

Annual Deaths Attributable to Obesity in the United States

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OBESITY IS A SERIOUS MEDICAL problem, increasing in prevalence, affecting millions,¹ and of great interest to the public. To articulate the burden of obesity, investigators have used indicators such as prevalence,^{1,2} economic cost,³ and association with risk factors and diseases.⁴ However, there is little published scientific information on the number of annual obesity-attributable deaths in the United States.

Mass media,⁵⁻⁸ scholarly journals,⁹⁻¹¹ and pharmaceutical handouts¹² have cited 300 000 deaths per year in the United States as being attributable to obesity, a number that may have been adapted from an analysis of precursors of premature death in the United States for 1980,¹³ attributing 289 502 deaths to "overnutrition." McGinnis and Foege¹⁴ estimated that, of US deaths in 1990, 309 000 to 582 000 were associated with unhealthy diet and exercise patterns. However, neither study estimated deaths attributed specifically to obesity.

We report a detailed analysis aimed at calculating the annual number of deaths attributable to obesity. It is important to clarify the quantity we are trying to estimate.

If we choose a particular year, ie, 1991, we can say, "Of the people who were alive at the beginning of 1991, how many fewer would have died by the end of that year if all of the obese people alive at the beginning of the year had not been obese

Context Obesity is a major health problem in the United States, but the number of obesity-attributable deaths has not been rigorously estimated.

Objective To estimate the number of deaths, annually, attributable to obesity among US adults.

Design Data from 5 prospective cohort studies (the Alameda Community Health Study, the Framingham Heart Study, the Tecumseh Community Health Study, the American Cancer Society Cancer Prevention Study I, and the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study) and 1 published study (the Nurses' Health Study) in conjunction with 1991 national statistics on body mass index distributions, population size, and overall deaths.

Subjects Adults, 18 years or older in 1991, classified by body mass index (kg/m²) as overweight (25-30), obese (30-35), and severely obese (>35).

Main Outcome Measure Relative hazard ratio (HR) of death for obese or overweight persons.

Results The estimated number of annual deaths attributable to obesity varied with the cohort used to calculate the HRs, but findings were consistent overall. More than 80% of the estimated obesity-attributable deaths occurred among individuals with a body mass index of more than 30 kg/m². When HRs were estimated for all eligible subjects from all 6 studies, the mean estimate of deaths attributable to obesity in the United States was 280 184 (range, 236 111-341 153). Hazard ratios also were calculated from data for nonsmokers or never-smokers only. When these HRs were applied to the entire population (assuming the HR applied to all individuals), the mean estimate for obesity-attributable death was 324 940 (range, 262 541-383 410).

Conclusions The estimated number of annual deaths attributable to obesity among US adults is approximately 280 000 based on HRs from all subjects and 325 000 based on HRs from only nonsmokers and never-smokers.

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and if those people had the hazard of those with a BMI [body mass index] just below the cutoff for obesity (eg, BMI 23-25 kg/m²)." For simplicity, we refer to this quantity as "the annual number of deaths attributable to obesity."

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METHODS

The year 1991 was chosen for analysis because of the availability of population (1990 US census¹⁵) and mortality statistics.¹⁶ Also, it was the midpoint of data collection for the Third National

with numerous organizations involving weight control products and services. Dr Manson was a consultant to Interneuron, Lexington, Mass, and Servier, Paris, France. Dr Stevens received travel reimbursement for speaking at Bristol-Myers Squibb, Princeton, NJ. Dr VanItallie received payment for work for the North American Association for the Study of Obesity, Silver Spring, Md, was a consultant to the Servier Foundation, Paris, and an unpaid consultant to ObeSys, United Kingdom, and has consulted for numerous organizations involving weight-control products.

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Health and Nutrition Examination Survey (NHANES III¹⁷), which provides the most recent, detailed population-based overweight and obesity-prevalence data.

Method of Calculation

We use formulae similar to the conventional formulae for attributable risk¹⁸ but account for “complications.” First, BMI exists along a continuum, and there is no single or universally accepted threshold above which people are labeled obese or overweight. Second, because persons go from being alive to dead over some time frame, use of relative risk (RR) estimates from studies without adjustment for time can bias results (though the bias may be small). The classes of quantities involved in calculation of number of obe-

sity-attributable deaths are described below and in TABLE 1.

