Smoking and Reverse Causation Create an Obesity Paradox in Cardiovascular Disease

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Objective: Many studies find that excess weight is associated with better survival among individuals with cardiovascular disease (CVD). Investigations were carried out to see whether this “obesity paradox” can be explained by biases.

Methods: The association between weight status and mortality in the US population ages 35 and above with CVD was investigated. Data were obtained from the National Health and Nutrition Examination Survey, 1988-2010, linked to mortality records through 2011. To minimize biases resulting from illness-induced weight loss, a reference category consisting of individuals who have always maintained normal weight was used. Age-standardized mortality rates and Cox models were estimated, comparing overweight/obesity (body mass index (BMI) ≥25.0 kg m⁻²) to normal weight (BMI 18.5-24.9 kg m⁻²).

Results: The paradox was present among those with overweight/obesity at the time of survey (hazard ratio (HR) = 0.89; 95% confidence interval (CI) 0.78-1.01). However, when the reference category was limited to the always-normal-weight, the paradox disappeared (HR = 1.16; 95% CI 0.95-1.41). When analysis was additionally confined to never-smokers, mortality risks were significantly higher in the overweight/obesity group (HR = 1.51; 95% CI 1.07-2.15; P = 0.021).

Conclusions: The findings provide support for the hypothesis that lower mortality among individuals with CVD and overweight/obesity is a product of biases involving reverse causation and confounding by smoking.

Introduction

Many studies find that excess weight is associated with lower mortality among individuals with cardiovascular disease (CVD) (1-6). A recent meta-analysis of 26 studies of patients with acute coronary syndrome concluded that individuals with overweight/obesity had lower mortality than those with normal weight, with hazard ratios of 0.60-0.70 (7). Although the mechanisms underlying the “obesity paradox” in CVD are not well understood, potential biological advantages of excess fat stores during periods of illness are often cited (8).

However, studies of the mortality consequences of obesity are subject to two major biases: reverse causation and confounding by smoking (9). These biases are typically enhanced when attention is confined to individuals who have entered a disease state (10). Whether the obesity paradox is a product of actual protection afforded by adiposity or of statistical biases has important clinical implications.

Reverse causation refers to instances in which weight is a consequence rather than a cause of illness. Low weight is often a result of disease, which can cause loss of appetite or increase metabolic demands, and is associated with higher mortality (11,12). Because the incidence of weight loss is typically higher among individuals suffering from an illness and because mortality is also higher, reverse causation is a greater threat to unbiased estimation of the mortality risks of obesity when analysis is confined to such individuals.

The applicability of smoking to the obesity paradox is a product of its being widespread, deadly, and inversely associated with obesity. Individuals with overweight/obesity are less likely to smoke than normal-weight individuals, a negative relationship that becomes stronger when individuals are selected into a disease state for which both smoking and obesity are risk factors. This result, a special case of what is commonly referred to as “selection bias” or
“collider-stratification bias,” has been demonstrated formally and empirically in a study of the obesity paradox in individuals with dysglycemia (10). The stronger negative correlation between smoking and obesity in the disease state, in turn, enhances the risk of residual confounding, producing a downward bias in the estimated mortality risk associated with obesity. Without identifying the key role of smoking, several other authors have hypothesized the operation of an unobserved risk factor that, having collided with obesity in the disease state, raises the relative mortality of the non-obese in that state (8,13-17). Glymour and Vittinghoff question the empirical significance of the bias (18). Other critics argue more generally that the paradox is so widespread that it must have biological rather than statistical roots (19).

The aim of the present article is to produce estimates of the association between weight status and mortality for individuals with CVD that are robust to biases related to reverse causality and smoking. Previous efforts to reduce the impact of reverse causation on the association between obesity and mortality have removed large fractions of the population from analysis. The exclusions may include people who have lost weight, people with a variety of illnesses, and people who die during the first several years of follow-up. These exclusions eliminate up to 80% of deaths (20). In the present study, we endeavor to minimize the effect of reverse causation by using a reference category that consists of individuals who have always been of normal weight, a strategy that has been employed in several previous studies (21,22). We compared the mortality of this group to that of individuals who had overweight/obesity at the time of the survey and to that of people who previously had overweight/obesity but had normal weight at survey. This latter group of weight losers should consist disproportionately of individuals who were losing weight as a result of illness. Their survival experience may also reflect the additional risks of having overweight/obesity at an earlier stage of life. By retaining weight losers in the analysis, we do not need to eliminate any individuals, years of exposure, or deaths.

