ORIGINAL ARTICLE

Adiposity as Compared with Physical Activity in Predicting Mortality among Women

Frank B. Hu, M.D., Walter C. Willett, M.D., Tricia Li, M.D., Meir J. Stampfer, M.D., Graham A. Colditz, M.D., and JoAnn E. Manson, M.D.

ABSTRACT

BACKGROUND

Whether higher levels of physical activity can counteract the elevated risk of death associated with adiposity is controversial.

METHODS

We examined the associations of the body-mass index and physical activity with death among 116,564 women who, in 1976, were 30 to 55 years of age and free of known cardiovascular disease and cancer.

RESULTS

During 24 years of follow-up, 10,282 deaths occurred — 2370 from cardiovascular disease, 5223 from cancer, and 2689 from other causes. Mortality rates increased monotonically with higher body-mass-index values among women who had never smoked (P for trend <0.001). In combined analyses of all participants, adiposity predicted a higher risk of death regardless of the level of physical activity. Higher levels of physical activity appeared to be beneficial at all levels of adiposity but did not eliminate the higher risk of death associated with obesity. As compared with women who were lean (i.e., they had a body-mass index lower than 25) and active (they spent 3.5 or more hours exercising per week), the multivariate relative risks of death were 1.55 (95 percent confidence interval, 1.42 to 1.70) for lean and inactive women, 1.91 (95 percent confidence interval, 1.60 to 2.30) for women who were obese (defined as a body-mass index of 30 or higher) but active, and 2.42 (95 percent confidence interval, 2.14 to 2.73) for inactive, obese women. Even modest weight gain during adulthood, independent of physical activity, was associated with a higher risk of death. We estimate that excess weight (defined as a body-mass index of 25 or higher) and physical inactivity (less than 3.5 hours of exercise per week) together could account for 31 percent of all premature deaths, 59 percent of deaths from cardiovascular disease, and 21 percent of deaths from cancer among nonsmoking women.

CONCLUSIONS

Both increased adiposity and reduced physical activity are strong and independent predictors of death.

From the Departments of Nutrition (F.B.H., W.C.W., T.L., M.J.S.) and Epidemiology (F.B.H., W.C.W., M.J.S., G.A.C., J.E.M.), Harvard School of Public Health; and the Channing Laboratory (F.B.H., W.C.W., M.J.S., G.A.C., J.E.M.) and the Division of Preventive Medicine (J.E.M.), Department of Medicine, Harvard Medical School and Brigham and Women's Hospital — all in Boston. Address reprint requests to Dr. Hu at the Department of Nutrition, Harvard School of Public Health, 665 Huntington Ave., Boston, MA 02115, or at frank.hu@channing.harvard.edu.

N Engl J Med 2004;351:2694-703.

OBESITY AND PHYSICAL INACTIVITY ARE major public health problems in the United States. Approximately two thirds of Americans are classified as overweight or obese (defined as having a body-mass index [the weight in kilograms divided by the square of the height in meters] of 25 or higher),[1] and the vast majority do not engage in regular physical activity.[2] Persuasive evidence indicates that both obesity and physical inactivity are risk factors for the development of major chronic diseases and premature death.[3] However, the optimal weight and levels of physical activity for longevity continue to be debated, and few epidemiologic studies have examined adiposity and physical activity simultaneously in relation to mortality. It has been suggested that higher levels of physical fitness can eliminate the effect of excess weight and obesity on morbidity and mortality and that, thus, obesity may be a less important determinant of mortality than is fitness. However, evidence in support of this hypothesis has been limited and inconsistent.[4,5] We therefore extended our previous analyses of body-mass index and mortality in the Nurses' Health Study[6] to 24 years of follow-up to address the long-term relationship between body-mass index and mortality and to examine whether higher levels of physical activity attenuate the association between the body-mass index and mortality.

METHODS

The cohort of the Nurses' Health Study was established in 1976, when 121,700 female registered nurses who were 30 to 55 years old completed a mailed questionnaire about their medical history and lifestyle. Women in the study have provided current information regarding lifestyle and health conditions every two years since 1976. After excluding women with reported cardiovascular disease and cancer in the baseline questionnaire, we included 116,564 women in the analysis of obesity and mortality. The 1980 questionnaire asked about weight at 18 years of age; about 80 percent of the participants provided the information. Beginning in 1980, diet was assessed with the use of validated semiquantitative questionnaires about the frequency with which certain foods were eaten.[7] The study was approved by the Human Research Committee at the Brigham and Women's Hospital in Boston; completion of the self-administered questionnaire was considered to imply informed consent.

