Mortality Attributable to Obesity Among Middle-Aged Adults in the US

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January 21st, 2008

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ABSTRACT

Obesity is considered a major source of premature mortality. We measure relative and attributable risks associated with obesity among middle-aged adults from the Health and Retirement Study (1992-2004). While class II/III obesity (BMI≥35.0) increases mortality by 53% compared to normal BMI (18.5-24.9), class I obesity (30.0-34.9) and overweight (25.0-29.9) are not associated with mortality. With respect to attributable mortality, obesity (BMI≥30.0) is responsible for only 2% of deaths in this population. Results are robust to confounding by diseases, SES, smoking, and other correlates. These findings challenge the viewpoint that obesity will stem the long-term secular decline in US mortality.

INTRODUCTION

Mortality among middle- and older-aged Americans continues to decline in the United States as evidenced by the most recent figures on life expectancy (National Center for Health Statistics 2006). This achievement, a continuation of the long-standing secular decline in mortality, may be threatened by the rapid rise in obesity levels (Olshansky et al. 2005). Obesity—a health risk that is largely determined by modifiable behaviors—is increasingly compared to cigarette smoking as a single source of premature deaths in the US (Marshall 2004; Parloff 2003; U.S. Department of Health and Human Services 2001). Middle- and older-aged Americans have not escaped the rising levels of obesity (Doshi, Polsky, and Chang 2007), and the fact that approximately 30% of adults over age 50 are obese (BMI≥30.0 kg/m^2) and an additional 40% are overweight (BMI 25.0-29.9) is well known (Ogden et al. 2006). The association between obesity and the early onset of many chronic illnesses and disability is also well known (Al Snih et al. 2007; Field et al. 2001; Reynolds, Saito, and Crimmins 2005). Recent investigations, however, suggest a limited role for obesity in shortening lifespan (Al Snih et al. 2007; Flegal et al. 2005). Moreover, claims that obesity is responsible for a substantial number of premature deaths in the US must rest on an empirical framework that translates individual-level mortality, usually estimated by relative risk, into attributable mortality at a national level. Such a framework is rarely implemented in research on obesity and mortality.

Diverging Estimates of Mortality Attributable to Obesity

The few studies that have measured mortality attributable to obesity have spawned considerable controversy. Allison et al. (1999a) estimated that between 280,000 and 325,000 adults deaths in the US in 1991 can be attributed to a BMI≥25.0 (overweight or obese).[i] In a well-publicized

study, Mokdad et al. (2004) updated these estimates for 2000 and reported that a BMI≥25.0 was responsible for 400,000 excess deaths among adults. In a follow-up letter by the same authors, this figure was revised down to 365,000 (Mokdad et al. 2005). According to Mokdad et al. (2004), the revised estimate of 365,000 excess deaths still placed higher weight status[ii] (BMI≥25.0) second to tobacco (435,000 attributable deaths) as the single most important cause of avoidable mortality in 2000. These two influential studies both relied on combining data from the same set of six epidemiological studies conducted during various times between 1948 and 1992. The larger of the studies used by these authors were the Framingham Heart Study (1948-1980), the American Cancer Society's first Cancer Prevention Study (1960-1972), the Nurses Health Study (1971-1992), and the National Health and Nutrition Examination Survey (NHANES) Epidemiological Follow-up Study (1971-1992). Relative risk estimates derived from the six studies were applied to the distribution of BMI and total number of deaths in 1991 (Allison et al. 1999a) and 2000 (Mokdad et al. 2004) to estimate attributable mortality. In a more recent paper, Flegal et al. (2005) also estimated attributable mortality for 2000 based on relative risks from three existing NHANES surveys and their mortality linkages (NHANES I, 1971-1992; NHANES II, 1976-1992; and NHANES III, 1988-2000). Flegal et al. (2005) estimated that approximately 112,000 deaths were attributable to obesity (BMI≥30.0) in 2000. They also estimated approximately 86,000 fewer deaths attributable to overweight but non-obese (BMI 25.0-29.9). Hence, the estimates by Flegal et al. (2005) result in a net of 26,000 deaths attributable to higher weight status (BMI≥25.0) as a whole in 2000, which is a figure far smaller than the 365,000 deaths estimated by Mokdad et al. (2005) for the same year.

The reasons for the divergent findings lie in numerous methodological differences among the studies. Major differences are that the earlier papers by Allison et al. (1999a) and Mokdad et al. (2004) used older data and did not fully account for variation in mortality risk by age (Couzin 2005; Flegal, Graubard, and Williamson 2004). Flegal et al. (2005) relied on mortality data that lasted through the 1990s. In contrast, four of the six studies in Allison et al. (1999a) and Mokdad et al. (2004) only possessed mortality data lasting into the 1970s or early part of the 1980s. Flegal et al. (2005) found that the relative risks associated with obesity was higher in the NHANES I mortality follow-up—a data set used by the earlier studies—compared to the latter two NHANES surveys suggesting a possible decline in mortality over time. They estimate that inclusion of the NHANES II and NHANES III relative risk estimates decreased their attributable death estimates in 2000 by more than 60%. Therefore, the estimates by Allison et al. (1999a) and Mokdad et al. (2004), which relied on older data, may not sufficiently reflect the contemporary association between weight status and mortality. Flegal et al. (2005) also stratified the analysis into three adult age groups (ages 25-59, 60-69, and 70+) allowing relative risks to vary by age. Allison et al. (1999a) and Mokdad et al. (2004) pooled adults aged 18 and over, while treating age only as a confounder and not an effect modifier. For the earlier papers, this may have resulted in a disproportionately high estimate of attributable deaths because the relative risk of obesity is thought to be smaller in the elderly compared to younger adults (Flegal et al. 2004).[iii]

The Present Study: Attributable Mortality using the Health and Retirement Study

In this study, we examine mortality attributable to obesity using a nationally representative birth cohort of middle-aged Americans from the Health and Retirement Study (HRS). As noted

above, age has previously complicated the estimation of attributable mortality. Hence, we draw on data from the HRS, which is specially designed to analyze birth cohorts of Americans over narrow age ranges and produce estimates generalizable to the national level. Respondents in our sample are Americans born between 1931 and 1941. They were ages 50-61 when first interviewed in 1992 and we follow them through 2004. The HRS is similar to other large-scale health surveys such as NHANES in that both data sources are nationally representative, collect data on a wide-range of health and social indicators, and are linked to the National Death Index. In the context of examining middle-aged adults, the HRS offers two important advantages. First, it contains a sample of almost 10,000 respondents of adults aged 50-61 increasing the precision of estimates for this specific age group. In comparison, NHANES III, a study conducted over a similar period as the HRS, contains only one-quarter the number of respondents within this age range. Second, SES can be an important confounder in the association between weight status and health (Lauderdale 2005) and has been overlooked in previous research. The HRS possesses very high-quality indicators of socioeconomic status (SES) including detailed measures of wealth (Smith 1995), which are not available in NHANES and other health surveys.

The association between weight status and mortality in middle-aged adults is increasingly important to determining the future direction of life expectancy in the US. The proportion of Americans who are in their fifties and sixties is expected to grow from approximately one-fifth to one-quarter of the US population over the next decade or so (U.S. Census Bureau 2005). Our target population is the 1931 to 1941 birth cohort. They are the predecessors to the numerically large baby-boom cohorts born between 1946 and 1964. Many baby boomers are now moving through the fifth and sixth decades of life, and this study provides insight into how weight status

is shaping their mortality in the current decade and will shape their mortality in the future. The shift toward an older population along with the fact that the majority of deaths in the US occur among individuals over age 50 highlight the importance of examining the association of weight status and mortality in those over age 50. We choose to examine middle-aged adults—those 50-73 over the study period—as opposed to an older sample for a number of reasons. Compared to older adults, middle-aged adults are less burdened by age-related comorbidities that can obscure the estimation of a causal relationship between weight status and mortality. Moreover, the changes in height and body mass composition that are common in older individuals complicate the measurement of weight status in the elderly (Gallagher et al. 1996; Janssen & Mark 2007). Finally, selective mortality, a force thought to reduce the effect of excess body weight on mortality because of depletion of at-risk subjects, is less influential among middle-aged adults in a low mortality population such as the US.

