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Overweight, Obesity, and Mortality in a Large Prospective Cohort of Persons 50 to 71 Years Old

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ABSTRACT

BACKGROUND

Obesity, defined by a body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) of 30.0 or more, is associated with an increased risk of death, but the relation between overweight (a BMI of 25.0 to 29.9) and the risk of death has been questioned.

METHODS

We prospectively examined BMI in relation to the risk of death from any cause in 527,265 U.S. men and women in the National Institutes of Health–AARP cohort who were 50 to 71 years old at enrollment in 1995–1996. BMI was calculated from self-reported weight and height. Relative risks and 95 percent confidence intervals were adjusted for age, race or ethnic group, level of education, smoking status, physical activity, and alcohol intake. We also conducted alternative analyses to address potential biases related to preexisting chronic disease and smoking status.

RESULTS

During a maximum follow-up of 10 years through 2005, 61,317 participants (42,173 men and 19,144 women) died. Initial analyses showed an increased risk of death for the highest and lowest categories of BMI among both men and women, in all racial or ethnic groups, and at all ages. When the analysis was restricted to healthy people who had never smoked, the risk of death was associated with both overweight and obesity among men and women. In analyses of BMI during midlife (age of 50 years) among those who had never smoked, the associations became stronger, with the risk of death increasing by 20 to 40 percent among overweight persons and by two to at least three times among obese persons; the risk of death among underweight persons was attenuated.

CONCLUSIONS

Excess body weight during midlife, including overweight, is associated with an increased risk of death.

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Substantial epidemiologic evidence indicates that obesity, defined by a body-mass index (BMI) (the weight in kilograms divided by the square of the height in meters) of 30.0 or more, is associated with an increased risk of death.[1] However, whether overweight (defined by a BMI of 25.0 to 29.9) increases the risk of death has not been established.[2] A substantial proportion of the U.S. adult population is overweight but not obese[3]; any association between overweight and mortality might have important clinical and public health implications.

Reverse causation owing to preexisting chronic disease and inadequate control for smoking status can distort the true relation between body weight and the risk of death, because chronic illness and smoking are associated with both decreased BMI and an increased risk of death.[4] Possible approaches to addressing these potential biases include disregarding deaths occurring in the initial period of follow-up and restricting the analysis to persons without preexisting disease or those who have never smoked. Another approach is to evaluate BMI earlier in life,[5] when it reflects typical adult weight largely unaffected by the onset of chronic disease. We examined the association between BMI and the risk of death in the National Institutes of Health (NIH)–AARP Diet and Health Study,[6] which is based on a cohort of more than half a million people who were 50 to 71 years old at baseline. At baseline this cohort was large enough to permit the use of restriction to minimize potential bias caused by preexisting disease and smoking. In addition, because information was available on subjects' weight at the age of 50 years, we were able to analyze the relation between BMI in midlife and the subsequent risk of death.

METHODS

STUDY POPULATION

The NIH–AARP Diet and Health Study was established in 1995–1996 when 567,169 questionnaires eliciting information on demographic and anthropometric characteristics, dietary intake, and numerous health-related behavioral patterns were returned by 18 percent of AARP members who were 50 to 71 years old and resided in six U.S. states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta and Detroit).[6] We excluded records from 179 persons with duplicate representation in our database; 321 persons who moved out of the study area; 261 persons who died before their questionnaires were received; 15,760 persons whose questionnaires were completed by a spouse or other surrogate respondent; 16,649, 4648, and 2085 persons with missing or extreme values for current height or weight, energy intake, or alcohol consumption, respectively; and 1 person who withdrew from the study. We analyzed the data from the remaining 527,265 participants (313,047 men and 214,218 women).

FOLLOW-UP

The vital status of cohort members was determined from 1995–1996 through December 31, 2005. Vital status was ascertained by annual linkage of the cohort to the Social Security Administration Death Master File on deaths in the United States,[7] with the most recent update on January 15, 2006. The design and maintenance of this cohort have been described elsewhere.[6,8] The NIH–AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the National Cancer Institute. All participants provided written informed consent. All authors vouch for the accuracy of the data and concur with the interpretation of the results.

ASSESSMENT OF HEIGHT, WEIGHT, AND OTHER POTENTIAL RISK FACTORS

Information on current height and weight, disease history, smoking habits, race or ethnic group, physical activity, and diet was collected by means of a self-administered, mailed questionnaire. The height and weight were used to calculate the BMI, which we divided into 10 categories (16.0 to 18.4, 18.5 to 20.9, 21.0 to 23.4, 23.5 to 24.9, 25.0 to 26.4, 26.5 to 27.9, 28.0 to 29.9, 30.0 to 34.9, 35.0 to 39.9, and 40.0 or more) that incorporated the definitions of underweight (less than 18.5), normal weight (18.5 to 24.9), overweight (25.0 to 29.9), and obesity (30.0 or more) proposed by the World Health Organization classification.[9] In a subanalysis, we calculated BMI in the cohort at the age of 50 years on the basis of recalled weight at that age from a supplementary questionnaire mailed to the entire cohort six months after baseline (rate of response, 60 percent).[6]

STATISTICAL ANALYSIS

Age-adjusted mortality rates were calculated by direct standardization[10] with the use of five-year age