Definitions of Overweight or Obesity and Reference Category

These quantities are the BMI thresholds used to define obesity and a nonoverweight reference category. We use T_1 (T for threshold) for the lower BMI limit of the reference group and T_2 for its upper BMI limit; T_3 is the BMI value above which subjects are categorized as overweight or obese. There are many thresholds that could be used for overweight or obese categorization and many possible reference groups. We used a BMI range of 23 to 25 kg/m² for the reference category, a close-to-average range corresponding to the upper end of current standards for acceptable weight.^{19,20}

Calculations were based on integer values of T_3 from 25 to 30 kg/m² (“overweight”), 30 to 35 kg/m² (“obesity”), and greater than 35 kg/m² (“severe obesity”)—cut points used by the World Health Organization (WHO)¹⁹ and the National Institutes of Health (NIH).²⁰ The hazard of mortality for those with BMIs greater than or equal to T_3 can then be compared with those of the reference group.

Population Characteristics

These quantities are estimated directly from existing data and describe the target population of interest. The target population is defined as adults (18 years or older) in the United States in 1991¹⁵ (total population size is N [185 105 441]). Total number of deaths in the target population in 1991

Table 1. Quantities Involved in Calculating Number of Deaths Attributable to Obesity*

Notation	Definition	Source of Estimates
Quantities Fixed by Choice		
T_1	The lower BMI limit of the reference group	Choice/convention (see “Methods” section for justification of specific values chosen)
T_2	The upper BMI limit of the reference group	
T_3	BMI value above which one categorizes a person as overweight or obese	
Quantities Directly Estimable From Data		
N	Total No. of people ≥ 18 y in the population	1990 US Census ¹⁸
M	Total No. of deaths among individuals ≥ 18 y expected to occur in the population during 1 y	1991 <i>MMWR Morb Mortal Wkly Rep</i> ¹⁹
$P(O)$	The probability of obesity, ie, $P(\text{BMI} \geq T_3)$	NHANES III ²⁰
$P(R)$	The probability of membership in reference category, ie, $P(\text{BMI} > T_1 \text{ and } < T_2)$	NHANES III ²⁰
$P(Q)$	The probability of nonobesity and nonmembership in reference category, ie, $1 - P(O) - P(R)$	NHANES III ²⁰
h	The HR for an obese or overweight person compared with a person whose BMI is in the reference category	Many useful data sets are available ⁴³
q	The HR for a nonobese person who is also not in the reference category compared with someone in the reference category	Many useful data sets are available ⁴³
Quantities Calculable From the Other Quantities Above		
$P(D)$	Probability of a member of the population dying in 1 y	M/N
λ	The hazard for a person in the reference category (ie, $\text{BMI} > T_1$ and $< T_2$)	Can be obtained by numerically solving the following equation for λ (see Appendix for derivation): $1 - P(D) = P(O) e^{-h\lambda} + P(R) e^{-\lambda} + (1 - P(O) - P(R)) e^{-q\lambda}$
$P(D O)$	Probability of a member of the population dying in 1 y given that he/she is obese or overweight	$1 - e^{-h\lambda}$
$P(D R)$	Probability of a member of the population dying in 1 y given that he/she is in the reference category	$1 - e^{-\lambda}$
$P(D Q)$	Probability of a member of the population dying in 1 y given that he/she is not in either the obese or overweight category or the reference category	$1 - e^{-q\lambda}$
ω	The number of deaths attributable to obesity or overweight, ie, the number of individuals in a given year who are expected to die who would not be expected to die if all obese or overweight persons had the same hazard as the average person in the reference category†	$M - N(P(R) P(D R) + P(O) P(D O) + P(Q) P(D Q))$

*BMI indicates body mass index; HR, hazard ratio.

†An equivalent formulation to that given at right is $\omega = A(P(O)) (P(D|O))N$, where A is the population-attributable fraction defined as $(RR-1)/RR$ and RR is the relative risk defined as $P(D|O)/P(D|R)$. We subtract from M the number of deaths expected to occur if all obese people had been in the reference category (the total number of deaths that currently occur). The number of deaths expected to occur if all obese people had been in the reference category is equal to the total population size (N) times the overall probability of deaths, which is a mixture of probabilities as given in the equation.

(2 110 687) is M .¹⁶ To quantify BMI population distribution, $P(O)$ is probability of obesity ($P[BMI \geq T_3]$). These values were derived from NHANES III data¹⁷ (Table 1). Probability of being in the reference category was also derived from NHANES III data.

The Relative Hazard Associated With Obesity

The hazard ratio (HR) for an obese or overweight person relative to a person in the BMI reference category is h . The HR for a nonobese person also not in the reference category relative to someone in the reference category is q . We estimate h and q from each data source (Table 1).

Calculated Quantities

The final quantities are calculable from quantities shown in Table 1. Mathematical expressions for quantities used to derive number of deaths attributable to overweight or obesity are given in the Appendix and Table 1 (a spreadsheet programmed to generalize these formulae to multiple cut points is available from the authors on request).

