

Cause-Specific Excess Deaths Associated With Underweight, Overweight, and Obesity

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IN A PREVIOUS STUDY,¹ WE ESTIMATED excess all-cause mortality associated with underweight, overweight, and obesity in the United States in 2000 using data from national surveys. We found significantly increased all-cause mortality in the underweight and obese categories and significantly decreased all-cause mortality in the overweight category compared with normal weight. To gain further insight into these findings, we now extend that work, using additional mortality data with longer follow-up, to examine the association of cause-specific mortality with different weight categories among US adults in 2004.

METHODS

The general approach used to estimate excess deaths builds on that of Allison et al.² Numbers of deaths in 2004 for people 25 years and older came from US vital statistics.³ We used underlying cause-of-death information that had been recoded using a standard list of 113 causes of death; details of the corresponding *International Classification of Diseases, Ninth Revision (ICD-9)* and *ICD-10* codes are shown elsewhere.⁴ We grouped deaths into 3 major categories: cardiovascular disease (CVD), cancer, and all other causes (ie, noncancer, non-CVD deaths). For some analyses, these categories were divided further. TABLE 1 shows the groupings and the total number of deaths from each cause in the United States,

Context The association of body mass index (BMI) with cause-specific mortality has not been reported for the US population.

Objective To estimate cause-specific excess deaths associated with underweight (BMI <18.5), overweight (BMI 25-<30), and obesity (BMI ≥30).

Design, Setting, and Participants Cause-specific relative risks of mortality from the National Health and Nutrition Examination Survey (NHANES) I, 1971-1975; II, 1976-1980; and III, 1988-1994, with mortality follow-up through 2000 (571 042 person-years of follow-up) were combined with data on BMI and other covariates from NHANES 1999-2002 with underlying cause of death information for 2.3 million adults 25 years and older from 2004 vital statistics data for the United States.

Main Outcome Measures Cause-specific excess deaths in 2004 by BMI levels for categories of cardiovascular disease (CVD), cancer, and all other causes (noncancer, non-CVD causes).

Results Based on total follow-up, underweight was associated with significantly increased mortality from noncancer, non-CVD causes (23 455 excess deaths; 95% confidence interval [CI], 11 848 to 35 061) but not associated with cancer or CVD mortality. Overweight was associated with significantly decreased mortality from noncancer, non-CVD causes (-69 299 excess deaths; 95% CI, -100 702 to -37 897) but not associated with cancer or CVD mortality. Obesity was associated with significantly increased CVD mortality (112 159 excess deaths; 95% CI, 87 842 to 136 476) but not associated with cancer mortality or with noncancer, non-CVD mortality. In further analyses, overweight and obesity combined were associated with increased mortality from diabetes and kidney disease (61 248 excess deaths; 95% CI, 49 685 to 72 811) and decreased mortality from other noncancer, non-CVD causes (-105 572 excess deaths; 95% CI, -161 816 to -49 328). Obesity was associated with increased mortality from cancers considered obesity-related (13 839 excess deaths; 95% CI, 1920 to 25 758) but not associated with mortality from other cancers. Comparisons across surveys suggested a decrease in the association of obesity with CVD mortality over time.

Conclusions The BMI-mortality association varies by cause of death. These results help to clarify the associations of BMI with all-cause mortality.

JAMA. 2007;298(17):2028-2037

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based on 2004 mortality data³ for people 25 years and older. Following the National Cancer Institute Obesity and Cancer Fact Sheet,⁵ we considered deaths from colon cancer, breast cancer, esophageal cancer, uterine cancer, ovarian cancer, kidney cancer, and pancreatic cancer to be deaths from obesity-related cancers.

All other data came from the National Health and Nutrition Examination Survey (NHANES) program of the National Center for Health Statistics. In

each survey a different nationally representative cross-sectional sample of the US population was examined. To estimate relative risks, we used baseline

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data from NHANES I, 1971-1975; NHANES II, 1976-1980; NHANES III, 1988-1994, and underlying cause-of-death mortality data through 2000 for these surveys (TABLE 2).⁶⁻¹² Height and weight were measured using standardized procedures. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Baseline age was age at the time of the examination.

We calculated relative risks for each category of causes of death using Cox proportional hazard models with age as the time scale.¹³ Because the proportional hazards assumption was not met across age, we divided the data into 3 age strata, 25 to younger than 60 years, 60 to younger than 70 years, and 70 years and older and fit models separately within each age stratum. Because age is the time scale, these age strata refer to attained age, rather than to age at baseline. For all analyses, we used BMI categories of 18.5 or less (underweight), 18.5 to less than 25 (normal weight, reference category), 25 to less than 30 (overweight), 30 to less than 35 (obesity grade 1), and 35 or greater (obesity grades 2 and 3).^{14,15} The model included BMI categories, sex, smoking status (never, former, current), race (white, black, other), and alcohol consumption categories in ounces per day (none, <0.07, 0.07- $<$ 0.35, and \geq 0.35).

To calculate the proportion of deaths in 2004 associated with each BMI level, we first calculated the relative risks for specific causes of death for all covariates from a data set that combined data from all 3 surveys (Table 2). We then applied each set of cause-specific relative risks from a given age group to the current distribution of the covariates (BMI group and all other covariates) in that age group in the general population, as estimated from the NHANES 1999-2002 cross-sectional survey data; for these purposes, non-Hispanic whites and blacks were categorized as white and black. Race was assessed by observation in NHANES I and II and by participant self-report in NHANES III and NHANES 1999-2002.