Table 1. Baseline Characteristics of 527,265 Men and Women According to BMI.*

Characteristic	BMI									
	<18.5	18.5–20.9	21.0–23.4	23.5–24.9	25.0–26.4	26.5–27.9	28.0–29.9	30.0–34.9	35.0–39.9	≥40.0
Men	1119	6992	36,788	46,486	56,236	49,882	49,029	51,857	11,306	3352
Age (yr)	63.6	63.0	62.8	62.7	62.5	62.4	62.2	61.8	61.1	60.3
Weight (kg)	61.8	64.9	71.4	76.8	81.6	86.1	91.7	101.5	116.5	136.9
Race or ethnic group (%)										
White	88.0	90.5	92.3	92.7	93.1	92.9	93.0	92.8	92.6	91.1
Black	2.3	2.7	2.0	2.0	2.3	2.7	2.9	3.5	3.7	4.6
Hispanic	2.5	1.4	1.4	1.8	1.9	2.0	2.0	1.8	1.7	1.7
Asian, Pacific Islander, or Native American	5.0	4.0	3.3	2.3	1.6	1.3	1.0	0.7	0.7	0.9
More than high-school education (%)	74.3	77.4	80.6	79.5	77.6	75.7	74.4	72.6	70.4	69.8
Smoking status (%)										
Currently smoking	27.3	24.5	15.5	12.9	11.4	10.8	10.5	10.1	9.4	9.2
Formerly smoked	40.7	39.7	47.0	51.7	54.8	57.2	59.1	60.2	61.2	60.2
Never smoked	28.8	32.4	32.1	32.1	30.3	28.6	26.9	26.0	25.3	26.9
Physical activity (times/wk)†	2.3	2.8	3.1	3.0	2.9	2.7	2.5	2.2	1.8	1.4
Alcohol intake (g/day)	16.2	15.8	15.4	15.7	15.7	15.6	15.7	14.6	12.8	9.4
Preexisting chronic disease (%)‡	38.2	31.7	26.6	25.8	25.9	26.5	27.5	29.2	30.3	30.3
Women	2617	18,800	43,774	29,304	23,831	22,714	23,276	31,434	11,899	6569
Age (yr)	62.5	61.9	61.9	62.1	62.2	62.1	62.1	61.9	61.3	60.6
Weight (kg)	59.9	54.0	59.8	64.9	68.8	72.5	77.2	85.0	98.5	117.2
Race or ethnic group (%)										
White	93.0	93.6	92.6	91.6	89.6	89.4	88.6	87.3	85.8	85.2
Black	2.5	1.7	2.4	3.7	5.3	5.8	6.9	8.2	9.9	10.4
Hispanic	0.8	1.1	1.7	1.9	2.2	2.0	1.8	1.9	1.7	1.8
Asian, Pacific Islander, or Native American	1.9	2.4	2.1	1.6	1.6	1.2	1.1	0.8	0.8	0.6
More than high-school education (%)	70.0	73.2	70.5	66.9	65.5	63.6	62.4	61.3	61.0	60.0
Smoking status (%)										
Currently smoking	33.4	23.3	18.3	16.7	15.9	14.8	13.6	12.1	10.2	9.1
Formerly smoked	26.2	32.7	35.5	37.0	37.5	37.9	38.3	38.9	40.5	42.7
Never smoked	37.4	41.2	43.2	43.4	43.4	44.3	45.3	46.3	46.3	45.1
Physical activity (times/wk)†	2.5	2.8	2.7	2.5	2.4	2.2	2.1	1.8	1.5	1.1
Alcohol intake (g/day)	7.2	7.1	6.6	6.0	5.4	4.9	4.3	3.3	2.6	1.9
Preexisting chronic disease (%)‡	25.6	19.4	18.3	19.2	19.6	19.9	21.5	22.5	25.1	26.9

* Percentages may not total 100 because of rounding or missing information. Race or ethnic group was self-reported.
† Physical activity was defined as activity that lasted at least 20 minutes and resulted in either sweating or an increase in breathing or heart rate.
‡ The chronic diseases are self-reported, physician-diagnosed cancer, heart disease, stroke, emphysema, and end-stage renal disease.

Table 2. Mortality Rates and Relative Risks of Death in Relation to BMI for All Men and for Selected Subgroups of Men.*

Variable	BMI									
	<18.5	18.5–20.9	21.0–23.4	23.5–24.9	25.0–26.4	26.5–27.9	28.0–29.9	30.0–34.9	35.0–39.9	≥40.0
All men										
No. of deaths	333	1513	5229	5768	6657	6021	6355	7488	2028	781
Age-standardized rate†	3520	2430	1520	1320	1270	1310	1440	1680	2260	3210
Multivariate relative risk	1.97	1.54	1.14	1.00‡	0.95	0.95	1.00	1.10	1.35	1.83
95% CI	1.76–2.20	1.45–1.63	1.10–1.18		0.91–0.98	0.92–0.98	0.96–1.04	1.06–1.14	1.28–1.42	1.70–1.97
Race or ethnic group										
White										
No. of deaths	304	1390	4849	5393	6195	5609	5938	6930	1862	710
Age-standardized rate†	3660	2460	1530	1320	1260	1310	1440	1670	2230	3220
Multivariate relative risk	1.99	1.54	1.14	1.00‡	0.94	0.95	1.00	1.08	1.32	1.82
95% CI	1.78–2.24	1.45–1.63	1.09–1.18		0.91–0.97	0.91–0.98	0.96–1.03	1.05–1.12	1.26–1.40	168–1.97
Black										
No. of deaths	8	40	148	133	175	165	176	282	81	36
Age-standardized rate†	4850	2560	2380	1720	1610	1490	1540	2020	2520	3390
Multivariate relative risk	1.90	1.40	1.34	1.00‡	0.96	0.89	0.92	1.16	1.44	1.68
95% CI	0.93–3.90	0.98–1.99	1.06–1.69		0.77–1.20	0.70–1.12	0.74–1.16	0.94–1.42	1.09–1.91	1.16–2.44
Hispanic										
No. of deaths	7	17	56	82	96	104	96	111	34	13
Age-standardized rate†	3060	2130	1100	1050	970	1110	1110	1340	2220	2750
Multivariate relative risk	2.31	1.97	1.11	1.00‡	0.94	1.04	1.02	1.17	1.79	2.42
95% CI	1.06–5.05	1.17–3.34	0.79–1.56		0.70–1.27	0.78–1.40	0.76–1.38	0.87–1.56	1.19–2.70	1.34–4.37
Asian, Pacific Islander, or Native American										
No. of deaths	7	40	104	92	91	56	56	59	15	7
Age-standardized rate†	1380	1500	920	910	1110	980	1380	2060	3120	2650
Multivariate relative risk	1.39	1.56	1.00	1.00‡	1.16	0.99	1.19	1.79	2.30	2.78
95% CI	0.64–3.03	1.07–2.26	0.76–1.33		0.87–1.55	0.71–1.38	0.85–1.67	1.28–2.50	1.31–4.03	1.27–6.08
Age										
50–55 Yr										
No. of deaths	15	111	274	310	353	347	389	594	216	113
Age-standardized rate†	1330	1260	540	480	440	470	520	660	970	1430