Data Sources for Estimation of HRs

We used several data sources to evaluate the extent to which results obtained were sensitive to a particular data set. Criteria used to select the data sets included (1) US source; (2) public availability or availability via extraction from published reports (ie, HRs for BMI cat-

egories); (3) not derived predominantly from ill, high-risk, or elderly subjects; and (4) well-documented characteristics. We chose 6 large prospective cohort studies meeting these criteria: the Alameda County Health Study,²¹ the Tecumseh Community Health Study,²² the Framingham Heart Study,²³ the American Cancer Society's Cancer Prevention Study I,²⁴ the Nurses' Health Study,²⁵ and the NHANES I Epidemiologic Follow-up Study²⁶ (TABLE 2). Instead of including every possible study that met the inclusion criteria, we focused on a few, readily accessible key studies, representing a relatively broad cross-section of studies, with which we analyzed the sensitivity of our results to derivation cohort.

ALAMEDA COUNTY HEALTH STUDY

The Alameda County Health Study²¹ followed 6928 persons selected in 1965 (response rate, 86%) to represent the noninstitutionalized adult population of Alameda County, California. Data included self-reported sociodemographic information (eg, age, sex, ethnicity, height, weight) and physical, cognitive, psychological, and social functioning.^{21,27} Of the original 6928 subjects, 6794 (98%) were used in our analysis. Sample racial and sociodemographic composition is representative of that in large, industrialized cities.²¹

FRAMINGHAM HEART STUDY

The Framingham Heart Study, initiated in 1948 to assess prospectively cardiovascular disease risk factors among a two-thirds sample of the residents of Framingham, Mass,²³ consisted of 5209 persons (response rate, 68.8%) between 28 and 62 years of age at entry, with all subjects examined biennially since study inception. Data collected included age, sex, measured height and weight, physical examination, and extensive cardiovascular history.²⁸⁻³⁰ Of the original 5209 subjects, 5166 (99%) were used in our analysis. Subjects were typically white and middle-class, with educational attainment comparable to that of the general population.

TECUMSEH COMMUNITY HEALTH STUDY

The Tecumseh County Health Study²² was initiated in 1959 to investigate health and disease determinants in the rural community of Tecumseh, Mich. Participants completed extensive questionnaires and had detailed medical examinations, including height and weight measurements. Eighty-eight percent (8641 persons) of residents participated in the first round of data collection (1959-1960). More than half (4864) were 18 years old or older during the first collection of data.^{22,31,32} Data collection has occurred periodically since then.^{22,31,32} Of the original 8641 subjects, 3905 (45%)

Table 2. Description of Data Sources

Study	N	Composition of Sample	Dates of Study	White, %	Female, %	Age at Entry, y	Weight and Height	Deaths During Study, No.	Source of Data
Alameda County Health Study ²¹	6794	Representative sample of Alameda County, California	1965-1975	79	54	16-94	Measured	704	Raw
Tecumseh Community Health Study ²²	3905	Representative sample of Tecumseh, Mich	1959-1985	100	52	35-69	Measured	708	Raw
Framingham Heart Study ²³	5166	% of residents in Framingham, Mass	1948-1980	100	55	28-62	Measured	1964	Raw
American Cancer Society Cancer Prevention Study I ^{24*}	829 636	Predominantly middle-class from 26 states	1960-1972	98	62	≥30	Self-report	124 229	Raw and published
Nurses' Health Study ^{25†}	115 195	Registered nurses	1976-1992	98	100	30-55	Self-report	4726	Published
NHANES I Epidemiologic Follow-up Study ²⁶	14 407	Representative sample of United States	1971-1992	78	60	25-75	Measured	4497	Raw

*Excludes subjects younger than 18 years, those with missing data, and women pregnant at baseline.
 †Excludes subjects with preexisting cancer, heart disease, and stroke at baseline.

with no missing data who were at least 18 years old were used in our analysis.

AMERICAN CANCER SOCIETY CANCER PREVENTION STUDY I

The American Cancer Society Cancer Prevention Study I²⁴ (CPS1) was conducted by questionnaire on more than 1 million male and female volunteers 30 years of age or older in 26 states. Enrollment extended from October 1959 to March 1960, and data collected included sociodemographic information, smoking status, and self-reported height and weight. Participants were followed through September 1971 (98%) and September 1973 (93%). Subjects were predominantly white and middle-class, with an average level of educational attainment higher than that of the US population. Participants were classified as never-smokers if they reported that they had never smoked cigarettes regularly. A total of 829 636 subjects (of whom 469 149 were classified as never-smokers) were used in our analyses.

To assess the sensitivity of the results relative to the baseline health status of the cohort, we analyzed the published data from the CPS1 cohort as reported by Stevens et al³³ because of the elimination from analyses of current and former smokers and subjects who, at study inception, reported poor health or history of heart attack, stroke, or cancer (other than skin cancer). After exclusions, 314 135 (62 116 men and 252 019 women) subjects who were never-smokers and reported no preexisting disease remained.