In contrast to prior studies on attributable mortality, which have in general combined estimates collected over many decades, we estimate relative and attributable risks over a recent period, 1992 to 2004. Given evidence that obesity-related relative risks may have declined (Flegal et al. 2005), this approach allows us to estimate the association between weight status and mortality using current data rather than relying on past estimates of relative risk. Finally, the effect of obesity on mortality has been judged against the well known effects of smoking on mortality, often without calculating attributable risk. Therefore, we also estimate smoking-attributable mortality as a point of comparison to that associated with obesity. To our knowledge, this comparison has not been previously made using a nationally representative data source.

Estimating Attributable Mortality

By "attributable mortality," we refer to the portion of deaths in a target population that would be avoided if a risk factor is entirely eliminated from the population. Alternatively, "attributable deaths" or "excess deaths" refer to the actual number of deaths in the target population that would be avoided if a risk factor were eliminated. The number of attributable deaths is obtained by multiplying the number of total deaths in a target population with its associated population attributable risk fraction (PAF). The PAF is the fraction of a particular disease (or in our case, deaths) that can be attributed to a risk factor and is based on both the relative risk and prevalence of that risk factor. An advantage of the PAF over other measures of association such as the relative risk or odds ratio is that the PAF provides a concise summary of the harm caused by a health-related risk factor and indicates the maximum societal benefit that can be achieved if efforts are successful at entirely eliminating a risk factor from the population. For example, PAFs are widely calculated by both governments and scientists to document the large mortality effect of smoking to support public anti-tobacco spending (Centers for Disease Control and Prevention 2002).

A contribution of this analysis is that we use data that is nationally representative of our target population of Americans born during 1931-1941. Hence, our estimates of relative risks, from which the PAF is directly based on, should closely mirror the actual associations operating in the target population. In contrast, most major studies on weight status and mortality have relied on convenience samples limited to specific segments of the population. These include the Nurses Health Study (Manson et al. 1995), the Physicians Health Study (Ajani et al. 2004), the National Institutes of Health—AARP cohort (Adams et al. 2006), and the second Cancer Prevention

Study (Calle et al. 1999), which was a snowball sample of friends of the American Cancer Society. Many of these samples over-represent whites and those with high SES (Calle et al. 2002; Schatzkin et al. 2001). Relative risks derived from convenience samples are not necessarily applicable to the US population (Malarcher et al. 2000; Sterling et al. 1993). This is important in the context of estimating attributable mortality because small deviations in relative risk can translate into substantial differences in attributable mortality (Flegal et al. 2004).

The Confounding Role of SES

Another contribution is that we account for confounding by SES across its multiple dimensions. In a highly influential critique of the published literature of the time, Manson et al. (Manson et al. 1987) highlighted the role of confounders (e.g., smoking) in estimating the association between weight status and mortality, but did not include SES. SES inequalities in health and mortality are some of the most well documented findings in the social sciences. In addition, weight status in the US is strongly patterned by SES, with differentials being most evident among women (Chang and Lauderdale 2005). Even analyses limited to specific occupation or professional cohorts may be subject to residual confounding by SES (Lauderdale 2005). Hence, SES is a potential source for divergent findings in the literature. African Americans, and to a lesser extent Hispanics, also exhibit higher average weight status compared with non-Hispanic Whites (Denney et al. 2004). Most published research has included race and ethnicity, but the failure to include the SES correlates of weight status can result in an over-estimation of the relative risks associated with higher weight status (BMI≥25.0).

Previous studies often control for education. Educational attainment is considered a desirable measure of SES because it can be easily obtained in most individuals, is relatively stable throughout adult life, and captures the degree to which individuals possess knowledge-based resources about healthy lifestyles (Elo and Preston 1996; Galobardes et al. 2006). However, increasing attention is now being given to the multidimensional nature of SES, and researchers are advocating the inclusion of multiple dimensions of SES to capture the complex pathways through which SES is associated with health endpoints (Braveman et al. 2005; Pollack et al. 2007). For example, household income is known to be independently associated with a wide array of health endpoints including mortality net of education (Bond Huie et al. 2003; Braveman et al. 2005). Household income is only moderately correlated with education in American adults (Braveman et al. 2005) and unlike education it can reflect changes in household circumstances in adulthood. With respect to weight status, overweight and obese individuals may face employment and income discrimination suggesting that income can vary considerably across weight status at any level of education (Averett and Korenman 1996; Baum and Ford, 2004). Household income also measures the ability of individuals to purchase healthy foods, which are often more expensive than nutritionally poor and calorie dense foods (Drewnowski and Specter 2004), and other resources (e.g., gym membership) that are associated with weight status.

Beyond education and income, a number of studies show that wealth is independently associated with many health endpoints (Duncan et al. 2002; Pollack et al. 2007). Wealth is robust to short-term fluctuations in income due to job loss or illness and is an indicator of accumulated economic resources over the life course. Households with higher wealth may be better able to afford high quality medical care or absorb the financial burden that arises from a new illness

(Smith 1999). In middle-aged adults who have long since completed their education and have been in the workforce for many years, accumulated wealth can differ markedly within any level of education or income (Krieger et al. 1997). Specific to weight status, households with higher wealth may reside in advantaged communities that provide a more favorable food environment (Baker et al. 2006; Chung & Myers 1999) as well as safe recreation places (e.g., parks) conducive toward physical activity. These and other neighborhood-level advantages have been shown to influence weight status (Chang 2006; Poortinga 2006; Popkin et al. 2005). To our knowledge no prior study has controlled for wealth, perhaps because it is not available in previous surveys such as the NHANES. The HRS contains detailed measurements of both income and wealth with relatively few missing cases (Smith 1995), and we will control for both of these dimensions of SES in addition to education.

The Importance of Preexisting Illnesses

Estimating the true causal effect of weight status on mortality raises complex methodological issues with respect to the role of confounding by preexisting illness. Many common illnesses including cancer and respiratory disease can cause substantial weight loss while increasing the risk of death (Manson et al. 1987). Ignoring the role of preexisting illness in initiating weight loss would lead to an under-estimation of the observed effect of weight status on mortality. However, preexisting illnesses (e.g., cardiovascular disease, cancers) could also be intermediary disease states on a causal pathway linking weight status to mortality. Hence, including the presence of preexisting illnesses as a control variable is not a straightforward solution, and the importance of confounding by illness remains controversial (Flegal et al. 2007; Manson et al. 2007). By excluding older adults in this analysis, we somewhat limit the role of preexisting

illnesses as a confounder, but this does not obviate the need to examine its effect on our estimates. Numerous methods have been employed to estimate the magnitude of confounding by illness but findings have been mixed (Adams et al. 2006; Ajani et al. 2004; Al Snih et al. 2007; Calle et al. 1999; Flegal et al. 2007; Sempos et al. 1998). One method is to stratify the analysis by health status to better estimate a true causal effect. The expectation is that those without a history of a major illness would exhibit higher effects of obesity on mortality compared to those with a preexisting condition. For example, using the second Cancer Prevention Study, Calle et al. (1999) found a stronger effect of obesity (BMI≥30.0) on mortality among those without a major illness (including heart disease, cancer, stroke, and respiratory disease) compared to those with a major illness across both sex and smoking status. In contrast, Flegal et al. (2007), reported no consistent pattern of increase in the association of obesity on mortality after excluding those with a history of major illness using combined data from NHANES I-III. Stratifying by time on study is another method used to account for confounding by illness guided by the assumption that the association between weight status and mortality in the early part of the study period is highly confounded by preexisting illnesses (Manson et al. 1987). In the National Institutes of Health-AARP Cohort of adults aged 50-71 studied over 10-years, Adams et al. (Adams et al. 2006) found that the relative risks associated with obesity (BMI≥30) were lower in the first 5 years of the study verses the final 5 years. For example, among men, the relative risk of death for those with a BMI of 30.0-34.9 (with reference to a BMI of 23.5-24.9) was 0.99 in the first 5 years of the study and increased to about 1.20 in the final 5 years. Similar increases in relative risk across time were reported for women. However, other techniques related to time on study such as excluding deaths occurring early in the study have been reported to have little effect on the association between weight status and mortality (Al Snih et al. 2007; Allison et al.

