 (0.838-1.231)	

1 Adjusted for age, sex, race/ethnicity, tobacco use alcohol use, physical activity level, NSAID use, personal history of cancer, personal history of CVD, personal history of diabetes, and CRP level.

2 Referent group

3 CRC= Colorectal Cancer

4 o-ORC= Other Obesity-related Cancer (i.e., breast, endometrial, pancreatic, prostate)

5 Body Mass Index stratified by waist circumference (BMI-W)