OVERALL AND ABDOMINAL ADIPOSITY

As a measure of overall obesity, we calculated the body-mass index. Self-reported weight was validated among 184 participants in the Nurses' Health Study who were living in the Boston area; self-reported weight was highly correlated with measured weight (r=0.96; mean difference [self-reported weight minus measured weight], −1.5 kg).[8] Weight as recalled at 18 years of age was also highly correlated with measured weight (r=0.87; mean difference [recalled weight minus measured weight], −1.4 kg) in the physical-examination records for the same age among 118 women from another cohort of female nurses.[9] In 1986, participants in the Nurses' Health Study reported direct measurements of their waists (at the umbilicus) and hips (at the largest circumference) to the nearest quarter of an inch.[10]

PHYSICAL ACTIVITY

In 1980 and 1982, women were asked to report the average number of hours they had spent each week during the previous year engaging in moderate physical activity (e.g., brisk walking) and in vigorous activity (e.g., strenuous sports and jogging). In 1986, women were asked to complete an eight-item questionnaire regarding the average time they spent per week walking, jogging, running, bicycling, swimming laps, playing tennis or squash, and participating in calisthenics. Similar data were collected in 1988, 1992, 1996, and 1998, which allowed us to calculate the average amount of time per week that was spent in moderate to vigorous activity (i.e., those, including brisk walking, that required 3.5 or more metabolic equivalents [MET] per hour) at each time point.[11] Our validation study indicated relatively good validity and reproducibility for the questionnaire.[12] The correlation between physical activity as reported in one-week recalls and that reported on the questionnaires was 0.79. The correlation between moderate-to-vigorous activity as reported in diaries and that reported on the questionnaires was 0.62. In a separate population of 103 women who were 20 to 59 years old, the correlation between the physical-activity score, as determined on a very similar questionnaire, and maximal oxygen consumption was 0.54.[13] In our previous analyses, the level of physical activity was a strong predictor of morbidity and mortality.[11,14-16]

END POINTS

Deaths were reported by the next of kin or the postal authorities or were ascertained through the Na-

tional Death Index. We estimate that follow-up for deaths was more than 98 percent complete.[17] For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin to review medical records. The underlying cause of death was assigned according to the *International Classification of Diseases, 8th Revision* (ICD-8). The primary end point in this analysis was death from any cause. We also conducted analyses according to the causes of death, which were divided into cancer (ICD-8 codes 140.0 through 207.9), cardiovascular disease (ICD-8 codes 390.0 through 458.9 and 795.0 to 795.9), and all other causes.

STATISTICAL ANALYSIS

In order to reduce the effects of underlying disease on weight, we used the baseline body-mass index in our analyses. We grouped women into nine categories according to the body-mass index as measured in 1976. We calculated the change between the weight at the age of 18 years and that in 1980 and grouped women into five categories. For all analyses, we excluded women who had reported cancer or cardiovascular disease at baseline. Person-years were calculated from the date of return of the 1976 questionnaire (for analyses of body-mass index) or the 1980 questionnaire (for analyses of physical activity) until the date of death or June 1, 2000, whichever came first. The relative risk of death was calculated as the rate of death among women within a given body-mass-index category as compared with that in the reference category. Age-adjusted analyses were conducted with the use of five-year age categories and the Mantel–Haenszel test.[18] The Cox proportional-hazards model[19] was used to adjust for age or other potential confounding variables, including smoking status, alcohol use, menopausal status and use or nonuse of hormone-replacement therapy, and presence or absence of a parental history of myocardial infarction before 60 years of age.

In our examination of the combined effects of physical activity and body-mass index on mortality, we used 1980 as the baseline. To represent long-term levels of physical activity most accurately and to reduce measurement error, we calculated the cumulative average number of hours of moderate-to-vigorous activity from all available questionnaires up to the start of each two-year follow-up interval.[15] In the secondary analysis, we controlled for the ratio of polyunsaturated to saturated fat consumed and for the intake of trans fat and fiber (all in quintiles). Likelihood-ratio tests were used to examine interactions between physical activity and obesity in relation to mortality with the comparison of nested models with and without the interaction variables of activity and obesity.

We calculated the population attributable risk conferred by excess weight (defined as a body-mass index of 25 or higher) and physical inactivity (defined as less than 3.5 hours per week of moderate-to-vigorous activity) to estimate the percentage of premature deaths in our cohort that, theoretically, would not have occurred if all women had been in the low-risk group (i.e, they were not overweight and engaged in regular exercise), assuming a causal relationship between the risk factors and mortality.[20] Statistical analyses were conducted with the use of SAS software, version 8.2. All reported P values are based on two-sided tests.

RESULTS

During 24 years of follow-up (approximately 2.7 million person-years), we identified 10,282 deaths — 2370 from cardiovascular disease, 5223 from cancer, and 2689 from other causes. We observed a J-shaped relationship between body-mass index and overall mortality in age-adjusted analyses (Table 1). However, when we restricted the analyses to women who had never smoked, in order to minimize confounding by this major cause of death,[21] we observed a direct monotonic relationship between the body-mass index and mortality. The lowest mortality was among women with a body-mass index of less than 23. There was a slight J-shaped relationship between body-mass index and mortality among former smokers, but the relationship was more evident among current smokers. Further adjustment for the number of cigarettes smoked per day and the duration of the period of smoking did not appreciably alter the relationship. Figure 1 shows multivariate relative risks of death from specific causes among women who had never smoked. The monotonic relationship held for deaths from cancer and, more strongly, for deaths from cardiovascular causes. For other deaths, the increased risk in the leanest group was primarily due to chronic obstructive pulmonary disease and cirrhosis.