1999b; Flegal et al. 2007; Sempos et al. 1998). Given some of these discrepancies, we will compare multiple approaches and provide further evidence toward evaluating the importance of confounding by illness. Here, we will compare multiple approaches including methods that stratify the sample and account for the effect of time on study.

Summary

We examine relative and attributable risk associated with higher weight status (BMI≥25.0) and mortality in a nationally representative cohort of middle-aged Americans aged 50-61 in 1992 and followed through 2004. In contrast to previous research on attributable mortality, this study estimates relative risks contemporaneous with estimates of attributable risk and excess deaths. We estimate these figures over a recent period (1992-2004) as opposed to using older data that may not reflect the current association of weight status and mortality. Given that obesity is often juxtaposed with cigarette smoking as a major source of preventable mortality, we also estimate smoking-attributable mortality as a point of comparison, which has not been done previously using a nationally representative data source. Contributions of this investigation also include: (1) focusing on a narrow age-range of middle-aged adults who comprise a rapidly growing segment of the US population, (2) relying on a nationally representative sample that closely mirrors the characteristics of the target population, (3) controlling for multiple dimensions of SES, which could not be done with previous data, and (4) using multiple methods to examine confounding by illness.

DATA & SAMPLE

The HRS is an ongoing probability-based longitudinal dataset of Americans aged 50 and over. The HRS possesses detailed information on a wide range of SES indicators, health status, and health-related behaviors. It consists of five nationally representative samples of selected birth cohorts born in the early and middle part of twentieth century. This analysis is based on the largest birth cohort comprised of individuals born between 1931 and 1941. They were first interviewed in 1992 at ages 50-61. HRS investigators provide vital status linkages with the National Death Index. Deaths are measured through 2004, which is the latest available year of mortality data currently available in the HRS. Analyses were conducted using the RAND HRS data file, which provides edited data on most key variables used in this investigation. We obtain more detailed data on cigarette smoking from the original 1992 HRS data file. The overall sample size of the cohort is 9,814. After accounting for missing data on covariates and vital status information we analyze a sample of 9,462 respondents—96% of the overall sample. We utilize the HRS-supplied sampling weights, which allow our results to be generalized to the noninstitutionalized population of Americans aged 50-61 in 1992. Approximately 15% (n=1,376) of the sample died by 2004. All analyses are conducted with STATA, version 9.0.

MEASURES

Weight Status

Weight status is measured by BMI to be consistent with the majority of studies in this area. BMI is treated categorically using current definitions advocated by the World Health Organization (2000) and the National Heart, Lung, and Blood Institute (1998). The classifications are: underweight (BMI<18.5), normal (BMI 18.5-24.9), overweight (BMI 25.0-29.9), obese I (BMI

30.0-34.9), obese II/III (BMI≥35.0). We combine obese II (BMI 35-39.9) and obese III (BMI≥40.0) because of the small percentage (~1%) of respondents in the latter category. BMI in the HRS is based on self-reports of height and weight. There is an ongoing debate on the validity of self-reported height and weight data (Ezzati et al. 2006; Nieto-Garcia et al. 1990; Spencer et al. 2002; Stunkard & Albaum 1981; Weaver et al. 1996; Yun et al. 2006). Previous studies have found self-reports to be a valid proxy for clinically measured values (Jeffery 1996; Spencer et al. 2002; Weaver et al. 1996). Using data from NHANES III (1988-1994)—a survey that contains both self-reported and clinically measured values for the same respondent—we found that the correlation between self-reported and clinically measured BMI is 0.94 for adults aged 50-61 (N=2,185) with no appreciable difference across sex. High correlations of this magnitude have been reported previously (Spencer et al. 2002; Weaver et al. 1996).

Other Predictor Variables

SES is measured by education, household income, and household wealth. Education is measured categorically: No High School Diploma, High School Diploma/GED, Some College, and College Degree. Alternative specifications such as years of schooling were explored and produced no substantive differences in results. An advantage of the HRS data over other nationally representative health surveys is that the it contains high-quality and detailed data on income and wealth with relatively few missing cases (Moon and Juster 1995). Due to the sensitive nature of disclosing information on assets, income and wealth data are normally subject to high non-response rates in surveys. In contrast to most health surveys, the HRS implemented a method of probing using progressively smaller income "brackets" if respondents were unwilling to provide a precise figure. This technique greatly reduced the amount of missing data

in the HRS (Smith 1995). Household income measures the income of both the respondent and their spouse. Household wealth measures total household assets after accounting for debts including the value of real estate, savings, retirement accounts, and investments. Based on published literature using the HRS, we measure both income and wealth continuously (Bond Huie et al. 2003). We logarithmically transform both income and wealth to produce more normal distributions. Given that wealth is negative in some respondents, we add a constant term to all values before taking the logarithm.

Cigarette smoking is an important confounder to include because smoking is strongly associated with a higher mortality risk and a lower weight status (Krueger et al. 2004). We construct five-categories of smoking exposure to capture incremental increases in the effect of smoking similar to published literature on smoking and mortality (Rogers et al. 2005). The categories are: (1) Never Smoker, (2) Former Smoker, (3) Current Light Smoker (<1 pack per day), (4) Current Moderate Smoker (1 to <2 packs per day), and (5) Current Heavy Smoker (2 or more packs per day). Other variables we include are sex and race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, Other race/ethnicity). Low levels of physical activity are associated with both obesity and higher mortality, and physical activity has been shown to confound the relationship between weight status and mortality (Ajani et al. 2004). Therefore, we also include physical activity, which is measured as a dummy variable indicating vigorous physical activity (≥3 times per week).

Previous studies in this area have invariably controlled for biological markers associated with weight status (e.g., blood pressure and cholesterol) often without justification (see Manson et al.

(1987) for a discussion). We do not control for biological risk factors because they are likely to be intermediaries on a causal pathway between weight status and mortality. Therefore, a similar problem of intermediary causal linkage arises with biological risk factors as with comorbidites discussed earlier. For example, obesity may result in high blood pressure that in turn increases the risk of cardiovascular mortality. Including such biological correlates would then reduce the relative risks that we estimate and is inconsistent with the objectives of this investigation—namely, to quantify the association between weight status and mortality independent of socio-demographic and behavioral confounders.

ANALYTICAL APPROACH

The first step of the analysis is to estimate relative risks of weight status. Consistent with the majority of published papers in this area, we utilize Cox proportional hazard regression models to estimate hazard ratios (HR), which are a form of relative risks. The hazard model predicting death from any cause has the form:

$$log\ h_i(a) = h(a) + \sum_j \beta_j X_j + \beta_{un} * UNDER + \beta_{ov} * OVER + \beta_{obi} * OBESEI + \beta_{obii} * OBESEII \qquad Eq.\ (1)$$

Where *i* subscripts an individual and *a* signifies age measured in days. $h(a)$ is the baseline hazard function. B_jX_j is an adjustment variable and its associated coefficient. *UNDER, OVER, OBESEI,* and *OBESEII* are dummy variables for each weight status category—underweight (BMI<18.5), overweight (BMI 25.0-29.9), obese I (BMI 30.0-34.9), and obese II/III (BMI≥35.0), respectively. A BMI of 18.5 to 24.9 is the reference category. Respondents become at-risk for death on their 50th birthday (respondents who enter the study after age 50 are censored until the age of interview in 1992). Respondents who survive through the follow-up period are censored at the end of the study on December 31st, 2004. Preliminary analysis showed

no significant interactions between weight status and sex and therefore we combine both sexes in all models. Age is used as the x-axis time scale variable (Korn et al. 1997). The proportionality assumption of the regression models was confirmed by testing the slope of the Schoenfeld residuals.