As described previously,¹ we calculated cause-specific attributable fractions for each BMI category by comparing the estimated risks from the current distribution of covariates with the estimated risks with BMI category set to normal weight, holding all else constant. The estimated number of excess deaths for each cause was then calculated by multiplying the total number of deaths in that age group in 2004 by the corresponding attributable fraction and summing over age. Standard errors were calculated by applying a delta method for complex sample de-

signs that takes into account uncertainties in the relative risks for BMI categories, the distribution of BMI, the distribution of covariates, and the estimated effects of covariates, as well as the added variability due to the complex sample designs of the NHANES surveys.¹⁶⁻¹⁸

Secondary analyses examining subgroups of mortality categories were performed by dividing the major mortality categories into finer groupings. The sum of the estimated excess deaths from these secondary analyses differs slightly from the estimated excess deaths in the

Table 1. Cause of Death and Number of Deaths Among US Adults 25 Years and Older in 2004 by Specified Cause

Cause of Death	Corresponding Numbers From 113-Causes-of-Death List ^a	No. (%) of Deaths of Persons in 2004, Aged \geq 25 y
CVD	53-74	858 723 (36.9)
Coronary heart disease	58-63	451 161 (19.4)
Other CVD	55-57, 64-74	407 562 (17.5)
Cancer	19-43	550 687 (23.7)
Lung cancer	27	158 058 (6.8)
Considered obesity-related ^b	21, 23, 25, 29, 31, 32, 34	173 717 (7.5)
All other cancers	All other numbers within cancer category	218 912 (9.4)
Noncancer, non-CVD disease	All other numbers	915 229 (39.4)
Diabetes and kidney disease	46, 97-113	115 115 (5.0)
Chronic respiratory disease	82-86	121 605 (5.2)
Acute respiratory and infectious disease	1-18, 76-81, 87-89	167 057 (7.2)
Injuries	112-135	137 640 (5.9)
Miscellaneous	All other numbers within noncancer, non-CVD categories	373 812 (16.1)
Total		2 324 639 (100)

Abbreviation: CVD, cardiovascular disease.

^aBased on Anderson et al.⁴

^bColon cancer, breast cancer, esophageal cancer, uterine cancer, ovarian cancer, kidney cancer, and pancreatic cancer.

Table 2. Descriptive Information About the Surveys Providing Mortality Data

	NHANES			Combined
	I	II	III	
Survey baseline, y	1971-1975	1976-1980	1988-1994	
Unweighted sample size ^a	12 655	9219	14 985	36 859
Age at baseline examination, y	25-75	30-75	>25	
Maximum follow-up, y	29.7	24.9	12.1	29.7
Person-years of follow-up, y	277 206	169 591	124 245	571 042
No. of deaths	5839	4140	2793	12 772
CVD deaths	2846	1861	1294	6001
Cancer deaths	1341	936	612	2889
Deaths from all other causes	1652	1343	887	3882

Abbreviations: CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

^aAfter exclusions for missing body mass index data.

whole category because they are derived from separately fitting different proportional hazard regressions, but the differences are small.

Estimates were made from the combined data to obtain more precision and to represent the US population over the more than 2 decades (1971-1994) covered by the baseline years of these surveys. Several issues arise in combining the surveys. For the present analyses, follow-up through 2000 was available for all surveys. As a result, NHANES I had more than 29 years of follow-up, NHANES II had more than 24 years of follow-up, and NHANES III had slightly more than 12 years of follow-up. Accordingly, the number of deaths contributed by the earlier surveys is larger than the number contributed by NHANES III.

One approach is to combine all data for all surveys, which gives the most weight to NHANES I, with its higher number of deaths. Another is to hold follow-up roughly constant across surveys. Willett et al¹⁹ have recommended that for studies of weight and mortality follow-up should not continue more than 10 or 15 years without remeasurement to limit weight misclassification. We report results from both approaches, using roughly balanced follow-up by limiting follow-up to no more than 15 years for each survey, *balanced follow-up*, or using all follow-up data for all surveys, *total follow-up*. Both approaches give less emphasis to the most recent data, since NHANES III has less than 15 years of follow-up and the fewest number of deaths.

Data were analyzed using the SAS System for Windows (Release 9.1) (SAS Institute Inc, Cary, North Carolina) and Research Triangle Institute's SUDAAN (Release 9.0) software programs (RTI International, Research Triangle Park, North Carolina). All analyses included sample weights that account for the varying probabilities of selection due to sampling and non-response. NHANES III and NHANES 1999-2002 underwent institutional review board approval and included

written informed consent. Institutional review board approval using current standards was not obtained for NHANES I or NHANES II, but internal human subject review was conducted. Estimates were considered significantly different from 0 if the 95% confidence interval (CI) did not include 0.

RESULTS

Cause-specific relative risks and 95% CIs for balanced and total follow-up are shown in FIGURE 1. The estimated numbers of excess deaths and 95% CIs by BMI category for CVD, cancer, and noncancer, non-CVD causes are shown in TABLE 3. The excess deaths from Table 3 expressed as a percentage of total deaths from the corresponding cause are shown in TABLE 4. For example, the 8674 excess CVD deaths associated with underweight shown in Table 3 represent 1% of the total 858 723 deaths from CVD in the United States that is shown in Table 1.

