The obesity paradox in the US population¹–³

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ABSTRACT

Background: Recently a number of studies have found a lower risk of dying for obese individuals than for normal-weight individuals. The explanation for these paradoxical findings has not yet been identified.

Objective: The objective was to assess whether this paradoxical pattern exists in the US population and whether it can be explained by reverse causation.

Design: Survival analyses were used to calculate the RR of all-cause mortality for obesity by using data from 35,673 participants in NHANES I (1971–1975), NHANES II (1976–1980), and NHANES III (1988–1994), which reported 7087 deaths during 3 different 15-y follow-up periods.

Results: With normal weight as a referent, a lower relative mortality risk of obesity was found only in NHANES III and only among men with a wide variety of preexisting serious illnesses. For this subgroup, the relative mortality risks in NHANES I, II, and III were 2.22 (95% CI: 1.45, 3.40), 0.89 (95% CI: 0.70, 1.15), and 0.65 (95% CI: 0.47, 0.91), respectively. Whereas the mortality rate among seriously ill normal-weight men did not change significantly between NHANES I and III, it did decrease significantly among seriously ill obese men, suggesting that reverse causation was not responsible for the lower relative mortality risk among seriously ill obese men in NHANES III.

Conclusions: Only obese NHANES male participants with a wide variety of serious illnesses experienced lower mortality risk than their normal-weight counterparts and only in NHANES III. Reverse causation seems unlikely to have played a role. These conclusions require confirmation. Am J Clin Nutr 2013;97:1195–200.

INTRODUCTION

Within the past decade there have been numerous reports of a lower mortality risk for obese individuals than for normal-weight individuals. These reports appear to be paradoxical. They contradict the well-accepted, empirically based idea that obesity confers elevated mortality risk. Some of these paradoxical reports resulted from studies that involved cohorts of elderly free-living persons, such as elderly US residents (1), US veterans (2), and residents of Jerusalem (3). Other studies used data from seriously ill patients, including patients on kidney dialysis (4), post–coronary revascularization patients (5), liver-transplant recipients (6), and patients with conditions such as wasting disease (7), AIDS (8), cancer (9), chronic obstructive pulmonary disease (10), heart failure (11), acute myocardial infarction (12), and peripheral arterial disease (13). Several investigators have used terms such as obesity paradox or reverse epidemiology to describe such findings (1, 4, 5).

Whereas a number of hypotheses have been proposed to explain the obesity paradox (4, 5, 14), no empirical evidence has yet confirmed any of these hypotheses as valid. One such hypothesis is reverse causation (4). Reverse causation is postulated to be caused by factors such as smoking and serious illness that simultaneously induce weight loss and increase mortality risk (15). These factors are theorized to increase mortality risk at low BMIs, and hence deflate mortality risks for obese individuals relative to normal-weight individuals, thereby yielding an artificially low mortality risk for obese persons. An analytic technique that is commonly used to abate reverse causation involves excluding smokers and participants with serious illness from the analysis. However, this technique cannot be applied in analyses involving samples of seriously ill participants.

The objective of the present analysis was to test the hypothesis that mortality risk is lower for obesity than for normal weight only among elderly and/or serious ill Americans. The analysis used data from the mortality-linked NHANES I, II, and III cohorts to assess the RR of mortality for obesity in different subgroups of participants during 3 different 15-y follow-up periods: 1973–1988, 1978–1993, and 1991–2006. The study also used a new technique to assess whether the obesity paradox pattern is likely to be caused by reverse causation in the US population.

SUBJECTS AND METHODS

NHANES I, II, and III cohorts

Data from 3 NHANES surveys were used for this analysis. These surveys were conducted in representative samples of the US population by the National Center for Health Statistics and

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²The National Center for Health Statistics (NCHS) is the original source of the NHANES data. The author is responsible for all analyses, interpretations, and conclusions, and not NCHS, which is responsible only for the data.

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Received June 30, 2012. Accepted for publication April 1, 2013. First published online May 1, 2013; doi: 10.3945/ajcn.112.045815.