In multivariate analyses, both excess weight or obesity and physical inactivity were significantly associated with increased mortality (Table 2). In the group of women who had never smoked, overall mortality was twice as high among those who were

Table 1. Body-Mass Index and Relative Risk of Death from All Causes during 24 Years of Follow-up.*

Group and Variable	Body-Mass Index†								
	<21.0	21.0–22.9	23.0–24.9	25.0–26.9	27.0–29.9	30.0–32.9	33.0–34.9	35.0–39.9	≥40.0
All women									
No. of deaths	2267	2259	1893	1184	1223	728	258	300	170
Person-yr	701,934	711,628	528,552	294,208	241,520	118,069	39,543	40,940	15,586
Age-adjusted relative risk (95% CI)	1.00	0.85 (0.80–0.90)	0.86 (0.81–0.91)	0.93 (0.86–1.00)	1.16 (1.08–1.25)	1.43 (1.31–1.55)	1.56 (1.38–1.78)	1.79 (1.59–2.02)	2.62 (2.24–3.06)
Multivariate relative risk (95% CI)	1.00	0.91 (0.86–0.97)	0.92 (0.87–0.98)	0.99 (0.93–1.07)	1.26 (1.18–1.36)	1.57 (1.44–1.71)	1.73 (1.52–1.97)	2.02 (1.79–2.29)	2.89 (2.47–3.38)
Women who never smoked									
No. of deaths	495	651	608	420	479	305	107	120	77
Person-yr	276,470	304,316	236,968	136,234	116,846	59,748	20,128	21,108	7853
Age-adjusted relative risk (95% CI)	1.00	1.03 (0.91–1.15)	1.11 (0.98–1.25)	1.27 (1.11–1.45)	1.67 (1.47–1.90)	2.10 (1.82–2.42)	2.26 (1.83–2.79)	2.43 (1.99–2.97)	4.07 (3.20–5.18)
Multivariate relative risk (95% CI)	1.00	1.02 (0.91–1.15)	1.09 (0.97–1.23)	1.23 (1.07–1.40)	1.61 (1.42–1.83)	1.96 (1.69–2.26)	2.10 (1.70–2.59)	2.29 (1.87–2.80)	3.71 (2.91–4.72)
Former smokers									
No. of deaths	327	401	378	208	229	149	60	86	47
Person-yr	152,326	169,776	126,367	68,642	56,992	27,913	10,322	11,296	4396
Age-adjusted relative risk (95% CI)	1.00	0.94 (0.81–1.09)	1.07 (0.92–1.24)	1.03 (0.87–1.23)	1.35 (1.14–1.60)	1.81 (1.49–2.20)	2.03 (1.54–2.68)	2.79 (2.20–3.54)	3.96 (2.92–5.38)
Multivariate relative risk (95% CI)	1.00	0.94 (0.81–1.09)	1.05 (0.91–1.22)	1.01 (0.85–1.21)	1.27 (1.07–1.51)	1.68 (1.38–2.04)	1.83 (1.39–2.42)	2.44 (1.92–3.11)	3.52 (2.59–4.80)
Current smokers									
No. of deaths	1430	1188	896	544	504	268	89	93	44
Person-yr	269,285	233,256	161,944	87,645	66,152	29,647	8753	8360	3225
Age-adjusted relative risk (95% CI)	1.00	0.86 (0.79–0.92)	0.84 (0.77–0.91)	0.92 (0.83–1.01)	1.15 (1.04–1.27)	1.40 (1.23–1.59)	1.66 (1.34–2.05)	1.88 (1.53–2.32)	2.28 (1.69–3.08)
Multivariate relative risk (95% CI)	1.00	0.86 (0.80–0.93)	0.83 (0.76–0.90)	0.90 (0.82–1.00)	1.13 (1.02–1.25)	1.34 (1.18–1.53)	1.60 (1.29–1.98)	1.79 (1.45–2.21)	2.07 (1.53–2.80)

* Multivariate relative risks were adjusted for age (<49, 50 to 54, 55 to 59, 60 to 64, or ≥65 years), smoking status (never smoked, former smoker, or current smoker [1 to 14, 15 to 24, or 25 or more cigarettes per day], adjusted only for the analyses for all women), parental history with respect to coronary heart disease, menopausal status and hormone use (never used hormones, used them in the past, or use them currently), level of physical activity (five categories), and alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, or ≥15 g per day). The physical-activity level and alcohol consumption were based on 1980 data. The numbers of deaths in the stratified analyses according to smoking status do not add up to the total number because of missing data on smoking status. P for trend <0.001 for all models. CI denotes confidence interval.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

obese (body-mass index, 30 or higher) as among those who were lean (body-mass index, less than 25). Mortality from cardiovascular disease was three times as high, and mortality from cancer was increased by 65 percent. Physical inactivity (less than one hour per week of exercise) was associated with a 52 percent increase in overall mortality, a doubling of mortality from cardiovascular disease, and a 29 percent increase in mortality from cancer. Adjustment for the body-mass index slightly attenuated these relative risks, but smoking status did not confound the associations.