The HRs estimated in the first part of the analysis are used to calculate the PAF. There are numerous methods available to estimate the PAF, which all share a common conceptual basis. The PAF indicates the fraction of cases (e.g., deaths) that would be avoided in a counterfactual situation where an exposure is entirely eliminated from a population. To calculate the PAF, the following formula is employed: (See Bruzzi et al. (1985) for a derivation; also discussed in Rockhill et al. (1998) and Benichou (2001)):

$$PAF_k = pd_k\left(\frac{RR_k - 1}{RR_k}\right) \qquad \textit{Eq. (2)}$$

Where PAF_k is the PAF for the k^{th} exposure category (e.g., overweight, obese I, obese II/III) and pd_k is the fraction of total deaths that are exposed to the k^{th} category. RR_k is the relative risk of the k^{th} category with reference to normal BMI (18.5-24.9) estimated by the HRs from the Cox regression models. Underweight (BMI<18.5) is treated as a non-exposed and non-reference category and does not enter into the calculation of attributable deaths. The PAF is additive across discrete categories of a risk factor. So, for example, the PAF for higher weight status can be obtained by summing the PAFs for the individual higher weight status categories (overweight+obese I+obese II/III. Similarly, we also calculate the PAF for current and former smoking by combining the individual categories. Equation (2) accounts for confounding by all other variables included in the Cox regression models. It does not account for interaction effects

between exposure and non-exposure variables.[iv] Confidence Intervals (95%) are derived using the jackknife method (Lehnert-Batar et al. 2006).

To calculate the number of attributable deaths, the PAF is multiplied with the actual number of deaths in the US occurring to the 1931-1941 birth cohort in 1999, which is the mean year of death in the sample. Previous research has combined relative risk estimates derived from data collected prior to 1990s with the total number of US deaths in 2000 (Flegal et al. 2005; Mokdad et al. 2004). In contrast, our approach will generate excess death estimates contemporaneous with the relative risk and PAF estimates.

RESULTS

Table 1 shows descriptive characteristics of the sample. Approximately 64% of the sample has a BMI≥25.0 reflecting that the majority of middle-aged Americans have a weight status above the range defined as normal. Approximately 16% of the sample is obese I (BMI 30.0-34.9) and 6% is obese II/III (BMI≥35.0). Approximately 35% of the sample falls within the normal range (BMI 18.5-24.9) with the remainder (1.3%) classified as underweight (BMI<18.5). The mean age of the sample is 55.6 years. Nearly 53% of the sample is female and approximately 81% is non-Hispanic white. The mean household income is $49,800 and the mean household wealth is approximately $236,000. These values reflect the skewed distribution of income and wealth and we logarithmically transform these values in the regressions.

Table 2 displays the HRs from the first series of Cox regression models. The objective of this initial portion of the analysis is to examine the HRs associated with higher weight status and then

progressively include sets of behavioral and socio-demographic characteristics that may act as confounders. Given that most published literature has controlled for sex, race, and behavioral attributes such as smoking, we begin by including these characteristics and then add SES in the final model to examine its contribution. Model I in Table 2 examines the relationship between weight status and mortality only adjusting for sex. In Model I, obese II/III (BMI≥35.0) is associated with a 55% increase in the mortality risk (HR=1.55 95% CI: 1.26, 1.91) compared to normal levels (BMI 18.5-24.9). The HR for underweight (BMI<18.5) is 4.35 (95% CI: 3.13, 6.05). While the two extreme ends of the BMI distribution are associated with excess mortality, the overweight (BMI 25.0-29.9) and obese I (BMI 30.0-34.9) categories are protective, though only the HR of overweight (BMI 25.0-29.9) is significant (HR=0.85; 95% CI: 0.74, 0.98). Adjusting for race/ethnicity in Model II does not alter the HRs substantially, although a slight decrease in the HR of obese II/III (BMI≥35.0) is observed (HR=1.55; 95% CI: 1.18, 1.80). This is most likely due to a relative large number of non-Hispanic Black respondents in the obese II/III category compared to other race/ethnicity groups. Model II shows a significantly elevated HR for non-Hispanic Blacks with respect to non-Hispanic Whites (HR=1.78, 95% CI: 1.56, 2.04). The mortality hazard for both Hispanics and the "other" race/ethnicity category did not significantly differ from non-Hispanic whites.

Model III further adjusts for the behavioral correlates of weight status, which are smoking status and vigorous physical activity. Model III retains the same general shape of the weight status and mortality relationship shown in Models I and II in that only obese II/III (BMI≥35.0) and underweight (BMI<18.5) are associated with higher mortality. The HRs for the higher weight status categories (overweight, obese I, obese II/III) did increase, though only moderately. The

largest increase is observed for obese II/III (BMI≥35.0) where the HR increased from 1.46 (Model II) to 1.67 (Model III). This change is largely driven by the inclusion of smoking status consistent with the fact that smokers tend to be thinner and at higher risk for mortality compared to never smokers. Model III also highlights the incremental increases in mortality associated with greater tobacco exposure where heavy smokers experience a nearly a four-fold increase (HR=3.97, 95% CI: 3.10, 5.07) in mortality compared to never smokers.

In the fully adjusted Model IV, we include the three measures of SES—education, income, and wealth. The effect on the higher weight status HRs is modest, although there is a decrease in the HR of obese II/III (BMI≥35.0) compared to Model III (1.67 verses 1.53). Model IV highlights the fact that education, income, and wealth each show significant gradients with respect to mortality. For example, those with at least a college degree have an approximately 30% reduced risk of mortality compared to those who did not complete high school. Similarly, increases in income and wealth are independently associated with lower mortality. Income and wealth only had a small effect on the HR of obese II/III (BMI≥35.0) after controlling for education (an additional 3% reduction was observed in a model that only controlled for education verses a model that included all three measures of SES; not shown in table).

Sensitivity Models

A critique of the statistical approach used in Table 2 is that the regression models do not account for confounding by illness (Manson et al. 1987; Willett et al. 2005). Advocates of the view that confounding by illness is important would argue that the HRs associated with the higher weight status categories (overweight, obese I, obese II/III) have been under-estimated. In this part of the

analysis, we implement a series of models that attempt to account for this confounding by changing model specifications based on varying theoretical assumptions (Tables 3 and 4). We reproduce Model IV (fully adjusted model, Table 2) in the second column of Table 3 to compare with our sensitivity models.

A straightforward method to account for confounding by illness is to control for the presence of disease. As discussed, this raises complex estimation issues because the presence of disease can act both as a confounder and as an intermediary factor on the pathway that causally links weight status with death. As a confounder, controlling for disease presence should increase the HRs of higher weight status (overweight, obese I, obese II/III) because it controls for the higher mortality rate among lower weight status (underweight, normal) due to wasting illnesses. In contrast, preexisting illnesses acting as an intermediary factor would tend to depress HRs when included because it captures some of the causal links between weight status and death. Model V (Table 3) controls for disease presence by including dummy variables for history of a major illness (i.e., heart disease, stroke, respiratory illness, and cancer) and favorable self-reported health. Self-reported health is included because it is a global measure of health status that may more accurately measure underlying or undiagnosed disease processes (Idler & Benyamini, 1997), which would include weight loss. Favorable health is defined as excellent, very good, or good (vs. fair or poor) self-reported health. Comparing Model IV to Model V in Table 3, we find the expected *decrease* in the HR for underweight (2.96 in Model IV to 2.41 in Model V) since we control for the disproportionate number of ill respondents in this category. Model V indicates virtually no change in the HRs for overweight (BMI 25.0-29.9) and obese I (BMI 30.0-34.9) compared to Model IV. Furthermore, the HR for obese II/III (BMI≥30.0) *decreased* (from

1.53 in Model IV to 1.29 in Model V) suggesting that at least in this highest BMI category adjusting for the intermediary linkages outweighed adjustment for confounding.