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have been described elsewhere (16–18). There were 12,544 adults who were 21–75 y of age without missing data on predictor, co-
variates or outcome variables in the 1971–1975 NHANES I. In the
1976–1980 NHANES II there were 9180 participants who were
30–75 y of age, and in the 1988–94 NHANES III there were
15,852 participants who were 21–90 y of age.

The acquisition and processing of the NHANES data were
approved by the institutional review board of Brooklyn
College.

### Survival analyses

Cox proportional hazards regression (19) was used to estimate
multivariate-adjusted RRs of mortality in different categories of
BMI. The proportionality assumption was checked by means of
scaled Schoenfeld residuals (20), and stratified baseline-function
analyses were used to assess the effects for covariates that appeared
not to have satisfied the proportionality assumption (21). Analytic
guidelines from the National Center for Health Statistics were used
to identify results that were potentially unreliable because of small
numbers of events (22). Model fit was assessed by means of the −2
log likelihood test. Time to event was days between the physical
examination and death or censorship. To avoid potential bias be-
cause of different lengths of follow-up (23) in the 3 NHANES
cohorts, the longest common follow-up period for the 3 cohorts,
15 y, was adopted in primary survival analyses. A sensitivity
analysis was conducted with a follow-up period of 10 y.

All analyses were performed with SAS version 9.2 and SAS-
Callable SUDAAN version 10.0.1 (SAS Institute). Sample weights
provided by NHANES researchers were used to account for
complex sampling and nonresponses.

### Predictor and covariates

The predictor was BMI, calculated as measured weight in kilo-
grams divided by measured height in meters squared. Covariates
were as follows: age in years, age squared, sex (male or female),
race (white or nonwhite), smoking status (never, former, or current),
preexisting serious chronic illness (yes or no), alcohol consumption
(never, less than weekly, weekly, or daily). Age squared was
included because it made a significant contribution to model fit
(20). The following self-reported highly prevalent causes of
serious illness were used to create the bivariate preexisting serious-
illness variable: heart attack, heart failure, stroke, cancer, and
emphysema. Covariates in the causal pathway between BMI
and mortality, such as blood pressure, were not included (15).

### Outcome variable

All-cause mortality was the outcome event. Deaths were iden-
tified by National Center for Health Statistics personnel through
systematic searches of the National Death Index. The reliability of
the National Death Index for epidemiologic purposes has been
previously estimated to have a sensitivity of 98% and a specificity
of 100% (24).

### BMI referent categories and upper age limit

The following BMI categories (in kg/m²) (25) were used in the
main analyses: ≤18.5 (underweight), 18.5 to <25 (normal
weight), 25 to <30 (overweight), and ≥30 (obese). For analyses
in which the referent category was the normal-weight category,
sensitivity analyses were conducted by using a BMI of 23 to
<25 as the normal-weight category.

To assess the effects of potential bias because of statistical
confounding referred to as reverse causation by obesity researchers
(15), separate analyses were conducted for obese participants by
using obesity in NHANES I as the referent BMI category. This
strategy effectively removes reverse-causation effects because it
removes the normal-weight category from the analysis, and reverse
causation is purported to be a result of artificially elevated mortality
risk in the normal-weight category. The elevation of risk is pos-
tulated to be a result of factors such as smoking and preexisting
serious illness (15). RR has been found to decrease with increasing age among
older participants in NHANES (23) and other (26) cohorts. The
percentages of participants aged >75 y were 0.21%, 0.05%,
and 6.02% in NHANES I, II, and III, respectively. In addition,
NHANES III participants aged >75 y accounted for 96.3% of
all deaths during follow-up in this age group in the 3 cohorts. An
upper age limit of 75 y was therefore imposed in all primary
analyses to ensure that comparisons of the relative mortality risk
across cohorts were meaningful. The lower ages were different in
the 3 surveys: 21 y in NHANES I and III and 30 y in NHANES II.
No attempt was made to create a uniform lower age limit because
there is no empirical evidence suggesting that the relative
mortality risk of obesity varies with age between 21 and 30 y
of age.