We next examined the combined effects of body-mass index and physical activity on mortality (Table 3). Excess weight and obesity predicted an increase in mortality regardless of the physical-activity level, and there was no evidence that higher levels of physical activity attenuated the association between obesity and mortality. As compared with women who were lean (i.e., who had a body-mass index lower than 25) and active (they spent 3.5 or more hours exercising per week), the multivariate relative risks of death were 1.55 (95 percent confidence interval, 1.42 to 1.70) for lean and inactive

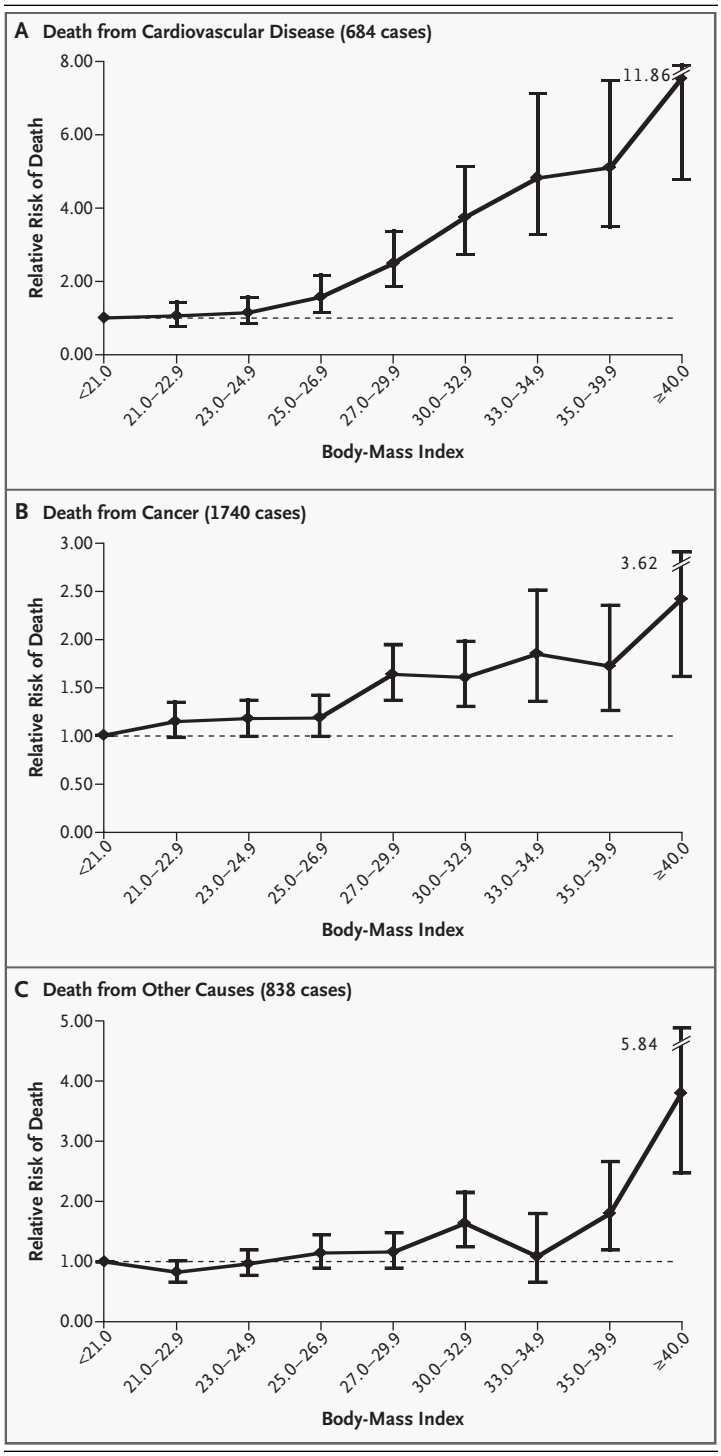

Figure 1. Multivariate Relative Risks of Death from Cardiovascular Disease (Panel A), Cancer (Panel B), and Other Causes (Panel C) According to Body-Mass Index among Women Who Had Never Smoked.

Risks were adjusted for age (<49, 50 to 54, 55 to 59, 60 to 64, or ≥65 years), presence or absence of a parental history of coronary heart disease, menopausal status and hormone use (never used hormones, used them in the past, or use them currently), physical activity (five categories; 1980 data), and alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, or ≥15 g per day; 1980 data). I bars denote 95 percent confidence intervals.

women, 1.91 (95 percent confidence interval, 1.60 to 2.30) for women who were obese (body-mass index, 30 or higher) but active, and 2.42 (95 percent confidence interval, 2.14 to 2.73) for inactive, obese women.

The association between physical activity and mortality was somewhat stronger among lean women than among overweight women, but the test for an interaction was not statistically significant (P=0.06 for overall mortality, P=0.37 for mortality from cardiovascular disease, and P=0.22 for mortality from cancer). Further adjustment for dietary factors (the ratio of polyunsaturated to saturated fat and the amount of trans fat and fiber) did not appreciably change the results. The designation of a higher level of physical activity (seven or more hours per week) as the cutoff point did not alter the overall findings.

In a secondary analysis for which 1986 was the baseline period, abdominal obesity (defined according to the waist-to-hip ratio) predicted increases in overall and cause-specific mortality that were independent of physical-activity levels. Women with the highest waist-to-hip ratios and the lowest levels of physical activity had the highest mortality (relative risk of death, as compared with women who had the lowest waist-to-hip ratio and the highest levels of physical activity, 2.84; 95 percent confidence interval, 2.25 to 3.57). Both the waist-to-hip ratio and the circumference of the waist were significant predictors of mortality after adjustments were made for body-mass index, physical activity, and other covariates (multivariate relative risks, from the lowest to the highest quintile, 1.00, 1.19, 1.40, 1.59, and 2.20 for waist circumference and 1.00, 1.14, 1.25, 1.51, and 1.84 for the waist-to-hip ratio; P<0.001 for both variables).

