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Original Contribution

Body Mass Index in Young Adulthood and Premature Death: Analyses of the US National Health Interview Survey Linked Mortality Files

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Knowledge of the association between body mass index (weight (kg)/height $(m)^2$) and premature death in young adulthood is very limited, especially for specific causes of death. Using the US National Health Interview Survey linked mortality files, the authors examined the relation between body mass index and premature death from all causes, cardiovascular disease (CVD), and cancer among 112,328 persons aged 18–39 years who participated in the National Health Interview Survey in the years 1987, 1988, and 1990–1995. During an average of 16 years of follow-up (ending on December 31, 2006), there were 3,178 deaths: 573 from CVD and 733 from cancer. Hazard ratios and 95% confidence intervals were estimated using multivariate proportional hazards models adjusting for age, gender, race/ethnicity, education, and smoking status. In analyses restricted to participants who had never smoked, the hazard ratios for death from all causes were 1.07 (95% confidence interval (CI): 0.91, 1.26) for overweight participants, 1.41 (95% CI: 1.16, 1.73) for obese participants, and 2.46 (95% CI: 1.91, 3.16) for extremely obese participants, compared with those of normal weight. Monotonically increasing risks for excess body weight were also observed for deaths from cancer and CVD. The associations found in this young cohort were much stronger than those in middle-aged or older populations.

body mass index; cardiovascular diseases; mortality; neoplasms

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; ICD-9, *International Classification of Diseases*, Ninth Revision; ICD-10, *International Classification of Diseases*, Tenth Revision; NHIS, National Health Interview Survey.

The ongoing obesity epidemic (1, 2) reinforces the importance of understanding the effects of adiposity among young people. The early onset of obesity leads to early disease initiation (3, 4), putting young people at higher subsequent risk of early mortality. Thus, prevention of obesity at a young age has the potential for great benefits. In particular, it may be easier and more beneficial to prevent obesity (5) or stabilize weight (6) among the young than to reverse it among older people after some of its effects are already present. However, few studies (7–11) have examined the association of adiposity in adolescence or young adulthood with premature death (before age 60 years), and even fewer studies (10, 11) have assessed multiple categories of excess body weight in relation to cause-specific mortality for major disease categories, because of small numbers of deaths. In fact, to our knowledge, there has been no published study in nationally representative samples of young adults in the United States.

One additional reason for studying the effect of adiposity among the young is that it offers the possibility of reducing the bias that probably afflicts studies of middle-aged and older adults, on whom the great majority of mortality studies have focused. These studies have generally found a body mass index (BMI; weight (kg)/height $(m)^2$) greater than 30, a frequently used measure of adiposity, to be associated with increased all-cause and cardiovascular disease (CVD) mortality (12–18). However, findings have been less consistent for slightly elevated BMI and for lower-than-normal BMI (13–21). One possible reason for the inconsistent findings is that the effect of adiposity may be biased by the presence of preexisting medical conditions, which can affect body mass

as well as mortality and can distort estimates, a bias sometimes called reverse causality (20). One approach to reduce this bias is to study younger subjects, at ages when few subjects may have preexisting medical conditions and possible resulting weight loss (7).

Thus, public health importance, a knowledge gap, and the possibility of reducing bias due to reverse causality motivated this study of the relation between BMI in young adulthood and mortality. In particular, we examined the relation between BMI (in 5 categories: <18.5, 18.5–<25.0, 25.0–<30.0, 30.0–<35.0, and ≥35.0) measured in young adulthood and premature death from all causes, CVD, and cancer, using linked mortality files from the National Health Interview Survey (NHIS), a follow-up study of nationally representative samples of the US noninstitutionalized population.

MATERIALS AND METHODS

Study population

This study was based on the NHIS linked mortality files. The NHIS, conducted by the National Center for Health Statistics, is a repeated large-scale household interview survey of a statistically representative sample of the US civilian noninstitutionalized population. The details of NHIS procedures can be found elsewhere (22). To assure at least 10 years of follow-up, we used the NHIS survey and underlying cause-of-death data for the years 1987, 1988, and 1990–1995, in which smoking information was available among randomly selected samples of the entire study populations. We restricted analyses to participants who were 18–39 years of age at the time of the NHIS interview and had complete information on smoking status, age, gender, education, race/ethnicity, height, and weight. We also excluded 668 persons with extreme BMIs (BMI <15.0 or >99.0). We simply deleted those participants with missing or extreme values, because they accounted for less than 5% (4,614/116,942) of the whole study population. The final analysis was based on 112,328 subjects.

Body mass index

BMI was calculated as weight in kilograms divided by the square of height in meters. In each baseline survey, the weight and height of each participant were self-reported (74.1%) or reported by an adult family member (25.9%). BMI was categorized as follows: <18.5, 18.5–<25.0, 25.0–<30.0, 30.0–<35.0, or ≥35.0. These categories correspond to those defined by the World Health Organization for ''underweight,'' ''normal body weight,'' ''overweight,'' ''obesity I,'' and ''obesity II and III'' (23).

Mortality outcomes

Mortality ascertainment was based primarily upon results from a probabilistic match between NHIS and National Death Index death certificate records. It has been reported that cause-of-death information in the National Death Index is accurate for major disease categories (24) and that the matching algorithm yields good agreement (98.5%) (25). A complete description of the matching method is given elsewhere (26). In this study, the primary endpoints were all-cause mortality, death from cancer, and death from CVD. Deaths due to cancer were identified by means of *International Classification of Diseases*, Ninth Revision (ICD-9), codes 140–208 or *International Classification of Diseases*, Tenth Revision (ICD-10), codes C00–C97; deaths due to CVD were identified by ICD-9 codes 390–434 and 436–448 or ICD-10 codes I00–I78 (27).