Methods

We used data from the National Health and Nutrition Examination Survey (NHANES) to examine the association between weight status and mortality among individuals with CVD. NHANES is a nationally representative study of the non-institutional population of the United States. Prior to 1999, data were collected on a periodic basis, after which it became a continuous survey with data released in 2-year cycles. In addition to self-reported data, clinical data are collected by trained medical personnel in mobile examination units. For the current study, we pooled NHANES III (1988-1994), with the continuous NHANES (1999-2010) (23,24). Information on mortality status through 2011 was obtained from the National Death Index (25).

We restricted the cohort to adults ages 35 and older at the time of survey. Younger adults were excluded because there were few deaths at those ages in the sample. Individuals who reported a prior diagnosis of coronary heart disease, stroke, congestive heart failure or angina by a physician or other health professional were defined as having CVD. After eliminating individuals with missing information on smoking, educational attainment, body mass index (BMI) and mortality status as well as individuals who were pregnant or in the underweight range at the time of survey (BMI of <18.5 kg m$^{-2}$), the total sample included 30,462 individuals, of whom 3,388 reported a prior diagnosis of CVD. In the latter group, there were 1,457 deaths during a median follow-up of 5.8 years.

We calculated BMI at the time of survey (BMI at survey) as the ratio of measured weight in kilograms to the square of measured height in meters. In addition to BMI at survey, we constructed a measure of maximum lifetime BMI (max BMI). Beginning in NHANES 3, respondents were asked to recall their maximum weight through a question that reads “Up to the present time, what is the most you have ever weighed?” Female respondents were instructed to exclude pregnancy from consideration. This information was used along with measured height at survey to calculate max BMI.

We constructed binary variables of weight status for BMI at survey using the categories normal weight (BMI of 18.5-24.9 kg m$^{-2}$) and overweight/obesity (BMI $\geq$25.0 kg m$^{-2}$). We additionally grouped individuals into categories according to their weight at maximum and survey: normal weight at both max and survey (“always-normal”); overweight/obesity at max and normal weight at survey (“weight losers”); and overweight/obesity at both max and survey. In the small number of instances in the CVD subpopulation in which BMI category at survey exceeded max BMI (n = 13), we substituted the former for the latter.

We calculated age-standardized mortality rates for individuals with CVD, comparing normal weight to overweight/obesity. Mortality rates were also estimated for each of the three weight trajectories defined above. The age-standardization procedure used 5-year age groups between 35 and 89 and an open-ended age group 90 and above. The US population in 2000 was used as the standard.

We then used Cox proportional hazards models with age as the underlying time scale to estimate hazard ratios for mortality. Models were adjusted for sex, race/ethnicity (non-Hispanic black, Hispanic, other), and educational attainment (less than high school, high school or equivalent, some college or greater). The first model used a reference category of people with normal weight at survey and compared their mortality to that of people with overweight/obesity at survey. The second model used a reference category of people who were always of normal weight and compared their mortality to that of weight losers (individuals in the normal-weight category who previously had overweight/obesity) and to that of people who had overweight/obesity at survey. Models were estimated for all individuals with CVD as well as for never-smokers with CVD. Former smokers who quit prior to the age of 25 were included in the latter group to increase sample size. The smoking restriction was carried out because smoking is a strong confounding variable that is simultaneously associated with lower weight and higher mortality (26). Smoking may be a particularly strong confounder in the present case as a result of collider bias produced by conditioning on CVD status.