NURSES' HEALTH STUDY

The Nurses' Health Study²⁵ (NHS) was established in 1976, when 121 700 female registered nurses 30 to 55 years of age completed questionnaires on medical history, height and weight, and health behavior. The subjects, 98% white, resided in 11 US states. The participation rate was more than 50%, fewer than 3% did not report height and weight, and mortality follow-up rate was more than 98%. The investigation of body weight and all-cause mortality reported by Man-

son et al³⁴ that provided the data herein was based on information about 115 195 women without diagnosed cardiovascular disease or cancer in 1976 who reported height and weight. The cohort was followed for 16 years, and relation of BMI to hazard of death was determined in all participants and in never-smokers. Using proportional-hazards analysis, Manson et al³⁴ determined the HR of dying for 7 BMI categories (<19 kg/m², 19-21.9 kg/m², 22-24.9 kg/m², 25-26.9 kg/m², 27-28.9 kg/m², 29-31.9 kg/m², and ≥32 kg/m²), with the leanest group as the referent. They expressed HRs as age-adjusted and adjusted for numerous potential confounders (eg, smoking, menopausal status, oral contraceptive and postmenopausal hormone use, and parental history of myocardial infarction before age 60). Manson et al³⁴ also adjusted for alcohol intake, saturated fat intake, and physical activity; however, HRs for these adjustments were virtually identical to those obtained with age- and smoking-adjustment only.

NHANES I EPIDEMIOLOGIC FOLLOW-UP STUDY

The NHANES I Epidemiologic Follow-up Study²⁶ (NHEFS) was designed to investigate relationships between clinical, nutritional, and behavioral factors assessed in NHANES I and subsequent morbidity, mortality, and functional limitation. This cohort is nationally representative of the US civilian noninstitutionalized population and includes all 14 407 persons who completed the medical examinations at baseline (1971-1975). Follow-up vital statistics were collected through 1992. Of the subjects, 96% have been successfully traced at some point through the 1992 follow-up, and 91% to 96% of those traced completed the follow-up interview.²⁶

Statistical Methods for Estimation of HRs

For each raw data set, the log of the HR of death from any cause was regressed on dummy codes for BMI categories defined by chosen thresholds: age (in-

cluding polynomials of age as needed), sex, and dummy codes for smoking status (any missing data on smoking were imputed for NHEFS) using Cox proportional hazards regression.³⁵ In the 5 raw data sets, proportionality assumption was checked and validated. Interactions of age and sex with BMI terms were not included because of our interest in estimating the average effect of overweight or obesity across both sexes and all adult ages. Although it is interesting to examine how obesity effects differ by age, sex, race, and other factors, the purpose of this article is to estimate total societal obesity burden in terms of mortality. However, our analysis does take into account differential effects of obesity by age and sex despite no corresponding interaction terms, simply by including both sexes and a cross section of ages in the derivation samples. For example, if there were an equal number of men and women in a sample with equal obesity rates by sex, and the RR of death given obesity was 2.0 in men and 1.5 in women, the estimated RR for the combined group would be 1.75; using this RR for the whole sample combined, we would get the same answer as if number of attributable deaths in women and men were calculated separately and added together. The differential effect of variations in BMI on mortality rate in different sex, age, and race groups has been described.^{33,36} As per Manson et al,³⁷ various health problems or risk factors such as hypertension that are partially due to obesity were not included in models because it is inappropriate to control for aspects of health considered intermediaries on the causal path from obesity to mortality.

As a sensitivity analysis, we repeated all analyses using data from only current nonsmokers (or never-smokers when data were available), because it is suggested that smoking status may confound the BMI-mortality relationship and that analyses of never-smokers yield the most valid estimates^{34,37} (see "Comment" section). Early deaths were not excluded as has sometimes been advocated,³⁸ in part because there is no

Table 3. Hazard Ratios (HRs) and 95% Confidence Intervals (CIs) Derived From the 6 Data Sources