CVD Mortality

For CVD, obesity, but not overweight, was significantly positively associated with excess mortality (Table 3). In secondary analyses, deaths due to CVD were subdivided into deaths from coronary heart disease (CHD) and deaths from other cardiovascular causes (including stroke). Estimates of excess deaths with balanced follow-up are shown in FIGURE 2 for these 2 subgroups. In balanced follow-up, obesity was associated with significantly increased mortality from both CHD (45 544 excess deaths; 95% CI, 24 785-66 303) and other forms of CVD (34 097 excess deaths; 95% CI; 13 848-54 346). Estimates from total follow-up were somewhat higher (CHD, 66 572 excess deaths; 95% CI, 50 582-82 562; other CVD, 42 650 excess deaths; 95% CI, 24 888-60 413). Neither underweight nor overweight was associated with significantly increased or reduced mortality from CHD or from other forms of CVD.

Cancer Mortality

For cancer, there was no significant association of excess mortality with any BMI category with either type of follow-up (Table 3). To investigate further, we subdivided cancer deaths into 3 subgroups: deaths from lung cancer, deaths from cancers considered in the literature to be obesity related (colon, breast, esophageal, uterine, ovarian, kidney, and pancreatic cancer), and deaths from all other cancers. Estimates of excess deaths with balanced follow-up are shown in Figure 2 for each of these 3 subgroups.

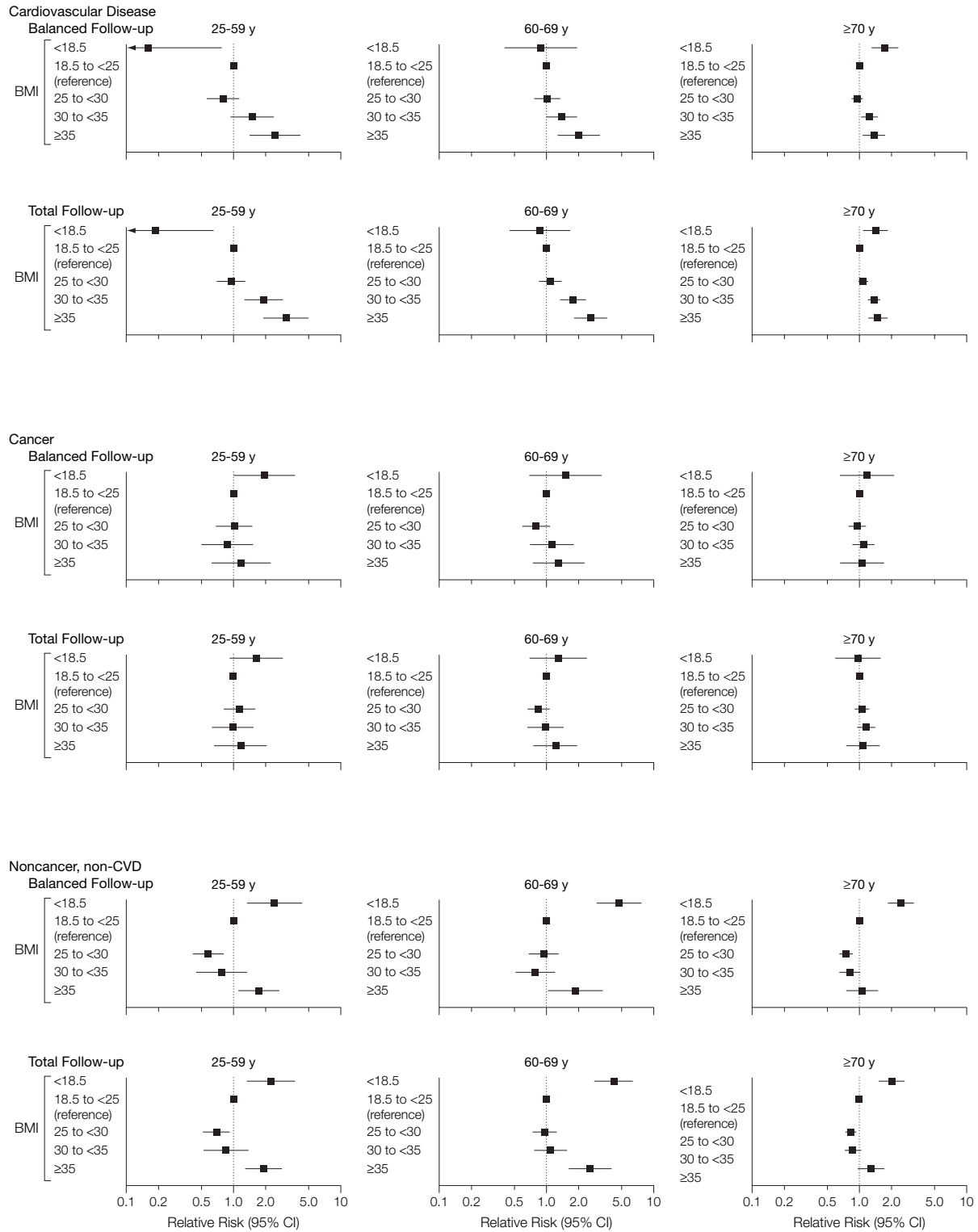
Lung cancer deaths showed no significant association with any BMI category; overweight and obesity were associated with a nonsignificantly reduced number of lung cancer deaths. Overall, obesity was associated with a significantly increased number of deaths from cancers considered obesity related, 19 732 excess deaths (95% CI, 4166-35 299), representing 11.4% of deaths from obesity-related cancers. With total follow-up, estimates were slightly lower (13 839 excess deaths; 95% CI, 1920-25 758). Overweight was not associated with excess deaths from cancers considered obesity related (Figure 2). Deaths from all other cancers had no relation with BMI (Figure 2).