Multivariate relative risk	2.01	2.10	1.08	1.00‡	0.88	0.92	0.96	1.16	1.57	2.10
95% CI	1.19–3.37	1.69–2.61	0.92–1.27		0.76–1.03	0.79–1.07	0.83–1.12	1.01–1.34	1.32–1.88	1.68–2.61
56–60 Yr										
No. of deaths	45	189	663	753	969	827	981	1282	410	190
Age-standardized rate†	2660	1520	930	800	830	770	910	1090	1480	2330
Multivariate relative risk	2.63	1.51	1.13	1.00‡	1.02	0.91	1.03	1.15	1.43	2.06
95% CI	1.95–3.56	1.29–1.77	1.02–1.25		0.92–1.12	0.82–1.00	0.94–1.13	1.05–1.27	1.27–1.62	1.75–2.42
61–65 Yr										
No. of deaths	105	434	1551	1679	2056	1892	2047	2425	666	269
Age-standardized rate†	3680	2440	1590	1340	1340	1380	1540	1760	2370	3620
Multivariate relative risk	2.15	1.54	1.18	1.00‡	0.99	0.98	1.07	1.15	1.39	1.93
95% CI	1.77–2.62	1.38–1.71	1.10–1.27		0.93–1.05	0.92–1.05	1.01–1.14	1.08–1.22	1.27–1.53	1.69–2.20
66–71 Yr										
No. of deaths	168	779	2741	3026	3279	2955	2938	3187	736	209
Age-standardized rate†	5040	3750	2470	2180	2030	2170	2310	2670	3540	4500
Multivariate relative risk	1.77	1.49	1.12	1.00‡	0.91	0.95	0.96	1.05	1.25	1.54
95% CI	1.52–2.07	1.38–1.62	1.07–1.18		0.87–0.96	0.90–1.00	0.91–1.01	0.99–1.10	1.15–1.36	1.34–1.77
Smoking status										
Current smoker§										
No. of deaths	145	597	1510	1464	1363	1078	1117	1222	272	101
Age-standardized rate†	6630	4520	3370	3080	2680	2640	2910	3320	3860	5000
Multivariate relative risk	1.90	1.38	1.08	1.00‡	0.88	0.82	0.91	1.00	1.09	1.42
95% CI	1.60–2.26	1.26–1.52	1.01–1.17		0.81–0.94	0.76–0.89	0.85–0.99	0.93–1.08	0.96–1.24	1.16–1.74
Former smoker§										
No. of deaths	129	629	2514	3002	3834	3557	3847	4580	1271	483
Age-standardized rate†	3280	2470	1490	1260	1290	1310	1430	1650	2250	3230
Multivariate relative risk	2.17	1.79	1.19	1.00‡	0.98	0.96	1.00	1.07	1.30	1.74
95% CI	1.82–2.59	1.64–1.95	1.13–1.26		0.93–1.03	0.91–1.01	0.95–1.05	1.02–1.12	1.22–1.39	1.58–1.92
Never smoked										
No. of deaths	46	226	1016	1085	1210	1146	1167	1374	392	164
Age-standardized rate†	1440	1050	850	780	760	880	990	1190	1760	2570
Multivariate relative risk	1.67	1.29	1.09	1.00‡	0.97	1.09	1.20	1.39	1.91	2.59
95% CI	1.24–2.24	1.12–1.49	1.00–1.19		0.89–1.05	1.00–1.18	1.10–1.30	1.28–1.51	1.70–2.15	2.20–3.06

Table 2. (Continued.)

Variable	BMI									
	<18.5	18.5–20.9	21.0–23.4	23.5–24.9	25.0–26.4	26.5–27.9	28.0–29.9	30.0–34.9	35.0–39.9	≥40.0
Preexisting chronic disease										
No. of deaths	210	881	2719	2841	3250	2945	3129	3735	997	372
Multivariate relative risk	1.91	1.60	1.20	1.00‡	0.94	0.91	0.94	0.98	1.10	1.41
95% CI	1.66–2.20	1.48–1.73	1.13–1.26		0.90–0.99	0.86–0.96	0.89–0.99	0.93–1.03	1.02–1.18	1.26–1.57
No preexisting chronic disease										
No. of deaths	123	632	2510	2927	3407	3076	3226	3753	1031	409
Multivariate relative risk	1.70	1.35	1.08	1.00‡	0.96	0.99	1.06	1.19	1.57	2.24
95% CI	1.42–2.04	1.24–1.47	1.02–1.13		0.91–1.01	0.94–1.04	1.00–1.11	1.14–1.25	1.47–1.69	2.02–2.49
Follow-up										
<5 Yr										
No. of deaths	200	754	2466	2565	2965	2570	2694	3111	841	329
Multivariate relative risk	2.32	1.61	1.20	1.00‡	0.95	0.91	0.94	0.99	1.17	1.54
95% CI	2.01–2.68	1.49–1.75	1.13–1.26		0.90–1.01	0.86–0.96	0.89–0.99	0.94–1.04	1.08–1.26	1.37–1.73
≥5 Yr										
No. of deaths	133	759	2763	3203	3692	3451	3661	4377	1187	452
Multivariate relative risk	1.58	1.46	1.09	1.00‡	0.95	0.98	1.05	1.19	1.52	2.11
95% CI	1.33–1.88	1.35–1.58	1.04–1.15		0.90–0.99	0.94–1.03	1.00–1.10	1.14–1.25	1.42–1.62	1.91–2.34

* The multivariate model used age as the underlying time metric and included the following covariates: race or ethnic group (white; black; Hispanic; or Asian, Pacific Islander, and Native American combined; or race or ethnic group missing), level of education (less than 8 years, 8 to 11 years, 12 years [high school], vocational school or less than 4 years of college, 4 or more years of college, or education level missing), smoking status (never smoked; quit smoking at least 10 years previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; quit smoking 1 to 9 years previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; quit smoking less than 1 year previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; currently smoking 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; or information on smoking status missing), physical activity (never, rarely, one to three times per month, one or two times per week, three or four times per week, five or more times per week, or information on physical activity missing; physical activity was defined as activity that lasted at least 20 minutes and resulted in either sweating or an increase in breathing or heart rate), and alcohol consumption (0, 0.01 to 4.9, 5.0 to 14.9, or 15.0 g or more per day). The stratified analyses excluded persons for whom information on the characteristic defining the stratum was missing. CI denotes confidence interval.

† Mortality rates are per 100,000 person-years, directly standardized to the age distribution of the cohort (according to sex).

‡ This group served as the reference group.

§ The multivariate risks are adjusted for the frequency of smoking (1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day).