Follow-up time was calculated from the quarter and year of NHIS interview to the quarter and year of death or the end of follow-up (December 31, 2006), whichever came first. We assumed that a participant's interview or death occurred at the middle of the quarter in which he/she was interviewed or died. For example, if a participant was interviewed in the first quarter of 1988 and died in the second quarter of 1998, then the follow-up time for this participant was $(1997 + 0.375) - (1987 + 0.125) = 10.25$ years. Participants who died in the same quarter and year as their NHIS interview were assumed to have 0.125 year of follow-up time. Participants who did not die by the end of follow-up were censored.

Statistical analysis

Age-adjusted mortality rates were calculated for each category of BMI through direct standardization to the age distribution of the entire study population with the use of 5-year age categories. To test the association of baseline BMI with premature death from all causes, CVD, and cancer, we fitted Cox proportional hazards regression models adjusting for potential confounders, including gender, age at baseline (years; continuous variable), education (less than high school, high school, or more than high school), race/ethnicity (white, black, or other), and smoking status (never, former, or current smoker). Additionally, we conducted subgroup analyses among never smokers to eliminate the confounding effect of smoking. BMI was primarily analyzed as a categorical variable, with a reference category of 18.5–<25.0. In supplemental analyses (see Web Table 1 (http://aje.oxfordjournals.org/)), we estimated hazard ratios for a 5-unit increment of BMI. For comparison, we fitted models using both age and amount of time in the study as the time scale. As Pencina et al. (28) reported, almost identical relative risk estimates were obtained for these 2 approaches with adjustment for age at baseline.

We tested for a linear trend in the BMI-mortality association by entering the BMI categories as a continuous variable into the regression models. The significance of interaction between gender and BMI was tested using the Satterthwaite adjusted chi-squared statistic (29). In sensitivity analysis, we examined the potential impact of preexisting medical conditions by restricting analyses to healthy participants (self-reported ''good,'' ''very good,'' or ''excellent'' health) or additionally excluding the first 5 years of follow-up. We tested the proportional hazards assumption by examining the relation between the scaled Schoenfeld residuals and survival time (30). No assumption violation was found for any variable included in the analyses.

All analyses were performed using SAS (release 9.2; SAS Institute Inc., Cary, North Carolina) and SUDAAN

(release 10.0; RTI International, Research Triangle Park, North Carolina) software, accounting for unequal probabilities of selection, nonresponse, and complex sample design. All *P* values calculated were 2-sided.

RESULTS

The cohort for this study consisted of 48,746 males and 63,582 females. The mean age at interview was 29.3 years (standard deviation, 6.0). During a median 16.1 years of follow-up, 3,178 deaths were documented, of which 733 were from cancer and 573 were from CVD. All deaths occurred before age 60 years, and the mean age at death was 41.8 years (standard deviation, 6.0). As compared with those with a lower BMI, participants with a higher BMI were older, less likely to be current smokers, less educated, and more likely to be black (Table 1 and Web Table 2). The detailed baseline characteristics of participants are presented in Table 1.

BMI and premature death from all causes

Among all participants, a J-shaped relation between BMI and premature death from all causes was observed, with a decreased risk for being overweight as compared with normal weight (Table 2). However, when analysis was restricted to never smokers, the hazard ratio for overweight was no longer less than 1, although the 95% confidence interval included 1. Among never smokers, the hazard ratios for premature death from all causes for overweight, obese, and extremely obese participants were 1.07 (95% confidence interval (CI): 0.91, 1.26), 1.41 (95% CI: 1.16, 1.73), and 2.46 (95% CI: 1.91, 3.16), respectively, compared with the normal BMI group (Table 2 and Figure 1); a significant trend of increasing risk of premature death with successively higher degrees of excess body mass was noted ($P < 0.001$). Little or no association between being underweight and premature death from all causes was observed. A slightly different pattern of association between BMI and all-cause mortality was found between male and female never smokers; a J-shaped relation was observed in males, whereas a monotonically increasing relation was observed in females (Table 3 and Figure 2).

BMI and premature death from CVD

Excess body weight was strongly related to an elevated risk of premature death from CVD, with a strong trend ($P < 0.001$) observed in both all participants and never smokers. However, the hazard ratio for each BMI category was much stronger in never smokers than in all participants. Among never smokers, the hazard ratios for overweight, obesity, and extreme obesity were 2.31 (95% CI: 1.50, 3.54), 4.34 (95% CI: 2.71, 6.96), and 8.36 (95% CI: 4.85, 14.40), respectively, compared with normal BMI (Table 2 and Figure 1). This monotonically increasing risk of premature CVD death for excess body weight was observed in both male and female never smokers, with comparable magnitudes (Table 3 and Figure 2). In analysis of major subgroups of CVD (ischemic heart disease, hypertensive heart disease, and stroke), a particularly strong positive association was observed for hypertensive heart disease (Web Tables 3 and 4).

BMI and premature death from cancer

Among all participants, cancer mortality among the overweight was associated with lower mortality, in comparison with those of normal weight (Table 2). Among never smokers, however, the risk of premature death from cancer monotonically increased with increasing BMI ($P = 0.001$). The hazard ratios for underweight, overweight, obese, and extremely obese never smokers were 0.63 (95% CI: 0.25, 1.61), 1.10 (95% CI: 0.82, 1.47), 1.25 (95% CI: 0.83, 1.88), and 2.28 (95% CI: 1.43, 3.64), respectively, compared with those with a normal-range BMI (Table 2 and Figure 1). However, when results were stratified by gender, such a monotonic increase in hazard ratios was seen only in female never smokers (Table 3 and Figure 2). In male never smokers, extreme obesity was associated with elevated cancer mortality, but moderately increased body weight (overweight and obesity) was not (Table 3 and Figure 2). Additional analysis of specific cancer sites (Web Tables 3 and 4) showed that overweight and obesity were associated with a higher risk of premature death from breast cancer (72 deaths).