BMI Category, kg/m ²	N = P (CAT)†	HR (h) and 95% CIs*					
		Alameda County Health Study ²¹		Framingham Heart Study ²³		Tecumseh Community Health Study ²²	
		All (N = 6794)	Nonsmokers Only (n = 2698)	All (N = 5166)	Nonsmokers Only (n = 2186)	All (N = 3905)	Nonsmokers Only (n = 1493)
<23	0.291	1.39 (1.2-1.7)	1.23 (0.9-1.6)	1.12 (0.9-1.3)	1.26 (0.9-1.6)	1.20 (0.9-1.5)	1.05 (0.7-1.5)
23 to <25	0.170	1.00	1.00	1.00	1.00	1.00	1.00
25 to <26	0.083	0.98 (0.7-1.3)	0.94 (0.6-1.4)	0.96 (0.8-1.1)	1.09 (0.8-1.5)	1.18 (0.9-1.6)	1.17 (0.7-1.8)
26 to <27	0.076	0.86 (0.6-1.2)	0.88 (0.5-1.5)	1.11 (0.9-1.3)	1.08 (0.8-1.5)	0.89 (0.7-1.2)	1.14 (0.7-1.9)
27 to <28	0.065	1.20 (0.8-1.7)	1.23 (0.7-2.0)	1.04 (0.9-1.2)	1.16 (0.9-1.6)	1.12 (0.8-1.5)	0.83 (0.5-1.4)
28 to <29	0.052	1.26 (0.8-1.8)	1.07 (0.6-1.9)	1.08 (0.9-1.3)	1.35 (0.9-1.8)	0.92 (0.6-1.3)	0.81 (0.5-1.4)
29 to <30	0.045	1.23 (0.8-1.9)	1.14 (0.6-2.2)	1.41 (1.1-1.7)	1.65 (1.2-2.3)	0.94 (0.6-1.4)	1.32 (0.7-2.6)
30-35	0.142	1.36 (0.9-1.9)	1.64 (1.1-2.5)	1.60 (1.4-1.8)	1.52 (1.2-1.9)	1.45 (1.1-1.9)	1.60 (1.1-2.4)
>35	0.077	2.79 (1.5-5.1)	2.76 (1.1-6.9)	1.94 (1.5-2.5)	1.96 (1.4-2.7)	1.87 (1.3-2.7)	1.52 (0.9-2.6)

*For a definition of h, see Table 1. BMI indicates body mass index.

†For each BMI category shown, the probability of being in that category, P(CAT), is derived from NHANES III raw data.²⁰ For each BMI category within each raw data set, the adjusted HR is given as derived on all subjects and as derived only on nonsmokers or never-smokers. Hazard ratios were adjusted for the BMI categories defined by chosen thresholds, age, sex, and dummy codes for smoking status.

‡Precise estimates of CIs for the Nurses' Health Study are not calculable from published data.

Table 4. Estimated Number of Deaths Attributable to Obesity in the United States in 1991*

BMI, kg/m ²	No. of Deaths Attributable to Obesity					
	Alameda County Health Study ²¹	Framingham Heart Study ²³	Tecumseh Community Health Study ²²	American Cancer Society Cancer Prevention Study I ²⁴	Nurses' Health Study ²⁵	NHANES I Epidemiologic Follow-up Study ²⁶
Based on Data From All Subjects in Each Data Set						
25 to <26	-1913	-5297	27 029	3018	-11 082	-4830
26 to <27	-15 833	15 269	-14 132	9394	-5005	16 277
27 to <28	21 046	4703	14 365	10 160	11 100	-3830
28 to <29	21 965	7976	-6588	13 228	19 783	38 561
29 to <30	16 912	32 065	-4618	17 122	25 804	5263
30-35	82 357	147 380	113 602	90 472	123 784	88 163
>35	216 619	123 297	117 759	100 867	122 384	96 507
Total	341 153	352 393	247 417	244 261	286 768	236 111
Based on Data From Nonsmoking or Never-Smoking Subjects in Each Data Set						
25 to <26	-6904	12 719	25 723	6460	0	-16 642
26 to <27	-14 543	10 380	19 464	12 102	8071	-10 293
27 to <28	24 326	17 286	-19 083	12 819	22 993	-4913
28 to <29	6121	29 509	-17 857	15 896	31 249	14 635
29 to <30	10 498	47 610	26 621	16 394	39 826	20 356
30-35	146 729	119 602	154 377	92 635	165 392	145 494
>35	217 183	119 354	73 588	106 235	108 635	159 593
Total	383 410	356 460	262 833	262 541	376 166	308 230

*Negative values for a body mass index (BMI) category occur when the estimated hazard ratio in that category is less than 1.0. Were such values statistically different (none were), this would imply that these BMI levels were "protective" relative to a BMI of 23 to 25 kg/m². Alternately, these negative values may represent random fluctuations owing to sampling variation.

published proof or formal statistical justification for merits of this technique. Contrarily, it was shown mathematically that the technique is not guaranteed to reduce bias due to occult disease when such bias is present and could even exacerbate such bias.³⁹ Also, simulations show that, under plausible scenarios of confounding due to occult disease, excluding early deaths may have little meaningful impact on results aside from reducing power and precision and can increase bias.⁴⁰ A meta-analysis involving nearly 2 million subjects found that, in practice, excluding early deaths has little discernible effect on the BMI-mortality relationship.⁴¹ Nevertheless, in sensitivity analysis herein, this technique is used in conjunction with several other methods, because certain published data on which we draw are based on this technique.