Noncancer, Non-CVD Mortality

For noncancer, non-CVD mortality, underweight was associated with a significantly positive number of excess deaths and overweight with a significantly negative number of excess deaths (Table 3). Obesity was not associated with any significant positive or negative excess noncancer, non-CVD mortality.

To investigate further, we divided noncancer, non-CVD deaths into 5 subgroups: (1) diabetes and kidney disease; (2) chronic respiratory disease, including bronchitis and emphysema; (3) acute respiratory and infectious disease, including pneumonia, tuberculosis, septicemia, and other infections; (4) injuries, including unintentional injuries, suicides, and homicides; (5) all other noncancer, non-CVD causes,

Figure 1. Cause-Specific Relative Risks by Age Group and Body Mass Index Category for Balanced and Total Follow-up



BMI indicates body mass index which is calculated as weight in kilograms divided by height in meters squared; CI, confidence interval (shown by error bars); CVD, cardiovascular disease.

Table 3. Estimated Number of Excess Deaths in the United States in 2004 Associated With Body Mass Index Levels, Based on the Combined NHANES I, II, and III Data Set

Cause of Death	Excess Deaths (95% Confidence Interval)			
	Underweight (BMI <18.5)	Normal Weight (BMI 18.5-25)	Overweight (BMI 25-30)	Obesity (BMI ≥30)
Balanced follow-up				
CVD	8674 (343 to 17 004)	0 [Reference]	-17 074 (-50 407 to 16 259)	81 072 (51 433 to 110 710)
Cancer	4144 (-1956 to 10 244)	0 [Reference]	-13 533 (-44 364 to 17 298)	14 930 (-13 721 to 43 582)
Noncancer, non-CVD	33 380 (17 435 to 49 326)	0 [Reference]	-107 674 (-148 738 to -66 610)	-560 (-41 201 to 40 081)
Total follow-up				
CVD	4097 (-1451 to 9645)	0 [Reference]	20 724 (-6092 to 47 540)	112 159 (87 842 to 136 476)
Cancer	1548 (-2451 to 5547)	0 [Reference]	6780 (-18 418 to 31 977)	15 252 (-7946 to 38 451)
Noncancer, non-CVD	23 455 (11 848 to 35 061)	0 [Reference]	-69 299 (-100 702 to -37 897)	35 594 (-1287 to 72 476)

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared. CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

including Alzheimer disease, Parkinson disease, liver disease, and any other noncancer, non-CVD causes not falling into the 4 categories above, including 303 deaths with no cause attributed. Diabetes and kidney disease were grouped together because there were too few diabetes deaths in the youngest age group to make acceptably precise estimates and because diabetes is an important cause of end-stage renal disease.

Balanced follow-up results are shown in FIGURE 3. Diabetes and kidney disease combined were associated with significantly increased mortality in overweight (13 904 excess deaths; 95% CI, 2534-25 273) and obesity (33 643 excess deaths; 95% CI, 20 640-46 645) categories. Results were higher with total follow-up (overweight, 15 872 excess deaths; 95% CI, 7973-23 772; obesity, 45 376 excess deaths; 95% CI, 35 532-55 219).

In each of the other 4 subgroups of noncancer, non-CVD deaths, overweight was associated with reduced mortality, and this association was statistically significant except for acute respiratory and infectious disease (Figure 3). Overall, obesity was not associated with noncancer, non-CVD mortality. However, for each of these 4 subgroups of noncancer, non-CVD deaths, grade 1 obesity tended to be associated with reduced mortality and grades 2 and 3 obesity with increased mortality. We then combined all 4 of these subgroups of noncancer, non-CVD deaths and found significantly reduced mortality among overweight (-89 680 deaths;

95% CI, -122 901 to -56 458) and grade 1 obesity (-39 595 deaths; 95% CI, -61 807 to -17 382) and significantly increased mortality among grades 2 and 3 obesity (23 702 deaths; 95% CI, 1736 to 45 669) with total follow-up. Overall, overweight and obesity combined were associated with increased mortality from diabetes and kidney disease combined (61 248 excess deaths; 95% CI, 49 685 to 72 811) and decreased mortality from other noncancer, non-CVD causes (-105 572 excess deaths; 95% CI, -161 816 to -49 328). With balanced follow-up, all estimates were lower than with total follow-up (diabetes and kidney disease combined: 47 546 excess deaths; 95% CI, 29 356-65 737; other noncancer, non-CVD causes: -133 310 excess deaths; 95% CI, -212 272 to -54 348).

Trends Over Surveys and Length of Follow-up

Cause-specific estimates of excess deaths associated with obesity were calculated using survey-specific relative risks (FIGURE 4). Because relative risks were applied to the NHANES 1999-2002 distribution of covariates, these estimates of excess deaths are not affected by differences between surveys in the prevalence of smoking and of other covariates. All-cause specific estimates were higher when using the NHANES I relative risks than when using the relative risks from the other surveys.