BMI and premature death from external causes and other causes

For deaths from all external causes combined and from suicide, overweight was associated with a lower risk (Web Tables 3 and 4). For ''other causes'' of death, overall a J-shaped association was observed. For acquired immunodeficiency syndrome, overweight and obesity were associated with a lower risk, whereas for diabetes, obesity and extreme obesity were strongly associated with a higher risk.

DISCUSSION

In this large prospective study of a nationally representative cohort of US adults under age 40 years, elevated risk of premature death (before age 60 years) from all causes, CVD, and cancer was monotonically associated with increasing excess body weight among never smokers. A particularly strong association was seen for premature death from CVD. Among never smokers, the risk of premature death from CVD was approximately 2 times higher for overweight participants, 4 times higher for obese participants, and 8 times higher for extremely obese participants, respectively, relative to those whose BMI was in the normal range.

Our findings of increasing risk of CVD death in association with increasing BMI are generally similar to findings from several large cohort studies based on middle-aged or older populations (13–19). However, the associations in our study were much stronger than those in any of the other studies (13–19). For example, according to results based on follow-up of subjects in the National Health and Nutrition Examination Survey (19), compared with normal weight, the hazard ratio for CVD death for extreme obesity was approximately 1.5 in persons aged 70 years or older, 2.0 in persons aged

Table 1. Baseline Characteristics and Numbers of Deaths Observed During Follow-up, According to Body Mass Index, Among 112,328 Participants Aged 18–39 Years, National Health Interview Survey, 1987–1995

	BMI[a] Category															Total		
	Underweight (BMI <18.5)			Normal Weight (BMI 18.5–<25.0)			Overweight (BMI 25.0–<30.0)			Obese (BMI 30.0–<35.0)			Extremely Obese (BMI ≥35.0)					
	No.	%	Mean (SD) or Median	No.	%	Mean (SD) or Median	No.	%	Mean (SD) or Median	No.	%	Mean (SD) or Median	No.	%	Mean (SD) or Median	No.	%	Mean (SD) or Median
Total	4,718	4.2		65,047	57.9		29,596	26.4		9,106	8.1		3,861	3.4		112,328	100.0	
Age group, years																		
18–29	3,093	65.6		34,722	53.4		12,629	42.7		3,537	38.8		1,359	35.2		55,340	49.3	
30–39	1,625	34.4		30,325	46.6		16,967	57.3		5,569	61.2		2,502	64.8		56,988	50.7	
Mean age, years			27.0 (6.0)			28.7 (6.1)			30.2 (5.8)			30.7 (5.7)			31.2 (5.5)			29.3 (6.0)
Gender																		
Male	650	13.8		25,046	38.5		17,714	59.9		4,108	45.1		1,228	31.8		48,746	43.4	
Female	4,068	86.2		40,001	61.5		11,882	40.2		4,998	54.9		2,633	68.2		63,582	56.6	
Education																		
Less than high school	697	14.8		8,095	12.4		4,403	14.9		1,672	18.4		786	20.4		15,653	13.9	
High school	1,749	37.1		23,878	36.7		11,858	40.1		4,005	44.0		1,736	45.0		43,226	38.5	
More than high school	2,272	48.2		33,074	50.9		13,335	45.1		3,429	37.7		1,339	34.7		53,449	47.6	
Race/ethnicity																		
White	3,932	83.3		54,336	83.5		23,882	80.7		6,807	74.8		2,710	70.2		91,667	81.6	
Black	470	10.0		7,834	12.0		4,871	16.5		2,073	22.8		1,076	27.9		16,324	14.5	
Other	316	6.7		2,877	4.4		843	2.9		226	2.5		75	1.9		4,337	3.9	
Smoking status																		
Never smoker	2,576	54.6		35,854	55.1		15,824	53.5		5,003	54.9		2,219	57.5		61,476	54.7	
Former smoker	492	10.4		9,193	14.1		4,820	16.3		1,477	16.2		564	14.6		16,546	14.7	
Current smoker	1,650	35.0		20,000	30.8		8,952	30.3		2,626	28.8		1,078	27.9		34,306	30.5	
Median duration of follow-up, years			16.4			16.1			15.9			15.6			15.6			16.1
No. of deaths																		
All causes	109			1,598			870			364			237			3,178		
Cancer	27			413			178			74			41			733		
Cardiovascular disease	7			196			191			102			77			573		

Abbreviations: BMI, body mass index; SD, standard deviation.

[a] Weight (kg)/height $(m)^2$.