Table 4 shows the association between a change in weight during adulthood (from the age of 18 years until 1980) and overall mortality and cause-specific mortality (from 1980 through 2000), according to the level of physical activity as assessed in 1980. Even a modest weight gain (4 to 10 kg) was significantly associated with an increase in mortality (relative

Table 2. Multivariate Relative Risks of Death from Any Cause and Death from Specific Causes According to Body-Mass Index and Physical Activity.*

Variable			
		Death from Any Cause	
BMI	<25.0	25.0–29.9	≥30.0
Relative risk (95% CI)			
All participants	1.00	1.13 (1.06–1.20)	1.69 (1.57–1.82)
Women who had never smoked	1.00	1.36 (1.22–1.51)	1.99 (1.76–2.25)
Physical activity (hr per wk)†	≥3.5	1.0–3.4	<1.0
Multivariate relative risk (95% CI)			
Without BMI	1.00	1.18 (1.10–1.26)	1.52 (1.41–1.63)
With BMI‡	1.00	1.14 (1.06–1.22)	1.44 (1.34–1.55)
		Death from Cardiovascular Disease	
BMI	<25.0	25.0–29.9	≥30.0
Relative risk (95% CI)			
All participants	1.00	1.39 (1.22–1.58)	2.70 (2.35–3.11)
Women who had never smoked	1.00	1.53 (1.19–1.97)	3.15 (2.45–4.06)
Physical activity (hr per wk)†	≥3.5	1.0–3.4	<1.0
Multivariate relative risk (95% CI)			
Without BMI	1.00	1.56 (1.33–1.83)	1.97 (1.67–2.33)
With BMI‡	1.00	1.46 (1.24–1.71)	1.75 (1.48–2.07)
		Death from Cancer	
BMI	<25.0	25.0–29.9	≥30.0
Relative risk (95% CI)			
All participants	1.00	1.11 (1.02–1.21)	1.34 (1.20–1.50)
Women who had never smoked	1.00	1.31 (1.13–1.52)	1.65 (1.39–1.97)
Physical activity (hr per wk)†	≥3.5	1.0–3.4	<1.0
Multivariate relative risk (95% CI)			
Without BMI	1.00	1.07 (0.98–1.17)	1.29 (1.17–1.42)
With BMI‡	1.00	1.05 (0.96–1.15)	1.25 (1.13–1.38)

* The body-mass index (BMI), the weight in kilograms divided by the square of the height in meters, was measured in 1980; levels of physical activity were updated through 2000. Relative risks were adjusted for age (<49, 50 to 54, 55 to 59, 60 to 64, or ≥65 years), smoking status (never smoked, former smoker, or current smoker [1 to 14, 15 to 24, or 25 or more cigarettes per day], adjusted only for the analyses for all women), parental history with respect to coronary heart disease, menopausal status and hormone use (never used hormones, used them in the past, or use them currently), level of physical activity (three categories, adjusted in the BMI analyses), and alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, or ≥15 g per day). P for trend <0.001 for all models. CI denotes confidence interval.
† Physical activity was defined as moderate to vigorous activity, including brisk walking.
‡ BMI was adjusted in three categories (<25, 25 to 29.9, and ≥30).

risk of death, 1.15; 95 percent confidence interval, 1.01 to 1.31). The increased mortality associated with weight gain was not mitigated by higher levels of physical activity. Weight loss was associated with an increase in mortality from cardiovascular disease among sedentary women.

In our cohort, the prevalence of either excess weight (a body-mass index of 25 or higher) or physical inactivity (less than 3.5 hours per week) was 80.7 percent among all participants and 81.6 percent among women who had never smoked as of 1992. We estimate that excess weight and physical inactivity together accounted for 26 percent of all premature deaths, 47 percent of deaths from car-

Table 3. Multivariate Relative Risks of Death from Any Cause and Death from Specific Causes According to Joint Categories of Body-Mass Index and Physical Activity.*