Another strategy commonly implemented is to condition the sample on healthy respondents (Models VI and VII). Theoretically, excluding sick respondents from the sample should eliminate confounding by illness to the extent that we are able to identify acutely ill respondents who have experienced resultant weight loss. On the assumption that confounding is important, we would expect the HRs for the underweight category to *decrease* and the HRs for the higher weight status categories (overweight, obese I, obese II/III) to *increase* compared to Model IV. Excluding unhealthy respondents, however, also raises problems with respect to the interpretation of the HRs. We may be inadvertently removing respondents who have long-standing illnesses like chronic heart disease that are, in part, attributable to obesity. Models VI and VII also eliminate a large percentage of deaths (approximately 45%) from the sample, thereby resulting in a loss of statistical power. Model VI limits the sample to respondents who report no history of major illness while Model VII is limited to those with favorable self-reported health. Models VI and VII both show the expected decrease in the HR of underweight in Models VI (HR=2.01) and VII (HR=1.48) compared to Model IV (HR=2.96). However, Models VI and VII provide little evidence supporting a strong role for confounding by illness. In both models, the overweight (BMI 25.0-29.9) and obese I (BMI 30.0-34.9) HRs were close to those reported in Model IV and there was no systematic pattern of increase. There seems to be more of an effect on the HRs for obese II/III (BMI≥35.0), though again no clear pattern emerges. Compared to Model IV, there is an increase in the HR of obese II/III (1.53 to 1.63) for Model VI while there appears to be a decrease (1.53 to 1.42) for Model VII.

In sum, the sensitivity models presented in Table 3 do not support a strong role for confounding by illness in biasing our original estimates of relative risk, yet the findings are somewhat mixed. The overweight and obese I categories generally did not change across the studies while there was more of an effect for obese II/III, though the direction of change was inconsistent.

As a final sensitivity analysis, we interact weight status and time on study (Table 4). The advantage of this approach is that we retain the complete sample and all deaths that have occurred. The theoretical justification is that the early period of the study is more highly confounded by illness than the latter period because acutely ill respondents who have experienced weight loss would die at a higher rate early on. This technique is similar to stratifying the analysis by time on study, which has been done previously, but interacting allows us to directly test the significance of the interaction term (Allison 1995) as well as treat potential changes in the HR as a continuous function of time.[v] Estimating the interaction model requires that we use time as the x-axis variable as opposed to age as we did in prior models (since we are interested in capturing interactions with time-on-study rather than age). We include age as a covariate. We also collapse overweight (BMI 25.0-29.9) and obese I (BMI 30.0-34.9) into one aggregated category (BMI 25.0-34.9) to reduce the number of interaction terms and increase the power of the model (Model VIII). The obese II/III (BMI≥35.0) remains intact. The normal category (BMI 18.5-24.9) is the reference category. Model VIII estimates an equation in the form:

$$\log h_i(t) = h_o(t) + \sum_j \beta_j X_j + (\beta_1 * OWOB + \beta_{int1} * OWOB * t) + (\beta_2 * OBII + \beta_{int2} * OBII * t) \quad \text{Eq. (3)}$$

Where $h_i(t)$ indexes the hazard of death for individual *i* at time *t* measured in days since interview (logarithmically transformed). *OWOB* is a dummy variable indicating a BMI between 25.0 and 34.9 (overweight and obese I). Accounting for the main and interaction terms, the effect of *OWOB* on mortality is interpreted as $(\beta_1 + \beta_{int1} * t)$. A positive β_{int1} would indicate that the effect of *OWOB* increases with time on study. This would be expected if the reference category contains a disproportionately large number of ill respondents who die early in the study. Similarly, the effect of *OBII* (obese II/III) is $(\beta_2 + \beta_{int2} * t)$. We also interact a dummy for underweight with time on study (not shown in equation (3) for clarity). Results in Table 4 shows that the HR of the interaction term for *LOW* is significant and less than 1.0 (HR=0.75; 95% CI: 0.57, 0.98)—HRs less than 1.0 are indicative of negative coefficients. This is consistent with the idea that many individuals who are underweight (BMI<18.5) are ill at baseline and die at a high rate in the early years of follow-up. The interaction terms for *OWOB and OBII*, nonetheless, are approximately 1.0 and nonsignificant. This suggests that the effect of the two higher weight status categories do not vary with time on study.

Attributable Mortality

We next calculate the PAF and number of excess deaths in the 1931-1941 birth cohort for 1999, which is the mean year of death in this sample (Table 5). In addition to estimating these figures for higher weight status (overweight, obese I, and obese II/III), Table 5 also presents estimates of smoking-attributable mortality as a point of comparison. The figures presented in Table 5 are based on results from the fully adjusted Model IV of Table 2. Given that the results from the sensitivity models presented in Table 3 may produce different estimates of attributable mortality

with respect to weight status, we also calculate attributable mortality based on these models and describe them below.

The PAF for each risk category is shown in the third column of Table 5. The value in each cell indicates the fraction of deaths that would be avoided if all individuals in the respective risk category are shifted to the reference category without changing any of their other attributes. Negative values are reflective of relative risks less than 1.0. They imply that mortality would *increase* if the risk category were eliminated. For example, the PAF of overweight (BMI 25.0-29.9) is -0.06 (95% CI: -0.16, 0.05) suggesting that the number of deaths would increase by 6% if all respondents in overweight (BMI 25.0-29.9) moved to the Normal range (BMI 18.5-24.9). The PAF for higher weight status as a whole (overweight+obese I+obese II) is -0.04 (95% CI: -0.16, 0.08). The PAF for obesity (BMI≥30) is slightly positive at 0.02 (95% CI: -0.04, 0.08). This translates into 6,098 (95% CI: -15,059, 27254) deaths in 1999 out of a total of 341,354 deaths occurring in the 1931-1941 birth cohort in 1999. Note that the estimated PAF and number of excess deaths for obesity (BMI≥30) is not statistically significant reflecting the fact that the PAF is very close to zero. Using the sensitivity models from Table 3, the PAFs for obesity (BMI≥30.0) would range from less than 1% (Model V) to about 3% (Model VII). Excess deaths based on a PAF of 3% for obesity (BMI≥30.0) would result in 10,003 deaths in contrast to the 6,098 deaths from the original model. Table 5 also clearly shows the much higher estimates for smoking-attributable mortality, where former and current cigarette smoking has a combined PAF of 0.42 (95% CI: 0.31, 0.53) and is responsible for nearly 145,000 deaths in 1999.

DISCUSSION

Mortality attributable to higher weight status (BMI≥25.0) continues to be a highly researched topic engendering much scientific controversy. In this nationally representative cohort of middle-aged Americans analyzed over the 1990s and 2000s, we found that higher weight status (BMI≥25.0) is not substantially associated with excess mortality as measured by both its relative and attributable risks. Within the higher weight status categories (overweight, obese I, obese II/III), only obese II/III (BMI≥35.0) was significantly associated with a relative risk greater than 1.0 (with reference to a BMI of 18.5-24.9). The estimated excess risk was approximately 50%. With respect to attributable mortality, the percentage of deaths due to obesity (BMI≥30.0) was small, approximately 2% (the range was 1%-3% if we consider sensitivity models) and not statistically significant. According to our primary estimates, approximately 6,000 deaths to the 1931-1941 cohort in 1999 can be attributable to obesity (BMI≥30). In contrast, the percentage of smoking-attributable mortality was 42%, resulting in more than 140,000 deaths in 1999, more than 20 times that associated with obesity (BMI≥30.0). Compared to the previously published estimates of obesity-attributable mortality (Allison et al. 1999b; Flegal et al. 2005; Mokdad et al. 2004), our results are most consistent with Flegal et al. (2005). They reported that approximately 5% of deaths among adults aged 25 and over in 2000 were attributable to obesity (BMI≥30.0) compared to our 2% estimate for middle-aged adults. Both Allison et al. (1999a) and Mokdad et al. (2004) calculated attributable mortality based on a BMI≥25.0, which was estimated to be 13% and 15% of deaths in 1991 and 2000, respectively, for adults aged 18 and over. Based on our analysis, we find a small *negative* estimate for mortality attributable to a BMI≥25.0 (PAF=-0.02). Our findings are robust to confounding by multiple and detailed socio-demographic and behavioral characteristics including three separate measures of SES, which have not been

accounted for previously. SES confounding was most evident in the highest obese II/III (BMI≥35) group. We also examined multiple procedures to account for confounding by illness, and, although there is no ideal statistical method to deal with confounding, we found no clear pattern of evidence to suggest that preexisting illnesses substantially bias our findings. An advantage of this study over most published papers in this area is that we relied on a nationally representative sample rather than on selected occupation groups or otherwise non-representative populations.