Table 2. Mortality Rates and Hazard Ratios for Premature Death From All Causes, Cardiovascular Disease, and Cancer, According to Body Mass Index, Among Participants Aged 18–39 Years, National Health Interview Survey, 1987–1995

Cause of Death	BMI[a] Category																		*P* for Trend
	Underweight (BMI <18.5)				Normal Weight (BMI 18.5–<25.0)[b]		Overweight (BMI 25.0–<30.0)				Obese (BMI 30.0–<35.0)				Extremely Obese (BMI ≥35.0)				
	No. of Deaths	MR[c]	HR	95% CI	No. of Deaths	MR	No. of Deaths	MR	HR	95% CI	No. of Deaths	MR	HR	95% CI	No. of Deaths	MR	HR	95% CI	
All causes																			
All participants[d]	109	164.8	1.16	0.94, 1.43	1,598	158.0	870	176.0	0.89	0.80, 0.98	364	233.2	1.29	1.14, 1.45	237	349.5	2.04	1.74, 2.40	<0.001
Never smokers[e]	31	93.7	1.10	0.72, 1.68	521	95.6	356	141.2	1.07	0.91, 1.26	145	175.0	1.41	1.16, 1.73	103	265.3	2.46	1.91, 3.16	<0.001
Cardiovascular disease																			
All participants	7	11.2	0.92	0.37, 2.26	196	19.9	191	37.7	1.60	1.25, 2.04	102	63.6	2.98	2.30, 3.87	77	113.4	5.25	3.89, 7.07	<0.001
Never smokers	3	8.9	2.50	0.66, 9.49	47	9.2	65	25.7	2.31	1.50, 3.54	40	47.5	4.34	2.71, 6.96	32	82.2	8.36	4.85, 14.40	<0.001
Cancer																			
All participants	27	46.7	0.96	0.64, 1.43	413	41.9	178	34.7	0.81	0.66, 0.98	74	45.4	0.97	0.75, 1.26	41	57.1	1.24	0.86, 1.78	0.79
Never smokers	6	21.1	0.63	0.25, 1.61	145	28.6	81	31.9	1.10	0.82, 1.47	31	36.7	1.25	0.83, 1.88	28	71.0	2.28	1.43, 3.64	0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MR, mortality rate.

[a] Weight (kg)/height $(m)^2$.

[b] Reference category (HR = 1).

[c] Age-standardized death rate per 100,000 person-years.

[d] In analyses including all participants, hazard ratios were adjusted for age at baseline (years; continuous variable), gender, race/ethnicity (white, black, or other), education (less than high school, high school, or more than high school), and smoking status (never, former, or current smoker).

[e] In analyses of never smokers, hazard ratios were adjusted for age at baseline (years; continuous variable), gender, race/ethnicity (white, black, or other), and education (less than high school, high school, or more than high school).

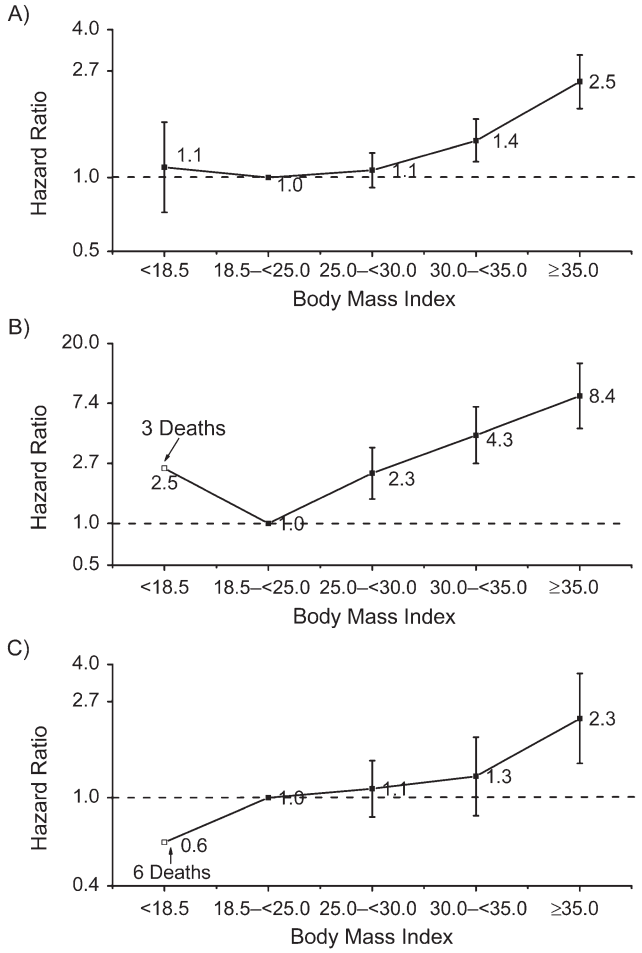

Figure 1. Multivariate hazard ratios for death from A) all causes, B) cardiovascular disease, and C) cancer according to body mass index (weight (kg)/height (m)^2) among never smokers aged 18–39 years, National Health Interview Survey, 1987–1995. Hazard ratios were adjusted for age at baseline (years; continuous variable), gender, race/ethnicity (white, black, or other), and education (less than high school, high school, or more than high school). Bars, 95% confidence interval.

60–69 years, and 2.5 in persons aged 25–59 years. Similarly, attenuated hazard ratios for excess body weight were observed in our supplemental analyses in the older age groups (Web Tables 5–9). The weaker association between CVD mortality and BMI at older ages is thought to reflect a real effect modification of age (31, 32), reverse causality (20), a survival effect (33), and reduced validity of BMI for measuring adiposity in older populations (34). In the only previous study that we found to have examined multiple categories of excess body weight in relation to CVD mortality in young adults (nonsmoking Korean men aged 20–39 years), the risk of death from CVD progressively increased with BMI in a pattern consistent with our results, although overall BMIs in that study were lower (10). A similar pattern of association between BMI and CVD mortality was also observed in a study carried out among 230,000 Norwegian adolescents (11). The strong association and monotonically increasing risk of CVD death with increasing excess body weight observed in the present study indicates the importance of weight management at younger ages to reduce premature death from CVD.