Variable	Physical Activity (hr/wk)		
	≥3.5	1.0–3.4	<1.0
Death from any cause			
BMI <25.0			
No. of deaths	807	1540	1091
Person-yr	352,531	457,290	215,188
Relative risk (95% CI)	1.00†	1.18 (1.09–1.29)	1.55 (1.42–1.70)
BMI 25.0–29.9			
No. of deaths	298	699	518
Person-yr	92,827	167,442	89,787
Relative risk (95% CI)	1.28 (1.12–1.46)	1.33 (1.20–1.47)	1.64 (1.46–1.83)
BMI ≥30.0			
No. of deaths	136	450	410
Person-yr	31,726	78,675	53,032
Relative risk (95% CI)	1.91 (1.60–2.30)	2.05 (1.82–2.30)	2.42 (2.14–2.73)
Death from cardiovascular disease			
BMI <25.0			
No.	118	299	211
Relative risk (95% CI)	1.00†	1.51 (1.22–1.87)	1.89 (1.51–2.37)
BMI 25.0–29.9			
No.	57	171	13
Relative risk (95% CI)	1.58 (1.15–2.16)	2.06 (1.62–2.60)	2.52 (1.96–3.25)
BMI ≥30.0			
No.	32	149	133
Relative risk (95% CI)	2.87 (1.94–4.25)	4.26 (3.33–5.44)	4.73 (3.68–6.09)
Death from cancer			
BMI <25.0			
No.	489	851	544
Relative risk (95% CI)	1.00†	1.09 (0.98–1.22)	1.32 (1.17–1.50)
BMI 25.0–29.9			
No.	170	373	255
Relative risk (95% CI)	1.22 (1.02–1.45)	1.20 (1.05–1.38)	1.39 (1.19–1.62)
BMI ≥30.0			
No.	66	187	165
Relative risk (95% CI)	1.57 (1.21–2.03)	1.44 (1.21–1.71)	1.68 (1.40–2.01)

* Relative risks were adjusted for age (<49, 50 to 54, 55 to 59, 60 to 64, or ≥65 years), smoking status (never smoked, former smoker, or current smoker [1 to 14, 15 to 24, or 25 or more cigarettes per day]), parental history with respect to coronary heart disease, menopausal status and hormone use (never used hormones, used them in the past, or use them currently), and alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, or ≥15 g per day). The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters. CI denotes confidence interval.

† Women with 3.5 days or more per week of physical activity and a BMI of 25.0 or less served as the reference group.

Table 4. Weight Change and Relative Risk of Death According to Level of Physical Activity among Women Who Had Never Smoked.*

Variable	Weight Loss ≥4.0 kg	No Change	Weight Gain				P for Trend
			4–10 kg	10.1–19.9 kg	20.0–39.9 kg	≥40.0 kg	
Death from any cause							
No. of deaths	112	376	563	606	479	87	
Person-yr	41,704	197,790	238,797	191,787	101,638	11,305	
Multivariate relative risk (95% CI)†	1.16 (0.93–1.44)	1.00	1.15 (1.01–1.31)	1.35 (1.18–1.53)	1.87 (1.63–2.14)	3.02 (2.39–3.83)	<0.001
Relative risk according to physical activity (95% CI)							
<1.0 hr/wk	1.38 (0.98–1.95)	1.00	1.19 (0.96–1.48)	1.40 (1.14–1.72)	1.86 (1.50–2.31)	3.01 (2.15–4.20)	<0.001
1.0–3.4 hr/wk	1.00 (0.64–1.56)	1.00	1.19 (0.93–1.53)	1.33 (1.04–1.72)	1.92 (1.48–2.49)	2.90 (1.85–4.55)	<0.001
≥3.5 hr/wk	1.04 (0.71–1.50)	1.00	1.10 (0.88–1.37)	1.32 (1.05–1.65)	1.92 (1.50–2.47)	3.56 (2.11–6.01)	<0.001
Death from cardiovascular disease							
No. of deaths	33	65	88	125	143	24	
Multivariate relative risk (95% CI)†	1.55 (1.00–2.40)	1.00	1.02 (0.74–1.41)	1.51 (1.12–2.04)	2.84 (2.11–3.83)	4.05 (2.52–6.51)	<0.001
Relative risk according to physical activity (95% CI)							
<1.0 hr/wk	2.01 (1.05–3.88)	1.00	1.20 (0.73–2.00)	1.80 (1.12–2.88)	2.75 (1.72–4.41)	3.40 (1.66–6.97)	<0.001
1.0–3.4 hr/wk	1.23 (0.54–2.78)	1.00	0.76 (0.42–1.38)	1.16 (0.67–2.02)	2.38 (1.41–4.03)	3.42 (1.44–8.13)	0.007
≥3.5 hr/wk	1.39 (0.59–3.28)	1.00	1.13 (0.63–2.03)	1.54 (0.86–2.73)	3.98 (2.27–6.96)	8.96 (3.50–23.0)	<0.001
Death from cancer							
No. of deaths	47	217	320	335	228	37	
Multivariate relative risk (95% CI)†	0.93 (0.67–1.28)	1.00	1.14 (0.96–1.33)	1.32 (1.12–1.58)	1.63 (1.35–1.97)	2.44 (1.71–3.46)	<0.001
Relative risk according to physical activity (95% CI)							
<1.0 hr/wk	0.86 (0.48–1.53)	1.00	1.07 (0.80–1.43)	1.28 (0.97–1.70)	1.53 (1.13–2.08)	2.92 (1.84–4.63)	<0.001
1.0–3.4 hr/wk	0.84 (0.43–1.64)	1.00	1.17 (0.84–1.63)	1.35 (0.97–1.88)	1.81 (1.28–2.56)	1.96 (0.97–3.98)	<0.001
≥3.5 hr/wk	0.95 (0.58–1.56)	1.00	1.20 (0.90–1.59)	1.34 (1.00–1.80)	1.59 (1.12–2.25)	1.57 (0.57–4.29)	0.003

* Weight change reflects a loss or gain during the period from age 18 until 1980.