After excluding the 3 NHANES II participants who were lost
to follow-up, the numbers of missing values in the combined
cohorts were as follows: BMI, 56 (0.14%), smoking status, 1859
(4.66%), illness status, 230 (0.58%), and alcohol consumption, 123
(0.31%). A sensitivity analysis was conducted to assess the effects
of the missing smoking data. After excluding participants with
missing data on predictor, covariates, or outcome variables there
were 35,673 participants and 7087 all-cause deaths during the
15 y of follow-up. A total of 12,544 participants in NHANES I
were 21–75 y of age, 9180 in NHANES II were 30–75 y, and
13,949 in NHANES III were 21–75 y of age. There were 2461,
2403, and 2223 deaths during follow-up in NHANES I, II, and
III, respectively. A sensitivity analysis was conducted without the
upper age limit.

### Interaction effects

Tests of interaction were conducted for cohort, serious illness,
smoking, sex, and age. The rationale was that a wide variety of
serious illnesses has been associated with the obesity paradox
and smoking, male sex, and advanced age are risk factors for many
serious illnesses. The forward-inclusion and backward-elimination
methods described by Kleinbaum et al (27) were used.

A cutoff of 55 y was selected for categorizing age because
Greenberg (23) found evidence suggesting that the relation between
mortality and BMI in the NHANES data differed between those
younger and older than 55 y of age.

### RESULTS

#### Baseline characteristics

Compared with normal-weight participants, obese participants
were older and a higher proportion of these participants were
nonwhite, nonsmokers, and nondrinkers (Table 1). In addition, obese participants were less likely to report being regular smokers or consumers of alcohol. Across cohorts, over time, there was a steady increase in the prevalence of obesity and a steady decrease in the prevalence of normal weight. There was also a steady decrease in the rate of smoking, and a steady increase in the proportion of participants who reported never using alcohol.

**Significant interactions**

Significant 2-way interactions were found for cohort and serious illness, cohort and smoking, cohort and sex, or cohort and age for mortality because of all causes. There were also one or more significant 2-way interactions involving age and serious illness, age and sex, illness and sex, smoking and age, smoking and serious illness, or smoking and sex. Separate survival analyses were therefore conducted in subgroups defined by categories of serious illness, smoking, sex, and age.

**Mortality risk of obesity with normal weight as the referent**

A significantly lower mortality risk for obesity than for normal weight was found only among men with serious illness and only in NHANES III (Table 2).

There were other subgroups with a relative mortality risk for obesity <1.00 in NHANES III, including older (aged >55 y) men and seriously ill participants. However, the CI for these subgroups included 1.00. There was no evidence of lower morality risk for obese women than for normal-weight women.

Obese seriously ill men, seriously ill participants, and older men showed a monotonic decreasing secular trend across cohorts in the relative mortality risk of obesity. However, there was no evidence of a monotonic decrease across cohorts for healthy, older obese males or for seriously ill obese females, which showed that there was only a monotonic decrease across cohorts for seriously ill obese men. There was also no evidence of a secular decrease across cohorts in the relative mortality risk of obesity for women.

In NHANES III, the maximum age was 90 y. Analyses were conducted to assess whether the inclusion of individuals older than 75 y would yield a significantly lower mortality risk for obese, healthy elderly men than for normal-weight, healthy elderly men. Without the 75-y upper age limit, there was no evidence of significantly lower mortality risk for obese, healthy elderly men than for normal-weight, healthy elderly men in NHANES III. For instance, for healthy men aged 55–90 y, the relative mortality risk for obesity was 1.05 (95% CI: 0.71, 1.55), with 529 total participants and 186 deaths among obese individuals. For healthy men aged 75–90 y, the relative mortality risk for obesity was 1.05 (95% CI: 0.71, 1.55), with 529 total participants and 54 deaths among obese individuals.