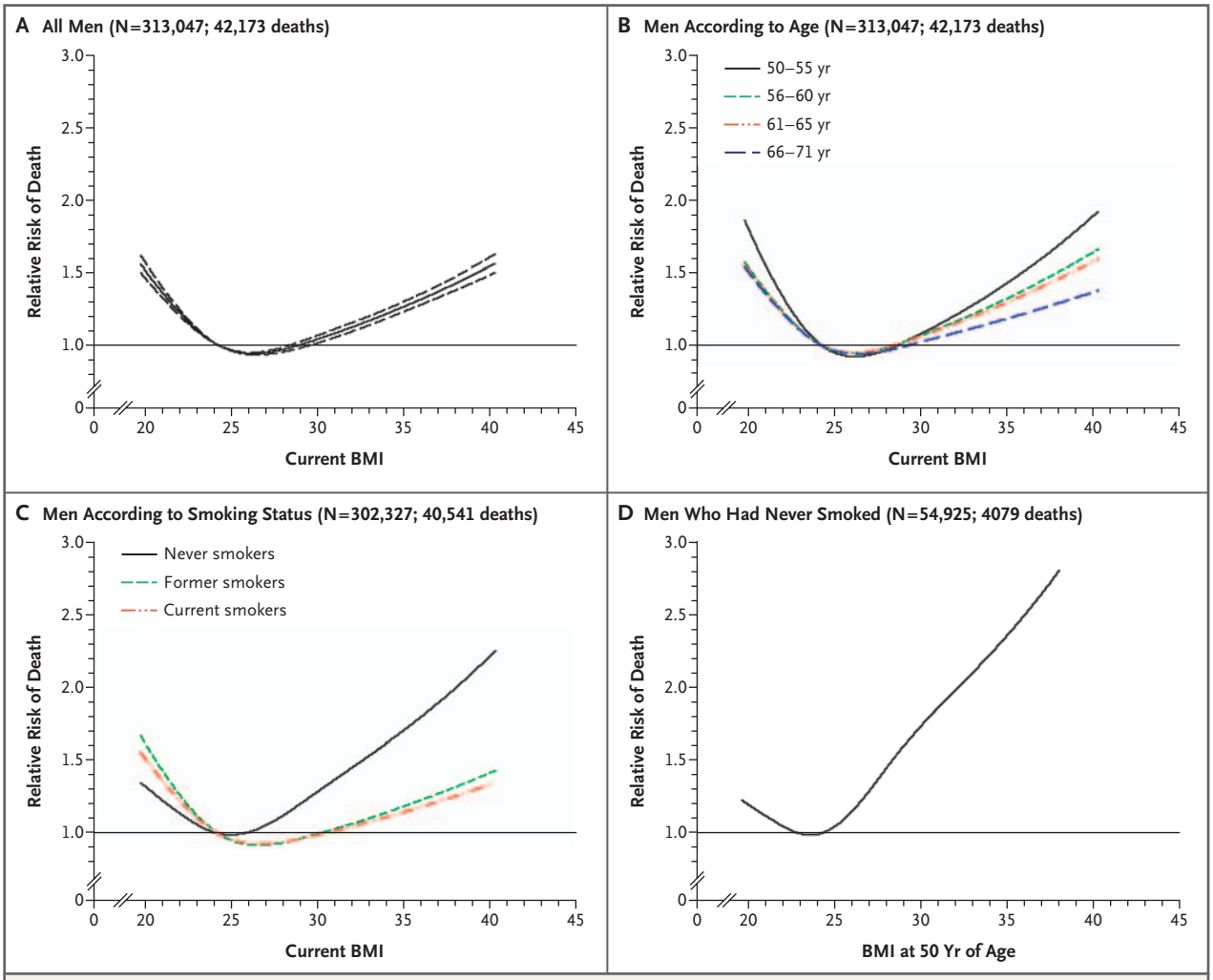

Figure 1. Multivariate Relative Risks of Death in Relation to BMI among Men.

In each panel, the lines are natural cubic splines showing the shape of the dose–response curve for mortality according to BMI on a continuous basis. Relative risks are indicated by solid lines, and 95 percent confidence intervals by dashed lines. Panels A, B, and C are based on current BMI values, whereas Panel D represents BMI at the age of 50 years. The reference point is the midpoint of the reference group (BMI, 23.5 to 24.9) for categorical analyses, with knots placed at the 5th, 25th, 75th, and 95th percentiles of the BMI distribution among all men. The graphic display is truncated at 1 percent and 99 percent of BMI on the basis of the distribution of baseline (current) BMI among all men (Panels A, B, and C) and BMI at the age of 50 years among men who had never smoked (Panel D). All models are adjusted for age, race or ethnic group, level of education, alcohol consumption, and physical activity. The model for all men is adjusted for smoking status and the number of cigarettes smoked per day. The models for men who were former or current smokers are adjusted for the number of cigarettes smoked per day; men for whom information on the number of cigarettes smoked per day was missing were excluded.

categories. Age-adjusted and multivariate relative risks were estimated by Cox regression analysis with age as the underlying time metric.[11] Multivariate models were adjusted for race or ethnic group, level of education, smoking status, physical activity, and alcohol consumption. We performed stratified analyses to assess whether the association between BMI and the risk of death varied according to race or ethnic group, age group, smoking status, presence or absence of chronic disease, and duration of follow-up. We also evaluated the relations between body-mass index and the risk of death according to sex and smoking status with nonparametric regression curves that used restricted cubic spline[12] graphs.

We calculated the population attributable risk,[13]

Table 3. Mortality Rates and Relative Risks of Death in Relation to BMI for All Women and for Selected Subgroups of Women.*

Variable	BMI									
	<18.5	18.5–20.9	21.0–23.4	23.5–24.9	25.0–26.4	26.5–27.9	28.0–29.9	30.0–34.9	35.0–39.9	≥40.0
All women										
No. of deaths	468	1878	3455	2237	1862	1888	1999	2983	1393	981
Age-standardized rate†	1980	1090	850	800	820	880	910	1030	1360	1880
Multivariate relative risk	2.03	1.30	1.07	1.00‡	1.00	1.06	1.07	1.18	1.49	1.94
95% CI	1.84–2.25	1.22–1.38	1.01–1.13		0.94–1.07	0.99–1.12	1.01–1.14	1.12–1.25	1.39–1.60	1.79–2.09
Race or ethnic group										
White										
No. of deaths	434	1754	3183	2045	1658	1688	1776	2617	1225	836
Age-standardized rate†	1970	1090	840	800	810	870	910	1030	1390	1870
Multivariate relative risk	2.04	1.30	1.06	1.00‡	1.00	1.05	1.08	1.19	1.54	1.95
95% CI	1.84–2.27	1.22–1.38	1.01–1.12		0.94–1.07	0.99–1.12	1.01–1.15	1.12–1.26	1.43–1.65	1.80–2.12
Black										
No. of deaths	14	44	117	99	106	98	128	239	113	101
Age-standardized rate†	2560	1560	1280	1010	940	860	910	1070	1140	1970
Multivariate relative risk	2.16	1.45	1.26	1.00‡	0.92	0.85	0.87	1.03	1.06	1.70
95% CI	1.23–3.79	1.02–2.07	0.96–1.64		0.70–1.21	0.64–1.13	0.67–1.14	0.82–1.31	0.81–1.40	1.28–2.25
Hispanic										
No. of deaths	1§	14	35	20	31	41	22	48	10	16
Age-standardized rate†	—	700	550	390	650	1000	550	880	560	1860
Multivariate relative risk	—	1.77	1.38	1.00‡	1.65	2.50	1.47	2.14	1.44	4.12
95% CI	—	0.89–3.52	0.79–2.39		0.94–2.91	1.46–4.28	0.80–2.71	1.26–3.62	0.67–3.09	2.09–8.12
Asian, Pacific Islander, or Native American										
No. of deaths	4§	30	59	25	34	22	26	20	14	2
Age-standardized rate†	—	690	690	590	980	890	1190	940	2180	—
Multivariate relative risk	—	1.29	1.19	1.00‡	1.66	1.38	1.65	1.28	2.21	—
95% CI	—	0.75–2.19	0.74–1.90		0.99–2.79	0.77–2.46	0.94–2.88	0.70–2.32	1.12–4.37	—