For the published summary statistics from the NHS cohort, we used established "dose-response" methods to estimate HRs for our BMI categories.⁴² The natural log of the HR was expressed as a function of mean BMI in the defined

American Cancer Society Cancer Prevention Study I ²⁴		Nurses' Health Study ²⁵		NHANES I Epidemiologic Follow-up Study ²⁶	
All (N = 829 636)	Nonsmokers Only (n = 410 817)	All (N = 115 195)	Nonsmokers Only (n = 50 211)	All (N = 14 407)	Nonsmokers Only (n = 1496)
1.07 (1.0-1.1)	1.05 (1.0-1.1)	1.06	0.91	1.04 (0.2-1.2)	1.24 (0.9-1.7)
1.00	1.00	1.00	1.00	1.00	1.00
1.02 (1.0-1.4)	1.04 (1.0-1.1)	0.92	1.00	0.96 (0.7-1.4)	0.88 (0.6-1.3)
1.06 (1.0-1.1)	1.08 (1.0-1.1)	0.96	1.06	1.11 (0.7-1.8)	0.91 (0.6-1.3)
1.08 (1.0-1.1)	1.10 (1.1-1.2)	1.09	1.20	0.96 (0.6-1.6)	0.95 (0.7-1.4)
1.14 (1.1-1.2)	1.16 (1.1-1.2)	1.21	1.34	1.40 (0.5-3.7)	1.16 (0.8-1.7)
1.21 (1.2-1.3)	1.20 (1.1-1.3)	1.32	1.50	1.06 (0.9-1.2)	1.26 (0.8-1.9)
1.35 (1.3-1.4)	1.36 (1.3-1.4)	1.49	1.66	1.33 (0.9-2.0)	1.61 (1.2-2.2)
1.72 (1.6-1.8)	1.76 (1.7-1.8)	1.89	1.80	1.68 (1.2-2.3)	2.24 (1.4-3.5)

BMI categories. These functions were based on simple linear interpolation between observed values and, for the highest BMI category, extrapolation from the slope between the penultimate and antepenultimate values. The HRs used were age-adjusted to maintain consistency with the raw data analyses of the 5 cohort studies. Mean BMI for each of our established categories was calculated from NHANES III data and used to estimate the HR within each category using the derived functions. We used the same procedure on the published statistics from the CPS1 subjects who were never-smokers, reported no preexisting disease, and no substantial weight loss.³³

RESULTS

TABLE 3 presents the inputs obtained for the 6 sets of analyses. For each BMI category, the probability of being in that category, P(CAT), is given as derived from NHANES III data. Also, for each BMI category within each raw data set, the adjusted HR and 95% confidence intervals are given as

derived on all subjects and for nonsmokers or never-smokers. The HRs generally increased with BMI, but elevation above 1.0 is not clear and consistent until BMIs reach the upper 20s. Also, although there is a tendency for HRs to be greater when calculated on nonsmokers only, the difference is slight and inconsistent, concurring with past research.⁴³

The top half of TABLE 4 provides numbers of deaths attributable to obesity in the United States in all subjects in each BMI category for each data set and the sum of all categories above a BMI of 25 kg/m². Negative values for a BMI category occur when an estimated HR is less than 1.0. Should statistically significant differences be found (none were) this would imply that the BMI levels were "protective" relative to a BMI of 23 to 25 kg/m². Alternately, these negative values may represent random fluctuations because of sampling variation. The overall values, however, are consistent among data sets. Across the 6 cohorts, the mean estimate of the annual number of obesity-

attributable deaths was 280 184 (range, 236 111-341 153).

The bottom half of Table 4 presents data based on HRs for nonsmokers only. The values estimated are not the number of deaths due to obesity in only nonsmokers or never-smokers. Rather, they are estimates of the number of deaths due to obesity in the total population consisting of both smokers and nonsmokers or never-smokers, assuming that HRs for obesity calculated on nonsmokers or never-smokers only offer the best estimates of HRs for all subjects, regardless of smoking status (see "Comment" section). The overall pattern was similar to HRs derived for all subjects. However, in the higher BMI categories, HRs tended to be higher in nonsmokers or never-smokers, expressed as larger numbers of attributable deaths in the higher BMI categories. Overall values are fairly consistent with a mean estimate of 324 940 annual deaths attributable to overweight or obesity (range, 262 541-383 410).

There are many possible ways to derive HR estimates for obesity effects. We have chosen 2 potentially conservative approaches, using all subjects or using nonsmoking or never-smoking subjects only. However, these approaches do not account for potential confounding from other sources (eg, prevalent chronic disease, unintentional weight loss, weight fluctuation). As a final set of sensitivity analyses, we used HRs from analyses of the 2 largest cohorts, the CPS1 and the NHS, in which there were efforts to control for these variables by excluding those whose weight fluctuated, those with ostensible ill health at baseline, and those who died early during follow-up. Based on published CPS1 statistics, we estimated that 330 324 annual deaths are attributable to overweight or obesity; using published NHS statistics, we estimated that number to be 418 154.