Our results indicate a considerably smaller association between higher weight status (BMI≥25.0) and attributable mortality compared to Allison et al. (1999a) and Mokdad et al. (2004). The age-dependent nature of the obesity and mortality association makes direct comparison with the Allison et al. (1999a) and Mokdad et al. (2004) findings difficult because both prior studies did not stratify the analysis by age. Therefore, they did not generate age-specific relative risks for middle-aged adults from which we can directly compare with our relative risk estimates. Our estimates of relative risks are generally consistent with those reported by Flegal et al. (2005) in their age-stratified analysis of adults aged 60-69 (the most comparable age group to our data). Using combined data from NHANES I-III, Flegal et al. (2005) reported significant excess mortality only in the highest BMI category—obese II/III (BMI≥35.0)—and not among the overweight (BMI 25.0-29.9) or mildly obese (obese I: BMI 30.0-34.9). In adults aged 60-69, Flegal et al.'s (2005) estimates of relative risks were 0.95, 1.13, and 1.63 for overweight, obese I, and obese II/III, respectively, similar to our estimates of 0.87, 0.92, and 1.53 (reference level for both studies was 18.5-24.9). The confidence interval for each category overlapped considerably across both studies. The relative risks reported by Flegal et al. (2005) were combined across

NHANES data ranging from 1971 to 2000 while our estimates may be more applicable to the association between weight status and mortality during the 1990s and 2000s. We used finer detailed measurements of confounding variables compared to Flegal et al. (2005). For example, we controlled for 5 categories of incremental exposure to cigarette smoking while Flegal et al. (2005) used 3 (never, former, current). We also included three aspects of SES—education, income, and wealth—while Flegal et al. (2005) only controlled for education (in sensitivity models).

In a study of adults aged 50-70 based on the National Institutes of Health-AARP cohort conducted between 1995 and 2005, a period highly similar to our analysis, Adams et al. (2006) reported relative risks for the higher weight status (BMI≥25) categories that were on average 15% higher than our estimates. Adams et al. (2006) controlled for similar characteristics as we do here including race/ethnicity, detailed smoking exposure, physical activity, and education. They used a higher reference category (BMI 23.5 to 24.9) in their analysis compared to our reference level of a BMI between 18.5 and 24.9, but in preliminary work, we found that the higher reference category had little effect on our results. The data used by Adams et al. (2006), although possessing a very large sample size of 500,000 respondents, was based on a mailed questionnaire to members of the AARP, which elicited a response rate of only 18%. The HRS data used in this analysis is based on multi-stage sampling and the included probability weights adjusted for non-response (Heeringa & Connor 1995). The higher bounds of our 95% confidence intervals were similar to the HRs reported by Adams et al. (2006). If we calculate attributable mortality based on the higher bounds of our confidence intervals we reach a rough estimate of 8% for obesity-attributable (BMI≥30.0) mortality. Hence, obesity (BMI≥30.0)

would still be accountable for far fewer deaths compared to current and former smoking and the estimated association is still substantially smaller than those reported by Allison et al. (1999a) and Mokdad et al. (2004).

This study relies on recent data analyzing mortality through 2004. Flegal et al. (2005) provides evidence that the relative risk of obesity may have declined since the early 1970s. They reported a general declining trend in the relative risks associated with higher weight status in NHANES I (1971-1975) verses NHANES II (1976-1980) and NHANES III (1988-1994). Other reports, however, suggest no such decline. For example, Calle et al. (2005) found no decline in relative risks between the 1980s and 2002 based on an analysis of the second Cancer Prevention Study. Gregg et al. (2005) provide *indirect* evidence supporting a declining risk of mortality among the obese. They found that obese individuals in 1999-2000 had lower levels of total cholesterol, high blood pressure, and smoking compared with higher weight status individuals in the 1960s and 1970s. These favorable trends occurred in all weight status groups but the reductions were proportionately larger among obese groups indicating a relative improvement in their health over time. Higher weight status individuals may have disproportionately benefited from better medical management of risk factors for cardiovascular disease. For example, the rapid dissemination of lipid lowering drugs (e.g. statins) that occurred over the 1990s has been shown to be highly effective in reducing cholesterol levels (Carroll et al. 2005). While the health-related risk factors among the obese may be declining, there is, nevertheless, emerging evidence of increasing disability among the obese (Alley and Chang 2007). Moreover, there has been a disproportionate rise in diabetes in this group relative to leaner individuals (Gregg et al. 2005). Taken in tandem with our findings of a weak effect of obesity on mortality, these unfavorable

trends may be a product of overweight and obese individuals living longer than in the past, but also acquiring a number of co-morbid conditions as they age. Two recent studies examining mortality and disability simultaneously in older populations show the stronger effect of obesity on disability verses mortality (Al Snih et al. 2007; Reynolds et al. 2005). These findings suggest that medical management and public health efforts may have only been partially successful at combating the deleterious consequences of excess body weight. Further investigations are needed to examine potential secular declines in the association between obesity and mortality over time, an analysis that we are unable to do in this study because of the nature of our data.

It has been suggested that existing diseases confound the association between weight status and mortality (Manson et al. 1987; Willett et al. 2005). However, statistical techniques used to account for confounding raise other methodological problems. We excluded older adults from this study to limit the problem of confounding (as well as related problems associated with compositional changes in body mass), but in a middle-aged population we would still expect the prevalence of chronic illness to be relatively high. Therefore, we implement multiple methods to account for confounding by illness. Models that alternatively controlled for health status, excluded those with unfavorable health status, and allowed HRs to vary with time on study did not indicate that our original estimates were substantially biased. Other recent papers have reached similar conclusions with respect to confounding by illness (Al Snih et al. 2007; Flegal et al. 2007). Nonetheless, given the complex causal pathways existing among weight status, disease, and death in population-based samples we cannot fully rule out the effect of confounding by illness.

Selective survival bias should minimally bias our results since we excluded older adults. Processes of selective mortality are useful in many different contexts to explain observed decreases in the mortality effect of risk factors as a cohort ages (Kohler and Kohler, 2000; Vaupel et al. 1979). For example, selective survival bias is commonly used as an explanation for the weak effects of higher weight status on mortality in elderly populations (Janssen and Mark 2007; Manson et al. 2007). In a cohort of middle-aged adults, however, selective survival bias is unlikely to explain the weak effect of higher weight status. This is because in a low mortality population such as the US, relatively few deaths occur before the fifth and sixth decades of life. Approximately 17% of the 1931-1941 birth cohort examined in this study died by age 50. For selective survival to be important, most early deaths would have to be in individuals who are overweight and obese. Yet, in the US, most deaths at the younger ages are attributable to accidents or cancer (Jemal et al. 2005). Accidents are a cause of death not likely to be associated with weight status and mortality from many types of cancers are shown to be weakly related to higher weight status (Flegal et al. 2007; Krueger et al. 2004).