The major difference was for CVD mortality. Estimates for 2004 using NHANES I relative risks indicated that

161 290 excess CVD deaths (95% CI, 123 788 to 198 791) were associated with obesity, representing 19% of all CVD deaths. The estimate for 2004 using the NHANES II relative risks was 88 657 excess CVD deaths (95% CI, 51 151 to 126 164), representing 10% of all CVD deaths, and using the NHANES III relative risks was 46 915 excess CVD deaths (95% CI, -5694 to 99 524), representing 5% of all CVD deaths. The higher estimates using NHANES I were not due to the longer follow-up in that survey because excess CVD mortality associated with obesity in NHANES I varied little by length of follow-up (15 years, 155 955 excess deaths; 95% CI, 103 844 to 208 065; 20 years, 168 383 excess deaths; 95% CI, 127 689 to 209 077; 25 years, 158 647 excess deaths; 95% CI, 119 053 to 198 242). Overweight was not significantly associated with positive excess CVD, cancer, or noncancer, non-CVD mortality based on any of the survey-specific or combined relative risks.

Sensitivity Analyses

To address the issue of potential confounding by illness-induced weight loss or smoking, sensitivity analyses for the major categories were conducted by simultaneously limiting the sample to never smokers without a history of the relevant disease (CVD, cancer, or chronic obstructive pulmonary disease) at baseline whose weight and height were measured before age 70 years and who did not die within the

first 3 years of follow-up. We used the BMI hazard ratios from this subgroup combined with hazard ratios from the full sample for other covariates to calculate a set of synthetic attributable fractions. This method isolates the effect on estimates of excess deaths for the whole population of the BMI hazard ratios in a selected subgroup while keeping the estimated risks for smoking and other covariates constant. These are sensitivity analyses and not estimates of attributable fractions either for the whole US population or for the selected subgroup.

For CVD mortality, with balanced follow-up, these exclusions reduced the attributable fractions for obesity and increased the attributable fraction for underweight. The attributable fraction for overweight became more negative. With total follow-up, changes were less than 1 percentage point for any BMI category, and the attributable fraction for underweight decreased from 0.5% to -0.3%.

For cancer mortality, with balanced follow-up, all attributable fractions were closer to 0 after the exclusions. With total follow-up, the attributable fraction for obesity increased from 2.8% to 4.8%, and attributable fractions for other BMI categories became closer to 0 after the exclusions.

For noncancer, non-CVD mortality, the attributable fraction for underweight became closer to 0 and for overweight increased from -11.8% to -7.7% for balanced follow-up or from -7.6% to -5.2% for total follow-up after exclusions. For obesity, the attributable fraction increased from -0.1% to 6.4% for balanced follow-up and from 3.9% to 7.4% for total follow-up.

COMMENT

We estimated the association of specific causes of mortality with BMI categories. For each cause, we estimated excess deaths in each BMI category, defined as deaths in 2004 in excess of those expected based on individuals of normal weight (BMI 18.5-<25). This approach provides a metric that can be summed over age groups while still allowing for variation in relative risks by age. It uses age-specific information on the prevalence of BMI cat-

egories and the population occurrence of specific causes of death, combined with relative risk information, to estimate the population-level burden of BMI-associated mortality, which cannot be assessed from relative risk estimates alone.

CVD Mortality

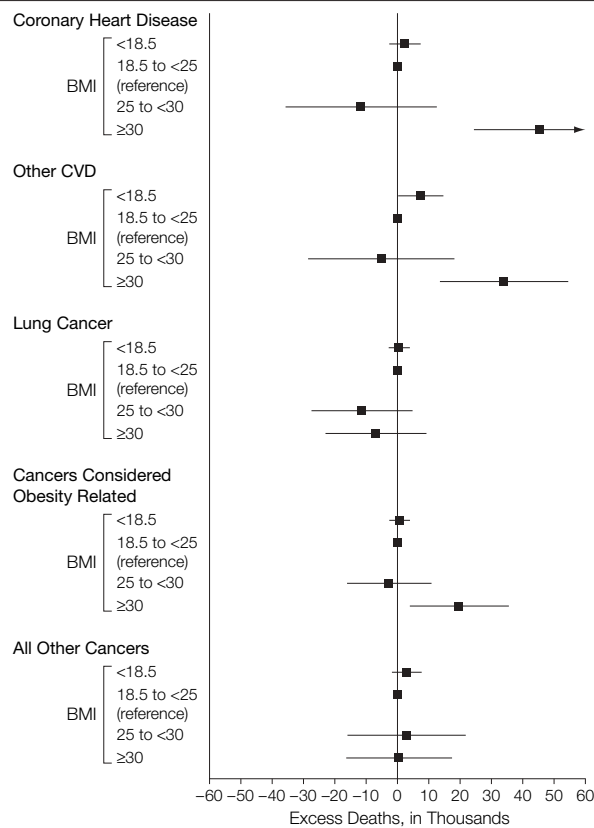
Cardiovascular disease accounted for 37% of adult deaths in the United States in 2004. Based on total follow-up, we found that 13% of total CVD mortality was associated with obesity (BMI ≥30);

Table 4. Excess Deaths as a Percentage of All Deaths from Specified Cause in the United States in 2004 Associated With Body Mass Index Levels, Based on the Combined NHANES I, II, and III Data Set