† Multivariate relative risks have been adjusted for age (<49, 50 to 54, 55 to 59, 60 to 64, or ≥65 years), smoking status (never smoked, former smoker, or current smoker [1 to 14, 15 to 24, or 25 or more cigarettes per day], adjusted only for the analyses for all women), parental history with respect to coronary heart disease, menopausal status and hormone use (never used hormones, used them in the past, or use them currently), level of physical activity (five categories, not adjusted in the stratified analyses), alcohol consumption (none, 0.1 to 4.9, 5.0 to 14.9, or ≥15 g per day), and body-mass index at age 18 as a continuous variable. CI denotes confidence interval.

diovascular disease, and 16 percent of deaths from cancer in the overall cohort, and for 31 percent of all deaths, 59 percent of deaths from cardiovascular disease, and 21 percent of deaths from cancer among women who had never smoked.

DISCUSSION

In this large cohort study of middle-aged women, the body-mass index and level of physical activity significantly and independently predicted mortality. A high level of physical activity did not eliminate excess mortality associated with obesity. Also, leanness did not counteract the increase in mortality conferred by inactivity. The lowest mortality was among physically active, lean women. Weight gain during adulthood was also a strong and independent risk factor for premature death, regardless of the level of physical activity.

Although obesity is clearly associated with an increase in mortality, the health consequences of being mildly to moderately overweight have been less clear. Many epidemiologic studies have suggested that leanness may be associated with an in-

crease in mortality.[3] However, there is little evidence that leanness is associated with a higher incidence of major chronic disease. To the contrary, even a body-mass index in the upper part of the normal range increases the risk of diabetes, hypertension, and coronary heart disease.[22] Although overall mortality is a simple and useful end point, epidemiologic studies of body weight and mortality are prone to methodologic biases that result from reverse causation (i.e., a low body-mass index is sometimes the result, rather than the cause, of underlying illness) and from confounding by smoking. These artifacts can lead to the J-shaped or U-shaped relationship between body-mass index and mortality and to a systematic underestimation of the effect of obesity on mortality.[21] In the present analyses, the linear relationship between body-mass index and mortality emerged only when the analyses were restricted to women who had never smoked. Our results are consistent with those of the Cancer Prevention Study II,[23] in which the relationship between body-mass index and mortality was substantially modified by smoking; among participants in that study who had never smoked, the mortality was lowest among women with a body-mass index of 22.0 to 23.4.

There is convincing evidence that increased levels of physical activity help reduce the risk of premature death.[3] Cardiorespiratory fitness, as measured by a treadmill-exercise test, is also a powerful predictor of mortality.[24] It has been hypothesized that physical fitness may eliminate the adverse effects of obesity on mortality. In an eight-year follow-up of 21,925 men 30 to 83 years of age in the Aerobics Center Longitudinal Study (in which 428 deaths occurred), Lee et al.[4] reported that physical fitness completely abrogated the excess mortality associated with increased body fat. However, in the Lipid Research Clinics Study,[5] both physical fitness and adiposity predicted overall mortality and mortality from cardiovascular disease, and physical fitness did not negate the association between obesity and excess mortality. Wessel et al.[25] recently reported that among 906 women who underwent coronary angiography for suspected ischemia, a higher level of self-reported physical fitness, but not a lower body-mass index, was significantly associated with a lower incidence of cardiovascular events. However, these results may be affected by residual confounding due to reverse causation, because existing coronary heart disease could lead to weight loss and could also limit exercise.

In the present study, we did not assess cardiorespiratory fitness. However, physical activity is the primary determinant of fitness that can be modified, and even moderate levels of physical activity (e.g., 30 minutes per day of brisk walking) can bring about levels of cardiorespiratory fitness that have been associated with a significant reduction in mortality.[26] In our study, the adverse effects of excess weight on mortality were persistent in both lower and higher physical-activity categories. Thus, our data do not support the hypothesis that a higher level of physical activity eliminates the excess mortality associated with increased body fat. Some unusually muscular persons with a body-mass index over 30 who are active and fit may have a relatively low risk of death, but such persons must be rare: only 2 percent of women in our study were both physically active and obese, and the overall risk of death in this group was twice that among lean and active women.

Measurement errors in self-reported levels of physical activity might have biased the association between physical activity and mortality toward the null hypothesis. In addition, obese participants might have exaggerated their physical-activity levels. However, our previous analyses demonstrated that the level of physical activity predicted the risk of diabetes[27] and coronary heart disease[14] in both lean and obese subjects. Because physical activity was assessed periodically during the follow-up period, our analyses with the use of the repeated measurements not only reduced errors in measurement but also took into account real changes in levels of physical activity over time.

Although our data are from women, they are broadly consistent with findings in two cohort studies of men,[28,29] which showed that the excess mortality associated with obesity was similar among physically active and sedentary men. In the Health Professionals Follow-Up Study,[29] the risk of death among lean and active men was not increased, but among the leanest men who were also sedentary, the risk of death was increased by a factor of two.

Because our study population is primarily white and is made up of registered nurses, the relative homogeneity of the cohort with respect to socioeconomic status and educational level reduces confounding and enhances the internal validity of the study. On the other hand, our results may not apply to other racial or ethnic groups. Previous studies of black and Hispanic populations have been limited but have generally found that broad ranges of the

body-mass index are associated with the lowest mortality.[30] Whether physical activity or fitness modifies the relationship between body-mass index and mortality in these populations remains to be studied.