For premature death from cancer, we found a monotonic increase in risk with increasing BMI ($P = 0.001$), with a significant 2.3-fold increased risk for extremely obese young adults, among participants who had never smoked. The monotonic relation between BMI and premature death from cancer largely reflects the association for females, since deaths in females accounted for 72.5% (211/291) of all deaths occurring in never smokers. In males, extreme obesity but not moderately increased body weight (overweight and obesity) was related to elevated risk of cancer death. This gender difference may have resulted from the combination of unstable estimates for males (based on 80 deaths), different distributions of cancer sites (Web Table 10), and/or a real difference in the association of BMI with mortality for some cancer sites, such as colorectal cancer (35, 36). Consistent with our results, a monotonically increasing risk of cancer death associated with excess body weight was also observed in several large prospective studies in middle-aged and older populations, such as Cancer Prevention Study II (37) and the Korean Cancer Prevention Study (38), but not in the National Health and Nutrition Examination Survey study (19). In 2 previous studies of young adults, investigators reported increased cancer mortality rates for excess body weight as well, but the elevated risks were not statistically significant, perhaps because of small numbers of cancer deaths (7, 39).

Notably, we observed a higher risk of death from breast cancer for overweight and obesity, even when analysis was restricted to deaths that occurred before 50 years of age. It is generally accepted that obesity is associated with a lower risk of developing premenopausal breast cancer (36) and a poor breast cancer prognosis (40). However, results regarding the association of BMI with premenopausal breast cancer mortality are less consistent. In a pooled analysis of data from 57 prospective studies, Whitlock et al. (13) found a 15% increased risk of premenopausal breast cancer death (<60 years of age) per 5-unit increase in BMI, while no significant results were observed in the United Kingdom Million Women Study (41) or in a pooled analysis of data from 39 Asia-Pacific cohort studies (42).

For all-cause mortality among never smokers, we observed a slightly higher risk for overweight and moderately increased risks for obesity and extreme obesity, with a significant linear trend ($P < 0.001$), compared with normal weight. The shape and magnitude of the relation between BMI and all-cause mortality reflects the combined effects of BMI on cause-specific mortality (Web Tables 3 and 4). Because the distribution of causes of death (Web Table 11) and the association of BMI with cause-specific mortality (such as cancer mortality) varied largely between genders, we observed different patterns of association of BMI with all-cause mortality between men and women. A J-shaped relation, with slightly lower risk among the overweight, was observed in male never smokers, whereas the hazard ratios increased monotonically in association with increasing BMI in female never smokers. Notably, when we censored persons who died from acquired immunodeficiency syndrome at the time of death, the gender difference diminished, since we then observed a higher risk

Table 3. Mortality Rates and Hazard Ratios for Premature Death From All Causes, Cardiovascular Disease, and Cancer, According to Body Mass Index and Gender[a], Among Never Smokers Aged 18–39 Years, National Health Interview Survey, 1987–1995

Cause of Death	BMI[b] Category																		*P* for Trend
	Underweight (BMI <18.5)				Normal Weight (BMI 18.5–<25.0)[c]		Overweight (BMI 25.0–<30.0)				Obese (BMI 30.0–<35.0)				Extremely Obese (BMI ≥35.0)				
	No. of Deaths	MR[d]	HR[e]	95% CI	No. of Deaths	MR	No. of Deaths	MR	HR[d]	95% CI	No. of Deaths	MR	HR[d]	95% CI	No. of Deaths	MR	HR[d]	95% CI	
All causes																			
Males	10	299.5	1.56	0.82, 2.95	270	140.0	213	146.7	0.93	0.75, 1.16	77	227.7	1.27	0.98, 1.65	49	463.9	2.66	1.89, 3.75	0.001
Females	21	73.4	0.99	0.59, 1.67	251	71.9	143	132.5	1.43	1.18, 1.73	68	137.8	1.67	1.27, 2.19	54	190.1	2.49	1.79, 3.47	<0.001
Cardiovascular disease																			
Males	1	18.5	3.45	0.45, 26.46	23	14.0	40	27.7	2.15	1.23, 3.78	22	65.1	4.25	2.31, 7.82	15	137.9	9.03	4.47, 18.25	<0.001
Females	2	7.5	2.19	0.42, 11.57	24	7.0	25	23.6	2.55	1.42, 4.61	18	34.8	4.36	2.22, 8.53	17	60.9	7.99	3.77, 16.93	<0.001
Cancer																			
Males	0	0.0			38	22.7	30	20.4	0.86	0.50, 1.50	5	14.6	0.55	0.19, 1.58	7	70.9	2.78	1.00, 7.75	0.578
Females	6	23.2	0.69	0.27, 1.78	107	31.8	51	46.3	1.24	0.90, 1.70	26	52.4	1.59	1.02, 2.50	21	71.5	2.23	1.38, 3.61	<0.001

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; MR, mortality rate.

[a] Satterthwaite adjusted chi-squared statistic for the interaction between gender and BMI: for all causes, $P = 0.017$; for cardiovascular disease, $P = 0.971$; for cancer, $P = 0.225$.

[b] Weight (kg)/height $(m)^2$.

[c] Reference category (HR = 1).

[d] Age-standardized death rate per 100,000 person-years.

[e] Hazard ratios were adjusted for age at baseline (years; continuous variable), gender, race/ethnicity (white, black, or other), and education (less than high school, high school, or more than high school).