Cause of Death	Excess Deaths as Percentage of Specified Cause (95% Confidence Interval)			
	Underweight (BMI <18.5)	Normal Weight (BMI 18.5-<25)	Overweight (BMI 25-<30)	Obesity (BMI ≥30)
Balanced follow-up				
CVD	1.0 (0.0 to 2.0)	0 [Reference]	-2.0 (-5.9 to 1.9)	9.4 (6.0 to 12.9)
Cancer	0.8 (-0.4 to 1.9)	0 [Reference]	-2.5 (-8.1 to 3.1)	2.7 (-2.5 to 7.9)
Noncancer, non-CVD	3.6 (1.9 to 5.4)	0 [Reference]	-11.8 (-16.3 to -7.3)	-0.1 (-4.5 to 4.4)
Total follow-up				
CVD	0.5 (-0.2 to 1.1)	0 [Reference]	2.4 (-0.7 to 5.5)	13.1 (10.2 to 15.9)
Cancer	0.3 (-0.4 to 1.0)	0 [Reference]	1.2 (-3.3 to 5.8)	2.8 (-1.4 to 7.0)
Noncancer, non-CVD	2.6 (1.3 to 3.8)	0 [Reference]	-7.6 (-11.0 to -4.1)	3.9 (-0.1 to 7.9)

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; CVD, cardiovascular disease; NHANES, National Health and Nutrition Examination Survey.

Figure 2. Excess Deaths by Body Mass Index Category for Subgroups of Cardiovascular Disease and Cancer Deaths—Balanced Follow-up



BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; CVD, cardiovascular disease. Error bars indicate 95% confidence intervals.

when balanced follow-up was used, giving less weight to the earlier data, our estimate was 9%. We found no significant association of overweight with CVD mortality. Simultaneously exclud-

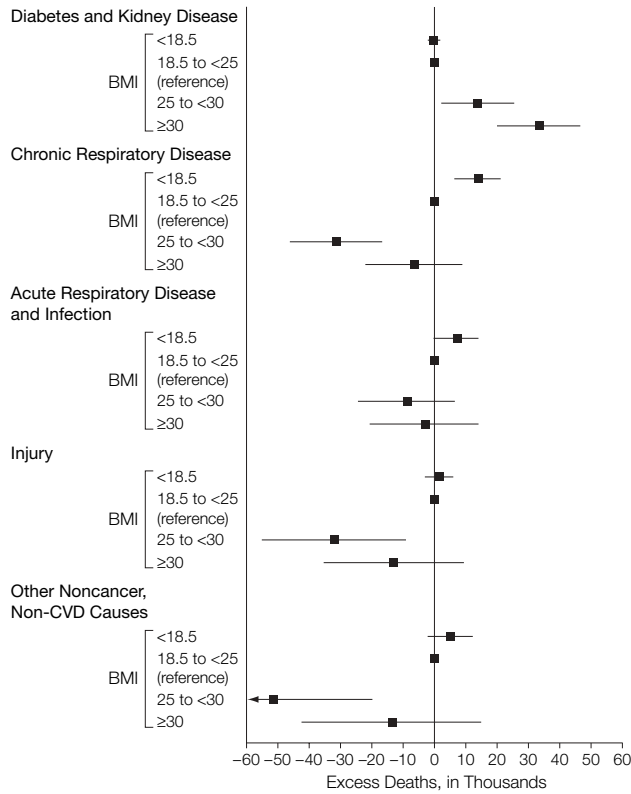
ing participants who reported a history of CVD, had ever smoked, died in the first 3 years of follow-up, or were measured after age 70 years had only small and nonsystematic effects on these

estimates. Thus, there was no indication that our results were biased by illness-induced weight loss prior to baseline (“reverse causation”) or residual confounding due to smoking.

Direct comparison of our results with other studies is difficult because studies use different BMI categories and referent groups and many lack measured heights and weights. Our attributable fraction estimates are somewhat higher than those from the Framingham Heart Study. Wilson et al²⁰ used the Framingham data to estimate that relative to normal weight (BMI 18.5-<25), obesity (BMI ≥30) accounted for 0.0% of CVD deaths in men and 10% of CVD deaths in women. In the Framingham study, relative to normal weight, overweight (BMI 25-<30) accounted for 2% of CVD deaths in men and -9% of CVD deaths in women, consistent with our finding of no significant association between overweight and CVD mortality.

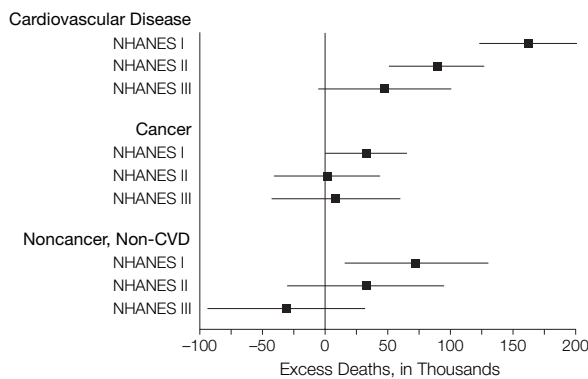
Several recent studies²⁰⁻²³ that used measured heights and weights and the same normal weight range as the referent BMI category used in our study found that CVD mortality had little relation to overweight with hazard ratios ranging between 0.9 and 1.1. Body mass index categories of 30 or higher, however, showed hazard ratios typically in the range of 1.4 to 1.8, similar to those observed in our study. Similar results were also found in a pooled analysis of 26 data sets with measured or self-reported heights and weights.²⁴

Figure 3. Excess Deaths by Body Mass Index Category for Subgroups of Noncancer, non-CVD Deaths—Balanced Follow-up



BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; CVD, cardiovascular disease. Error bars represent 95% confidence intervals.