**Relative mortality risks with obesity in NHANES I as the referent**

Reverse causation is thought to be caused by factors such as serious illness and smoking (15), which induce weight loss and simultaneously increase mortality risk, and hence increase the mortality rate in the normal-weight category (and thereby artificially deflate survival-analysis RRs for obesity when the normal-weight category is the referent category). If reverse causation is the explanation for the RR for all-cause mortality for obesity (with normal weight as the referent) being significantly lower than 1.00 only for men with serious illness, and only in NHANES III (Table 2), then an increase in reverse causation would have occurred only in seriously ill men between NHANES I and III and would have manifested as a higher mortality rate among normal-weight, seriously ill men in NHANES III compared with NHANES I. However, the RR of mortality for normal-weight, seriously ill men in NHANES III, with normal-weight, seriously ill men in

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Baseline characteristics of participants in NHANES I, II, and III according to body weight category5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NHANES I</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Ideal weight</td>
</tr>
<tr>
<td>18.5 to &lt;25</td>
<td>49.3</td>
</tr>
<tr>
<td>≥30</td>
<td>49.3</td>
</tr>
<tr>
<td>Age (y)</td>
<td>49.3</td>
</tr>
<tr>
<td>Unweighted n</td>
<td>5885</td>
</tr>
<tr>
<td>Percentage of cohort in BMI range</td>
<td>46.9</td>
</tr>
<tr>
<td>Age (y)</td>
<td>44.7 ± 0.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.2 ± 0.02</td>
</tr>
<tr>
<td>Female (%)</td>
<td>58.5</td>
</tr>
<tr>
<td>Nonwhite (%)</td>
<td>8.7</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>Never</td>
</tr>
<tr>
<td></td>
<td>Former</td>
</tr>
<tr>
<td></td>
<td>Current</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>Never</td>
</tr>
<tr>
<td></td>
<td>Less than weekly</td>
</tr>
<tr>
<td></td>
<td>Weekly</td>
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<td>Daily</td>
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</table>

5 Age was significantly greater for obesity than for ideal weight in all 3 cohorts (P < 0.05, by ANOVA). Across cohorts in both BMI categories there were significant differences in rates of obesity, ideal weight, smoking, and alcohol consumption by chi-square test; and across BMI categories in ≥2 cohorts there were significant differences in ethnicity, rates of smoking, and alcohol consumption.

2 Mean ± SEM (all such values).
Relative mortality risk of obesity from all causes in NHANES I, II, and III

<table>
<thead>
<tr>
<th>Obese subgroup</th>
<th>N (no. of deaths)</th>
<th>RR (95% CI)</th>
<th>N (no. of deaths)</th>
<th>RR (95% CI)</th>
<th>N (no. of deaths)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy men aged 55 y</td>
<td>2136 (539)</td>
<td>1.54 (1.22, 1.94)</td>
<td>1624 (447)</td>
<td>1.09 (0.96, 1.24)</td>
<td>3794 (662)</td>
<td>1.31 (1.13, 1.51)</td>
</tr>
<tr>
<td>Seriously ill men</td>
<td>1776 (381)</td>
<td>1.51 (1.19, 1.90)</td>
<td>1385 (326)</td>
<td>1.14 (0.97, 1.34)</td>
<td>3365 (468)</td>
<td>1.50 (1.24, 1.83)</td>
</tr>
<tr>
<td>Women aged 55 y</td>
<td>360 (158)</td>
<td>1.52 (1.08, 2.16)</td>
<td>239 (121)</td>
<td>1.08 (0.84, 1.31)</td>
<td>429 (194)</td>
<td>0.97 (0.74, 1.24)</td>
</tr>
<tr>
<td>Male participants</td>
<td>1483 (330)</td>
<td>1.36 (1.02, 1.81)</td>
<td>1022 (247)</td>
<td>1.18 (0.95, 1.46)</td>
<td>2361 (346)</td>
<td>1.67 (1.34, 2.09)</td>
</tr>
<tr>
<td>Female participants</td>
<td>659 (270)</td>
<td>1.16 (0.98, 1.36)</td>
<td>602 (200)</td>
<td>1.01 (0.83, 1.23)</td>
<td>1433 (316)</td>
<td>1.06 (0.87, 1.28)</td>
</tr>
</tbody>
</table>
| Older and seriously ill obese men both exhibited relative mortality risks below 1.00 in NHANES II and III (Table 3). Also, seriously ill men and older men exhibited monotonically decreasing relative mortality risks across cohorts (Table 3). As in the analysis with normal weight as the referent (Table 2), these patterns in Table 3 were not present for healthy, older obese males, suggesting that they applied only to seriously ill obese men. It is also worth noting that no paradoxical patterns were observed for any subgroups of women in Table 3.