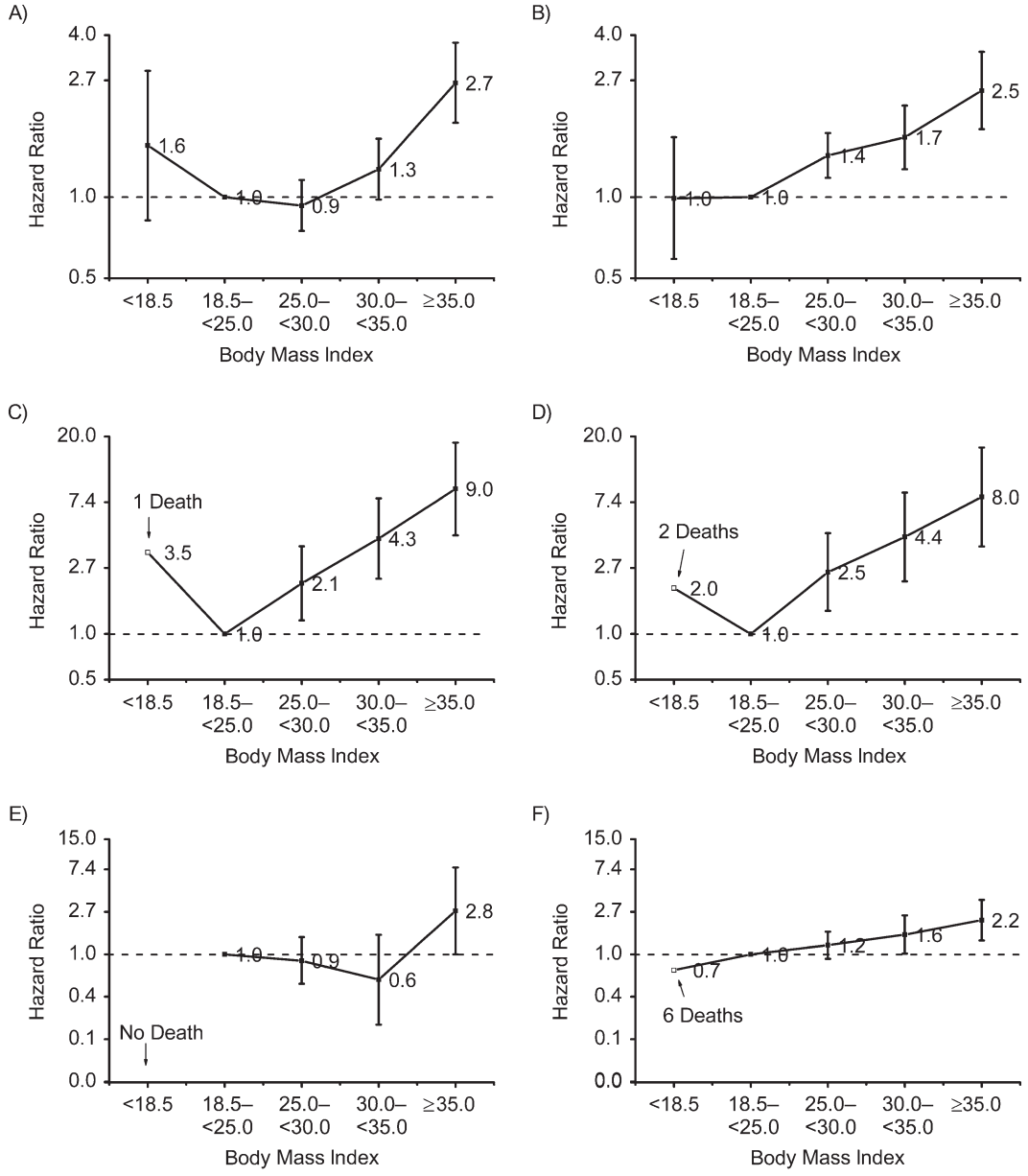

Figure 2. Multivariate hazard ratios for death from all causes (panel A, males; panel B, females), cardiovascular disease (panel C, males; panel D, females), and cancer (panel E, males; panel F, females) according to body mass index (weight (kg)/height (m)^2) and gender among never smokers aged 18–39 years, National Health Interview Survey, 1987–1995. Hazard ratios were adjusted for age at baseline (years; continuous variable), gender, race/ethnicity (white, black, or other), and education (less than high school, high school, or more than high school). Bars, 95% confidence interval.

for being overweight compared with normal weight among male never smokers. Generally similar to our study, previous studies in young adults or adolescents (7, 8, 11) found an elevated risk for excess body weight. Because of differences in study design (demographic characteristics of the study population, age at BMI measurement, and length of follow-up) and analytical method (BMI classification and smoking adjustment), the magnitude of the association between BMI and all-cause mortality varied across these studies.

In primary analyses, we did not account for preexisting medical conditions, which are expected to be uncommon in young adults (94.2% reported good or excellent health). However, in supplemental analyses, we assessed how these relatively uncommon preexisting medical conditions may have affected our primary results by restricting analyses to self-rated healthy participants with or without additional exclusion of the first 5 years of follow-up. The results of restriction-only analyses were quite similar to those in our

primary analyses, except for underweight (Web Table 6), but higher hazard ratios for higher BMI groups were observed in restriction-plus-exclusion analyses (Web Table 7). The slightly increased risk for underweight in the primary analyses disappeared in both supplemental analyses (no estimates were statistically significant), providing some evidence for the idea that a moderate degree of underweight in young, healthy adults may not be associated with an increased risk of premature death.