Figure 4. Cause-Specific Excess Deaths Associated With Obesity by Survey—Total Follow-up



NHANES indicates National Health and Nutrition Examination Survey; CVD, cardiovascular disease. Error bars represent 95% confidence intervals.

Cancer Mortality

Cancer accounted for approximately 24% of total deaths among US adults in 2004. Our results showed little or no association of excess all-cancer mortality with any of the BMI categories. None of the estimates of excess deaths was statistically significantly different from 0. Simultaneously excluding participants who reported a history of cancer, had ever smoked, died in the first 3 years of follow-up, or were measured after age 70 years had only small and unsystematic effects on these estimates; thus, there was no apparent bias due to illness-induced weight loss prior

to baseline or residual confounding by smoking.

We divided cancers into lung cancer (29% of cancer deaths among adults in the United States), cancers considered in the literature to be associated with obesity (32% of cancer deaths), and other cancers (40% of cancer deaths). We found that obesity was significantly associated with 11% of deaths from cancers considered to be obesity-related. Mortality from lung cancer and other cancers showed no significant association with underweight, overweight, or obesity.

Our findings about cancer mortality are consistent with several recent reports. Danaei et al²⁵ estimated that 3% of cancer mortality in developed countries was associated with overweight and obesity. Ni Mhurchu et al,²⁶ using a years-of-life-lost approach, estimated that 4% of cancer mortality in New Zealand was associated with having a BMI higher than 21. Kuriyama²⁷ found that 4.5% of cancer deaths in Japanese women and -0.2% in Japanese men were associated with overweight and obesity. Calle et al²⁸ found significantly reduced cancer mortality in the overweight category for men in the large Cancer Prevention Study II cohort, based on self-reported heights and weights. Calle et al²⁸ estimated that 4.3% of cancer deaths among men and 14.3% of cancer deaths among women in the United States were associated with obesity, although their attributable fraction estimates were not fully adjusted for the covariates in their models.²⁹ Our finding of nonsignificant relative risks of all-cancer mortality among overweight and obese individuals is in agreement with a number of other studies.^{21,30-36} In addition, relative incidence rates for all cancer tend to be null or small for the overweight category and modestly elevated for categories of obesity,^{28,37} consistent with our results.

Noncancer, non-CVD Mortality

Noncancer, non-CVD deaths accounted for approximately 39% of total deaths among adults in 2004. Although noncancer, non-CVD causes make up a substantial portion of adult mortality,

they are often not considered to be weight-related. However, we found that these other deaths were significantly elevated in the BMI category of underweight, were significantly reduced in the BMI category of overweight, showed a negative or null association with obesity grade 1, and showed a modest significantly positive association with obesity grades 2 and 3. Several other studies have reported similar results. The large Cancer Prevention Study II study showed an inverse or null relation between BMI and noncancer, non-CVD mortality among never smokers who were healthy at baseline, up to a BMI of approximately 32 for men and 28 for women.³⁸ The British Regional Heart Study of men found a statistically significant inverse relation between BMI and noncancer, non-CVD mortality.³⁹

Combined diabetes and kidney disease mortality, however, was significantly positively associated with increased mortality in both the overweight and obese categories. The other 4 subgroups of noncancer, non-CVD causes (chronic respiratory disease, acute respiratory and infectious disease, injuries, and miscellaneous causes) showed significantly decreased mortality in the overweight and grade 1 obesity categories and significantly increased mortality in the obesity grades 2 and 3 category.

Excess Mortality by BMI Categories

It has been suggested that excess mortality in the underweight is due to weight loss associated with cancer or cardiovascular disease.⁴⁰ Our results, however, as well as those of Jee et al,⁴¹ He et al,⁴² and others, suggest that excess mortality among the underweight is primarily associated with noncancer, non-CVD causes and not with cancer or cardiovascular disease. Jee et al⁴¹ found significantly increased mortality from respiratory causes (including tuberculosis, chronic obstructive pulmonary disease, asthma, and pneumonia) with decreasing BMI in a large Korean cohort; this inverse association was seen both in smokers and in nonsmokers and persisted when the

first 5 years of deaths were excluded. He et al⁴² found that underweight was associated with increased mortality even after the simultaneous exclusion of ever-smokers or those with cancer, CVD, chronic obstructive pulmonary disease, or end-stage renal disease at baseline and those who died within the first 3 years of follow-up. In our results, excess mortality among the underweight was primarily related to chronic respiratory conditions, as others have found.^{32,33,41} This finding may be partly due to weight loss associated with chronic obstructive pulmonary disease, although among such patients, low BMI has also been shown to be a risk factor for mortality independently of disease severity.^{41,43-45}

The primary contribution to excess mortality among the obese was CVD, with smaller contributions from obesity-related cancers and from diabetes and kidney disease combined. Comparisons across surveys suggested a decrease in the association of obesity with CVD mortality over time. This finding is consistent with a number of population trends. National mortality data for 2004 showed a decrease in age-adjusted death rates to a historically low figure.³ Age-adjusted CVD mortality rates have been decreasing over the previous 4 decades.³ The prevalence of several CVD risk factors has decreased at all weight levels.⁴⁶

Some evidence suggests that modestly higher weights may improve survival in a number of circumstances,⁴⁷⁻⁵² which may partly explain our findings regarding overweight. Overweight is not strongly associated with increased cancer or CVD risk, but may be associated with improved survival during recovery from adverse conditions, such as infections or medical procedures, and with improved prognosis for some diseases. Such findings may be due to greater nutritional reserves or higher lean body mass associated with overweight.