COMMENT

Using relative hazards associated with elevated BMI in 6 US studies, the national distribution of adult BMI, and estimates of population size and total deaths from the same era, we esti-

mated the annual number of deaths attributable to obesity to be about 280 000. The mean estimate based on analyses of HRs measured in nonsmokers or never-smokers was about 325 000 and that found using HRs from ostensibly healthy, weight-stable nonsmokers or never-smokers was about 374 000. Among BMI categories examined, the largest proportion of deaths attributable to overweight or obesity (more than 80%) occurred in persons with BMIs of at least 30 kg/m². During the NHANES III survey, about 40.5 million Americans (about 22% of adults) had BMIs at that level.

In 1990, an analysis by Hahn et al⁴⁴ of excess mortality in the United States due to 9 chronic conditions involving the Framingham and El DuPont de Nemours data sets estimated that obesity contributed to 261 988 deaths. However, deaths attributable to obesity were calculated only from coronary heart disease (CHD), stroke, and diabetes; other chronic diseases were ignored and potential protective aspects of obesity, especially in the elderly (eg, hip fracture reduction), were not considered.

Distributions of age, sex, smoking, health status, ethnicity, and socioeconomic status in a cohort can affect the estimated HR. For example, Stevens et al³³ found that HR for obesity decreased steadily with advancing age. Hence, if cohort age distributions vary, this disparity could yield different average HRs associated with BMI. Methodological factors can also affect the BMI-mortality association and may contribute to the variation in our results, eg, there are possible effects of differing follow-up durations, although there was no clear association between follow-up duration and magnitude of estimates among the cohorts examined.

Our primary analyses, adjusting only for sex, smoking, and age, may provide conservative estimates of annual number of deaths attributable to obesity and do not control for confounding from prevalent chronic disease at baseline or residual confounding from cigarette smoking, both of which are as-

sociated with lower body weight and increased mortality. Thus, these analyses may underestimate risks of excess weight. In analyses controlling for these variables (using CPS1 and NHS data), mean annual number of deaths attributable to obesity was estimated to be 374 239.

Smoking has received much attention in BMI and mortality analyses. In Table 3, HRs of nonsmokers whose BMIs exceeded 29 kg/m² were generally higher than those of a combined group of smokers and nonsmokers; were higher in the CPS1 after exclusion of subjects with possible preexisting illness; and were highest in the NHS, a relatively healthy group without cancer or cardiovascular disease. Because some evidence suggests that smoking and preexisting illness confound the obesity-mortality relationship,^{34,37} we separately estimated attributable deaths using HRs calculated from all subjects and nonsmokers or never-smokers and performed a sensitivity analysis involving ostensibly healthy, weight-stable never-smokers. The exclusion of subjects with a potentially confounding trait yields HRs free of confounding by the trait, but validity of application of the HRs to a mixed population (with and without the trait) cannot be known with certainty.

The differences observed between analyses based on HRs from all subjects vs those from nonsmokers or never-smokers prompts the question, "Which of the estimates presented is more reasonable?" If one is prepared to believe that in self-defined smokers, there is no variation in the degree to which persons are exposed to those components of cigarettes that influence both body weight and mortality rate (ie, all smokers smoke an identical amount in an identical way or at least that the classification into smokers and nonsmokers reasonably captures the biological mechanism[s] by which smoking influences mortality rates), then there is no residual confounding by smoking after controlling for it statistically or by stratification. In this case, best estimates of BMI's causal effect on mortality rate will come from a sample of both smokers and

nonsmokers (top part of Table 4). Alternately, if one is prepared to believe that the causal effect of BMI on mortality rate is identical for all levels of smoking status (ie, no interaction or effect modification), then samples of never-smokers should give more unbiased estimates of the true effect of BMI on mortality rate, even for mixed populations consisting of both smokers and nonsmokers (bottom part of Table 4). Finally, for those who think there may be both residual confounding among smokers and effect modification, the best estimates may lie between the top and bottom parts of Table 4. Similar comments apply to exclusion of individuals whose weight fluctuates or who are apparently unhealthy. With respect to whether residual confounding or effect modification is likely, the literature is divided.^{20,37,43} The results of our analysis, both with and without smokers, suggests that there is some effect modification or residual confounding. However, the effect of eliminating smokers from the data set does not seem to be a lowering of risk in the very lean nor a lowering of the BMI mortality curve nadir, but rather a slight increase in obesity hazard relative to average-weight persons. We have no way of knowing whether residual confounding or effect modification is the more likely explanation.