Our analyses used de-identified secondary data and therefore approval was not required by an ethics committee. All calculations incorporated sample weights that adjust for unequal probabilities of selection and nonresponse. Analyses were performed using Stata 13 (StataCorp, TX). Variances were estimated using Taylor series linearization with the SVY routine.
Results

Table 1 describes characteristics of the NHANES cohort and the CVD subpopulation. Individuals with CVD were on average older (64.6 vs. 53.4 years) and less likely to have completed high school compared to the NHANES cohort as a whole. They were more likely to have been diagnosed with diabetes (26.8 vs. 9.9%), cancer (15.0 vs. 8.2%), and emphysema (9.2 vs. 2.5%). The CVD subpopulation had a higher prevalence of overweight/obesity at survey (76.6 vs. 67.7%) and a lower fraction that had always been of normal weight (8.4 vs. 18.8%). Individuals in the CVD subpopulation who had normal weight at survey were more likely to have previously had overweight or obesity than in the NHANES cohort as a whole (64.3 vs. 41.8%).

Table 2 compares the age-standardized prevalence of smoking in the CVD subpopulation to the value in the larger NHANES cohort, disaggregating by weight status to focus on the critical relationship between smoking and weight. Overall, 25% of the NHANES cohort and 30% of those with CVD were current smokers, but there were large observed differences in the rate of current smoking by weight status and these differences were sharper in the CVD subpopulation than in the entire NHANES cohort. In the NHANES cohort, the prevalence of current smoking was 32% higher in individuals with normal weight compared to those with overweight/obesity, whereas in the CVD subpopulation the prevalence was 53% higher.

Table 3 presents age-standardized death rates and hazard ratios by weight status at survey among those with CVD. Individuals with overweight/obesity had a death rate 26% below that of normal-weight individuals, providing a clear manifestation of the obesity paradox among those with CVD. The paradox is also evident in the hazard ratios shown in the second column of Table 3. The hazard of dying was 11% lower among those with overweight/obesity at survey than among those with normal weight. However, when analysis was limited to never-smokers, the obesity paradox was attenuated in age-standardized mortality rates and eliminated altogether in the hazard model.

We noted earlier that a large fraction (64%) of the normal-weight population with CVD had previously had overweight or obesity.

### Table 1: Descriptive statistics for the NHANES cohort and CVD subpopulation

| Characteristic                  | NHANES cohort | CVD subpopulation |
|--------------------------------|---------------|-------------------|
| No. of participants            | 30,462        | 3,388             |
| Age at survey (years)          | 53.4          | 64.6              |
| Race/ethnicity (%)             |               |                   |
| Non-Hispanic white             | 76.6          | 78.3              |
| Non-Hispanic black             | 10.3          | 11.6              |
| Hispanic                       | 9.3           | 6.7               |
| Other                          | 3.9           | 3.4               |
| Education (%)                  |               |                   |
| Less than high school          | 22.7          | 37.1              |
| High school or equivalent      | 28.7          | 27.1              |
| Some college or higher         | 48.7          | 35.8              |
| Smoking status (%)             |               |                   |
| Never                          | 46.2          | 35.7              |
| Former                         | 31.0          | 43.6              |
| Current                        | 22.7          | 20.7              |
| Over/obese at survey (%)       | 67.7          | 76.6              |
| Over/obese at max (%)          | 81.2          | 91.6              |
| Weight status: max - survey (%)|               |                   |
| Normal - normal                | 18.8          | 8.4               |
| Over/obese - normal            | 13.5          | 15.1              |
| Over/obese - over/obese        | 67.7          | 76.6              |
| Prior chronic disease diagnosis (%)|         |                   |
| Diabetes                       | 9.9           | 26.8              |
| Cancer                         | 8.2           | 15.0              |
| Emphysema                      | 2.5           | 9.2               |

CVD: cardiovascular disease; Over/obese: overweight/obesity. Normal weight defined as BMI in the range 18.5–24.9 kg m⁻². Overweight/obesity defined as BMI ≥25.0 kg m⁻². CVD defined as a prior diagnosis of congestive heart failure, coronary heart disease, angina, or stroke. Sample restricted to adults ages 35 and above at the time of survey. Means and percentages adjusted using sample weights. Source: National Health and Nutrition Examination Survey (NHANES).