Age										
50–55 Yr										
No. of deaths	38	141	262	150	119	106	136	254	127	109
Age-standardized rate†	970	420	330	310	330	290	370	480	540	750
Multivariate relative risk	2.64	1.35	1.11	1.00‡	1.01	0.88	1.12	1.39	1.56	2.07
95% CI	1.85–3.78	1.07–1.69	0.90–1.35		0.80–1.29	0.68–1.12	0.89–1.42	1.13–1.70	1.23–1.98	1.60–2.66
56–60 Yr										
No. of deaths	56	274	554	337	309	311	315	524	269	231
Age-standardized rate†	1040	650	570	520	570	610	600	730	940	1380
Multivariate relative risk	1.58	1.19	1.11	1.00‡	1.06	1.11	1.11	1.29	1.59	2.23
95% CI	1.19–2.10	1.02–1.40	0.97–1.27		0.91–1.23	0.95–1.30	0.95–1.30	1.13–1.48	1.35–1.87	1.88–2.65
61–65 Yr										
No. of deaths	150	565	1088	699	571	608	649	941	446	323
Age-standardized rate†	2450	1180	930	870	860	960	980	1080	1420	1980
Multivariate relative risk	2.35	1.29	1.10	1.00‡	0.97	1.09	1.07	1.15	1.46	1.89
95% CI	1.97–2.81	1.16–1.44	1.00–1.21		0.87–1.08	0.97–1.21	0.96–1.19	1.05–1.27	1.29–1.65	1.65–2.16
66–71 Yr										
No. of deaths	224	898	1551	1051	863	863	899	1264	551	318
Age-standardized rate†	3010	1860	1370	1320	1350	1440	1490	1640	2260	3040
Multivariate relative risk	1.92	1.34	1.03	1.00‡	1.01	1.04	1.06	1.14	1.49	1.84
95% CI	1.66–2.22	1.23–1.47	0.96–1.12		0.92–1.10	0.95–1.14	0.97–1.16	1.05–1.23	1.34–1.66	1.63–2.10
Smoking status										
Current smoker¶										
No. of deaths	243	808	1197	726	535	451	454	628	224	134
Age-standardized rate†	3390	2200	1780	1760	1730	1630	1780	2120	2550	3230
Multivariate relative risk	1.87	1.24	1.01	1.00‡	0.96	0.88	0.94	1.10	1.28	1.61
95% CI	1.62–2.17	1.12–1.37	0.92–1.11		0.86–1.07	0.78–0.99	0.83–1.05	0.99–1.22	1.10–1.49	1.33–1.93
Former smoker¶										
No. of deaths	123	590	1233	819	711	774	832	1242	616	461
Age-standardized rate†	1910	1040	850	790	830	930	980	1100	1500	2110
Multivariate relative risk	2.45	1.41	1.13	1.00‡	1.00	1.10	1.09	1.13	1.39	1.75
95% CI	2.03–2.96	1.27–1.57	1.04–1.24		0.91–1.11	0.99–1.21	0.99–1.20	1.04–1.24	1.25–1.54	1.56–1.97

Table 3. (Continued.)

Variable	BMI									
	<18.5	18.5–20.9	21.0–23.4	23.5–24.9	25.0–26.4	26.5–27.9	28.0–29.9	30.0–34.9	35.0–39.9	≥40.0
Never smoked										
No. of deaths	80	419	908	599	548	591	654	1009	500	362
Age-standardized rate†	850	570	500	480	530	600	640	730	1020	1490
Multivariate relative risk	1.70	1.21	1.06	1.00‡	1.09	1.21	1.27	1.38	1.82	2.52
95% CI	1.35–2.15	1.06–1.37	0.96–1.18		0.97–1.22	1.08–1.36	1.13–1.42	1.25–1.53	1.62–2.06	2.20–2.88
Preexisting chronic disease										
No. of deaths	239	845	1404	1000	803	822	886	1293	695	447
Multivariate relative risk	2.02	1.32	1.01	1.00‡	0.94	0.98	0.94	0.95	1.21	1.29
95% CI	1.75–2.32	1.21–1.45	0.93–1.09		0.85–1.03	0.89–1.07	0.86–1.03	0.87–1.03	1.10–1.34	1.15–1.45
No preexisting chronic disease										
No. of deaths	229	1033	2051	1237	1059	1066	1113	1690	698	534
Multivariate relative risk	1.86	1.26	1.12	1.00‡	1.05	1.11	1.15	1.34	1.61	2.42
95% CI	1.61–2.14	1.16–1.37	1.04–1.20		0.97–1.14	1.02–1.21	1.06–1.25	1.24–1.44	1.47–1.77	2.18–2.68
Follow-up										
<5 Yr										
No. of deaths	237	845	1506	967	832	820	821	1246	561	400
Multivariate relative risk	2.24	1.35	1.08	1.00‡	1.03	1.05	1.00	1.10	1.30	1.65
95% CI	1.95–2.59	1.23–1.48	1.00–1.17		0.94–1.13	0.95–1.15	0.91–1.10	1.01–1.20	1.17–1.44	1.46–1.86
≥5 Yr										
No. of deaths	231	1033	1949	1270	1030	1068	1178	1737	832	581
Multivariate relative risk	1.85	1.26	1.06	1.00‡	0.98	1.06	1.14	1.25	1.66	2.20
95% CI	1.60–2.12	1.16–1.37	0.98–1.13		0.91–1.07	0.98–1.15	1.05–1.23	1.16–1.34	1.52–1.81	1.99–2.43

* The multivariate model used age as the underlying time metric and included the following covariates: race or ethnic group (white; black; Hispanic; or Asian, Pacific Islander, and Native American combined; or race or ethnic group missing), level of education (less than 8 years, 8 to 11 years, 12 years [high school], vocational school or less than 4 years of college, 4 or more years of college, or education level missing), smoking status (never smoked; quit smoking at least 10 years previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; quit smoking 1 to 9 years previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; quit smoking less than 1 year previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; currently smoking 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; or information on smoking status missing), physical activity (never, rarely, one to three times per month, one or two times per week, three or four times per week, five or more times per week, or information on physical activity missing; physical activity was defined as activity that lasted at least 20 minutes and resulted in either sweating or an increase in breathing or heart rate), and alcohol consumption (0, 0.01 to 4.9, 5.0 to 14.9, or 15.0 g or more per day). The stratified analyses excluded persons for whom information on the characteristic defining the stratum was missing. CI denotes confidence interval.