It is important to interpret the associations we report in terms of possible causal effects. The potential threats to validity of estimated causal effects of adiposity are many, and include the challenge of defining clearly the effect of interest in a way that corresponds to the study contrast (43), confounding by smoking and preexisting medical conditions, misclassification, and, of course, reverse causality (44). Although we cannot claim to have fully addressed all of these biases, use of a young, nonsmoking cohort should have reduced the impact of some, including two of those likely to be particularly strong—residual confounding by smoking and reverse causality. The strong associations we found, particularly for CVD, probably reflect a negative impact of excess body weight and other associated aspects of lifestyle on premature mortality, but we emphasize that the exact magnitude is difficult to determine precisely (43). If the true effect magnitudes were the same as those reported in this study and a weight reduction intervention could reduce the body weight and mortality rate for all overweight (BMI $\geq$25.0) young adults to the levels we found among those of normal weight, an estimated 11.0%, 51.1%, and 9.9% of deaths from all causes, CVD, and cancer, respectively, could be prevented among never smokers.

A strength of our study is that this is the first study to have assessed the association of BMI with premature death in a nationally representative cohort of US young adults, in whom preexisting medical conditions are less common and the relation between BMI and mortality is less likely to be importantly affected by reverse causality. Notably, the large sample size allowed us to examine the association between BMI and cause-specific mortality for both moderately and extremely elevated body weight. A limitation of our study is that we calculated BMI from self-reported or proxy-reported height and weight. Although the correlation between self-reported and measured BMI values is usually very high (about 90%), underweight people tend to overestimate their BMI and overweight people tend to underestimate their BMI (45, 46). This dependent measurement error could have biased the relative risk estimates in either direction (46). The bias is expected to be small for overweight and obese groups, but we should use particular caution in interpreting results for underweight and extreme obesity (46). Reither and Utz (47) found that proxy-reported BMI tended to underestimate self-reported BMI in the NHIS surveys. We performed additional analyses restricted to participants with self-reported BMI and noted that the hazard ratio for each BMI category changed very little. Another limitation is that only BMI, an indicator of general adiposity, was measured in our study. It would have been preferable to have additional information on waist circumference or waist:hip ratio, two commonly used measures of central adiposity which have been reported to be stronger predictors of death than BMI in some studies. A third limitation of our study is that we did not account for potential confounding effects of alcohol use and physical activity. However, the effects of these two factors should have been small. The association between alcohol use and body weight seems to be weak, especially for young adults (48, 49), so confounding by this factor is probably unimportant (50). In a meta-analysis of 49 studies (51), the summary relative risks of all-cause mortality for an elevated BMI were almost identical between studies that included physical activity as a covariate (relative risk = 1.23) and studies that did not (relative risk = 1.24).

In summary, in this large, nationally representative prospective study of young adults, elevated risk of premature death from all causes, cancer, and CVD was strongly associated with increasing excess body weight above the range labeled as normal by the World Health Organization, with the strongest association being observed for CVD. These relative associations were stronger than those usually reported for older adults and were monotonic in nonsmokers, although excess body weight may cause more deaths in older adults because of their high mortality rates.

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REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA*. 2010; 303(3):235–241.
2. Popkin BM, Gordon-Larsen P. The nutrition transition: worldwide obesity dynamics and their determinants. *Int J Obes Relat Metab Disord*. 2004;28(suppl 3):S2–S9.
3. Burke V. Obesity in childhood and cardiovascular risk. *Clin Exp Pharmacol Physiol*. 2006;33(9):831–837.
4. Daniels SR. Complications of obesity in children and adolescents. *Int J Obes (Lond)*. 2009;33(suppl 1):S60–S65.
5. Gill T, King L, Caterson I. Obesity prevention: necessary and possible. A structured approach for effective planning. *Proc Nutr Soc*. 2005;64(2):255–261.
6. Lloyd-Jones DM, Liu K, Colangelo LA, et al. Consistently stable or decreased body mass index in young adulthood and longitudinal changes in metabolic syndrome components: the Coronary Artery Risk Development in Young Adults Study. *Circulation*. 2007;115(8):1004–1011.
7. van Dam RM, Willett WC, Manson JE, et al. The relationship between overweight in adolescence and premature death in women. *Ann Intern Med*. 2006;145(2):91–97.
8. Neovius M, Sundström J, Rasmussen F. Combined effects of overweight and smoking in late adolescence on subsequent