Some limitations of our study should be noted. The results depend on projecting the experience of past cohorts onto the present, which may be inac-

curate. The underlying cause of death may be misidentified on death certificates. In particular, diabetes may be underreported as an underlying cause. One study showed that only 39% of the death certificates of individuals with diabetes who died of CVD mentioned diabetes.⁵³ This misclassification could lead to underestimating the excess obesity-associated deaths for diabetes as the underlying cause and overestimating the excess obesity-associated deaths for CVD as the underlying cause. The estimates reported herein are for statistical associations of BMI with mortality. A variety of other factors associated with both weight and mortality, however, such as physical activity levels, body composition, and differences in medical treatment by weight, could be responsible for part or all of the observed associations.⁵⁴ Our study does not address the association of BMI levels with risk factors such as hypertension or dyslipidemia nor with disease incidence or morbidity. In addition, our study does not address potential effects of weight loss or gain on associations between BMI and mortality.

Although it is desirable to use the experience of recent cohorts, doing so limits the follow-up time. The experience of cohorts with long follow-up may not reflect current conditions, however. Over a long follow-up, baseline values of BMI or other covariates may change considerably. For example, as follow-up lengthens, individuals who were overweight at baseline may move into the obese category and acquire the higher risks more characteristic of the obese category but would still be classified as overweight rather than obese in the analysis. Such changes could distort the apparent risk associated with overweight. Thus inaccuracies might be introduced either by including data from less recent cohorts with long follow-up or by including data from a more recent cohort with shorter follow-up. We found little or no change with increasing follow-up in estimated cause-specific excess deaths associated with obesity. When similar lengths of follow-up were used for each survey, es-

timates were slightly lower, in part because of an apparently weaker obesity-CVD mortality association in more recent surveys. Estimates for total follow-up thus tended to be higher than those for balanced follow-up, not because follow-up was longer but because they gave more weight to the earlier surveys, particularly NHANES I, in which the association of obesity with mortality was stronger.

Many factors influence mortality risk in addition to weight. Some variability among studies in estimates of association between BMI and all-cause mortality may reflect differences in age, sex, and other risk factors, apart from BMI, including secular effects on studies conducted at different times. The relative proportions of different causes of death in various cohorts can also influence this association. Study exclusions designed to control confounding may alter the observed BMI-mortality association by changing the relative proportions of different causes of death.⁵⁵ The associations of BMI with all-cause mortality represent the net effect of a variety of associations that vary by cause of death. Understanding these cause-specific associations helps interpret our previous findings for all-cause mortality¹ and may help explain differing associations between BMI and all-cause mortality found in the literature.

CONCLUSIONS

We found that underweight was associated with increased mortality, primarily from noncancer, non-CVD causes. Overweight was associated with significantly increased mortality from diabetes and kidney disease combined; was associated with significantly decreased mortality from other noncancer, non-CVD causes; and was not associated with mortality from cancer or cardiovascular disease. The net result was that overweight was associated with significantly decreased all-cause mortality overall. Obesity was associated with significantly increased mortality from CVD, from some cancers, and from diabetes and kidney dis-

ease combined but showed little or no association with other cancers and with other causes of death. Obesity also was associated with increased mortality overall, primarily due to its association with CVD mortality. Thus, our data indicate that the association of BMI with mortality varies considerably by cause of death. These results help to clarify our earlier findings¹ of excess overall mortality associated with underweight and obesity but not with overweight.

Author Contributions: Dr Flegal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Flegal, Graubard, Williamson, Gail.

Acquisition of data: Flegal, Graubard.

Analysis and interpretation of data: Flegal, Graubard, Williamson, Gail.

Drafting of the manuscript: Flegal, Graubard, Williamson, Gail.

Critical revision of the manuscript for important intellectual content: Flegal, Graubard, Williamson, Gail.

Statistical analysis: Graubard, Gail.

Financial Disclosures: None reported.

Funding/Support: There was no external funding for this work.

Role of the Sponsor: All data used in this study were collected by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention. The NCHS was responsible for the design and conduct of the surveys and collected and managed the original data. The Centers for Disease Control and Prevention and the National Cancer Institute reviewed and approved this report before submission.

Disclaimer: The findings and conclusions in this report are those of the authors and not necessarily those of the agency.

Additional Contributions: We thank Christine S. Cox, MA, and Robert N. Anderson, PhD, both of the National Center for Health Statistics, Centers for Disease Control and Prevention, for her assistance with the NHANES I, II, and III mortality data and for his assistance with the 2004 mortality data. We also thank Rachel Ballard-Barbash, MD, and D. Michal Freedman, PhD, of the National Cancer Institute; Edward Gregg, PhD, and Juliette Kendrick, MD, of the National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease and Prevention, and Susan Yanovski, MD, of the National Institute for Diabetes and Digestive and Kidney Diseases for reviewing and commenting on earlier drafts of the manuscript, all of whom reviewed this as part of their regular duties.

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