This study has limitations. First, we use BMI as a proxy for adiposity while other anthropometric measures may be more suitable (Kalmijn et al. 1999; Price et al. 2006; Seidell and Visscher 2000; Visscher et al. 2001). Currently, most nationally representative data sources use BMI as a measure of weight status because of its ease of collection and availability. By using BMI in this study, we are able to compare our results with many major studies examining weight status and mortality. The usefulness of BMI verses other measures of weight status such as waist circumference and the waist-to-hip ratio is still not fully explored with respect to middle- and older-aged adults (Price et al. 2006; Simpson et al. 2007). For example, Woo et al.

(Woo et al. 2002) found that in a sample of adults aged 70 and over, both BMI and waist circumference similarly predicted disease outcomes and mortality while the waist-to-hip ratio was not predictive of these events. In a sample of women aged 30-55, Manson et al. (Manson et al. 1995) also found that the waist-to-hip ratio was more weakly related to overall mortality as compared with BMI over a 16-year period (though, waist-to-hip ratio was a strong predictor of heart disease mortality). Nonetheless, future data collections should explore multiple measures of weight status that can be effectively collected in the context of population-based health surveys. We also measure BMI in middle adulthood while it is likely that the deleterious health effects of excess body weight accumulate over a lifetime (Jeffreys et al. 2003). Given that requisite large-scale data containing both weight status measurements early in life and mortality measurements later in life are not readily available, most research examining obesity and mortality have taken an approach similar to ours. Numerous studies have found that childhood and adulthood BMI are moderately and positively correlated (Casey et al. 1992; Guo et al. 1994; Serdula et al. 1993) suggesting that many respondents in our study who were obese in 1992, when BMI was measured, also were obese when they were younger (i.e., middle adulthood BMI proxies for BMI at younger ages). Moreover, a previous study reported similar patterns for weight status and mortality between recall measurements of early life BMI (age 21) and BMI measurements taken at the older ages (Corrada et al. 2006).

Finally, the HRS cohort used here is only nationally representative to the non-institutionalized population while deaths in our target population would include deaths of those residing in institutions. It is unlikely that this difference affected our results. Based on the 2000 Census of Population, only 1.1% of Americans aged 50-61 resided in institutional settings. It is also likely

that some respondents in our sample entered institutions after they were interviewed. Deaths occurring to these individuals are still captured by the mortality linkages used here. Therefore, this analysis is still able to capture a portion of deaths occurring in institutionalized individuals.

Despite concerns that increasing obesity levels will threaten future life expectancy improvements in the US, our findings lend support toward a weak effect of obesity on current mortality as indicated by both its relative and attributable risks. An important contribution of our analysis is that we focus on middle-aged adults, a group that is at high risk for cardiovascular and other chronic conditions that link higher weight status to death and has not been well studied relative to other age groups. It is becoming increasingly evident that higher weight status (BMI≥25.0) is not strongly associated with excess mortality among older adults over aged 70 (Al Snih et al. 2007; Flegal et al. 2005; Grabowski and Ellis 2001; Reynolds et al. 2005). Our results extend this pattern to middle-aged adults who are ages 50-73 over the study period. This finding is important because in order for obesity to have a large effect on mortality indicators such as life-expectancy it would have to be responsible for a substantial burden of premature deaths at the middle and older ages—where the majority of deaths in the US occur. Yet, we found that only a BMI≥35.0 is associated with excess mortality, which is a minority of all individuals who possess higher weight status (BMI≥25.0). The excess mortality in this group is not insubstantial. It is approximately 50% higher than normal BMI levels (BMI 18.5-24.9), similar to the mortality difference observed between non-Hispanic blacks and non-Hispanic whites at the middle ages.

There have been substantial differences in past estimates of obesity-related attributable mortality. Reasons for these differences are numerous and complex, partly reflecting differences in sample

composition, techniques used to account for age effects, and the time period of data sources. This investigation examined a nationally representative sample of middle-aged adults across a narrow age range based on data that was specially designed for birth cohort analysis and possessed high-quality information on deaths and socio-demographic indicators. Additional studies using data collected over a recent period will help further evaluate whether obesity is a large source of premature mortality and help assess whether there have been secular declines in the association between obesity and mortality. In sum, our findings suggest that obesity is not a large source of attributable mortality among middle-aged adults and that prior estimates of obesity-related attributable mortality potentially overestimate the current association between obesity and mortality.

FOOTNOTES:

[i] Allison et al. (1999a) refer to these estimates as obesity-attributable deaths, although their calculations were actually based on BMI values that encompass both overweight (BMI 25.0-29.9) and obese (BMI≥30) categories according to current definitions set forth by the World Health Organization (2000) and the National Heart, Lung, and Blood Institute (1998).

[ii] The term weight status is commonly employed as term for weight adjusted by height. Here, we use "higher weight status" to signify a BMI≥25.0. Consistent with current definitions, we use overweight to refer to a BMI of 25.0 to 29.9 and obese to refer to a BMI≥30.0.

[iii] Flegal et al. (2004) show that estimates of obesity-related attributable risk is highly sensitive to effect modification by age (different relative risks of higher weight status by age). They contend

that the method used by Allison et al. (1999a) and later by Mokdad et al. (2004) cannot fully account for effect modification by age and would likely lead to an overestimation of obesity-related attributable deaths. This is because the prior studies did not stratify by age and essentially applied relative risks from a pooled sample to adults of all ages including those over age 70. The bias partly arises from the fact that the samples used to derive relative risk estimates have different distributions of age and other characteristics compared with the target US population in 1991. In simulated models, Flegal et al. (2004) show that the magnitude of the overestimation is approximately 17%. Differential treatment of age, then, could only partly account for differences in attributable mortality across the studies. Since Allison et al. (1999) and Mokdad et al. (2004) did not stratify by age we cannot ascertain relative and attributable risks specifically in those under age 70, which would be relevant to this analysis.

[iv] Benichou (2001) and Flegal et al. (Flegal et al. 2004) review an alternate method to calculate the PAF (termed "weighted sum") that accounts for interaction effects as well as confounding. The "weighted sum" method estimates unadjusted relative risks of the exposure variable for each unique combination of confounder variables (subgroups or levels). The relative risks along with the proportion of exposed cases for each level are then summed to estimate the PAF. In contrast to Eq. (2), which relies on a single adjusted estimator of relative risk, the "weighted sum" method allows the relative risk to vary across subgroups, thereby accounting for interaction effects between the exposure variable and other variables. We do not use this method here for a number of reasons. First, an important justification for implementing the "weighted sum" method is to account for the strong interactions between age and weight status reported previously. Here, we examine a narrow age-range and it is unlikely that age in this context has a

strong modifying role (preliminary models failed to show any significant interactions between age and weight status). Second, unlike most prior work in this area, we include very detailed information on numerous confounding variables (e.g., five levels of smoking, three measures of SES). To gain precise estimates of relative risk using the "weighted sum" method, we would have to forgo the detail of confounding variables to obtain a manageable number of subgroups. Moreover, in preliminary analysis we also did not detect significant interactions between weight status and important potential modifiers such as sex, race/ethnicity, and SES that have been included in our models.

[v] Previous studies have stratified the follow-up period by two or more time-periods often using cut-points of between 2 and 5 years. Generally, there has been no theoretical justification as to the appropriateness of using these specific cut-points. By measuring time continuously and using interaction terms, we are able to assess an overall trend in the interaction.

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Table 1. Descriptive characteristics of the 1931-1941 HRS birth cohort at 1992 interview (N=9,462).