There are several limitations of the current analysis that may point to future investigations. We analyzed BMI at a single point in time only, and it would be interesting to evaluate mortality as a function of BMI changes. Also, our calculations assume that all (controlling for age, sex, and smoking) excess mortality in obese people is due to obesity. However, it is not definitively established that if currently obese persons were to lose weight or were to never become obese, they would not still have a higher mortality rate. Also, our estimates may be biased toward higher numbers due to confounding by unknown factors. Given these considerations, studies of the potential mortality-reducing effects of intentional weight loss by medically advisable procedures in obese persons would be of

Appendix

Derivation of Equation for λ

The probability of surviving (1 minus the probability of death) is a mixture of the probability of surviving for persons in the obese or overweight, reference, and other categories. This can be expressed as follows:

$$1-P(D) = P(O)[1-P(D|O)] + P(R)[1-P(D|R)] + P(Q)[1-P(D|Q)].$$

Assuming the population structure and characteristics are stable (ie, that death rates and birth rates are maintaining the population at equilibrium), the hazard rate, averaged across all members of the population at any 1 point in time, must be constant over time. A constant hazard rate implies an exponential survival distribution. This means that

$$1-P(D|O) = P(S|O) = e^{-h\lambda\tau}, \\ 1-P(D|R) = P(S|R) = e^{-\lambda\tau}, \text{ and} \\ 1-P(D|Q) = P(S|Q) = e^{-q\lambda\tau}.$$

where S denotes the event of survival and τ denotes time. Because we are considering 1 year, if we measure time in years, then the τ drops out, leaving

$$1-P(D|O) = P(S|O) = e^{-h\lambda}, \\ 1-P(D|R) = P(S|R) = e^{-\lambda}, \text{ and} \\ 1-P(D|Q) = P(S|Q) = e^{-q\lambda}.$$

Thus, $1-P(D) = P(O)e^{-h\lambda} + P(R)e^{-\lambda} + P(Q)e^{-q\lambda}$.

great benefit. Also, we chose BMI cutoffs for overweight and obesity used by the NIH and WHO. Had we set the BMI thresholds higher, the number of attributable deaths would have been reduced. Alternately, had we relied only on studies in which the BMI-mortality association increases in a monotonic (not "U-shaped") manner³⁴ and set either the threshold for overweight and the reference category lower, the number of attributable deaths would have increased substantially.

Regarding generalizability, our estimates are national estimates for the overall population of US adults, be-

cause the BMI distribution on which our calculations are based is derived from a nationally representative sample (NHANES III). Therefore, the overall estimates will be valid for the US adult population to the extent that our HR estimates, which in only 1 case are based on a nationally representative sample, are valid estimates for the US population. Most of our samples overrepresent whites and may have overrepresented middle- and upper-socioeconomic status subjects. The sole nationally representative sample (NHEFS) yielded slightly lower estimates than the others. Our estimates are also best applied to 1991. For 1999 and beyond, 2 factors are likely to increase the number of obesity-attributable deaths: continued growth in population size, and the apparently continuing increase in both the population proportion that is obese and severely obese.¹ Indeed, this latter trend implies that our approach to calculating risks in BMI categories (vs a continuous model) with older data sets probably underestimates the total number of deaths due to obesity in general and in the highest BMI category in particular. However, this may be offset by the fact that when most of the cohort studies used were initiated, there were fewer intervention strategies to reduce risk factors associated with obesity and fewer medical therapies for postponing death from obesity-related diseases. An increase in the efficacy and availability of such interventions would reduce HRs associated with obesity.

Our estimates are limited to a societal rather than individual perspective. It would be interesting to use BMI-mortality data to calculate expected years of life lost for the individual. In such an analysis by Stevens et al,⁴⁵ this way of viewing the burden of obesity showed that moderate obesity generally results in a 1- to 3-year reduction in life expectancy, depending on age. It would also be interesting to examine cause-specific mortality, which we have not done in this article. Integrating cause-specific mortalities (T.B.V. and J.E.M., unpublished data, August 1999) gener-

ates a total that can serve as a validity check on the current results; preliminary findings show consistency between those results and results herein.

Obesity is a major cause of mortality in the United States. Aside from mortality rate, however, obesity substantially increases morbidity⁴ and impairs quality of life.⁴⁶ In essence, the health impact of obesity far exceeds what we have presented herein. This, combined with the relative consistency in the estimates from the 6 cohort studies, makes it clear that obesity is a major public health problem in the United States.

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So it is that medicine is surely deeply involved in the social organization of our life, and that, if there is meaning in the phrase "doctor-patient relation," this implies the recognition of the patient as a social being who lives in a network of relations, and not in the chance isolation of sickness.

—Ida M. Cannon (1877-1960)