† Mortality rates are per 100,000 person-years, directly standardized to the age distribution of the cohort (according to sex).

‡ This group served as the reference group.

§ Mortality rates and relative risks of mortality are not reported for cells with five or fewer deaths.

¶ The multivariate risks are adjusted for frequency of smoking (1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day).

which is an estimate of the percentage of premature deaths in the cohort that would not have occurred if all persons had been of normal weight at the age of 50 years, given the assumption of a causal association between weight and the risk of death. Because the relation of BMI to the risk of death differed between current or former smokers and those who had never smoked, we calculated the population attributable risk according to sex both for the entire cohort and for the subgroup of subjects who had never smoked. The analysis was adjusted for confounding factors and modification of effects according to age.

RESULTS

During a maximum follow-up of 10 years (4,821,757 person-years), 42,173 men and 19,144 women died. As compared with men and women in the reference group (BMI, 23.5 to 24.9), overweight and obese men and women had a lower percentage of current smokers, a lower level of education, and were less physically active (Table 1).

Among all men (Table 2 and Fig. 1A) and women (Table 3 and Fig. 2A), including smokers and those with preexisting disease, there was a U-shaped relation between current BMI and the risk of death, with the highest risk in the lowest and the highest categories of BMI. Overweight was not associated with an increased risk of death among men but was weakly associated with an increased risk of death among women. The associations between obesity and the risk of death were slightly stronger among Hispanic men and women and among Asian, Pacific Islander, or Native American men and women than among white or black men and women. The elevated risks associated with both extremely high and extremely low values of BMI declined slightly with increasing age in both men and women (Tables 2 and 3 and Fig. 1B and 2B). In analyses stratified according to smoking status, we observed stronger associations between obesity and an increased risk of death among those who had never smoked than among former and current smokers. Underweight was most strongly associated with an increased risk of death among former and current smokers (Tables 2 and 3 and Fig. 1C and 2C).

To address the potential effect of bias owing to preexisting disease and disease-related weight loss, we conducted separate analyses for participants with and those without preexisting chronic conditions at enrollment (Tables 2 and 3). We also divided the follow-up into earlier and later periods. In both men and women, the relation of obesity to the risk of death was consistently stronger among participants without preexisting chronic disease than among those with preexisting chronic disease. In separate analyses of the first five years of follow-up and the subsequent five years of follow-up, the association between obesity and the risk of death was stronger in the second than in the first follow-up period.

We also examined relations between BMI and the risk of death within racial or ethnic groups and age categories after restricting the analysis to those without preexisting disease who had never smoked. These relations within each age group were similar to those from the age-stratified analyses in the full cohort (data not shown). The number of deaths among nonwhites was insufficient to allow firm conclusions to be drawn about the relations between BMI and the risk of death among those who had never smoked and were free of preexisting disease.

The prevalence of chronic conditions increased markedly with age: the percentages of participants who reported physician-diagnosed heart disease, emphysema, stroke, end-stage renal disease, or cancer were 13.9 percent among men and women who were 50 to 55 years of age at enrollment, 19.2 percent among those 56 to 60 years of age, 26.2 percent among those 61 to 65 years of age, and 33.1 percent among those 66 to 71 years of age. Among both men and women 65 years of age or older, weight loss after the age of 50 years was more strongly associated with the risk of death than was weight gain (data not shown).

We attempted to correct for potential bias from disease-related weight loss by using participants' recalled weight at the age of 50 years to examine the relation of BMI to the risk of death, after confirming that the association between current BMI and the risk of death in the subcohort of respondents to the supplemental questionnaire was consistent with that for the entire cohort (data not shown). In addition, we confirmed that persons classified as overweight or obese at baseline who died by the end of the follow-up period were as likely to respond to the supplemental questionnaire as their counterparts of normal weight (the response rates were 54.5 percent and 55.9 percent, respectively).