mortality: nationwide cohort study. *BMJ*. 2009;338b496. (doi: 10.1136/bmj.b496).
9. Bender R, Jöckel KH, Trautner C, et al. Effect of age on excess mortality in obesity. *JAMA*. 1999;281(16):1498–1504.
10. Park HS, Song YM, Cho SI. Obesity has a greater impact on cardiovascular mortality in younger men than in older men among non-smoking Koreans. *Int J Epidemiol*. 2006;35(1): 181–187.
11. Bjørge T, Engeland A, Tverdal A, et al. Body mass index in adolescence in relation to cause-specific mortality: a follow-up of 230,000 Norwegian adolescents. *Am J Epidemiol*. 2008; 168(1):30–37.
12. McGee DL, Diverse Populations Collaboration. Body mass index and mortality: a meta-analysis based on person-level data from twenty-six observational studies. *Ann Epidemiol*. 2005;15(2):87–97.
13. Whitlock G, Lewington S, Sherliker P, et al. Body mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. Prospective Studies Collaboration. *Lancet*. 2009;373(9669):1083–1096.
14. Berrington de Gonzalez A, Hartge P, Cerhan JR, et al. Body mass index and mortality among 1.46 million white adults. *N Engl J Med*. 2010;363(23):2211–2219.
15. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. *N Engl J Med*. 2008;359(20):2105–2120.
16. Hu FB, Willett WC, Li T, et al. Adiposity as compared with physical activity in predicting mortality among women. *N Engl J Med*. 2004;351(26):2694–2703.
17. Jee SH, Sull JW, Park J, et al. Body mass index and mortality in Korean men and women. *N Engl J Med*. 2006;355(8): 779–787.
18. Yan LL, Daviglus ML, Liu K, et al. Midlife body mass index and hospitalization and mortality in older age. *JAMA*. 2006; 295(2):190–198.
19. Flegal KM, Graubard BI, Williamson DF, et al. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA*. 2007;298(17):2028–2037.
20. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. *N Engl J Med*. 1995;333(11):677–685.
21. Adams KF, Schatzkin A, Harris TB, et al. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med*. 2006;355(8):763–778.
22. Centers for Disease Control and Prevention. *National Health Interview Survey*. Atlanta, GA: Centers for Disease Control and Prevention; 2011. (http://www.cdc.gov/nchs/nhis.htm). (Accessed April 18, 2011).
23. WHO Expert Committee on Physical Status. *Physical Status: The Use and Interpretation of Anthropometry*. Geneva, Switzerland: World Health Organization; 1995.
24. Gittelsohn A, Royston PN. Annotated bibliography of cause-of-death validation studies. *Vital Health Stat 2*. 1982;(89):1–42.
25. National Center for Health Statistics. *NHANES I Epidemiologic Follow-up Survey (NHEFS)—Calibration Sample for NDI Matching Methodology*. Hyattsville, MD: National Center for Health Statistics; 2009. (http://www.cdc.gov/nchs/data/datalinkage/mort_calibration_study.pdf). (Accessed March 31, 2011).
26. Office of Analysis and Epidemiology, National Center for Health Statistics. *The National Health Interview Survey (1986–2004) Linked Mortality Files: Mortality Follow-up Through 2006. Matching Methodology*. Hyattsville, MD: National Center for Health Statistics; 2009. (http://www.cdc.gov/nchs/data/datalinkage/matching_methodology_nhis_final.pdf). (Accessed December 13, 2010).
27. Anderson RN, Miniño AM, Hoyert DL, et al. *Comparability of Cause of Death Between ICD-9 and ICD-10: Preliminary Estimates*. (National vital statistics reports, vol 49, no. 2). Hyattsville, MD: National Center for Health Statistics; 2001.
28. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. *Stat Med*. 2007;26(6):1343–1359.
29. Centers for Disease Control and Prevention. *NHANES Web Tutorial Frequently Asked Questions (FAQ)*. Atlanta, GA: Centers for Disease Control and Prevention; 2010. (http://www.cdc.gov/nchs/tutorials/NHANES/FAQs.htm). (Accessed December 13, 2010).
30. Grambsch PM, Thernau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81(3):515–526.
31. Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903–1913.
32. Lewington S, Whitlock G, Clarke R, et al. Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55,000 vascular deaths. Prospective Studies Collaboration. *Lancet*. 2007;370(9602):1829–1839.
33. Villareal DT, Apovian CM, Kushner RF, et al. Obesity in older adults: technical review and position statement of the American Society for Nutrition and NAASO, The Obesity Society. *Am J Clin Nutr*. 2005;82(5):923–934.
34. Micozzi MS, Harris TM. Age variations in the relation of body mass indices to estimates of body fat and muscle mass. *Am J Phys Anthropol*. 1990;81(3):375–379.
35. Pischon T, Nöthlings U, Boeing H. Obesity and cancer. *Proc Nutr Soc*. 2008;67(2):128–145.
36. Renehan AG, Tyson M, Egger M, et al. Body mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. *Lancet*. 2008;371(9612): 569–578.
37. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348(17): 1625–1638.
38. Jee SH, Yun JE, Park EJ, et al. Body mass index and cancer risk in Korean men and women. *Int J Cancer*. 2008;123(8): 1892–1896.
39. Burton A, Martin R, Galobardes B, et al. Young adulthood body mass index and risk of cancer in later adulthood: historical cohort study. *Cancer Causes Control*. 2010;21(12):2069–2077.
40. Carmichael AR. Obesity and prognosis of breast cancer. *Obes Rev*. 2006;7(4):333–340.
41. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. *BMJ*. 2007;335(7630):1134. (doi: 10.1136/bmj.39367.495995.AE).
42. Parr CL, Batty GD, Lam TH, et al. Body mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. *Lancet Oncol*. 2010; 11(8):741–752.
43. Hernán MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes (Lond)*. 2008;32(suppl 3):S8–S14.
44. Flanders WD, Augestad LB. Adjusting for reverse causality in the relationship between obesity and mortality. *Int J Obes (Lond)*. 2008;32(suppl 3):S42–S46.
45. Nyholm M, Gullberg B, Merlo J, et al. The validity of obesity based on self-reported weight and height: implications for

population studies. *Obesity (Silver Spring)*. 2007;15(1):197–208.
46. Keith SW, Fontaine KR, Pajewski NM, et al. Use of self-reported height and weight biases the body mass index-mortality association. *Int J Obes (Lond)*. 2011;35(3):401–408.
47. Reither EN, Utz RL. A procedure to correct proxy-reported weight in the National Health Interview Survey, 1976–2002. *Popul Health Metr.* 2009;7:2. (doi: 10.1186/1478-7954-7-2).
48. Suter PM. Is alcohol consumption a risk factor for weight gain and obesity? *Crit Rev Clin Lab Sci.* 2005;42(3):197–227.
49. Pajari M, Pietiläinen KH, Kaprio J, et al. The effect of alcohol consumption on later obesity in early adulthood—a population-based longitudinal study. *Alcohol Alcohol*. 2010;45(2):173–179.
50. Flanders WD, Khoury MJ. Indirect assessment of confounding: graphic description and limits on effect of adjusting for covariates. *Epidemiology.* 1990;1(3):239–246.
51. Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. *Obes Rev.* 2003;4(4):257–290.