### Table 2: Age-standardized smoking prevalence by weight status for the NHANES cohort and CVD subpopulation

|                  | All     | Normal weight | Overweight/obesity | Ratio (2/3) |
|------------------|---------|---------------|--------------------|-------------|
| NHANES cohort    |         |               |                    |             |
| Never-smoker     | 0.46    | 0.45          | 0.47               | 0.95        |
| Former smoker    | 0.28    | 0.25          | 0.30               | 0.84        |
| Current smoker   | 0.25    | 0.30          | 0.23               | 1.32        |
| CVD subpopulation|         |               |                    |             |
| Never-smoker     | 0.35    | 0.31          | 0.35               | 0.88        |
| Former smoker    | 0.36    | 0.28          | 0.38               | 0.73        |
| Current smoker   | 0.30    | 0.41          | 0.27               | 1.53        |

CVD: cardiovascular disease. Normal weight defined as BMI in the range 18.5–24.9 kg m⁻². Overweight/obesity defined as BMI ≥25.0 kg m⁻². Smoking prevalence age-standardized to the US 2000 Census using 5-year age groups between 35 and 89 and open-ended category 90+. Estimates weighted using sample weights. Sample restricted to adults ages 35 and above at the time of survey. Source: National Health and Nutrition Examination Survey (NHANES).
Table 4 shows mortality rates and hazard ratios (HR) from analyses differentiating normal-weight individuals who previously had overweight/obesity from those who were always normal weight. Among individuals with CVD who had normal weight at survey, those who transitioned to normal weight from overweight/obesity had significantly elevated mortality risks compared to individuals who were consistently normal weight (HR = 1.48; 95% CI 1.19-1.85; P = 0.001). Clearly, including the weight losers with the always-normal group raises the death rate in the reference category and helps to create a paradox. When the always-normal group was used as the reference category in the hazard model, both the weight losers and those who had overweight/obesity at survey had hazard ratios above 1 (Table 4).

When the sample was restricted to never-smokers in the bottom panel of Table 4, the hazard ratio associated with overweight/obesity became larger in magnitude and statistically significant (HR = 1.51; 95% CI 1.07-2.15; P = 0.021). Combining the modified reference category with the restriction on smoking has produced a sharp reversal of the obesity paradox.

It is worth noting that, by themselves, both the smoking restriction and the refinement of the reference category eliminated the paradox in hazard models. Restriction to never-smokers in Table 3, using the conventional reference category, produced hazard rates for overweight/obesity of 1.06. Using the restricted reference category but applying the model to all smoking groups in Table 4 produced a

| BMI category | Total CVD sample | Never-smokers only |
|--------------|------------------|--------------------|
|              | Mortality rate    | Hazard ratio       |
|              | Est. | 95% CI | Est. | 95% CI | P value |
| Normal weight at survey | 38.60 | (26.83-50.37) | 1.00 | 1.00 | 0.001 |
| Overweight/obesity at survey | 28.47 | (23.64-33.29) | 0.89 | (0.78-1.01) | 0.076 |
| Normal weight at survey | 21.36 | (5.62-37.11) | 1.00 | 1.06 | 0.576 |
| Overweight/obesity at survey | 21.04 | (16.26-25.81) | 1.06 | (0.87-1.29) | 0.021 |

BM: body mass index; Est.: estimate; CI: confidence interval; CVD, cardiovascular disease. Normal weight defined as BMI in the range 18.5-24.9 kg m\(^{-2}\). Overweight/obesity defined as BMI ≥25.0 kg m\(^{-2}\). Cox proportional hazards models adjusted for gender, race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), and educational attainment (less than high school, high school, some college or greater). Analysis time specified as age at exposure. Proportional hazards assumption confirmed by testing the slope of Schoenfeld residuals by BMI category. Estimates weighted and account for complex survey design. Sample restricted to adults ages 35 and above at the time of survey. Entry years for cohort members are 1988-2010 with mortality follow-up through 2011.