We observed a J-shaped relation between BMI at

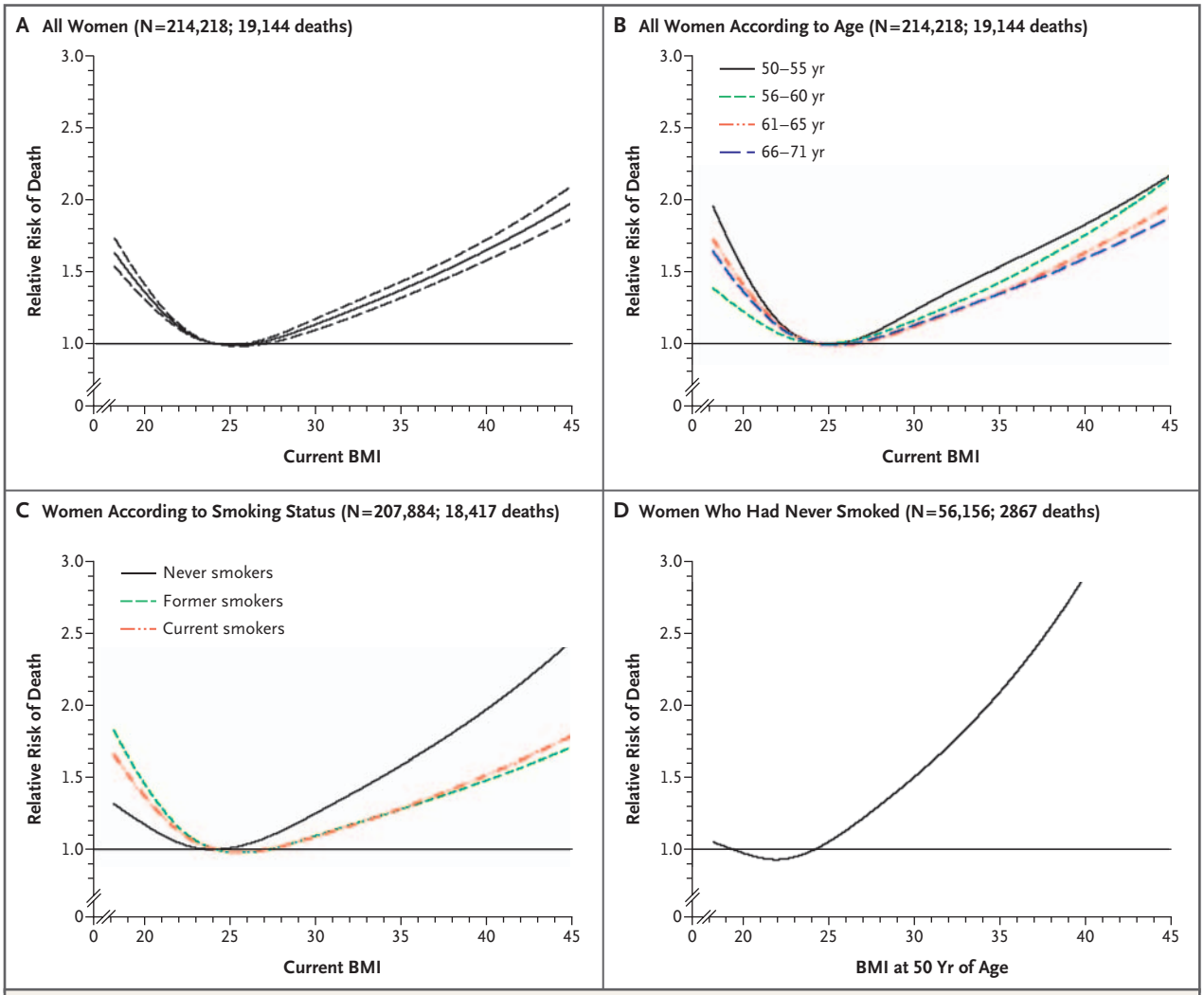

Figure 2. Multivariate Relative Risks of Death in Relation to BMI among Women.

In each panel, the lines are natural cubic splines showing the shape of the dose–response curve for mortality according to BMI on a continuous basis. Relative risks are indicated by solid lines, and 95 percent confidence intervals by dashed lines. Panels A, B, and C are based on current BMI, whereas Panel D represents BMI at the age of 50 years. The reference point is the midpoint of the reference group (BMI, 23.5 to 24.9) for categorical analyses, with knots placed at the 5th, 25th, 75th, and 95th percentiles of the BMI distribution among all women. The graphic display is truncated at 1 percent and 99 percent of BMI on the basis of the distribution of baseline (current) BMI among all women (Panels A, B, and C) and BMI at the age of 50 years among women who had never smoked (Panel D). All models are adjusted for age, race or ethnic group, level of education, alcohol consumption, and physical activity. The model for all women is adjusted for smoking status and the number of cigarettes smoked per day. The models for women who were former or current smokers are adjusted for the number of cigarettes smoked per day; women for whom information on the number of cigarettes smoked per day was missing were excluded.

the age of 50 years and the risk of death in both men and women, with a trend toward increased risk across the entire range of overweight and obese categories (Table 4). In contrast, the relation of underweight to the risk of death on the basis of BMI at the age of 50 years was weaker in both men and women than that noted in analyses based on current BMI.

When we further restricted the analysis of BMI at the age of 50 years to participants who had never smoked, we observed significant increases in the risk of death throughout the range of above-normal categories of BMI in both men and women (Table 4 and Fig. 1D and 2D). As compared with men with a BMI of 23.5 to 24.9 at the age of 50 years, morbidly obese men (BMI of 40.0 or more)

Table 4. Relative Risk of Death in Relation to BMI at the Age of 50 Years among Men and Women.*

Variable	BMI at 50 Yr of Age									
	<18.5	18.5–20.9	21.0–23.4	23.5–24.9	25.0–26.4	26.5–27.9	28.0–29.9	30.0–34.9	35.0–39.9	≥40.0
All men										
No. of deaths	133	796	3567	3812	4113	3262	2728	2910	627	212
Age-adjusted relative risk	1.81	1.36	1.06	1.00†	1.01	1.13	1.27	1.66	2.26	3.22
95% CI	1.52–2.15	1.26–1.47	1.02–1.11		0.97–1.06	1.08–1.19	1.21–1.34	1.58–1.74	2.07–2.46	2.80–3.70
Multivariate relative risk	1.47	1.18	1.05	1.00†	1.00	1.09	1.18	1.46	1.86	2.40
95% CI	1.24–1.75	1.10–1.28	1.00–1.09		0.95–1.04	1.04–1.15	1.13–1.24	1.39–1.53	1.71–2.03	2.08–2.76
Men who had never smoked										
No. of deaths	18	122	622	651	708	621	544	605	136	52
Multivariate relative risk	1.29	1.14	1.04	1.00†	1.05	1.31	1.49	1.96	2.46	3.82
95% CI	0.81–2.06	0.94–1.39	0.94–1.17		0.94–1.17	1.17–1.46	1.33–1.67	1.75–2.19	2.04–2.97	2.87–5.08
All women										
No. of deaths	228	1383	2630	1472	977	894	761	964	376	263
Age-adjusted relative risk	1.87	1.11	0.97	1.00†	1.10	1.19	1.32	1.62	2.11	3.08
95% CI	1.63–2.15	1.03–1.19	0.91–1.03		1.02–1.20	1.09–1.29	1.21–1.45	1.49–1.76	1.88–2.36	2.70–3.51
Multivariate relative risk	1.54	1.05	0.96	1.00†	1.08	1.15	1.28	1.51	1.90	2.76
95% CI	1.34–1.77	0.98–1.13	0.90–1.03		1.00–1.17	1.06–1.25	1.17–1.40	1.40–1.64	1.69–2.13	2.42–3.15
Women who had never smoked										
No. of deaths	32	297	685	402	303	265	245	380	149	109
Multivariate relative risk	1.27	1.01	1.00	1.00†	1.21	1.19	1.37	1.99	2.57	3.79
95% CI	0.89–1.82	0.87–1.18	0.88–1.13		1.05–1.41	1.02–1.39	1.16–1.60	1.73–2.29	2.12–3.11	3.06–4.70

* The multivariate model used age as the underlying time metric and included the following covariates: race or ethnic group (white; black; Hispanic; or Asian, Pacific Islander, and Native American combined; or race or ethnic group missing), level of education (less than 8 years, 8 to 11 years, 12 years [high school], vocational school or less than 4 years of college, 4 or more years of college, or education level missing), smoking status (never smoked; quit smoking at least 10 years previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; quit smoking 1 to 9 years previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; quit smoking less than 1 year previously after having smoked 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; currently smoking 1 to 10, 11 to 20, 21 to 30, 31 to 40, 41 to 60, or more than 60 cigarettes per day; or information on smoking status missing), physical activity (never, rarely, one to three times per month, one or two times per week, three or four times per week, five or more times per week; or information on physical activity missing; physical activity was defined as activity that lasted at least 20 minutes and resulted in either sweating or an increase in breathing or heart rate), and alcohol consumption (0, 0.01 to 4.9, 5.0 to 14.9, or 15.0 g or more per day). The stratified analyses excluded persons for whom information on the characteristic defining the strata was missing. CI denotes confidence interval.