Characteristics	% or Mean (SD)
BMI Categories, %	
Underweight (<18.5)	1.3
Normal (18.5-24.9)	35.2
Overweight (25.0-29.9)	41.1
Obese I (30-34.9)	16.1
Obese II/III (≥35)	6.3
Age (years)	55.6 (3.2)
Male	47.5
Race/Ethnicity	
White, non-Hispanic	81.2
Black, non-Hispanic	10.2
Hispanic	6.4
Other	2.2
Education	
< HS Degree	23.0
HS Degree/GED	38.8
Some College	19.8
College Graduate +	18.4
Income ($1,000s)	49.8 (50.3)
Wealth ($1,000s)	236.3 (452.8)
Smoking Status	
Never Smoker	36.0
Former Smoker	36.9
Light Smoker (<1 pack per day)	9.0
Moderate Smoker (1 to <2 packs)	14.1
Heavy Smoker (≥2 packs)	4.1
Vigorous Physical Activity (≥3 times per week)	19.6
Deaths, 1992-2004 (n=1,376)	14.5

Notes: Data reflect sampling weights.

Table 2. Cox regression HRs predicting death from any cause, 1992-2004 (N=9,462)

Characteristics	Model I (+ sex)	Model II (+ race)	Model III (+ behaviors)	Model IV (+ SES)
BMI Categories (Normal, 18.5-24.9)				
Underweight (<18.5)	4.35*** [3.13, 6.05]	4.24*** [3.05, 5.88]	3.09*** [2.16, 4.39]	2.96*** [2.08, 4.21]
Overweight (25.0-29.9)	0.85* [0.74,0.98]	0.84* [0.73, 0.96]	0.88 [0.77, 1.01]	0.87 [0.76, 1.00]
Obese I (30.0-34.9)	0.91 [0.77,1.09]	0.87 [0.73, 1.04]	0.96 [0.80, 1.15]	0.92 [0.77, 1.10]
Obese II/III (35.0+)	1.55*** [1.26,1.91]	1.46*** [1.18, 1.80]	1.67*** [1.35, 2.06]	1.53*** [1.24, 1.90]
Male	1.88*** [1.66, 2.12]	1.88*** [1.67, 2.12]	1.67*** [1.48, 1.89]	1.75*** [1.55, 1.90]
Race/Ethnicity (White, non-Hispanic)				
Black, non-Hispanic	-	1.78*** [1.56, 2.04]	1.76*** [1.53, 2.03]	1.43*** [1.23, 1.67]
Hispanic	-	0.93 [0.75, 1.16]	0.98 [0.78, 1.23]	0.76* [0.60,0.97]
Other	-	1.03 [0.66, 1.60]	1.14 [0.74, 1.76]	1.08 [0.69, 1.69]
Smoking Status (Never Smoker)				
Former Smoker	-	-	1.67*** [1.41, 1.96]	1.63*** [1.38,1.92]
Light Smoker (<1 pack per day)	-	-	2.45*** [1.99, 3.03]	2.25*** [1.82, 2.79]
Moderate Smoker (1 to <2 packs)	-	-	3.45*** [2.89, 4.11]	2.99*** [2.50, 3.58]
Heavy Smoker (≥2 packs)	-	-	3.97*** [3.10, 5.07]	3.23*** [2.51, 4.14]
Vigorous Physical Activity (<3 x per week)	-	-	0.81** [0.69, 0.95]	0.83* [0.71, 0.97]

(cont.)

(Table 2, continued)

Characteristics	Model I (+ sex)	Model II (+ race)	Model III (+ behaviors)	Model IV (+ SES)
Education (Less than HS)				
HS Diploma/GED	-	-	-	0.87 [0.75, 1.01]
Some College	-	-	-	0.85 [0.71, 1.02]
College Graduate +	-	-	-	0.71** [0.57, 0.89]
Income[a]	-	-	-	0.94*** [0.91, 0.97]
Wealth[a]	-	-	-	0.46** [0.30, 0.73]

*** p<.001; **p<.01; *p<.05
Note: 95% Confidence intervals shown in brackets. Data reflect sampling weights.
[a] continuous in ln($1,000) units

Table 3. Cox regression models predicting mortality under different assumptions about the role of confounding by illness, 1992-2004

Characteristics	Model IV – Fully Adjusted Model from Table 2	Model V – Control for Major illness and Self-Reported Health	Model VI – Limited to No History of Major Illness	Model VII – Limited to Excellent/ V. Good/Good Self-Reported Health
BMI Categories (Normal, 18.5-24.9)				
Underweight (<18.5)	2.96*** [2.08, 4.21]	2.41*** [1.75,3.32]	2.01* [1.14, 3.54]	1.48 [0.74,2.93]
Overweight (25.0-29.9)	0.87 [0.76, 1.00]	0.89 [0.77,1.03]	0.88 [0.73, 1.05]	0.84 [0.70,1.01]
Obese I (30.0-34.9)	0.92 [0.77, 1.10]	0.88 [0.74,1.06]	0.99 [0.79, 1.25]	1.05 [0.82,1.33]
Obese II/III (35.0+)	1.53*** [1.24, 1.90]	1.29* [1.04,1.61]	1.63*** [1.23, 2.17]	1.42* [1.02,1.97]
Sample (No.)	9,462	9,462	7,589	7,325
Deaths (No.)	1,376	1,376	784	730

*** p<.001; **p<.01; *p<.05

Note: 95% Confidence intervals shown in brackets. All models control for sex, income, smoking status, race, wealth, education, and physical activity. Model IV is the fully adjusted model from Table 2 reproduced here to compare sensitivity models (Models V-VII). Data reflect sampling weights.

Table 4. Interaction of higher weight status (BMI≥25.0) with time on study

Characteristics	Model VIII
Main Effects (Normal, 18.5-24.9)	
LOW (<18.5)	4.83*** [3.04, 7.64]
OWOB (BMI 25.0-34.9)	0.86 [0.65, 1.15]
OBII (BMI≥35)	1.59* [1.04, 2.41]
Interaction Effects	
*LOW*time*	0.75* [0.57, 0.99]
*OWOB*time*	1.00 [0.85, 1.17]
*OBII*time*	0.97 [0.77, 1.22]
Sample (No.)	9,462
Deaths (No.)	1,376

*** p<.001; **p<.01; *p<.05

Note: 95% Confidence intervals shown in brackets. Model controls for age, sex, race, education, income, wealth, smoking status, and physical activity. Time is logarithmically transformed. Data reflect sampling weights.

Table 5. PAF and number of excess deaths associated with higher weight status (BMI≥25.0) and cigarette smoking

Characteristics	Hazard Ratio Fully Adjusted Base Model (Model IV)	Population Attributable Risk Fraction	Excess Deaths, 1999
Overweight	0.87 [0.76, 1.00]	-0.06 [-0.16, 0.05]	-19,116 [-5, 5173, 16,412]
Obese I	0.92 [0.77, 1.10]	-0.01 [-0.07, 0.04]	-4,733 [-22896, 13,431]
Obese II/III	1.53*** [1.24, 1.90]	0.03 [<0.00, 0.06]	10,830 [-19, 21,679]
Total – Higher Weight Status (BMI≥25)	-	-0.04 [-0.16, 0.08]	-13, 018 [-54,596, 28,559]
Total – Obesity (BMI≥30)	-	0.02 [-0.04, 0.08]	6,098 [-15,059, 27254]
Former Smoker	1.63*** [1.38,1.92]	0.14*** [0.05, 0.22]	46,682*** [17,926, 75,436]
Current Light Smoker	2.25*** [1.82, 2.79]	0.07*** [0.03, 0.11]	24,009*** [11,012, 37,005]
Current Moderate Smokers	2.99*** [2.50, 3.58]	0.16*** [0.11, 0.21]	53,541*** [35911, 71,170]
Current Heavy Smoker	3.23*** [2.51, 4.14]	0.06*** [0.03, 0.09]	19,913*** [9,715, 30,110]
Total – Cigarette Smoking	-	0.42*** [0.31, 0.53]	144,414*** [106587, 181,701]
Total Deaths, 1999	-	-	341,354

*** p<.001; **p<.01; *p<.05

Note: 95% Confidence intervals shown in brackets. Model IV is the fully adjusted model from Table 2. Attributable risk and excess deaths are calculated in 1999, the mean year of death of the sample. The 1931-1941 birth cohort was ages 57-68 in 1999. Data reflect sampling weights.