In conclusion, we found that both the body-mass index and the level of physical activity were important and independent predictors of mortality and that a higher level of physical activity does not appear to negate the risk associated with adiposity. Women who were both lean and physically active had the lowest mortality. Also, our data on women who were followed for 24 years continue to show a monotonic relationship between the body-mass index and mortality among those who have never smoked, with the lowest mortality among women with a body-mass index of less than 23. Furthermore, even a moderate weight gain during adulthood was associated with an increase in mortality that was independent of the physical-activity level. Thus, public health campaigns should emphasize both the maintenance of a healthy weight and regular physical activity.

Supported by grants (HL24074, HL34594, P30 DK46200, and CA87969) from the National Institutes of Health. Dr. Hu is the recipient of an American Heart Association Established Investigator Award.

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999-2000. JAMA 2002;288:1723-7.
2. Simpson ME, Serdula M, Galuska DA, et al. Walking trends among U.S. adults: the Behavioral Risk Factor Surveillance System, 1987-2000. Am J Prev Med 2003;25:95-100.
3. Katzmarzyk PT, Janssen I, Ardern CI. Physical inactivity, excess adiposity and premature mortality. Obes Rev 2003;4:257-90.
4. Lee CD, Blair SN, Jackson AS. Cardiorespiratory fitness, body composition, and all-cause and cardiovascular disease mortality in men. Am J Clin Nutr 1999;69:373-80.
5. Stevens J, Cai J, Evenson KR, Thomas R. Fitness and fatness as predictors of mortality from all causes and from cardiovascular disease in men and women in the Lipid Research Clinics Study. Am J Epidemiol 2002;156:832-41.
6. Manson JE, Willett WC, Stampfer MJ, et al. Body weight and mortality among women. N Engl J Med 1995;333:677-85.
7. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985;122:51-65.
8. Willett W, Stampfer MJ, Bain C, et al. Cigarette smoking, relative weight, and menopause. Am J Epidemiol 1983;117:651-8.
9. Troy LM, Hunter DJ, Manson JE, Colditz GA, Stampfer MJ, Willett WC. The validity of recalled weight among younger women. Int J Obes Relat Metab Disord 1995;19:570-2.
10. Rimm EB, Stampfer MJ, Colditz GA, Chute CG, Litin LB, Willett WC. Validity of self-reported waist and hip circumferences in men and women. Epidemiology 1990;1:466-73.
11. Rockhill B, Willett WC, Manson JE, et al. Physical activity and mortality: a prospective study among women. Am J Public Health 2001;91:578-83.
12. Wolf AM, Hunter DJ, Colditz GA, et al. Reproducibility and validity of a self-administered physical activity questionnaire. Int J Epidemiol 1994;23:991-9.
13. Jacobs DR Jr, Ainsworth BE, Hartman TJ, Leon AS. A simultaneous evaluation of 10 commonly used physical activity questionnaires. Med Sci Sports Exerc 1993;25:81-91.
14. Manson JE, Hu FB, Rich-Edwards JW, et al. A prospective study of walking as compared with vigorous exercise in the prevention of coronary heart disease in women. N Engl J Med 1999;341:650-8.
15. Hu FB, Stampfer MJ, Colditz GA, et al. Physical activity and risk of stroke in women. JAMA 2000;283:2961-7.
16. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. N Engl J Med 2001;345:790-7.
17. Stampfer MJ, Willett WC, Speizer FE, et al. Test of the National Death Index. Am J Epidemiol 1984;119:837-9.
18. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J Am Stat Assoc 1963;58:690-700.
19. Cox DR, Oakes D. Analysis of survival data. London: Chapman and Hall, 1987.
20. Rothman KJ, Greenland S. Modern epidemiology. 2nd ed. Philadelphia: Lippincott-Raven, 1998.
21. Manson JE, Stampfer MJ, Hennekens CH, Willett WC. Body weight and longevity: a reassessment. JAMA 1987;257:353-8.
22. Willett WC, Dietz WH, Colditz GA. Guidelines for healthy weight. N Engl J Med 1999;341:427-34.
23. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med 1999;341:1097-105.
24. Blair SN, Cheng Y, Holder JS. Is physical activity or physical fitness more important in defining health benefits? Med Sci Sports Exerc 2001;33:Suppl:S379-S399.
25. Wessel TR, Arant CB, Olson MB, et al. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. JAMA 2004;292:1179-87.
26. Stofan JR, DiPietro L, Davis D, Kohl HW III, Blair SN. Physical activity patterns associated with cardiorespiratory fitness and reduced mortality: the Aerobics Center Longitudinal Study. Am J Public Health 1998;88:1807-13.
27. Hu FB, Sigal RJ, Rich-Edwards JW, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. JAMA 1999;282:1433-9.
28. Ajani UA, Lotufo PA, Gaziano JM, et al. Body mass index and mortality among US male physicians. Ann Epidemiol 2004;14:731-9.
29. Baik I, Ascherio A, Rimm EB, et al. Adiposity and mortality in men. Am J Epidemiol 2000;152:264-71.
30. Stevens J. Obesity and mortality in African-Americans. Nutr Rev 2000;58:346-53.