Source: National Health and Nutrition Examination Survey.
Discussion

Confounding by smoking and reverse causality are major sources of bias in estimating the association between weight status and mortality. We have shown that these biases are enhanced in the population with CVD, in which both the prevalence of illness is higher and the negative correlation between BMI and smoking is stronger than in the source population. Our results show that simultaneously addressing both confounding by smoking and reverse causality leads to a striking reversal of the obesity paradox. Having overweight/obesity was associated with a non-significant 11% reduction in mortality relative to normal weight in a conventional model that used BMI at survey to assess weight status. However, when the reference category was defined to include only those who have always been of normal weight and the sample was restricted to never-smokers, overweight/obesity was associated with a statistically significant 51% increase in mortality. The two biases were of roughly equal importance in accounting for the obesity paradox. We interpret these results as evidence that the obesity paradox is an artifact of reverse causation and confounding by smoking rather than a real biological phenomenon as previous studies have argued (19).

A set of related studies examines the role of cardiorespiratory fitness in the obesity paradox among those with CVD. McAuley and Beavers review five studies of individuals with known or suspected CVD (27). They find in all cases that an obesity paradox persists among patients with low cardiorespiratory fitness, whereas among patients with high fitness, the obesity paradox is missing in three studies and maintained in two [see also (8)]. Smoking is one of the key risk factors for developing poor cardiorespiratory function (28). In that sense, the effect modifications associated with smoking and with cardiorespiratory fitness are mutually reinforcing.

It is worthwhile to ask why there is a widespread “obesity paradox” while similar paradoxes are rare in epidemiology. We believe that the explanation lies in part in the inverse correlation between obesity and another prominent source of attributable risk, cigarette smoking (29). If two variables are positively associated, failure to properly control one would typically produce an overestimate of the impact of the other (30). In this case, no “paradox” is observed but rather an exaggeration of the impact of a variable already suspected of influencing the outcome. Such exaggerations often help to confirm a hypothesis. As a result, they may not receive the scrutiny that they deserve. Exaggerations are common in observational studies because so many risk factors are positively associated. A paradox occurs, on the other hand, when results are contrary to expectations. Such a result is more likely when risk factors are negatively correlated and when the confounding variable is omitted or poorly measured. Future studies of the obesity paradox should recognize the great threat to unbiased estimation posed by the negative correlation between smoking and obesity.

Another likely explanation for widespread findings of an obesity paradox is that the reference group in analyses of BMI and mortality—the normal-weight group—is often a mix of low-risk, stable-weight individuals and high-risk individuals who have lost weight (21). In the present analysis, we showed that in individuals with CVD, a majority of individuals in the normal-weight category at the time of survey previously had overweight or obesity. These individuals have much higher mortality than those who were consistently normal weight throughout life, suggesting that their presence in the normal-weight category is often related to illness. Illness itself is not expected to change the value of other exposures that predict death from CVD such as hypertension or high fasting plasma glucose. But it often produces weight loss, an association that biases analyses of the mortality consequences of obesity unless proper caution is taken.

This study has several limitations. First, we relied on recalled maximum weight, which may be subject to measurement error. Measurement error could inflate or reduce the estimated mortality risks depending on the direction of the misreporting; however the threat posed is likely to be small as we have adopted a simple binary measure of weight status for the analysis in this article. Second, to construct maximum lifetime BMI, we combined recalled weight with measured height at survey. Height loss between max and survey could lead to max BMI being overestimated for some individuals. This may lead to underestimating of the mortality risks associated with obesity.

This study did not directly investigate biologic mechanisms that may reduce mortality among individuals with obesity who have developed CVD, so we cannot conclude that any such mechanism is invalid. We can, however, conclude that large statistical biases may arise in the analysis of associations between obesity and mortality among those with CVD. We have shown that adjusting for these biases leads to eliminating the obesity paradox altogether. The main sources of bias result from reverse causation and confounding by smoking. Such biases are present in many studies of the mortality risks of obesity but they are exaggerated when attention is confined to those in a disease state such as CVD.

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