† This group served as the reference group.

had a multivariate relative risk of death of 3.82 (95 percent confidence interval, 2.87 to 5.08). The corresponding relative risk among women was 3.79 (95 percent confidence interval, 3.06 to 4.70). The increased risk of death among underweight participants remained but was diminished and not significant, with only 18 underweight men and 32 underweight women who died (Table 4).

Excess weight accounted for approximately 7.7 percent of all premature deaths among men and 11.7 percent of all premature deaths among women in the overall cohort. It accounted for 18.1 percent of all premature deaths among men who had never smoked and 18.7 percent of all premature deaths among women who had never smoked.

DISCUSSION

In this large prospective study, obesity was strongly associated with the risk of death in both men and women in all racial and ethnic groups and at all ages. After we accounted for potential bias owing to preexisting disease and residual confounding by smoking status by using midlife BMI values and restricting the analysis to participants who had never smoked, we found that even moderate elevations in BMI conferred an increased risk of death. The risk among participants who were overweight at the age of 50 years was 20 to 40 percent higher than that among participants who had a BMI of 23.5 to 24.9 at that age. The risk among obese subjects was two to at least three times that of participants with a BMI of 23.5 to 24.9. The risk of death among underweight participants was attenuated.

Excess body fat has long been recognized as a harbinger of disease and early death.[14] Nearly a half-century ago, insurance records showed that life expectancy was diminished in obese persons.[15] Epidemiologic studies subsequently confirmed the link between obesity and an increased risk of death.[1] Several studies showed that after smokers and those who died in the early years of follow-up were excluded, above-normal weight (BMI greater than 25.0), including overweight, was associated with an increased risk of death from any cause.[16-24]

However, whether moderate elevations in BMI (i.e., overweight) truly increase the risk of death is controversial.[2] Several studies reported no increase in the risk of death among overweight subjects even after those who died during the initial years of follow-up were excluded or subjects were stratified according to smoking status.[25-29] Recently, Flegal et al. reported that overweight was not associated with an excess risk of death in the nationally representative samples of U.S. adults drawn from the National Health and Nutrition Examination Survey.[29] They speculated that possible causes for their finding might be improved medical management of obesity-related chronic disease or differences between the U.S. general population and populations in other studies.[29] Others have suggested that inadequate control for the combined effects of smoking and chronic illnesses could be the explanation.[30] Smoking is associated with both a lower BMI and an increased risk of death and can therefore distort the relation between BMI and the risk of death. Statistical adjustment for smoking status does not fully address the problem; the adjusted findings represent a potentially complex combination of the associations between BMI and the risk of death among current smokers, former smokers, and those who have never smoked. Restriction of analyses to persons who have never smoked is a powerful tool for addressing this potential bias. Our cohort included more than 186,000 men and women who had never smoked. When we restricted our analyses to these persons, the relation of obesity to the risk of death was substantially strengthened, and significant increases emerged in the risk of death, even among overweight participants.

Preexisting disease is linked to both decreased weight and an increased risk of death. Bias related to preexisting disease can be circumvented by restricting the analysis to healthy subjects and excluding those who died during the first years of follow-up (when deaths are more likely to reflect preexisting disease). In our data, the association between overweight or obesity and the risk of death among both men and women was strengthened by the use of these techniques.

An alternative approach to addressing bias related to preexisting disease is to examine weight at an earlier age (50 years in our study), a time of life reflecting typical adult weight and largely unaffected by the onset of diagnosed disease. When we analyzed BMI at the age of 50 years in relation to the risk of death, the results were stronger than those based on the current BMI after the exclusion of participants who died during the early years of follow-up. This suggests that within the

10-year time frame of our study, using weight at a younger age was more effective in accounting for preexisting disease than using current BMI and excluding participants who died during the initial years of follow-up. Finally, we observed the strongest associations between BMI and the risk of death when we combined analytic techniques for addressing bias from both preexisting disease and smoking by examining the relation of adiposity to the risk of death using BMI at the age of 50 years among those who had never smoked.

Large prospective studies are especially valuable for determining a more precise dose–response gradient for the connection between BMI and the risk of death. Our large cohort enabled us to estimate risks of death according to narrow categories of BMI with great precision and to discern not only an elevated risk for most categories of overweight but also substantially enhanced risk among the obese.

Although we did not compare our participants' assessments of height and weight with directly measured values, self-reported height and weight are generally known to be accurate. The correlation between BMI based on self-reported height and weight and that based on measured height and weight is typically greater than 0.9,[31] and weight recalled from 28 years previously by elderly people has been reported to have a correlation of more than 0.8 with measured weight at that time.[32] Some evidence suggests that obese persons are more likely to underestimate their weight than are persons of normal weight.[33] This bias may be offset if underweight persons at higher risk for death report normal weight and are thus misclassified in the reference group. On balance, and given the strong correlation between self-reported and measured weight, including weight at the age of 50 years, the combined effect of random and systematic reporting error on the observed association between BMI and the risk of death is probably minimal.

We adjusted for several variables, including level of education, race or ethnic group, alcohol consumption, and physical activity, which allowed us to minimize the potential for confounding by these factors. Because we cannot rule out the possibility that unmeasured or unknown confounding factors accounted for the associations observed in our study, we cannot conclude with complete certainty that the relation between adiposity and the risk of death is causal.

The biomedical foundation for an association between excess body fat and the risk of death is well established. Medical complications of adiposity include hypertension, type 2 diabetes mellitus, cardiovascular disease, pulmonary disease, and cancer.[34] Pathophysiologic processes that could plausibly mediate the connection between BMI and the risk of death include insulin resistance, lipid abnormalities, hormonal alterations, and chronic inflammation.[35,36]

The NIH–AARP Diet and Health Study is a contemporary investigation with vital status ascertained from 1995–1996 through the end of 2005. Many of the participants, who were 50 to 71 years old at baseline, are from the baby-boomer generation. Much has been written recently about the rise in obesity — and its medical consequences — in this segment of the population.[37,38] Even against the background of advances in the management of obesity-related chronic diseases in the past few decades, our findings suggest that adiposity, including overweight, is associated with an increased risk of death.

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The views expressed are those of the authors.

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