Secondary analyses

The analyses in Tables 2 and 3 were repeated to test the effects of the following: 1) a shorter follow-up period (10 y); 2) a narrower BMI referent category (23 to <25); 3) exclusion of NHANES I participants for whom smoking was retrospectively assessed in 1982–1984; 4) extra covariates in the model, such as physical activity (% maximum), marital status (married, single, widowed, or separated/divorced), and educational level (ordinal, 0–17 completed years of school); and 5) inclusion of participants over the age of 75 y, who were all in the NHANES III, in the analysis. The results of these secondary analyses were essentially the same as those in Tables 2 and 3. There were fewer deaths in the 10-y follow-up analyses, so that the 95% CIs were slightly wider, and a few cells contained <50 deaths, so their results are potentially unreliable.

<table>
<thead>
<tr>
<th>Obese subgroup</th>
<th>N (no. of deaths)</th>
<th>Referent</th>
<th>N (no. of deaths)</th>
<th>RR (95% CI)</th>
<th>N (no. of deaths)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy men aged 55 y</td>
<td>208 (105)</td>
<td>1.58 (1.07, 2.32)</td>
<td>240 (107)</td>
<td>1.17 (0.88, 1.54)</td>
<td>363 (132)</td>
<td>1.25 (0.93, 1.70)</td>
</tr>
</tbody>
</table>

The RR of all-cause mortality was calculated from the multivariate-adjusted RR of mortality determined by Cox regression analyses by using data from the mortality-linked NHANES cohorts for 35,673 participants in NHANES I, NHANES II, and NHANES III, in which there were 7087 deaths during 15 y of follow-up. The referent BMI category (in kg/m²) was 18.5–25, and the following covariates were included in the model: age in years, age squared, sex (male or female), race (white or nonwhite), smoking status (never, former, or current), preexisting serious chronic illness (yes or no), and alcohol consumption (never, less than weekly, weekly, or daily).
DISCUSSION

The main finding of this analysis in the NHANES I, II, and III cohorts is that mortality risk was lower for obese participants than for normal-weight participants only for men with serious chronic illnesses and only in NHANES III. This paradoxical pattern was associated with a decrease over time across cohorts in the relative mortality risk of obesity. The fact that the paradoxical result occurred only among participants with serious illness accords with the fact that the participants in many previous studies that arrived at this paradoxical finding were also seriously ill (4–13). The main findings also proved to be robust in 5 different sensitivity analyses. The main findings are unique in showing the mortality risk of obesity in samples of the US population during 3 different 15-y follow-up periods (1973–1988, 1978–1993, and 1991–2006), covering 3 decades, and 2) in all NHANES participants and in different subgroups on the basis of health status and sex. These findings could be helpful in future research on the causes of the obesity paradox.

The present finding of a lower relative mortality risk for obese men than for normal-weight men with a wide range of preexisting illnesses accords with previously published findings in patients with a wide range of serious conditions—from AIDS (8) to chronic obstructive pulmonary disease (10) to heart failure (11). These findings suggest that the lower relative mortality risk for seriously ill obese participants is not related to a specific disease process but to the severity of the patient’s clinical condition. Also, the present finding that a lower relative mortality risk for obesity than for normal weight occurred only in NHANES III accords with the fact that most previously published reports of this pattern appeared within the past 2 decades. This is true of all such studies cited here, and almost all studies they cited found the same paradoxical pattern.

In the present study, one of the previously hypothesized explanations, reverse causation, does not appear to be an explanation for the study's main finding: a lower mortality risk for obese participants than for normal-weight participants that occurred only for men with serious chronic illnesses and only in NHANES III. As detailed above, reverse causation is a result of factors such as serious illness that induce weight loss and simultaneously increase mortality risk, and hence elevate the mortality rate in the normal-weight category, and that thereby artificially deflate the relative mortality risk for obesity when the normal-weight category is the referent category. However, in the present analysis, the mortality rate among normal-weight, seriously ill men did not change between NHANES I and III, showing that reverse causation could not be the explanation. On the other hand, the mortality rate among obese, seriously ill men was found to decrease between NHANES I and III, thereby providing a good explanation for the study’s main finding. This conclusion is strengthened by the fact that this decrease in mortality rate for obesity and the lower relative mortality risk for obese participants than for normal-weight participants were both only found among seriously ill, obese men.

Of all the previously published hypotheses concerning the obesity paradox, the selection bias (11, 28) seems best able to explain the present findings. This hypothesis posits that seriously ill obese men have lower mortality risk than seriously ill, normal-weight men because clinicians use appropriate diagnostic and treatment methods at an earlier stage of the disease and more intensively for the obese subjects as a result of the empirically established, well-publicized high mortality risk for obese persons. Evidence and logic supporting the selection bias as the explanation, and that suggest that this bias is more likely to act in male and seriously ill patients, are presented in the Supplemental Material under “Supplemental data” in the online issue. There are factors other than the selection bias that may help explain the present findings, and several of them are outlined in the Supplemental Material. On the other hand, there are some previously published hypotheses that involve biological factors associated with adiposity and improvements in medical treatment that do not seem to explain the present findings. They are also presented in the Supplemental Material.

The fact that female, but not male, subjects exhibited a relative mortality risk higher than 1.00 in NHANES III is noteworthy. This might be a result of the following: 1) a lower level of reverse causation among women than men; 2) the selection bias, in that clinicians may tend to use appropriate diagnostic and treatment methods at an earlier stage of the disease and more intensively for obese men than for obese women because men have a higher mortality rate (29); or 3) other factors. The focus of the present analysis does not allow for exploration of these options. However, even if reverse causation is the explanation, reverse causation is not the explanation for the main finding in the present analysis, as outlined previously.

In the present analysis, neither healthy, elderly, obese female nor healthy, obese male NHANES participants exhibited a lower relative mortality risk than their equivalent normal-weight participants. This was true even in NHANES III in which the upper age was 90 y. Some (1–3), but not all (30, 31), previous studies using cohorts of community residents found that healthy individuals do show this pattern. Literature reviews have found that the majority of such studies have not found a lower relative mortality risk for obese participants than for normal-weight participants (32, 33).

The relatively small size of the NHANES cohorts limited the range of analyses that could be performed in the present study. For instance, larger cohorts would have enabled more detailed analysis of the risk of mortality from specific chronic conditions, such as cardiovascular disease, cancer, emphysema, or diabetes. It is possible that a larger cohort or a longer follow-up period than the 15 y available for the present analysis would eliminate the obesity-paradox findings. Also there are no data on waist or hip circumference in NHANES I or II, so that the role of central adiposity could not be investigated. Some investigators, such as Pischon et al (34), have found that different measures of adiposity yield different estimates of the relative mortality risk of obesity. Other investigators, including Flegal and Graubard (35), have found that different measures do not yield important differences.

The present study also has some strengths. The study’s predictor, BMI, was based on measured rather than self-reported values for body weight and height. Also, the fact that each NHANES cohort was sampled from the US population during 3 different time periods allowed for the analysis of secular changes that yielded important evidence on possible causes of the lower mortality risk for obese participants than for normal-weight participants. In conclusion, this analysis found that mortality risk was lower for obese than for normal-weight participants only for men with serious chronic illnesses and only in NHANES III. This paradoxical pattern was associated with a decrease over time across...
cohort in the relative mortality risk of obesity. The present results do not support reverse causation as an explanation for the paradox. They do suggest that the paradox could be a result of clinicians using appropriate diagnostic and therapeutic techniques more intensively and earlier in the disease process for obese male patients than for other patients. These conclusions require confirmation.

JAG designed, conducted, and is responsible for all aspects of the research reported in this article. The author had no conflicts to declare.

REFERENCES